RAMESH KHANNA
RAYMOND T. KREDIET
EDITORS

Nolph and Gokal's Textbook of Peritoneal Dialysis

THIRD EDITION

Springer

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Third edition

Ramesh Khanna · Raymond T. Krediet
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Foreword by Karl D. Nolph

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Editors
Ramesh Khanna
University of Missouri – Columbia
Columbia, MO, USA
khannaR@health.missouri.edu

Raymond T. Krediet
University of Amsterdam
The Netherlands
C.N.deBoer@amc.uva.nl

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Foreword

The Nolph and Gokal *Textbook of Peritoneal Dialysis* in its third edition covers the history of peritoneal of dialysis from its early beginnings to the present and updates the many advances since the second edition was published. This book continues to represent a major source of knowledge about this dialysis therapy.

Two of the previous editors, Drs. Ram Gokal and Karl D. Nolph, are now retired from their full-time academic careers, and Drs. Ramesh Khanna and Ray Krediet, who were co-editors of the second edition, have skillfully assumed the total responsibility for editing this third edition. They have graciously included the names of Drs. Nolph and Gokal in the title of the third edition, and I thank them for this honor. Drs. Gokal and Nolph were the two co-editors of the first edition.

The 31 chapters included in this scholarly and comprehensive review of the history, science, and clinical practice of peritoneal dialysis should be a valuable resource for all those who have an interest in the therapy from any perspective.

The science reviewed includes peritoneal membrane structure and function, the peritoneal microcirculation, solute and water transport via the peritoneal membrane and lymphatics, animal models of peritoneal dialysis, pharmacological manipulation of transport, pharmacokinetics during peritoneal dialysis, and the chemistry and physiologic effects of various peritoneal dialysis solutions.

Epidemiology and demographic studies are included in chapters dealing with the current status of the therapy, survival outcome comparisons with patients on peritoneal and hemodialysis, and peritoneal dialysis in developing countries.

Clinical chapters review what is known about peritoneal dialysis in the elderly, long-term patients, children, and diabetics. The challenges of anemia, fast transport, achieving adequacy and volume control, changing peritoneal morphology and function, maintaining good quality of life, peritonitis, ultrafiltration failure, protein-energy malnutrition, renal osteodystrophy, cardiovascular disease and inflammation, vascular calcification, and other noninfectious complications are reviewed extensively in separate chapters. There are also individual chapters on peritoneal dialysis access and exit-site care, connectology, and automated peritoneal dialysis. There is a chapter dealing with intraperitoneal chemotherapy. A very important chapter is the one dealing with the nephrology nurse's role in organizing and managing a peritoneal dialysis program.

The completeness of the reviews and the breadth of topics imply that the book should be useful for medical students, medical residents, nephrology fellows, nephrologists (both clinical and academic), researchers (clinical, translational and basic), nurses, dieticians, social workers, bioengineers, pharmacologists, epidemiologists, and many others.

The authors of each chapter are highly qualified to write their respective chapters and most of the authors are among the top leaders in area of knowledge they review.

This book is being published at a time when, in my opinion and that of many others, peritoneal dialysis is underutilized. It is a therapy with a long list of advantages for many patients. It is also, for many, a good therapy with which to commence chronic dialysis therapy. One of the reasons for underutilization is clearly lack of knowledge of and lack of experience with peritoneal dialysis among nephrologists. Although nephrology training programs are expected to provide education and experience with peritoneal dialysis to their nephrology fellows, many programs are poorly equipped and/or motivated to do a good job in this regard. My hope is that this book, which contains state-of-the-art knowledge about peritoneal dialysis, will be a useful tool for those involved in worldwide efforts to increase understanding of peritoneal dialysis and what it has to offer many patients.

Karl D. Nolph, M.D.
Curators' Emeritus Professor of Internal Medicine
Division of Nephrology
University of Missouri School of Medicine
Columbia, Missouri

Contents

Contributors

G. Abraham
Professor of Medicine, Sri Ramachandra Medical College and Research Institute, Chennai, India

S.R. Alexander
Stanford University School of Medicine, Stanford, California, USA

J. Axelsson
Karolina Institutet, Divisions of Renal Medicine and Baxter Novum, Stockholm, Sweden

J.M. Bargman
University of Toronto General Hospital, Toronto, Ontario, Canada

P. Blake
Professor of Medicine, Division of Nephrology, Department of Medicine, London Health Sciences Centre and University of Western Ontario, London, Ontario

E.W. Boeschoten
Hans Mak Instituut, Naarden, The Netherlands

J.D. Bower
Chair of Nephrology and Hypertension, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA

J.M. Burkart
Wake Forest University Health Sciences Center, Bowman Gray School of Medicine, Winston Salem, North Carolina, USA

J.J. Carrero
Karolinska Institutet, Divisions of Renal Medicine and Baxter Novum, Stockholm, Sweden

M. Chan
Karolinska Institutet, Divisions of Renal Medicine and Baxter Novum, Stockholm, Sweden

A.S. De Vriese
AZ Sint-Jan AV, Department of Internal medicine, Brugge, Belgium

O. Devuyst
Division of Nephrology, Université catholique de Louvain Medical School, 10 Avenue Hippocrate, Brussels, Belgium

N.V. Dombros
Professor of Internal Medicine/Nephrology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

M. Feriani
Ospedale Umberto 1, Reparto di Nefrologia e Dialisi, Mestre-Venezia, Italy

M.F. Flessner
University of Mississippi Medical Center, Jackson, Mississippi

L. Fried
VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania

L. Gotloib
Ha'Emek Medical Center, Department of Nephrology, Afula, Israel

D.N. Granger
LSU Health Sciences Center, Department of Molecular & Cellular Physiology, Shreveport, Louisiana

E. Grapsa
Alexandra Hospital, Renal Unit, Athens, Greece

A. Gupta
Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

O. Heimbürger
Karolinska Institutet, Divisions of Renal Medicine and Baxter Novum, Stockholm, Sweden

A.J. Hutchison
Manchester Institute of Nephrology and Transplantation, Dialysis Unit, Manchester, United Kingdom

A.A. Kaptein
Department of Medical Psychology, Leiden University Medical Center, Medical Psychology, Leiden, The Netherlands

P. Kathuria
Department of Medicine, University of Oklahoma College of Medicine, Tulsa, Oklahoma, USA

R. Khanna
University of Missouri School of Medicine, Columbia, Missouri, USA

R.T. Krediet
Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

N.H. Lameire
University Hospital Ghent, De Pintelaan 185, Ghent, Belgium

V. Liakopoulos
Medical School, University of Thessaly, Larissa, Greece

B. Lindholm
Karolinska Institute, Div. of Renal Medicine and Baxter Novum, Stockholm, Sweden

M. Luongo
Massachusetts General Hospital, Boston, Massachusetts

I.C. MacDougall
Dept. of Renal Medicine, King's College Hospital, London, United Kingdom

P.J. Margetts
Dept. of Medicine, McMaster University, Div. of Nephrology, St. Joseph's Hospital, Hamilton, Ontario, Canada

K. Matsubara
Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden

R. Mehrotra
David Geffen School of Medicine at UCLA, and Los Angeles Biomedical Research Institute, Los Angeles, California, USA

M. Misra
University of Missouri School of Medicine, Columbia, Missouri, USA

S. Mujais
Renal Division, Baxter Healthcare Corporation, McGraw Park, Illinois, USA

D. Negoi
Assistant Professor of Clinical Medicine, Division of Nephrology, Department of Internal Medicine, University of Missouri School of Medicine, Columbia, Missouri, USA

W.K. Nichols
University of Missouri, School of Medicine, Columbia, Missouri, USA

A.R. Nissenson
David Geffen School of Medicine at UCLA, Department of Medicine, Division of Nephrology, Los Angeles, California, USA

K.D. Nolph
University of Missouri School of Medicine, Columbia, Missouri

D.G. Oreopoulos
Toronto Western Hospital, Toronto, Ontario, Canada

B. Piraino
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

B. Pratap
Sri Ramachandra University, Madras, India

B. Prowant
University of Missouri School of Medicine, Columbia, Missouri

A. Rastogi
David Geffen School of Medicine at UCLA, Department of Medicine, Division of Nephrology, Los Angeles, California

E. Ritz
University of Heidelberg, Department of Internal Medicine, Division of Nephrology, Im Neuenheimer Feld 162, Heidelberg, Germany

F. Schaefer
University Hospital for Children and Adolescents, Heidelberg, Germany

W. Smit
Department of Nephrology, Academic Medical Cente,r University of Amsterdam, Amsterdam, Netherlands

P. Stenvinkel
Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden

D.G. Struijk
Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

M.S.Y. Thong
Department of Clinical Epidemiology, Leiden University Medical Center, Medical Psychology, Leiden, The Netherlands

N.V. Topley
School of Medicine Cardiff University, Cardiff, United Kingdom

Z.J. Twardowski
University of Missouri School of Medicine, Columbia, Missouri

W. Van Biesen
University Hospital Ghent, Renal Division, Ghent, Belgium

R. van Westrhenen
Dutch Medicines Evaluation Board, Clinical Assessor FT1, The Hague, Netherlands

A. Vardhan
Institute of Nephrology & Transplantation, Manchester Royal Infirmary, Oxford Road, Manchester MI3 9WL, United Kingdom

B.A. Warady
Children's Mercy Hospital, Kansas City, Missouri

R. White
LSU Health Sciences Center, Shreveport, Louisiana, USA

K. Yeates
Division of Nephrology, Department of Medicine, Kingston General Hospital and Queens University, Kingston, Ontario

M.I. Yilmaz
Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden

M.M. Zweers
Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

Chapter 1
History of Peritoneal Dialysis

D. Negoi and K.D. Nolph

The concept of the uremic syndrome caused by blood and tissue accumulation of toxic substances normally excreted in the urine was an established idea in the middle of nineteenth century [1, 2]. In the late 1800 s, renal insufficiency and concurrent uremic intoxication were treated only by simple and ineffective measures such as blood letting, dietary changes, digitalis, infusion of normal saline followed by forced diuresis, purgation, and diaphoresis [1, 3]. The period of time surrounding the beginning of the twentieth century was marked by intense research and growth in scientific knowledge that allowed the birth of clinical dialysis, a lifesaving therapy for patients with renal failure.

The Discovery of Principles of Dialysis: Diffusion and Ultrafiltration. Thomas Graham and Henri Dutrochet

The development of peritoneal dialysis in early 1900 s as a form of renal replacement therapy was made possible by remarkable progress in science and medicine that took place in the eighteenth and nineteenth centuries. In the field of physical chemistry, it was Thomas Graham (1805–1869) who completed vast work that included the discovery of laws of diffusion of gases (Graham's law: the rate of diffusion of a gas is inversely proportional to the square root of its molecular weight), investigation of osmotic force, and separation of chemical or biological fluids by dialysis [4–7]. His work represents the theoretical foundation upon which clinical dialysis could later develop. Graham was born in Glasgow, Scotland; his father wanted him to study theology and enter the Church of Scotland. He became a student at the University of Glasgow in 1819, were he was attracted by the field of chemistry and attended lectures in chemistry against his father's wishes. His passion and dedication for this science caused him later to alienate his father. Graham became professor of chemistry at numerous colleges, his lectures being attended by aspirants in chemistry and medicine, as their training was similar during that time. Between 1846 and 1861, he published an important series of papers in the *Philosophical Transactions of the Royal Society:* "The motion of gases" in 1846, followed by "The motion of gases part II" 3 years later, "The Bakerian lecture on osmotic force" in 1854, and "Liquid diffusion applied to analysis" in 1861 [4]. His studies led him to the innovative distinction between "crystalloids" and "colloids," which he defined based on their ability to diffuse through a semi-permeable membrane and crystallize. He introduced the concept of "semi-permeable" membrane and redefined the term *dialysis*. In his experiments, he separated solutions containing sugar or gum arabic from water, using sheets of vegetable parchment impregnated with starch, acting as a "dialytic septum." He noted that sugars can cross the semi-permeable membrane and called them crystalloids, as opposed to gum arabic, which did not cross the vegetable, semi-permeable membrane, and called these types of substances colloids. He wrote: "The molecules are moved by force of diffusion. . . It may perhaps be allowed to me to apply the convenient term *dialysis* to the method of separation by the method of diffusion through a system of gelatinous matter" [4]. As mentioned by Gottschalk, prior to this new meaning given to the term *dialysis*, this was used "to describe dissolution of strength or weakness of the limbs, coming from the Greek, to part asunder" [4].

Graham also suggested that animal tissue could be used as a functioning semi-permeable membrane and showed that the rate of diffusion of different molecules is inversely related to the molecular size. He also demonstrated that urea, which is present in the urine, can be dialyzed through semi-permeable membranes. Because of these brilliant

D. Negoi (✉)
Assistant Professor of Clinical Medicine, Division of Nephrology, Department of Internal Medicine, University of Missouri School of Medicine - Columbia, Missouri, USA
e-mail: negoid@health.missouri.edu

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discoveries that proved that solutes can be "dialyzed" or separated from a fluid using a semi-permeable membrane, he is considered to be the "father of modern dialysis."

Prior to Graham, it was René Henri Joachim Dutrochet (1776–1846) who introduced the term *osmosis* to describe the movement of water through membranes that hamper the passage of solutes but allow the passage of water down concentration gradients of salts [5]. This is an early description of osmotic induced ultrafiltration. Some authors consider Dutrochet as being the "grandfather of dialysis" because he discovered the principle that explains osmotic ultrafiltration [5].

The Peritoneal Cavity and the Peritoneal Membrane

Egyptian morticians observed the peritoneal cavity as early as 3000 B.C. and recorded their observation in the Ebers papyrus [8, 9]. They described it as a "definite entity in which the viscera were somehow suspended" [8]. In the Roman times it was Galen, the Greek physician, who made thorough descriptions of the peritoneal cavity and peritoneum, which he observed by treating injuries of the gladiators [9].

Extensive knowledge of the peritoneal cavity started to accumulate in the last half of the nineteenth century, as the abdomen was often explored due to developments in abdominal surgery (see Table 1.1). In the early 1860 s, von Recklinghausen [10, 11] comprehensively described the peritoneal cavity, even proposing it was lined entirely by mesothelial cells and noting the lymphatic drainage. In 1877**,** Georg Wegner**–** from the Surgical Clinic of the University of Berlin – published his "surgical comments on the peritoneal cavity" [12]. His observations were the results of experiments in rabbits where he injected hypertonic solutions of sugar, salt, or glycerin in an animal's peritoneal cavity and found that intraperitoneal fluid volume increased. When hypotonic solutions were injected in the peritoneum, their volume decreased. In 1893, Beck described the peritoneal mesothelium and possible connections of the peritoneal cavity with lymphatics [13] and Kolossow described paths between the mesothelial cells, which he did not believe were connected with the lymphatic system [13]. The famous English physiologist E.H. Starling and his collaborator from Guy's Hospital in London, A.H. Tubby, specifically studied the transport of fluids and solutes across the peritoneal membrane and published their result at the end of nineteenth century [14]. They determined that solute exchange was primarily between solutions in the peritoneal cavity and blood, lymphatic transport being considered negligible. They reproduced Wegner's results and also studied the transport of indigo carmine and methylene blue and concluded that, as with water, they can cross the peritoneal membrane in both directions.

Further insight into peritoneal physiology was acquired in the early years of the twentieth century. Some of the most well-known works during that period of time are those published by Cunningham, Putnam, and Engel. Cunningham [8, 15] studied the absorption of glucose from the peritoneal cavities of rats in 1920 and reviewed extensively the peritoneal structure and function in 1926. At the same time, Putnam described the dog peritoneum "as a dialyzing membrane" and brought more evidence that the peritoneum was a semi-permeable membrane that allowed bidirectional water and solute transport on the basis of the principles of osmosis and diffusion. His experiments were complex, including observations on dwell time, flow rate, fluid removal, and exchange of various solutes [16]. Advanced animal studies were done by Engel, who published his conclusions in 1927 [17]. He showed that animals could not tolerate extensive ultrafiltration and that solute clearance is directly proportional with its molecular size, the flow rate of the intraperitoneal fluid, peritoneal surface area, and blood flow. These were the times when the first attempts of therapeutic peritoneal dialysis were done in humans.

Table 1.1 Pioneering animal studies of the peritoneal membrane

Investigator	Findings	Date
Recklinghausen [10, 11]	Described mesothelium and lymphatic drainage	1862–1863
Wegner [12]	Transport of solutes and water across the peritoneum	1877
Beck [13]	Described mesothelium	1893
Kolossow [13]	Described intermesothelial paths	1893
Starling and Tubby [14]	Transport of solutes and water across the peritoneum	1894
Cunningham [8, 15]	Peritoneal transport and structure	1920–1926
Putnam [16]	Described the peritoneum "as a dialyzing membrane"	1923
Engel [17]	Peritoneal transport	1927

The Birth of Clinical Dialysis

In 1913–1914, Abel, Rowntree, and Turner developed a device they called the "artificial kidney" or "vivi-diffusion apparatus" using semi-permeable collodium membranes specifically designed to substitute the role of the kidneys in eliminating toxic substances when these organs are failing [4, 18]. Although they experimented with this apparatus only in animals, their intention was to develop a method of extracorporeal dialysis that could be used in humans. Their work was terminated in 1914 because of World War I. The first human hemodialysis was done in 1924 in Germany by Georg Haas, who apparently was unaware of Abel's work in the United States [6]. Also in Germany, Heinrich Necheles had great interest in "external" dialysis, and was searching for a better dialysis membrane for his dialyzers [19]. His work with goldbeater's skin, which was a commercial preparation of visceral peritoneum from calves' abdomen, must have stimulated Ganter to perform peritoneal dialysis [19].

First Attempts at Peritoneal Dialysis – Georg Ganter (1923)

Georg Ganter from Würtzburg, Germany is credited with the first publication regarding application of peritoneal dialysis to treat uremia. He was aware of the hemodialysis attempts of his contemporaries, and was captivated by the idea of using a patient's own natural membranes for dialysis. He considered that application of external dialysis at the bedside would be complicated due to difficulties in establishing the extracorporeal circuit and toxic effects of the hirudin, which was used as anticoagulant [20].

In 1923, Ganter published the result of his investigations in humans and animals in his only paper, entitled "On the elimination of toxic substances from the blood by dialysis" [21]. He described his 1918 attempt to remove uremic toxins in a young man with glomerulonephritis using pleural lavage. He removed a pleural effusion and replaced the fluid with a single infusion of 750 mL of a sodium chloride solution and noted clinical improvement. The patient still died a few days after discharge, probably because Ganter did not recognize that uremic toxins will build up again [7]. He then carried out experiments on rabbits and guinea pigs made uremic by ligation of ureters and found that intraperitoneal instillation of saline solution improved the symptoms of uremia and blood urea nitrogen levels. In order to perform fluid exchanges, he used drainage tubes implanted in the peritoneal cavity and instilled saline solutions in volumes of approximately 50 mL, which were left in the peritoneal cavity for about 3 h. After this period of time the fluid was drained, with an average volume of 10–30 mL being recovered. The procedure was then repeated up to four times. He found that, after each exchange, there was almost complete equilibration of nonprotein nitrogen in the dialysate with blood concentrations and that some of the instilled fluid was absorbed. He also noted improvement in the animal's uremic symptoms after peritoneal lavage: their appetite and activity level were improved after each exchange. Ganter used this procedure in a woman with acute uremia from bilateral ureteral obstruction due to uterine carcinoma: her condition improved transiently after a single intraperitoneal infusion of 1.5 L of physiologic saline. In another patient with a coma due to diabetic ketoacidosis, he instilled 3 L of saline intraperitoneally, and the patient's mental status improved transiently.

His unprecedented clinical experience with intermittent peritoneal dialysis was limited, but he envisioned that this procedure could become a new form of therapy and recognized a few aspects of primary importance in its applicability: adequate access is extremely important to maintain good inflow and outflow, peritoneal infection is the most common complication and the use of sterile solutions can help prevent this complication, a large volume of dialysate is necessary in order to remove the uremic toxins, and he suggested 1–1.5 L per exchange. Dwell time also influences solute clearance and it was considered necessary that the fluid remain in the peritoneal cavity until the equilibrium between the blood and dialysate is reached. Additionally, he recommended the use of hypertonic solutions to promote fluid as well as toxin removal.

Unfortunately, Ganter did not continue research in the field of peritoneal dialysis, which evolved very slowly in the following years, probably because most of the attempts were unsuccessful in saving the life of patients.

Early Experience in Peritoneal Dialysis (1923–1950)

In 1950, Odel and his colleagues [22] summarized and analyzed the published experience with peritoneal lavage (dialysis) between 1923 and 1948 and formulated some recommendations based on published results and their own experience. They found only five papers published on this topic from 1923 to 1938 (including Ganters' paper) and as many as 33 papers between 1946 and 1948. No papers were published during World War II (1939–1945), but the

number of fatal renal failure cases caused by trauma in both civilian and military patients brought this problem to the center of attention and stimulated research. They identified 101 reported patients treated by peritoneal lavage, including three patients treated by the authors. Sixty-three of the patients had reversible causes of renal failure, 32 had irreversible renal lesions, and two had an indeterminate diagnosis. Of the 101 patients reported in that 25-year period, only 36 survived: 32 patients with reversible uremia, two of the patients considered to have irreversible renal lesions, and two of those with indeterminate renal diagnosis. The most common causes of death were pulmonary edema (40%), uremia (33%), and peritonitis (15%).

The peritoneal dialysis technique was applied in a very diverse way: 22 of the reported patients received intermittent treatments, with 1–6 lavages for exchanges of 15 min to 6 h duration and 75 of the patients received continuous treatment of 1 to 21 days duration. In four cases the type of intraperitoneal lavage was unknown. There was also a great variety of solutions used for peritoneal lavage with 14 different types reported: different concentrations of sodium chloride and dextrose solutions, Ringer's, Rhoads', Hartmann's two modified Tyrode's, "A," "P," modified "P" solutions, Kolff's and two unknown.

Rubber catheters introduced in the peritoneal cavity with the help of trocars, as well as glass or stainless steel tubes with multiple perforations, were used for inflow of the dialysis fluid into the peritoneal cavity, while mushroom-tip catheters of large bore, or stainless steel sump drains "similar to those perforated suction tubes used in operating rooms" were used for drainage of the peritoneal fluid from the peritoneal cavity. Catheter complications were very common and difficult to deal with: these included leakage of fluid, especially around the rigid tubes, bacterial contamination of the tubes, outflow obstruction caused by pocketing of the omentum, visceral perforation caused by the rigid tubes, and intra-abdominal hemorrhage. Other complications were noted: depletion of plasma proteins, sometimes to critical levels, in addition to derangements of the acid–base, electrolytes, and water balance. Odel and his colleagues were convinced that composition of the fluid used for dialysis was of the greatest importance and the main cause of experimental and clinical peritoneal dialysis failure was related to the imbalance of water and electrolytes. They advocated the use of a solution that would not change the normal electrolyte composition of the plasma, would permit maximal diffusion of waste products from the blood, would permit mild dehydration (moderately hypertonic solution), and would not irritate the peritoneum (the solution needs to have a pH close to that of the plasma).

It is worth noting that the early investigators were aware of the fact that peritoneal lavage aided in removal of metabolic waste products, but the concept of adequate dialysis had yet to be discovered. Frequently, the duration of dialysis was too short, or if time of dialysis was longer, the amount of dialysis fluid was not sufficient to achieve sufficient removal of waste products.

Although mortality with peritoneal lavage was high, it offered hope for effective therapy in some patients, especially in patients with reversible causes of renal failure, who were able to recover renal function before the peritoneal dialysis procedure failed.

Of the papers published after World War II, the most important are considered to be those of doctors Howard Frank, a surgical intern, Arnold Seligman, trained in chemistry, and Jacob Fine, their mentor and chief of service at Beth Israel Hospital in Boston. They worked under contract with the "Office of Scientific Research and Development" (OSRD), the federal agency created by President Franklin D. Roosevelt in 1941 to promote research for military purposes in medicine and weapons technology [23]. Their task was to work on treatments for acute renal failure in trauma patients, and because they wanted to avoid the use of anticoagulants they opted for peritoneal lavage as a good possibility. As the literature regarding the use of natural membranes was limited at the time they embarked on their project, the team began by doing very elegant studies of peritoneal irrigation in non-nephrectomized and nephrectomized uremic dogs [24]. They calculated the optimal flow rate and volume of peritoneal irrigation fluid in order to obtain the maximum urea clearance and to prevent uremia, compared the blood urea clearance by peritoneal irrigation with clearance through the kidneys, and experimented with irrigation of various parts of the gastrointestinal tract and pleural cavity, which proved to be ineffective means of urea removal. The irrigation fluid used was Ringer's solution containing glucose, which was later changed to a Tyrode's solution, in their search for the right solution. Their uremic, nephrectomized dogs survived for 3–10 days with peritoneal dialysis and none of them died of uremia, but rather of peritonitis. Their method involved the use of two catheters introduced into the peritoneal cavity, one of them used for inflow of irrigation fluid and the other one for drainage. Continuous irrigation of the peritoneal cavity was done for 20 h daily for 2 days and 8–12 h daily thereafter, with the outflow rate being modified in order to prevent overdistension of the peritoneal cavity. Encouraged by the results of their experimental work in dogs, in 1945 they decided to try the treatment on a patient who presented to the emergency room at Beth Israel Hospital with acute renal failure from sulfathiazole administration [23, 25]. Their treatment was successful and the patient recovered after 7 days of dialysis, using the same technique as described before. This technique can be called an "intermittently continuous irrigation," because the fluid was introduced in the peritoneal cavity by continuous irrigation, but there were periods of time when the irrigation was stopped and so peritoneal dialysis did not take place. It is interesting that their papers do

not make any reference to the first successful use of continuous peritoneal dialysis in a patient with urinary tract obstruction by Wear, Sisk, and Trinkle, and they were probably unaware of this achievement [22, 26]. Fine's group's success became known immediately and gave an impulse to others to use their technique. Motivated by their own accomplishment, they continued work on peritoneal dialysis and tried to perfect their work. They treated 18 more patients, but only four survived [22]. They found that peritonitis was the greater risk associated with the procedure, and the main reason for considering this method was still in the investigational phase [27]. They improved the irrigation fluid by decreasing the sodium chloride concentration to 0.74% to reduce the risk of hyperchloremia, added gelatin, and increased the glucose concentration to increase the fluid tonicity so they were able to control edema. Bicarbonate was used in the irrigation fluid to combat acidosis. The bicarbonate solution was sterilized separately and added to the solution before irrigation was initiated. Their closed system was bulky and seemed complicated, and the procedure required the constant attendance of a nurse (see Figs 1.1 and 1.2). The dialysis solution was sterilized and

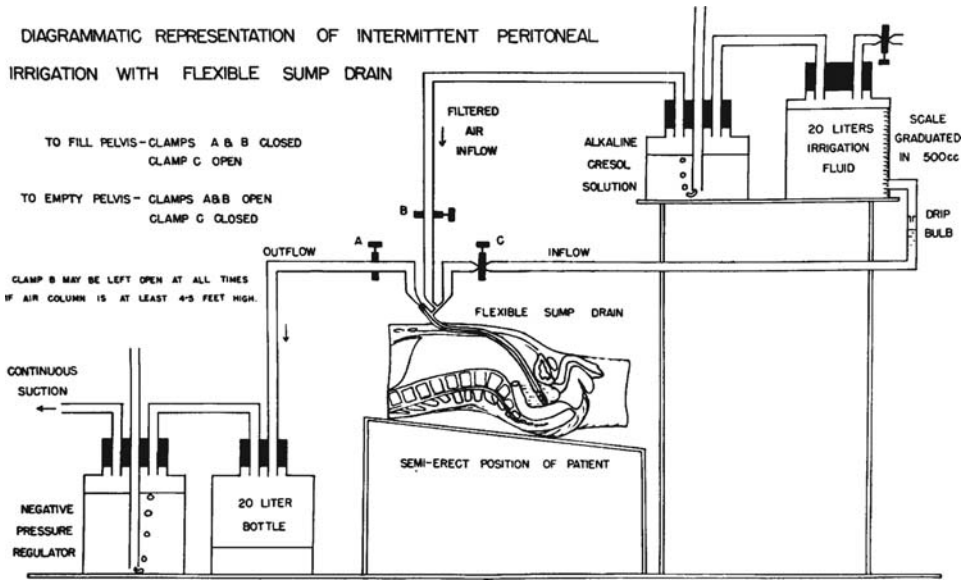

Fig. 1.1 Schematic representation of closed system used by Frank, Seligman, and Fine (From Annals of Surgery 1948, with permission)

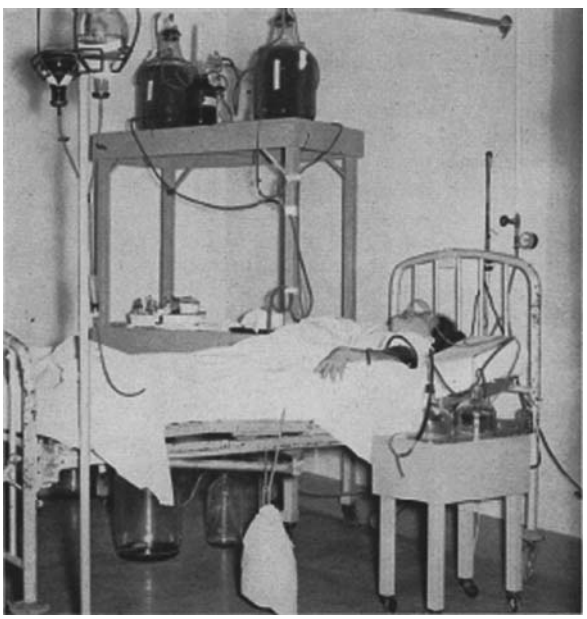

Fig. 1.2 Closed system used by Frank, Seligman, and Fine (From Annals of Surgery, 1948 with permission)

administrated from special 20-L Pyrex bottles, which required a large autoclave and were difficult to manipulate. The access was somewhat improved by introduction of a flexible sump drain that could be used as a two-way system if a separate inflow tube was not available. Most of the patients were treated with continuous flow technique, but they also used intermittent peritoneal lavage in some of the patients, with 0.5–2-L fill volumes depending on patient tolerability and 15 min to 3 h dwell time [27]. After finishing his internship, Frank remained at Beth Israel Hospital as a thoracic surgeon and member of the faculty at the Harvard Medical School and Arnold Seligman went to John Hopkins University School of Medicine, where he followed both a surgical and chemistry career [23].

The next major step in the development of peritoneal dialysis was the work done by Arthur Grollman, from Southwestern Medical School in Dallas, Texas [28]. It is interesting that, in reality, Grollman did not believe in the value of peritoneal dialysis for treatment of acute renal failure, which he thought could be managed by conservative measures if they were properly applied [28]. His main interest was actually to find a simple way to prolong life of nephrectomized dogs, which he used to study the role of kidneys in hypertension [29] His procedure involved the instillation by gravity of the irrigating fluid in the peritoneal cavity of the dogs, using a needle introduced in the peritoneal cavity through the flank [28]. The fluid was left in the abdomen for variable periods of time, and then removed using the same size needle connected by an adapter to a rubber tube. The drainage was followed by refilling. The procedure was carried out twice daily in the morning and late afternoon and kept the dogs alive for 30–70 days after bilateral nephrectomy, compared to the previously reported average of 10 days. Although he called this technique an intermittent peritoneal lavage, it was actually a continuous type of peritoneal dialysis in the way we classify it today, because he did not have periods of a "dry" abdomen. He called it intermittent because it did not involve continuous instillation of the dialysis fluid, but rather the fluid was left to dwell in the peritoneal cavity for various periods of time. He considered that more frequent exchanges were not necessary to prolong a dog's life, but could further decrease the level of urea and other catabolites. His kinetic studies showed that urea reaches equilibrium in 2 h after filling the peritoneal cavity of dogs with 1 L of fluid containing different concentrations of glucose. He also paid attention to the volume of fluid removed with peritoneal lavage using various concentrations of glucose in the dialysis solutions and using variable periods of time. In humans, he found equilibrium time for urea, electrolytes, creatinine, and glucose after 2 h, using 2–3 L instillation volumes of dialysis solution. He described the use of his method in five human patients. The dialysis fluid composition was modified based on patient needs and "intermittent" exchanges of 2 h duration were done for 16–48 h. The access used was for the first time a plastic tube, "to which omentum does not attach itself" [28]. The single plastic catheter was kept in place for the entire procedure and was used for both inflow, when it was attached through a needle to the infusion bottle, and outflow, when it was connected to an adapter and rubber tube for drainage. One of his patients survived, two others had some improvement in their clinical condition but died after peritoneal dialysis was stopped, and the other two did not improve at all with peritoneal dialysis. He did not have any peritonitis in humans; there was one episode in a dog dialyzed for 70 days, due to a break in the aseptic technique. Grollman considered his method superior to the continuous lavage previously described because of its simplicity and possibly increased efficiency in removal of the waste products. His technique did not require "the complex apparatus, multiple incisions, and constant attention necessary when one utilizes a constant perfusion technique as advocated by previous investigators" [28]. Additionally, he considered that continuous irrigation can create a "channeling" of the fluid between the inflow and outflow and be less efficient in urea removal due to decrease in available surface for exchange.

The Modern Era of Peritoneal Dialysis

The modern era of peritoneal dialysis started with Morton Maxwell in 1959 [30]. Maxwell started training in renal physiology with Homer Smith at the New York University School of Medicine in 1948. After he joined the staff of the VA Hospital in Los Angeles, California, he purchased a Kolff twin-coil kidney machine and started using it. He found this procedure "formidable" and expensive, with narrow applicability due to necessity of dedicated medical staff with special training, who had to work long hours to prepare the machine, deliver the treatment, and clean up after a 6-h-long session [31]. He turned his attention to peritoneal dialysis and found Grollman's technique promising in its simplicity and worked on refining it. One of the obstacles he wanted to eliminate was the laborious way of extemporaneous preparation of dialysis solutions. Access-related complications were also a great limiting factor in peritoneal dialysis and he started experimenting with different catheters. Maxwell introduced a semi-rigid nylon catheter with a curved tip and numerous tiny distal perforations, which, similar to plastic catheters, caused less omental reaction than the rubber and metal tubes. Because it was semi-rigid, it did not have the tendency to kink as did other plastic catheters developed in the early 1950 s, and, by decreasing the diameter and increasing the number of very

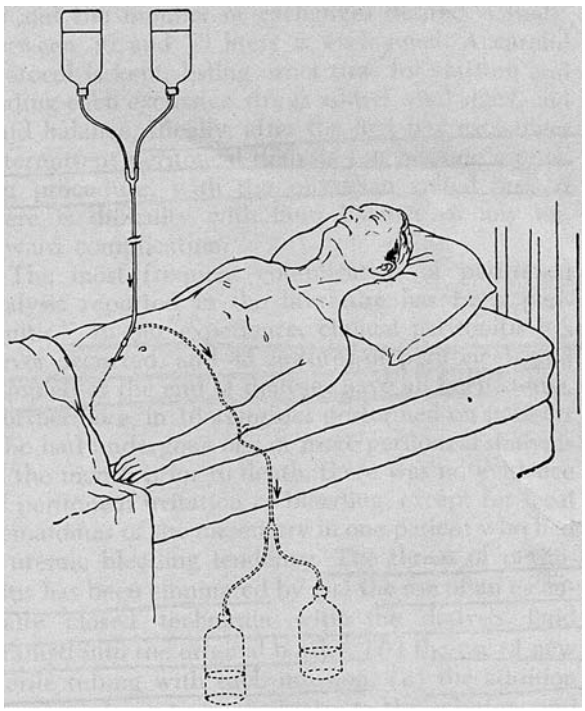

Fig. 1.3 Maxwell's paired bottle technique (From JAMA 1959, with permission)

small perforations in the distal end, he prevented portions of the omentum from entering the catheter and this resulted in better performance. He convinced the Don Baxter Company of Glendale, California, and Cutter Laboratories of Berkeley, California, to produce a standard dialysis solution in 1-L sterile glass bottles, special Y-type administration tubing, and the new type of catheter [29, 30]. The peritoneal dialysis procedure involved insertion of the catheter into the peritoneal cavity through an incision of the abdominal wall, below the umbilicus, using a 17 French Duke trocar set [31]. Then the catheter was attached to the Y-tubing, previously connected to 2 L of warmed dialysis solution (see Fig. 1.3). The paired bottles were hung above the bed level and the dialysis fluid was allowed to flow into the peritoneal cavity. The tubing was clamped when the bottles were empty with some fluid still present in the administration tubing, and the bottles were then lowered onto the floor. After 1 h dwell time, the clamps were removed and the fluid was permitted to flow out of the peritoneal cavity. When the drainage was complete, a new pair of dialysate bottles was connected to the catheter using new tubing. This "intermittent" procedure was continued for 12–36 h as required buy the clinical situation and proved to be "mechanically successful" in 76 instances [31]. Maxwell and his colleagues specifically reported only six cases in their classical paper, with five survivors and one death after transient improvement with dialysis. Those patients who recovered had acute renal failure, barbiturate poisoning, intractable edema, hypercalcemia, and acute on chronic renal failure due to ureteral blockage.

The new dialysis solution contained sodium in a concentration of 140 mEq/L, chloride 101 mEq/L, calcium 4 mEq/L, magnesium 1.5 mEq/L, dextrose 15 g/L, and, for the first time, lactate 45 mEq/L. The lactate was replacing bicarbonate in the dialysis solution, eliminating the problem of precipitation of calcium salts. Potassium was excluded from the commercial dialysis solution because most of the patients with acute renal failure had hyperkalemia, but, if needed in patients with low serum potassium levels, it could be added to one of the bottles using a hypodermic syringe. The 1-L bottles were much easier to handle than the large carboys introduced by Fine's group and generally used up to that point. If there was need for addition of other substances to the dialysis solution (potassium, dextrose, prophylactic antibiotics, heparin), they were added to one of the two bottles used for each exchange, a maneuver that, from their perspective, decreased the risk of peritonitis. Actually, they reported that in their experience peritonitis never occurred, although in fact the risk of contamination was still increased because the system was disconnected with each exchange.

Their experience in patients with chronic renal failure was unsatisfactory, but they imagined that with further improvement of the technique, peritoneal dialysis could become more efficient so that it could be applied for shorter sessions of 6–8 h duration. Theoretically, chronic patients could be admitted to the hospital at certain intervals and receive the peritoneal dialysis treatment, "in the same manner patients with refractory anemia are given transfusions at

the present time" [31]. Although the procedure was still not ready for use in the treatment of chronic uremia, the fact that now it became a simpler nursing procedure and the dialysis solution was commercially available in 1-L bottles allowed it to be accepted and used more commonly as a treatment for acute renal failure. The new catheter used by Maxwell seemed to have fewer complications than previously used catheters and became widely used.

At the same time, at the U.S. Navy Hospital in Oakland, California, Paul Doolan and his team started research in dialysis, being stimulated once more by war casualties due to acute renal failure and hyperkalemia in the Korean War (1950–1953) [32]. Their goal was again to find a simple way to dialyze patients on the battle field or at the bedside, and found that peritoneal dialysis applied using Grollman's intermittent flow technique was most appropriate. In the same year, 1959, they published their experience with the use of intermittent peritoneal lavage in ten patients [33]. They used dialysis solutions that were prepared in the hospital, with a lower content of sodium (128 meq/L), glucose used as an osmotic agent, and bicarbonate 28 mmol/L added as a buffer and, to avoid precipitation of calcium salts, they administered calcium parenterally. Potassium was added to the dialysis fluid as required by the clinical situation. Doolan and Murphy developed a polyvinyl chloride catheter with a straight intra-abdominal segment with multiple side holes, transverse ridges, and spiral grooves to avoid kinking and omental obstruction. William Murphy was the president of the Cordis Corporation and manufactured this catheter, but it did not become widely used because it was difficult to insert, sometimes even requiring laparotomy. Nevertheless, Doolan and his group used the catheter to successfully carry out intermittent flow peritoneal dialysis. The work of Maxwell and Doolan and the introduction of plastic catheters and commercially available "rinsing" solutions contributed to the widespread acceptance of peritoneal dialysis in the early 1960 s as a clinically feasible technique.

Long-Term Peritoneal Dialysis

The first chronic renal failure patient treated with long-term peritoneal dialysis was Mae Stewart, a 33-year-old black woman from San Francisco who had complications from a recent childbirth [32, 34]. In late 1959, she was referred to see Dr. Richard Ruben at Mt. Zion Hospital in San Francisco for management of her renal failure. Previously that year, Ruben had worked with Doolan at Oakland Naval Hospital, where he acquired the skills necessary to perform peritoneal dialysis. He started Stewart on peritoneal dialysis with the help of his colleagues, doctors A.E. Lewis and E. Hassid. She improved after the first dialysis session, with a decrease in serum creatinine form 20 to 13 mg/dL, but after a week her condition deteriorated again. They decided to leave the catheter in place in case they might need to use it again. As it turned out, the patient had small, shrunken kidneys and chronic renal failure due to glomerulonephritis, so her uremic symptoms returned after several days. She continued to receive in-hospital, weekly peritoneal dialysis treatments, using the same catheter left in place, so the Murphy-Doolan catheter was the first one used for chronic peritoneal dialysis. She was allowed to go home between treatments, where she was able to continue to take care of her family. Sometimes during treatments, she was disconnected from the closed system after inflow and was allowed to ambulate.

She was kept on intermittent or "periodic" peritoneal dialysis for 7 months, and the catheter was replaced only once at 3 months after starting the treatment. Intraperitoneal antibiotics were administered occasionally to prevent the occurrence of peritonitis. Later during the treatment, the patient developed pericarditis, refused to continue further treatments, and died. Mae Stewart was the first patient maintained on chronic dialysis; she started treatment in January 1960 several months before Clyde Shields started chronic hemodialysis in Seattle in March 1960. Ruben and his collaborators wrote a report of this case and submitted it to the New England Journal of Medicine, but the manuscript was rejected for publication.

During the early 1960 s, many centers were trying to use "periodic" peritoneal dialysis in patients with end-stage renal failure. The results were disappointing mainly because of frequent episodes of peritonitis due to access infection or contamination during the repeated maneuvers of changing the bottles [35]. Survival was commonly limited to only few months. As the nylon catheters were found to be unsatisfactory for long-term use, many attempts in different centers were being made to design a safe and easy method to insert an access device that would permit reliable dialysate flow and limit the infectious and mechanical complications. During that time, significant results in chronic dialysis were accomplished at the University of Washington in Seattle, where Belding Scribner and Wayne Quinton were able to maintain end-stage renal disease patients on chronic hemodialysis. However, the number of patients was much higher than what they could accommodate, and also some of the patients were running out of sites for hemodialysis access, requiring other forms of chronic therapy. Scribner, the same as others during that time, thought that peritoneal dialysis could be a good alternative to hemodialysis and invited Dr. Fred Boen, an Indonesian physician working in Holland, to come to Seattle and work on peritoneal dialysis [36, 37]. Boen had become known for his work on the kinetics of peritoneal dialysis, which was the subject of his M.D. thesis and was later published [38]. In January 1962, Boen and his team in Seattle began a program of long-term peritoneal dialysis, one of the first in the world. Around the

same time, John Merrill started doing chronic peritoneal dialysis in Boston, at the Peter Bent Brigham Hospital, Harvard Medical School. Both groups presented their 3 months experience in April 1962 at the American Society for Artificial Internal Organs Meeting in Atlantic City, New Jersey [39–41]. At the same meeting, Dr. J. Garrett from the Albany Medical College, New York, mentioned that he had maintained a patient on intermittent dialysis for 9 months [42]. The Seattle group developed the first automatic peritoneal dialysis machine, which was designed with the goal of minimizing the risk of contamination of the dialysis solution at the time of each exchange and also to reduce the need for nursing attendance [40]. They returned to the closed system developed earlier by Frank, Seligman, and Fine and designed a similar but automatic one. The sterile dialysis solution was contained in 20-L carboys from where it was pumped into an elevated reservoir where the fill volume was preset, usually at 2 L. From there the fill volume would enter in the peritoneal cavity using gravity flow. The inflow, dwell, and outflow times were monitored by the system's timers, which controlled the opening of the clamps and made the procedure automatic. They used a dwell time of 30 min. The disadvantage of the system was that the 20-L glass bottles were bulky and difficult to handle and, again, required special equipment for preparation and sterilization of the dialysis solution. The advantage was that it eliminated the need for frequent system openings during each exchange by replacing the individual 1-L bottles with large carboys containing the sterile dialysis solution; this way they decreased the risk of peritonitis by contamination. Later, they used a 48-L carboy, which made it possible to use a single container and a completely closed system for each dialysis session.

Boen's group, the same as Merrill's group in Boston [41], tried to use a permanent, indwelling peritoneal device in order to make frequent access into the peritoneal cavity easier. Their idea was to create an artificial and permanent conduit or channel through the abdominal wall, which would allow easy passage of a catheter into the peritoneal cavity and eliminate the need for repeated paracentesis.

Boen's access was the modification of a system developed by Garrett [40]. It was initially a Teflon hollow tube, replaced later by a silicon rubber, which was surgically implanted in the abdominal wall with one exit at the skin and the other one in the peritoneal cavity (see Fig. 1.4). The hollow tube had two perpendicular discs, one located just below the peritoneum in the peritoneal cavity and the other one in the abdominal wall. This tube allowed the repeated introduction of a catheter into the peritoneal cavity. At the end of the treatment, the catheter was withdrawn from the tube, which was then capped. The cap looked like a button at the skin surface and Boen's device was later called "Boen's button" or the "silastic button." Others tried to create a subcutaneous access button, which required cannulation through multiple stab wounds in the skin [43]. The overall performance of these buttons turned out to be poor. Merrill reported the use of such a device in five patients who received two to 17 dialysis treatments [41]; one of the patients had acute renal failure and did not recover, two patients were dialyzed intermittently for 2 months and the other two for 3 months. One of them was even able to do eight dialysis treatments at home, with the help of her spouse. None of the patients developed clinical peritonitis, but all of them had technical failure of the access device: occlusion of the lumen due to fibrous tissue or omentum, bowel penetration, or disruption of the conduit. Garrett was also not getting good results with his button device, even after further improvements [42].

Kevin Barry and his team from the Walter Reed Army Institute of Research, Washington, D.C., considered the permanent, artificial intra-abdominal conduit as a viable access option, and in order to make it easier to insert without

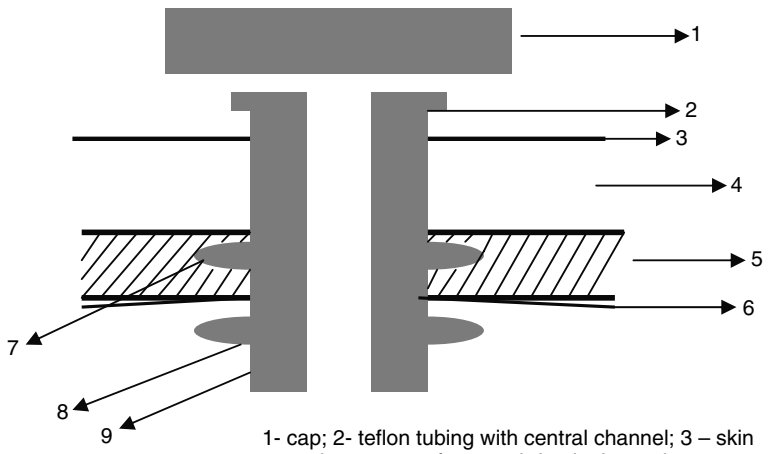

Fig. 1.4 Schematic representation of the "Boen's Button

the need of a surgical procedure, they developed a flexible, polyvinyl cannula implanted with the help of a trocar [44, 45]. The cannula had a balloon at the intraperitoneal end, which kept the device in place after it was expanded by infusion of saline. This device was able to accommodate the standard, nylon catheter. They recruited 116 investigators from several countries to participate in trials involving these polyvinyl cannulae [45]. Frequent complications were noted, including fluid leaks, separation of the intraperitoneal balloon, massive bleeding, and bowel perforation. This device has never gained popularity. Norman Lasker was one of those who used the Barry pericannula with some success [46, 47], but abandoned this method later in favor of the Roberts and Weston stylet catheter [47].

Other investigators were trying to find ways to use implanted, indwelling catheters without the need for artificial conduits. Gutch, for instance, from the Medical Service and Dialysis Unit of the V.A. Hospital in Lincoln, Nebraska, experimented with long-term catheters of different materials and found that silicon catheters were the least irritating and caused the least protein loss in the dialysis fluid [48, 49]. He reported the use of such silicone catheters for as long as 17 months, which was a significant achievement in survival of peritoneal dialysis patients; of note, this group preferred to dialyze patients daily, rather than two or three times a week, which was the common dialysis schedule during that time. Insertion of the catheter was done as usual, through a 24 French trocar.

In 1964, Boen and his group became convinced that chronic indwelling conduits or catheters of any material were not practical for long-term peritoneal dialysis because of frequent episodes of peritonitis and adhesion formation causing technical difficulties and poor general condition [50]. Their experience in humans was limited to only two patients, but none of them did well using Boen's button; their research in rats had demonstrated that polyethylene, Teflon, or silastic indwelling tubes inevitably produced adhesions and infections. As a result, Boen started using the "repeated puncture technique": a new puncture and a new nylon catheter were used each time the patient was dialyzed. Using this technique in combination with the closed sterile dialysis system and their automatic cycling machine, their second patient had no peritonitis for more than 8 months, compared with the development of peritonitis after 10 weeks when using Boen's button. The patient was dialyzed once weekly for 14–22 h and maintained a good quality of life. The trocar used for the repeated puncture was the one described by McDonald [51, 52]. Dr. Harold McDonald was a urologist who became familiar with peritoneal dialysis while training at the Peter Bent Brigham Hospital in Boston, with John Merrill's group in the early 1960 s. There he witnessed an unsuccessful event of catheter insertion for peritoneal dialysis and became interested in developing a tool that could facilitate catheter placement and resolve the pericatheter leakage. He designed a smaller, 14 French trocar, with a triface pointed tip. The common catheters used at that time were 11 French in size and were introduced using a 24 French Duke or Ochner paracentesis trocar. This new trocar made a smaller hole in the abdominal wall for catheter insertion, which helped in diminishing leakage around the catheter.

The Tenckhoff Catheter

In 1963, Henry Tenckhoff, a German physician, accepted a fellowship position at the University of Washington in Seattle, where he replaced Charles Mion, who was returning to France [36]. Tenckhoff also developed his interest in nephrology and dialysis while working in Boston with John Merrill. He could not nurture his interest for dialysis in Germany, and decided to return to the United States to continue working in dialysis. In 1964, Boen's team started training patients for home intermittent peritoneal dialysis using the repeated puncture technique and the Seattle, automatic closed system [36, 53]. The patients were trained in the hospital and then sent home with the dialysis equipment; the dialysis solution was prepared in the hospital, sterilized in the 40-L glass containers, and delivered to the patient's home at regular intervals. Dialysis was done weekly, usually on weekends. Tenckhoff had to go to the patient's home and insert the peritoneal dialysis catheter and start the dialysis treatment, which was carried out for 20–22 h each session. After this time, the patient with the help of the spouse, would terminate the treatment, turn off the machine, and remove the catheter. Initially they used the McDonald trocar to insert the catheter, but afterwards they started using the Weston and Roberts stylet catheter, which helped further in reducing the problems of bleeding and leakage. The procedure was simple and allowed long-term survival without peritonitis. In 1965, the Seattle group had treated one patient at home for 1 year, and another patient was treated using the same technique, but in the hospital, for 2 years. Soon it became clear that more than once weekly treatments were needed for the home peritoneal dialysis patient, and Tenckhoff had to go now twice a week to the patient's residence to start dialysis. Although the previous experience with permanent, indwelling catheters was not favorable, Tenckhoff recognized that, in order to make home peritoneal dialysis a viable procedure, a safe, permanent access to the peritoneal cavity was crucial [54]. Of the previously designed catheter, he believed that the Palmer–Quinton catheter was most appropriate for chronic use, with some improvements.

Russell Palmer, a Canadian physician from Vancouver, was one of the first to do hemodialysis in North America, starting in 1946 [55]. In the early 1960 s he also became interested in peritoneal dialysis and became familiar with the work done in Seattle, including with the work of Wayne Quinton in developing the silicone arteriovenous fistula for hemodialysis. He asked Quinton to help him design a permanent peritoneal dialysis access and, after experimenting with different materials, they decided to use silicon rubber. Their final product was an 84-cm-long catheter, with a lumen of 2 mm [56]. The intraperitoneal portion was coiled and had numerous perforations extending 23 cm from the tip. At the middle of the length of the catheter, there was a triflange step for placing the catheter in the deep fascia and peritoneum. The catheter was introduced surgically in the peritoneal cavity through a midline incision located about 5 cm below the umbilicus. From this level, the extraperitoneal portion was tunneled under the skin and the exit site was in the left upper quadrant. This long, tunneled portion was designed to decrease the risk of infection due to migration of bacteria from the skin. The external portion of the catheter was capped between dialysis treatments. Although this design was innovative and allowed peritoneal dialysis treatments for more than a year, peritonitis continued to occur [57].

Tenckhoff took this catheter a step further and designed the access that is even today most commonly used for peritoneal dialysis [58]. The most important improvement was the addition of two Dacron felt cuffs, obviating the need for the triflange step, which was eliminated from the new design [54]. At that point it was recognized that Dacron felt attached to the catheters improves tissue fixation, permits tissue ingrowth, and this way creates a barrier that reduces the chances of infection. McDonald also created a permanent silicon peritoneal catheter equipped with a Teflon velour skirt in the subcutaneous tissue and a Dacron sleeve in the intramural portion [59]. After extensive animal studies, Tenckhoff and Schechter decided that they would use a silicon catheter, of 40 or 75 cm length [54]. Two Dacron felt cuffs were attached to the silastic catheter in two places, dividing the catheter into three portions: the intraperitoneal portion was a straight 20-cm tube with 60 perforations in the area15 cm from the tip. Some of the catheters also had a curled intraperitoneal section, similar to the one described by Palmer. One of the Dacron felt cuffs was located in the peritoneal cavity, abutting the parietal peritoneum. The intramural section was also tunneled under the skin, but in an arcuate pattern and varied in length from 45 to 10 cm. They shortened this segment as they felt that the presence of the two cuffs closed the catheter sinus tract at both sides and thus decreased the risk of bacterial invasion. The second cuff was placed in the subcutaneous tissue just beneath the skin. They also recommended the arcuate tunnel so that the external part of the catheter and the sinus were directed caudally. In 1968, Tenckhoff and Schechter presented their 4-year experience in eight patients: one catheter had been used without complication for as long as 14 months in one of the patients [54]. Although the Tenckhoff catheter has not completely eliminated the risk of peritonitis, it was a major breakthrough and became the most important factor in promoting peritoneal dialysis in other centers.

The Growth of and Disappointment with Intermittent Peritoneal Dialysis

The next limiting steps in the widespread use of home peritoneal dialysis was represented by the difficulties in providing the adequate supply of sterile peritoneal dialysis fluids to the increasing number of patients using this technique and patients' problems in handling the large and heavy bottles [60]. The Seattle group was still preparing the dialysate in their hospital's "fluid factory" and was shipping the 40-L containers to the patients' homes. Charles Mion in France was using smaller, 10-L plastic containers connected in series for closed-circuit peritoneal dialysis [61]. The next proposal was to design a machine that could make sterile dialysate in the home of the patients, obviating the need for shipping large quantities of dialysate. Harold McDonald from the Department of Surgery – Urology, State University of New York, Downstate Medical Center, Brooklyn, New York, created a system that used tap water and dialysate concentrate, which could be integrated in an automatic peritoneal dialysis machine for hospital or home use [62]. Cold tap water, after going through a purifying and warming system, was mixed with the dialysate concentrate, and the resulting dialysis solution was further sterilized by passing through a 0.22-μ millipore filter before entering the peritoneal cavity. McDonald presented his system at the American Society for Artificial Internal Organs Meeting in 1969 [62]. At the same meeting, Tenckhoff presented the first system of water purification, which was developed by the Seattle group [60]. The latter experimented with different methods of water or dialysate purification, including bacterial filtration, heat sterilization, and UV-light irradiation, and found that heat sterilization using a pressure boiler tank was the only way to achieve perfect sterilization. This system was further improved and allowed production of large quantities of safe, sterile dialysate in the hospital and at home; its disadvantages were the large weight and bulkiness, high cost, and requirement for high pressure and temperatures to operate. As a result of progress made in water treatment technology, Tenckhoff and his team were able to design a new, much smaller and extremely efficient and safe system [63]. This system used the reverse osmosis method to produce large quantities of sterile, pyrogen-free water from tap water and contributed to the increase in the number of home peritoneal dialysis patients, making the

Seattle center one of the largest centers for home intermittent peritoneal dialysis in the 1970 s. In 1973, they reported the experience of 12,000 peritoneal dialysis treatments in 69 patients [61]. In 1977, 161 dialysis patients had been on dialysis at this center. The other large peritoneal dialysis center in North America at that time was in Toronto, Canada, [61]. In Europe, Charles Mion, formerly trained in Seattle, was directing the third most important center in the world, which was located in Lyon, France [64].

Dimitrios Oreopoulos accepted a position at the Toronto Western Hospital in 1970, to manage a four-bed intermittent peritoneal dialysis program with approximately 16 ambulatory patients [64]. He acquired knowledge about peritoneal dialysis while training in Belfast, Ireland, where he was using the Deane prosthesis to establish access. At the beginning of his experience in Toronto, he was able to maintain patients on peritoneal dialysis for up to 20 months, and their chronic peritoneal dialysis patient population increased steadily to close to 40 patients in a few years. At the same time, one of Oreopoulos' former colleagues from Belfast, Dr, Stanley Fenton, started working at the Toronto General Hospital. Fenton had trained in Seattle with Scribner and Tenckhoff after leaving Belfast and before coming to Toronto. He had a few Tenckhoff catheters, which he showed to Oreopoulos who tried them and was so impressed with the results that he abandoned the Deane prosthesis and converted all patients to Tenckhoff catheters. Having this reliable permanent peritoneal access available, Oreopoulos began sending patients home with reverse osmosis systems. During the early 1970 s. the president of American Medical Products visited Toronto and introduced a simpler cycler machine to Oreopoulos, the one designed by Lasker.

Norman Lasker [47, 65] was another pioneer in peritoneal dialysis, who had visited Seattle and studied the automated systems developed by Tenckhoff. He considered they were superior over the manual technique and the wider application of peritoneal dialysis could be facilitated if simpler machines would be available. With the help of Gottscho Packaging Equipment Company, he designed a simpler "peritoneal dialysis cycler." Ira Gottscho was a business man whose daughter died of kidney disease and he established a foundation in her memory. Lasker's peritoneal cycler was simple, efficient, and easy to use: it used gravity principles and eliminated pumps, and used commercially available 2-L bottles of dialysis solution and presterilized disposable tubing and bags. By connecting four bottles, an 8-L reservoir was obtained each time [47, 65].

Oreopoulos was the first to see the value of Lasker's work and had 40–45 patients use his cycler [64]. Another innovation was also available in Canada: in 1973–1974, Baxter provided dialysis solution (Dianeal) in plastic bags and all patients started using this product, which became available in the United States in 1978.

The high cost of care of dialysis patients was an additional factor that held back the dissemination of peritoneal dialysis. In the United States, new renal care legislation was approved in 1972 and Medicare started to cover medical expenses of end-stage renal disease patients in 1973 [47, 66], making peritoneal dialysis affordable. This modality was available not only in the hospital, but also as a home therapy, being delivered intermittently, usually three to four times a week for about 10 h per session [67]. As more experience started to accumulate, it became evident that real long-term success could not be achieved with intermittent peritoneal dialysis. In a 1979 analysis of the outcomes of chronic peritoneal dialysis therapy at the Seattle center, it was found that the cumulative technical survival rate was 72% for 1 year, 43% for 2 years, and only 27% for 3 years [68]. One of the leading causes of intermittent peritoneal dialysis failure was inadequate dialysis. Different approaches had been investigated in humans and animal models to increase the efficiency of intermittent peritoneal dialysis and summarized by Gutman also in 1979 [69]: increase of dialysate flow rate from the standard of 4 L/h to 12 L/h allowed only modest increase in clearance and was expensive, and increases in the dwell volumes over 3 L were uncomfortable for the patients. Other modalities explored were the use of tris-hydroxymethyl aminomethane (THAM) to increase the permeability of the peritoneal membrane, use of vasodilators to increase the effective surface area of the peritoneum, or the use of hypertonic solutions to increase solute removal by solvent drag [69]. None of these methods found applicability and intermittent peritoneal dialysis remained inferior to hemodialysis in terms of achievable small solute clearance. For this reason, peritoneal dialysis was considered a "second-hand" therapy for chronic renal failure until a new form of peritoneal dialysis was born in Austin, Texas.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

In 1975, a young, otherwise healthy patient entered the chronic hemodialysis program directed by Jack Moncrief at the Austin Diagnostic Clinic in Austin, Texas [67]. Each arteriovenous fistula that was created in this patient failed, and in the absence of a hemodialysis access, he was advised to move to Dallas, where an intermittent peritoneal dialysis program was available. He refused to relocate and his doctors were in the situation of losing this young father of four children due to the impossibility of providing life-saving dialysis therapy.

One of Moncrief's collaborators was Robert Popovich [67], a young biomedical engineer formerly trained in Seattle under Belding Scribner and Albert Babb. The case of their unfortunate patient was reviewed during a routine weekly meeting and the team decided to try peritoneal dialysis but in a new form, which would allow complete equilibration of plasma urea with peritoneal fluid and thus maximum urea removal with each dwell. They calculated what was the minimum volume of dialysis fluid required to remove the urea generated daily on a 1 g/kg protein diet, knowing that dialysate urea equilibrates with plasma urea in 2 h. In a 70-kg man who eats 1 g of protein per kilogram of body weight, daily urea generation will be 7,000 mg per day. They decided that a level of 70 mg/dL for the blood urea nitrogen was desired. If at equilibrium dialysate urea concentration will be 70 mg/dL, then 10 L of dialysate are required daily in order to remove the generated urea and maintain a constant plasma urea concentration. The commercial dialysate solutions were available in 2-L glass bottles. Their prescription was for 2-L fill volumes, dwell time of at least 3 h, and a total of five exchanges per day. This prescription was applied to the patient using a Tenckhoff catheter as access, and improved and controlled the patient's chemistries, volume, and clinical status [67]. Moncrief and Popovich called this procedure the "portable/wearable equilibrium peritoneal dialysis technique" and they submitted the results of their first application of the technique as an abstract to the American Society of Artificial Organs in 1976 [67, 70]. This abstract was not accepted for presentation, probably because the name was confusing. In January 1977, Moncrief and Popovich attended the National Institute of Health Contractors Meeting, where they met Karl Nolph [71], who was practicing nephrology at the University of Missouri in Columbia, Missouri. Nolph became interested in the new technique and decided to start collaboration with the Austin group. During their initial discussions, they agreed that "continuous ambulatory peritoneal dialysis" (CAPD) might be a more appropriate name for the new modality [71]. They published the experience with nine patients treated for 136 patient weeks in a classical article that established the use of CAPD [72]. The procedure was simple and involved the continuous presence (i.e., all day long, 7 days a week) of dialysis solution in the peritoneal cavity. Manual exchanges were done 4–5 times a day, and the dialysis catheter was capped between the exchanges, allowing participation in daily activities. The dialysis was called "portable" or "internal" and did not require the presence of a machine [72]. Other advantages of CAPD were identified: it allowed continuous, steady state chemistries after a few weeks because there was constant removal of waste products from the body; the procedure could be done by the patient unaccompanied at home or "anywhere" dietary restriction was not necessarily severe (later it has been recognized that sodium restriction is actually very important); CAPD was better tolerated from the cardiovascular perspective; and larger molecule clearance was significantly higher compared with hemodialysis. CAPD did not eliminate one of the most important problems encountered in peritoneal dialysis, namely peritonitis. On the contrary, the risk of peritonitis was higher because of increased number of connections per day. Their patients had peritonitis, on average, every 10 weeks [72].

Two further modifications of the technique contributed to the decrease of peritonitis rates and facilitated worldwide acceptance of CAPD: the first was the use of dialysate in plastic bags, introduced by Oreopoulos in Canada, and the second was the introduction of the innovative Y-set connector system by Buoncristiani in Italy [64, 71, 73, 75].

CAPD with Plastic Bags

In 1976, Jack Rubin [64, 71], one of the fellows trained at Toronto Western Hospital under Dr. Oreopoulos, was accepted by Dr. Nolph to come for further training and research at the University of Missouri in Columbia, Missouri. He became involved in the emerging CAPD program and was impressed with the new technique. A year later, he returned to Toronto and tried to convince Oreopoulos to adopt this new, continuous procedure that seemed to be better than the typical intermittent peritoneal dialysis. Because of the high peritonitis rates, he was hesitant to introduce it, until one of his patients, who had been on intermittent peritoneal dialysis for about 2 years, had to be admitted with complications related to uremia. She was severely underdialyzed, and Oreopoulos decided to give CAPD a try: she was started on CAPD on September 27, 1977 [64]. Her improvement was so dramatic that he decided to convert all his almost 40 home intermittent peritoneal dialysis patients to CAPD and was able to do this in only a few weeks [71, 73]. Patients' acceptance was excellent and the patient population continued to grow at a fast rate at his center [64]. Because, at the time, dialysis solutions were available in plastic bags were only available in Canada, they adopted a slightly different technique: after filling the peritoneal cavity with 2 L of dialysis solution, the tubing connecting the bag with the dialysis catheter was clamped and the plastic bag was wrapped around the patient, without disconnecting the bag from the catheter. After 6 h, the empty bag was placed on the floor, the tubing was unclamped, and the dialysate was allowed to drain by gravity. When the drainage was complete, the bag was disconnected from the system and a new bag was connected to the permanent catheter to repeat the cycle. They initially used the standard Y-set for acute peritoneal dialysis. The unused arm of the Y-tube was closed and tightly wrapped with the bag, making the

tubing system bulky and uncomfortable. Oreopoulos was trying to improve the tubing by eliminating the redundant part and create a straight tube with a Luer connector for connection with the catheter at one end and a spike for connection with the plastic bag at the other end. After consulting with his Baxter representative, he realized they had the straight tube available from the reverse osmosis machine [64]. They started using this tube and developed the Toronto Western Hospital Technique for CAPD, known also as the "spike technique" [73, 74]. With this technique, their rate of peritonitis was decreased to one episode every 10.5 patient months [74]. As a result of this remarkable improvement and with substantial pressure from the groups in Columbia, Missouri, and Austin, Texas, and also from the National Institutes of Health, the Food and Drug Administration (FDA) finally approved the use of the plastic bags in the United States in October 1978 [64, 71].

The Y-Set and "Flush Before Fill" Technique

In the 1980 s, Dr. Umberto Buoncristiani [73] from Perugia, Italy, published incredible results with an innovative Y-set, which resulted in a significant drop in the peritonitis rates to one episode to every 40 patient-months [73]. Buoncristiani was searching for an original technique in part because his patients were refusing to switch from the intermittent modality to the more efficient CAPD, as they found the "wearable bag" distasteful [75]. He was more concerned about the high rate of peritonitis and was also trying to develop a system to decrease the risk of infection. He realized that the "contaminating act" takes place at the time when a connection is made between a new bag and the transfer set, followed by the filling phase, when the infused fluid carries bacteria into the peritoneal cavity [75]. He reintroduced the Y-tubing, connected with one arm to the catheter, and the other two arms of the "Y" to bags, one containing dialysate and the other one empty. With this technique, after the connections are made, before the draining is started, some fresh dialysate is washed out into the drainage bag, flushing with it any bacteria that might have contaminated the tubing at the time of the connection. This is followed by drainage of dialysate into the empty bag and then filling of the abdominal cavity with the new solution. After the infusion is finished, the two bags are disconnected and the Y-set is filled with an antiseptic. This technique is known as "flush before fill" or "flush after connect," and the system is known as "the disconnect system" [73, 75]. The results were impressive, but they were not easily accepted in North America. The Italian group carried out a prospective, randomized controlled study to compare the Y-set with the standard spike system [76]. Their results were published in 1983 and were again remarkable: the peritonitis rate was one episode every 33 patient-months in the Y-set group, compared to one episode every 11.3 patient-months in the standard system [76]. A multicenter, randomized clinical trial was then carried out in Canada [77] and the results confirmed the Italian experience: their Y-connector group had one episode of peritonitis in 21.53 patient-months compared to one episode in 9.93 patient-months in the standard system group [77]. Subsequently, the Y-set technique has been accepted worldwide as standard.

With these changes, the use of CAPD increased considerably all over the world, a trend that continued through the early 1990 s.

Automated Peritoneal Dialysis (APD)

The use of machines for peritoneal dialysis was left behind for a while, as the CAPD technique proved to be much simpler and efficient than intermittent peritoneal dialysis [78]. After long-term use of CAPD, new problems have been discovered: patients were losing motivation after long periods of time using manual peritoneal dialysis; adequate dialysis was difficult to attain after the residual renal function was lost, especially in large patients, requiring an increase in the total volume of daily dialysis solution; recurrent peritonitis, especially due to touch contamination, continued to remain a problem and one of the main causes of technique failure. Interest in using the machines for peritoneal dialysis was re-established in early 1980 s.

Diaz-Buxo and his collaborators [79] introduced an automated cycler to deliver three exchanges at night, during sleep. In the morning before disconnection, the machine filled the peritoneal cavity with fresh dialysate to be drained at night, when the patient connected again to the machine. The main goal of this modality was to reduce the number of manually performed connections, and thus decrease the risk of touch contamination and peritonitis. This procedure was also a continuous one, as the fluid was always present in the peritoneal cavity and it was thus called "continuous cyclic peritoneal dialysis" (CCPD). The dwell time was supposed to be for at least 3 h, allowing complete equilibration, and small solute clearance was comparable with CAPD. Basically, the CCPD schedule was a reversal of the CAPD schedule, with the three shorter dwells performed at night and one long dwell during the day.

Around the same time, Price and Suki [80] described an "automated modification of prolonged-dwell peritoneal dialysis" (PDPD) [80], which was comparable to CAPD in improving blood chemistries and had lower peritonitis rate than CAPD, similar to results reported by Diaz-Buxo [79].

The continuous development of simpler cyclers and patient preferences has driven an increase in the use of cyclers over the years. This technique became more appealing for physicians after the development of the peritoneal equilibration test (PET) as a tool of defining peritoneal transport characteristics of individual patients [81]. Cycler-based prescription made it easier to deliver increased number of short time dwells for high transporters and maintain them on peritoneal dialysis. Later, the CANUSA study [82] showed a strong, positive correlation of the total small solute clearance with survival. National Kidney Foundation – Dialysis Outcome Quality Initiative (NKF – KDOQI) guidelines were published in 1997 and recommended a target weekly Kt/V of 2.0 for CAPD and 2.1 for CCPD, based on results of the CANUSA study [83]. The need to achieve these high targets drove an increase in APD utilization, because the use of automated machines allowed easier delivery of higher daily dialysate volumes. Subsequent reanalysis of the CANUSA study [84] showed that the decrease in the solute clearance over time was caused by uncompensated loss of residual renal function, suggesting that lower peritoneal clearance targets might be appropriate. This was confirmed by another landmark study, the ADEMEX study in 2002 [85]. Even so, APD use has increased significantly since its reintroduction, probably because it allows positive changes in the lifestyle of dialysis patients.

Peritoneal Dialysis Catheters

The Tenckhoff catheter remains the gold standard for peritoneal dialysis access and is the most widely used [58]. Individual dialysis centers' preferences for dialysis catheters are based on their particular experience and availability of other catheters. Various improvements were tried over the years in many centers, with the purpose of finding the best design with the lowest rates of mechanical and infectious complications.

In Toronto, Dr. Oreopoulos, in collaboration with Gabor Zellerman, attached three silicon discs to the intraperitoneal segment in order to prevent obstruction and migration of the catheter [39, 64]. This catheter was further improved and two variations were described a few years later [86]: Toronto Western Hospital – type 1 and 2. The first type was a double cuff straight catheter with two silicone discs attached to the intraperitoneal segment, and the type 2 was further equipped with a Dacron disc and a silicone ring at the base of the intraperitoneal cuff, which was meant to improve the seal at the peritoneal hole and prevent leaks [86].

In 1980, Ash et al. [87] introduced a "column disc catheter," which was abandoned later in favor of the "T-fluted" Ash catheter [88]. In 1983, the Valli catheter was described: the intraperitoneal segment was enclosed and protected from omental obstruction by a silastic balloon with many holes, which also was supposed to help self-positioning [89].

The permanently bent intramural segment, known as the "swan neck" [90], decreased the risk of external cuff extrusion and it was introduced by Twardowski et al. in 1986. Two somewhat similar designs were introduced later: the Cruz (pail-handle) catheter in 1992 and the "Swan neck with elongated superficial cuff (Moncrief–Popovich)" in 1993 [39]. Twardowski and his collaborators at the University of Missouri, Columbia, Missouri, introduced several more modifications [39]: a Swan neck Missouri catheter has a slanted flange and bead attached below the deep cuff, to improve catheter fixation and decrease leaks; the Swan neck presternal catheter was introduced in 1992 and has a long, tunneled segment with the exit site located in the presternal area. This design was intended to decrease the rate of peritonitis.

Conclusion

Development of peritoneal dialysis has been a fascinating intellectual, scientific, and medical journey. Table 1.2 illustrates the most important moments in the history of peritoneal dialysis, and the most important scientists who made the development of this life-saving treatment possible and applicable to patients afflicted with severe kidney disease. In recent years, there has been a trend for a decrease in peritoneal dialysis utilization, a trend that is more pronounced in the United States and Canada. As a peritoneal dialysis modality, APD is becoming the preferred one, with most of the new peritoneal dialysis patients opting for cycler therapy. At the end of 2004, there were 1,371,000 dialysis patients worldwide and 11% of them were on peritoneal dialysis. Thirty percent of the 149,000 global peritoneal dialysis patients and 60% of the U.S. patients were on APD [91]. The decrease of peritoneal dialysis utilization is thought to be multifactorial, but there is no doubt for those who use it that it remains a very important tool in an integrated renal replacement program. Patient survival in peritoneal dialysis seems to be better on the first

Table 1.2 Milestones in the development of clinical peritoneal dialysis

Investigator	Description	Date
Ganter [20, 21]	First human peritoneal dialysis	1923
Wear, Sisk, and Trinkle [22, 26]	First successful treatment of ARF with PD	1938
Frank, Seligman, and Fine [23–25, 27]	Seminal studies of PD in ARF in animals and humans	1946–1948
Grollman [28]	Long-dwell PD for uremia in animals and humans	1951
Maxwell [31]	IPD for ARF, commercially available dialysis solutions, and nylon catheter	1959
Doolan [33]	IPD for ARF, PVC catheter	1959
Ruben [32, 34]	First long-term IPD for CKD	1959
Boen [36, 37, 40]	First program of long-term PD First automatic peritoneal dialysis machine	1962
Boen [50]	Repeated puncture technique	1964
Tenckhoff [54]	Tenckhoff catheter	1968
Popovich and Moncrief [72]	CAPD	1978
Oreopoulos [64]	CAPD with plastic bags	1977
Buoncristiani [75]	"Flush before fill"	1980
Diaz-Buxo [79] Price and Suki [80]	APD/CCPD	1981

ARF – acute renal failure, PD – peritoneal dialysis, IPD – intermittent peritoneal dialysis, PVC – polyvinyl chloride, CKD – chronic kidney disease, CAPD – continuous ambulatory peritoneal dialysis, APD – automated peritoneal dialysis, CCPD – continuous cyclic peritoneal dialysis.

2 years of treatment than with hemodialysis [92] and the technique survival at 5 years is around 50–70% [93]. Peritoneal dialysis can no longer be viewed as a second class treatment and with further technological improvement in cyclers and newer, biocompatible peritoneal dialysis solutions, and capability to deliver adequate dialysis in terms of solute and fluid removal, there is a hope that peritoneal dialysis will continue to grow.

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Chapter 2
Current Status of Peritoneal Dialysis

R. Mehrotra and E.W. Boeschoten

It was in 1923 that Ganter performed the first peritoneal dialysis (PD) in a woman with renal failure [1]. However, the early experience with intermittent peritoneal dialysis (IPD) was discouraging and led to the belief that PD was not an appropriate renal replacement therapy for patients with end-stage renal disease (ESRD) [2]. The introduction of the concept of continuous ambulatory peritoneal dialysis (CAPD) by Popovich et al. in 1976 [3] was initially met with scepticism, but the successful clinical experience in nine patients at two centers in the United States [4, 5] convinced skeptics about the potential of the technique as a viable alternative to hemodialysis. Over the last decades, PD has grown worldwide to become the third most common modality for renal replacement. In this chapter, we will present a brief overview of the major advances in the care of patients undergoing PD.

PD: The Technique

A major innovation early on was the introduction of sterile plastic bags for dialysate [6]. Since then, the basic PD system consists of a PVC bag containing 1.5–3.0 L of dialysate, a transfer set, and a catheter access to the peritoneal cavity. Significant advances in the technique of PD have occurred during the subsequent decades.

Trends in Connectology

The initial bag-and-spike system was recognized to result in an unacceptably high incidence of peritonitis from touch contamination. In Italy, a double-bag Y-set device was developed that used a disconnect system with a flush before fill technique [7]. The early success in Italy was confirmed in several other centers [8–10] and is now the system of choice for PD. Over 90% of all patients in North America, Europe, Australia, and New Zealand now use these disconnect devices [11, 12]. The increased monetary cost of the twin-bag system is more than offset by the reduction in peritonitis rates [13].

Trends in Catheter Design

Tenckhoff's design of the indwelling silicone rubber catheter with two dacron cuffs was instrumental in making IPD a viable long-term therapy for renal replacement [14] and it still remains the most widely used catheter worldwide [15–17]. Several variations in the catheter design have been introduced and include the number of cuffs (single vs. double), design of the subcutaneous pathway (permanently bent or "swan-neck" vs. straight) and the intra-abdominal portion (straight vs. coiled) [18]. Double-cuff catheters were thought to be associated with a lower incidence of both peritonitis [16, 19, 20] and exit-site infections [21, 22]. However, in a prospective randomized comparison no significant differences between catheters with single or double cuffs could be established with respect to catheter survival, episodes of peritonitis, and exit site infections [23]. The benefit of the swan-neck design was demonstrable in the United States Renal Data System (USRDS) study only after adjusting for possible center effects [16]. Similarly, no convincing evidence exists for the superiority of the coiled design of the intraperitoneal portion of the catheter [18]. Finally, a downward-directed exit site was thought to result in a reduction in the incidence of exit-site infections and peritonitis

R. Mehrotra (✉)
David Geffen School of Medicine at UCLA, and Los Angeles Biomedical Research Institute, Los Angeles, California, USA
e-mail: rmehrotra@labiomed.org

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[19, 24], but in a prospective comparison, catheter types employing downward and lateral tunnel-tract and exit-site configurations produced equivalent outcomes for infectious and mechanical complications [25].

Innovations in connectology and catheter design have resulted in a 1-year catheter survival of over 80% [24]. The skills of the surgeon or nephrologist involved in the implantation of the catheter and the dedication of the PD team involved in postoperative catheter care now seem to be the most important predictors of cather survival and complications.

Trends in Peritoneal Dialysis Solutions (PDS)

Initially, glucose-based dialysate was the only PDS available. The osmotic agent glucose was buffered with lactate (or, in the early years, with acetate) to produce a low pH of 5.2 to avoid the caramelization during heat-sterilization of the PDS. The limitations of the currently available bioincompatible glucose-based solutions are now widely recognized [26]. The areas of concern are the role of glucose in the nonenzymatic glycation, formation of advanced glycosylation end-products (AGE) and glucose degradation products (GDP), and the unphysiological pH and buffer combinations. Glucose and GDPs are the most likely causative agents being responsible for ultrafiltration failure in PD patients [27–29] (Fig. 2.1). To overcome these and other concerns, alternative solutions have been designed, each targeted to achieve a clinical goal (Table 2.1).

In order to minimize acidity of the peritoneal fluid and reduce GDP production, multibag systems are currently commercially available. In these systems, the buffer is separated from the glucose solution, allowing the glucose to be stored at a very low pH and thus minimizing the formation of GDPs during heat-sterilazation. Low GDP solutions have been marketed and demonstrate improved biocompatibility. Preliminary evidence shows a salutary effect on preservation of residual renal function and retrospective analyses suggest a survival advantage with these solutions [30, 31]. These findings, however, need to be confirmed in prospective, randomized clinical trials.

Icodextrin (Extraneal®) is a glucose polymer that has undergone clinical trials since the early 1990 s. The molecular size of the icodextrin molecule is substantially larger than that of glucose and is removed from the peritoneal cavity slowly via the lymphatics. This allows for sustained ultrafiltration during the long dwells. The use of 7.5% icodextrin for an overnight exchange in patients with CAPD can generate 3.5 times greater ultrafiltration at 8 h than the 1.5% dextrose solution and similar to the 4.25% dextrose solution [32]. The amount of ultrafiltration with icodextrin can be further augmented by adding nitroprusside and this is associated with an increase in urea and creatinine clearances [33]. When used instead of standard glucose solutions for the long daytime dwell in patients on continuous cyclic peritoneal dialysis (CCPD), it generates significantly greater ultrafiltration, increased peritoneal clearance, and increased sodium removal [34, 35]. In high-average and high transporters, the ultrafiltration during the long daytime CCPD dwell with icodextrin is superior to that obtained with 4.25% dextrose [36]. In short-term clinical studies, no

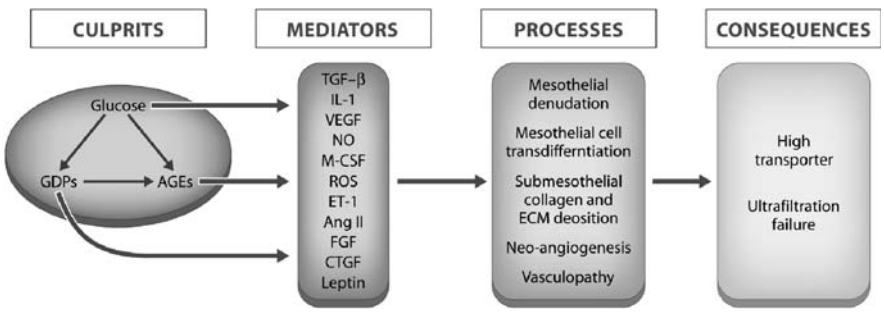

Fig. 2.1 Pathophysiologic mechanisms underlying peritoneal membrane damage with long-term use of bioincompatible peritoneal dialysis solutions. Reproduced from reference [29], with permission

Table 2.1 Biocompatibility of the new peritoneal dialysis solutions

	Low GDP solutions	Bicarbonate/lactate	Amino acid	Icodextrin
Improved pH	√	√	√	
Bicarbonate buffer		√		
Iso-osmolar				√
Reduced GDPs	√	√	√	
Reduced AGE formation	√	√	√	√
Glucose-sparing			√	√

significant adverse effects were noticed although serum maltose levels increased in both CAPD and CCPD patients [32, 37]. In later observations, the development of a skin rash appeared to be the most common treatment-related side effect of the use of icodextrin [38, 39]. There was no increase in the episodes of bacterial peritonitis, and during such episodes no further increase in maltose concentration occurred [40]. In response to an excess of cases of aseptic peritonitis in PD patients using icodextrin, a global recall of some batches of icodextrin PDS was issued in May 2002. Extensive analysis revealed that these cases were due to contamination of dialysate with *Alicyclobacillus* [41]. This problem has been resolved. With the recognition of the importance of ultrafiltration in determining patient outcome, icodextrin PDS are increasingly being used in clinical practice in many countries.

Nutrineal® is a 1.1% amino acid–containing solution with an ultrafiltration capacity equivalent to 1.5% dextrose PDS. Nutrineal® contains no glucose and GDPs and, like icodextrin, has been shown to be more biocompatible to the peritoneal membrane than the conventional PDS [42, 43]. Even though Nutrineal® induces anabolism in malnourished PD patients [44], the clinical benefit of improvement in nutritional status in randomized, controlled trials has been modest [45–47]. Providing a surfeit of calories, as obtained with co-administering amino acid and glucose PDS during night-timing cycling, may enhance the nutritional benefits of these solutions [48].

To gain the maximum benefits of biocompatibility and avoidance of glucose and GDP exposure, it is likely that future developments will focus on a combination of products. More prospective outcome-based studies, particularly focusing on the systemic effects of the new solutions, compared to those obtained by comparing these solutions with conventional PDS, will be required to convince health-care providers to pay the higher costs of the new solutions.

Automated Peritoneal Dialysis

Automated peritoneal dialysis (APD) refers to all forms of peritoneal dialysis employing a cycler to perform the dialysis exchanges. APD regimens include CCPD, IPD, nocturnal intermittent peritoneal dialysis (NIPD), and tidal peritoneal dialysis (TPD). In early experiences with CCPD this modality was shown to be accompanied by lower rates of peritonitis and hospital admissions, whereas it was as effective as CAPD with a Y-connector for patient and technique survival [49]. However, some of the later studies have not been able to confirm the lower incidence of peritonitis in APD patients [50]. The most important advantage of APD compared to CAPD seems the better quality of life and its surrogate, 'patient preference' [50, 51].

Assisted Peritoneal Dialysis

CAPD and APD are home-based dialysis modalities such that patients are trained to perform the treatment themselves. However, in many societies, the elderly, who generally have a higher co-morbidity burden, constitute a progressively larger cohort of incident dialysis patients. These patients are less likely to start or to continue on peritoneal dialysis because they are not able to perform the PD exchanges or to operate the PD cyclers themselves. Many centers have demonstrated the feasibility and safety of assistance for PD treatment by district or private nurses, at the patient's home, for physically dependent or elderly patients [52–54]. However, in a study from France, patients undergoing assisted PD appeared to have a higher risk of peritonitis than family-assisted patients, unless additional regular home visits were organized by the original training center [55]. Therefore, regular home visits by the training center may be necessary to optimize the care provided by the home nurse.

Epidemiology

Patient Numbers on PD

During the 1980 s there occurred a rapid growth in the utilization of PD. This rapid growth continued between 1990 and 1995, with annual global growth rates reaching 15% for the period 1991–1994 [11]. At the end of 1997 the chronic PD population worldwide was estimated to be 115,000, representing 14% of global dialysis patients [56]. However, since then the growth in use of PD has been slower than the increase in the number of patients undergoing maintenance dialysis worldwide [57, 58]. At the end of 2004, 149,000 patients were undergoing PD, representing 11% of the total dialysis population (i.e., 1,371,000). The reasons for this slow-down in the proportion of PD patients seem multifactorial. As the utilization of PD is declining, particularly among the elderly [54, 59], and the elderly are the largest and

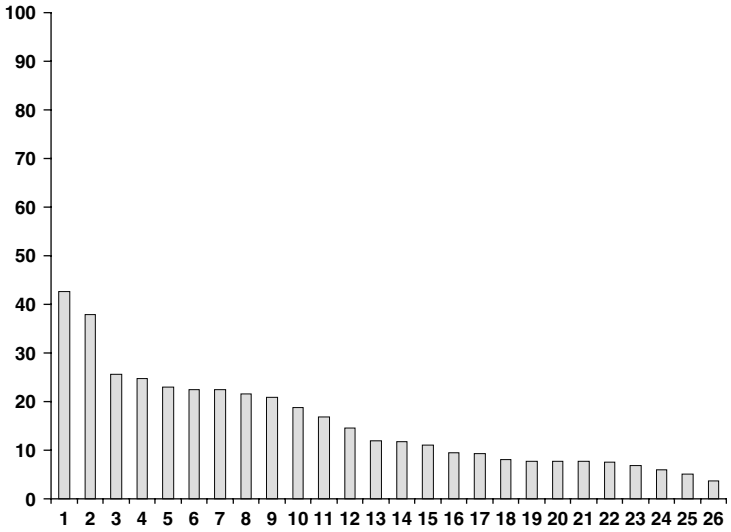

Fig. 2.2 Percentage of prevalent dialysis patients on PD in selected countries worldwide. Data obtained from reference [57]. Index for countries: 1, New Zealand; 2, Iceland; 3, Netherlands; 4, Denmark; 5, Korea; 6, Australia; 7, Sweden; 8, Scotland; 9, Finland; 10, Canada; 11, Norway; 12, Philippines; 13, Italy; 14, Turkey; 15, Israel; 16, Malaysia; 17, Greece; 18, Russia; 19, Taiwan; 20, United States; 21, Uruguay; 22, Czech Republic; 23, Thailand; 24, Chile; 25, Germany; 26, Japan

fastest growing group of patients with chronic disease, barriers to self-care PD may contribute. Also, the burden of unrealistic high solute clearance targets might have reinforced the notion of PD as an 'inadequate' therapy for renal replacement [60]. Finally, institutional changes in the delivery of dialysis therapy – e.g., proliferation of hemodialysis units and corporatization of dialysis care in the United States – are important contributors to this declining trend.

The wide variations in the utilization of PD in different countries are striking [61]. The proportion of patients on dialysis treated with PD varies from 2 to 4% in countries such as Chile, about 5 to 10% in France, Germany, and the United States, 20 to 30% in the Scandinavian countries, The Netherlands, Australia, and Canada, and >75% in Mexico and Hong Kong (Fig. 2.2) [58, 61]. Even within the same country there are wide variations in the use of PD. In the United States, the prevalence of PD in 2004 ranged from 5% in New York to 10.8% in Network 16 (Alaska, Idaho, Montana, Oregon, and Washington) [57]. In Italy, the disparity in use of PD among regions has increased, varying from 0 to 55% [62]. Finally, in France, there are large differences in the use of PD and the percentage of patients treated with PD can vary from 0 to 22% between different towns in the same region [63]. On the other hand, more recently, in Romania, the share of the dialysis pool of incident patients has increased from 10% in 1995 to 29% in 2004 [64]. The reasons for these differences are multiple and complex and are discussed in a subsequent section.

Growth of Automated PD (APD)

While in the 1980 s and the early 1990 s the growth in PD was almost entirely due to the expansion of CAPD programs, it is the growth in automated PD that is sustaining the ongoing increase in the number of patients on PD [58, 65, 66]. This growth has been mainly driven by patient preference and the development of new, simpler cyclers [67]. It is anticipated that the use of APD will continue to expand.

Factors Affecting the Choice of PD

The disparity in the use of PD in different countries and different parts of the same country has stimulated tremendous interest in elucidating the factors that determine the choice of PD as the modality for renal replacement. A large number of factors impact upon this choice (Table 2.2).

Medical and Psychsocial Factors and Patient Education

For technical reasons, PD is the modality of choice in infants and small children with ESRD [68]. The presence of medical contraindications to PD is more frequent than that for maintenance HD [69]. In a recent analysis from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study, previous major abdominal surgery was the most common medical contraindication followed by cystic kidneys, poor lung function, chronic inflammatory

Table 2.2 Factors determining the utilization of peritoneal dialysis in different parts of the world

Economic factors
Cost of peritoneal dialysis fluids and manpower
Health care system
Physician/facility reimbursement
Resource availability
Psychosocial factors
Physician bias
Educational deficits (physician/patient)
Time of referral
Patient preference/lifestyle attributes
Medical factors
Age
Cardiovascular instability
Availability of vascular access
Abdominal pathology

bowel disease, and poor cardiac condition. Poor cardiac condition was the most frequent medical contraindication to HD. Most patients deemed to have a social contraindication to PD were judged by the nephrologist to be incapable of performing the treatment by themselves. The percentage of patients having any contraindication to PD increases with age. However, studies show that up to 70% of adults have neither medical nor social contraindications to either maintenance HD or chronic PD [70–72].

Predialysis care is associated with a greater probability of selection of PD [69, 73–75]. However, if one accounts for the adequacy of education about dialysis modalities, delayed referral may not be as strong an impediment to the selection of home dialysis modalities [71, 76]. Consistent with these observations, adequate predialysis education is associated with a far higher probability of choosing home dialysis [77]. Furthermore, structured, two-step patient education has been shown in a randomized, controlled trial to be associated with significant increase in the proportion of patients that plan to start home dialysis therapy [78].

Physician Bias and Patient Education

Physician bias probably also plays an important role in the utilization of PD [62, 63, 79]. The nature of patient education is dependent on the physician bias, and in nonurgent situations the decisions of patients depend mostly on the information provided by their doctors. In the Dialysis Morbidity and Mortality Study (DMMS), Wave 2, only 25% of the patients who chose HD reported that PD was discussed with them, whereas 68% of the patients who chose PD reported that HD was discussed with them [80]. In fact, 84% of the PD patients but only 47% of the HD patients enrolled in the DMMS Wave 2 study appeared to contribute substantially to the decision about their own dialysis modality. A more recent study from the United States confirms the finding that the majority of patients are not presented with the choice of either chronic PD, home HD, or renal transplantation (66, 88, and 74%, respectively) [71]. An incomplete presentation of treatment options is an important reason for underutilization of home dialysis therapies and probably delays access to transplantation. In societies where such an impediment exists, reimbursement for pre-ESRD education may ensure timely access to different renal replacement therapies.

Economic Factors

The effect of economic factors on the selection of dialysis modality may vary by the region of the world. In Europe and America, it appears that the greater the involvement of the "public" (as opposed to "private") facilities in the provision of dialysis care, the larger the proportion of dialysis patients on chronic PD (Fig. 2.3) [62, 63, 79, 81, 82]. In these areas of the world, the cost of health-care workers in the provision of dialysis therapy is greater than the cost of dialysis supplies. Thus, the delivery of personnel-intense therapy like hemodialysis is more expensive than a therapy that uses a larger amount of supplies, viz., PD [82]. However, in many Asian and African countries, manpower is substantially cheaper than the cost of dialysis supplies, which are often imported from Western countries. This makes hemodialysis more economical than PD in these societies [83]. Manufacture of dialysis solutions in the developing countries has gone a long way in making PD affordable in some of these societies.

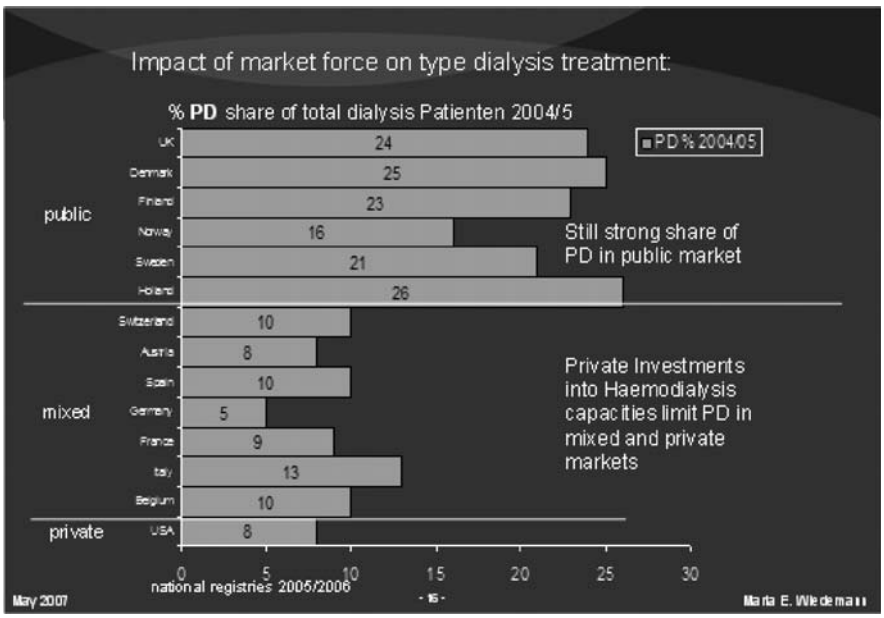

Fig 2.3 Use of PD as a modality for dialysis in various countries during the mid-1990s, based upon the funding of the dialysis provider. The top panel (Japan, USA) shows predominantly private dialysis providers; the middle panel (Germany, Belgium, Austria, Spain, France, Italy) shows a mixture of public and private providers, and the bottom panel (Switzerland, Sweden, Norway, Netherlands, Denmark, Finland, Canada, UK) shows predominantly public providers [81]

Physician reimbursement is significantly influenced by the health-care system and has been identified as a most important determinant of the choice of PD by some [62, 63, 79]. However, financial incentives in Canada (province of Ontario), Germany, and the United States have not translated into a greater utilization of PD [84, 85].

Outcome of PD

HD and PD: Comparative Survival

The current practice of care of the ESRD patient is based on the premise that HD and PD are equivalent therapies. Over the past 20 years, many studies have compared mortality risks in HD and PD [86–94]. Even though at first the results of these studies appear conflicting, some common themes have emerged. First, that the relative risk for death for PD versus HD varies by time over therapy such that most subgroups of patients have a survival advantage during the first 1–2 years of therapy [95]. Second, the lower the co-morbidity burden, the greater is the initial survival advantage associated with PD. In contrast, a higher co-morbidity burden diminishes the advantage of PD and may even be associated with an increased risk after 1–2 years [95]. Not withstanding these conclusions, it remains unclear if any of the differences in the outcomes can be attributed to the dialysis modality and may simply represent residual confounding from the inability of our statistical tools to adjust for differences in the patient characteristics. Given these caveats, patient choice should probably take precedence in the selection of dialysis modality.

Technique Survival

Technique failure is often used to describe the outcome of PD patients and usually implies cessation of use of PD due to transfer to HD, after censoring for death or transplantation. Based on the published studies, technique survival varies considerably in different countries as well as between different centers in the same country [15, 96–101]. The difference in technique success between PD and HD is greatest in the youngest patients and progressively diminishes in the other age groups [102]. Furthermore, some racial groups may have a lower short-term technique survival than others [97] and patients who are referred late are more likely to be transferred to HD than those who are referred early [103]. With improvements in patient selection, training, and aggressive management of complications, it is possible to obtain 1-year technique survival in excess of 80% [104, 105].

If death and transplantation are excluded, infectious complications have been the most common reason for transfer-out from PD [24, 106, 107]. However, with refinements in technology there has been a significant reduction in the rates of infectious complications. This has been paralleled by an increasing recognition of the importance of

small solute clearance and ultrafiltration capacity. Consistent with the importance of ultrafiltration, retrospective studies have demonstrated that it may be possible to prolong the time for which patients are treated with PD with the use of icodextrin PDS [108, 109].

Adequacy of Small Solute Clearances

In the early years of PD it was commonly accepted that subjective clinical judgment was enough for determining that a patient was well dialyzed [110]. Even though the concept of urea kinetic modeling was first extended to PD in the mid-1980 s [111], it was not until the 1990 s that this issue was systematically investigated [112–115]. The multicenter CANUSA study [115] showed that both total weekly Kt/V_{urea} and creatinine clearance (peritoneal + renal) were strong predictors of patient survival, and survival improved continuously with increasing total small solute clearance, without an apparent threshold. Higher dialysis dose, including residual renal function, was also associated with better technique survival and less hospitalization. The similar results from the study of Maiorca et al. [114] supported the CANUSA findings and both provided the evidence for the DOQI guidelines published in 1997 [116]. The DOQI guidelines recommended a target Kt/V_{urea} of 2.0 per week and creatinine clearance of 60 L/week/1.73 m^2 body surface area for CAPD. Somewhat higher levels were recommended for APD. Reanalysis of the CANUSA study, however, revealed that the effect of solute removal on outcome was entirely attributable to the effect of residual renal function [117]. In order to bypass the influence of residual renal function, the effect of the dialysis dose on outcome has been evaluated in four studies of anuric subjects; these studies suggest a minimum threshold of peritoneal Kt/V_{urea} of 1.5–1.7 [118–121]. However, as none of these studies was randomized, confounding cannot be excluded. Consistent with these observational studies, two randomized controlled clinical trials were unable to demonstrate an improvement in survival by increasing the peritoneal small solute clearances within the range currently achieved in clinical practice [122, 123].

Based on these observations, various expert groups now recommend a minimum, total Kt/V_{urea} of 1.7 [60, 124]. Furthermore, it has been recognized that besides solute removal, achievement of euvolemia should be an important goal of adequate dialysis [120, 124].

Residual Renal Function

Not surprisingly, residual renal function (RRF) influences morbidity, mortality, and quality of life in chronic dialysis patients [117, 125–129]. RRF not only contributes to small solute removal, but, probably even more importantly, allows for better volume control and larger-molecular weight solute clearances and continued endocrine and metabolic function [60]. As RRF has a major impact on the outcomes of chronic dialysis patients, its preservation is of major importance.

Decline Rate of Residual Renal Function in PD

Several studies have shown that RRF is better preserved in PD than in HD patients [130–133]. In the NECOSAD study, a large prospective cohort of HD and PD patients in the Netherlands [133], the decline of RRF in HD and PD patients was most pronounced during the first 3 months after the start of treatment. At all time points (0, 3, 6, and 12 months) unadjusted RRF values were higher in PD patients when compared to HD patients. Also after adjustment for baseline variables, PD patients had a 30% higher RRF than HD patients ($p < 0.0001$). Moreover, after adjustment for baseline RRF, the relative difference increased over time, especially during the first 6 months. However, the absolute decrease in both groups was about equal. Proteinuria, a higher diastolic blood pressure, hypotensive episodes in HD, and episodes with dehydration in PD appeared to be associated with a more rapid decline of RRF. In contrast to other studies [134, 135], but in line with the study of de Fijter et al. [136], no detrimental effect of APD on RRF could be found.

Preservation of Residual Renal Function

Considering the importance of RRF to the outcome of dialysis treatment, we need to develop treatment plans that focus on preserving RRF in PD patients [137]. This begins with regular monitoring of RRF and this should be done with a 24-h collection of urine every 1–3 months to measure volume and urea and creatinine clearances. In view of

substantial tubular secretion of creatinine at low GFRs, arithmetic mean of urea and creatinine clearance may be a better measure [138, 139]. Blood pressure should be well controlled and hypotensive episodes should be avoided. Randomized, controlled clinical trials have demonstrated that the benefit of angiotensin converting enzyme inhibitors and angiotensin receptor blockers is seen even at the low levels of glomerular filtration rates reported in patients undergoing PD [140, 141]. The use of diuretics for the preservation of RRF is controversial [142]. Loop diuretics produce an increase in diuresis and may result in a clinically meaningful improvement in fluid balance. However, loop diuretics have no effect on preserving solute clearances [143]. Finally, nephrotoxic agents like aminoglycosides, nonsteroidal anti-inflammtory drugs, and iodinated contrast agents should be avoided as far as possible.

Incremental Peritoneal Dialysis: Are Renal and Peritoneal Clearances Equivalent?

Even though targets have been set for small solute clearance clearances for patients undergoing maintenance dialysis, patients with chronic renal failure are allowed to dwindle to clearances far below the adequacy target before dialysis is initiated [115, 144, 145]. Based on the similar relationship between dietary protein intakes and clearances in pre-dialysis patients and PD patients, the 1997 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended that the level of small solute clearances considered to provide adequate CAPD at that time (weekly Kt/V_{urea}, 2.0) be considered the level of renal function at which chronic dialysis should be initiated [116, 146]. The PD subcommittee of the KDOQI recommended that chronic dialysis may be initiated in an incremental fashion such that the sum of the renal and dialytic weekly Kt/V_{urea} should remain near 2.0 at all times. Even though scientific evidence for this approach was lacking, "incremental dialysis" seemed rational. In subsequent studies, this approach could not be validated [147, 148]. A reason for this lack of evidence may have been the assumption that renal and peritoneal solute clearance are equivalent. Even when the measured small solute clearances are identical, clearances for middle and larger molecular weight solutes may differ considerably. Furthermore, the kidney has many other metabolic and endocrinologic functions. Therefore, 1 mL/min of solute clearance by the kidney is of more value to the patient than 1 mL/min solute clearance by the kidney [137].

Nutritional Status

Protein energy wasting at the time of initiation of dialysis, and subsequently, is an important surrogate marker of an adverse patient outcome. This observation makes the assessment of nutritional status and prevention of protein energy wasting an important clinical priority.

Prevalence of Protein Energy Wasting

Protein energy wasting is widely prevalent in the PD population [115, 149, 150]. It is estimated that 40% of PD patients have protein energy wasting, with 5–10% of patients demonstrating severe malnutrition [151]. Since peritoneal glucose absorption contributes to the total energy intake of a PD patient, suboptimal protein intakes are probably more important than suboptimal energy intakes as a cause of nutritional decline [151].

The Malnutrition Inflammation Atherosclerosis (MIA) Syndrome

Several studies have shown that malnutrition, inflammation, and atherosclerotic vascular disease are inter-related and each is associated with mortality [152–155]. The combination of these three conditions has been referred to as the MIA syndrome [156]. Several theories have been proposed to explain the supposed links between the three components of the MIA syndrome [155, 157, 158], but the mechanisms involved are not yet clear. Stenvinkel et al. [156] suggested two types of protein energy wasting in ESRD patients: the first type (type 1) is associated with the uremic syndrome per se or factors associated with uremia such as physical inactivity, underdialysis, dietary restrictions, and psychosocial factors. This type is characterized by a modest reduction in serum albumin due to a low dietary intakes. Significant co-morbidity and signs of inflammation are usually not present in type 1 protein energy wasting and this condition may be addressed by eliminating the causative factors. On the other hand, type 2 protein energy wasting, characterized by significant co-morbid conditions, severe hypoalbuminemia, and an inflammatory response evidenced by higher levels of CRP and pro-inflammatory cytokines, may be more difficult to treat.

Losses of Nutrients in the Dialysate

From the beginning of the CAPD era, it has been recognized that PD is associated with protein losses in the dialysate [159–162]. In the guidelines for nutrition in chronic renal failure, these losses have been taken into account [163, 164]. A recent study suggests that APD may be associated with somewhat higher protein losses compared to previous reports in CAPD patients, and the magnitude of these losses may be related to the number of nighttime exchanges and the duration of dwell [165]. Protein and amino acid losses accounted for an average of 15% of total nitrogen appearance, accounting for almost a third of the increase in dietary protein requirements in CPD patients.

Strategies to Improve Protein Energy Wasting in PD Patients

Several interventions have been shown to improve protein energy wasting in dialysis patients [151]. It is unclear, however, if improvement in nutritional status will result in a reduction in morbidity or mortality of our patients. A detailed discussion is beyond the scope of this chapter but are summarized in Table 2.3 and some of the key issues are summarized below.

Residual Renal Function

RRF plays an important role in maintaining the nutritional status of patients on chronic dialysis [115, 149, 166]. In an international study, loss of RRF correlated with muscle wasting and contributed to anorexia and the symptoms of severe malnutrition [149]. Likewise, in the Canadian–USA (CANUSA) multicenter study, after 6 months of initiation of PD there was a progressive decline in nutritional parameters with declining residual renal function [115]. Hence, preserving residual renal function should be an important goal.

Small Solute Clearances

Several cross-sectional studies have shown a relationship between the peritoneal clearances, dietary protein intake, and the nutritional status of patients [167, 168]. In the CANUSA study, during the first 6 months of CAPD, the addition of dialytic clearances resulted in a marked increase in solute clearances. This was associated with significant improvements in several estimates of nutritional status (subjective global assessment, protein catabolic rate, and lean body mass) and these changes were significantly correlated with the estimates of the dose of dialysis [169].

Table 2.3 Recommended interventions to improve nutritional status in PD patients

Treat reversible causes of anorexia
Improve/maintain small solute clearances
Prokinetic agents for gastroparesis
Treat *Helicobacter pylori* infection
Increase supply of nutrients
Nutritional counseling
Appetite stimulants
Oral supplements
Enteral supplements
Intraperitoneal amino acids
Correct metabolic acidosis
Anabolic hormones
Recombinant human growth hormone
Insulin-like growth factor I
Nandrolone acetate
L-carnitine
Potential anti-inflammatory therapies
Treatment of co-morbid conditions

Source: Adapted, with permission, from reference [151]

Correction of Metabolic Acidosis

The adverse impact of chronic metabolic acidosis on nutritional status has long been recognized [170]. Two randomized, controlled clinical trials among patients undergoing PD have demonstrated that correction of metabolic acidosis is associated with improvement of nutritional status and reduced hospitalization rates [171, 172].

Use of Intraperitoneal Amino Acid (IPAA) Solutions

Earlier studies with amino-acid solutions enrolled small numbers of patients, were uncontrolled, and used solutions not available commercially. However, three trials supported the use of these solutions. Two metabolic balance studies have demonstrated that IPAA solutions induce anabolism, particularly when a surfeit of calories (as with glucose-based dialysate) is provided [44, 48]. However, subsequent randomized, controlled clinical trials have demonstrated that the nutritional benefits of IPAA solutions may be modest (reviewed in [151]).

Obesity

Early papers on CAPD focused on weight gain during peritoneal dialysis as an undesirable complication [173–176]. Many PD patients experience significant weight gain upon initiation of therapy, but weight usually stabilized thereafter [174, 176]. The weight gain appears to correlate with the daily amount of glucose absorbed from the dialysate [173] and seems to be most prominent in patients who are already obese at the start of treatment [174]. More recently, the impact of obesity on outcomes of dialysis patients has been questioned. Unlike the observations in the general population, in HD patients obesity appears to be associated with improved survival [177]. The advantage associated with obesity in PD patients appears, though, to be less pronounced [178, 179]. In a report from the Australian and New Zealand registry, among patients undergoing PD, obesity was associated with worse outcomes [180] and a higher risk for peritonitis [181]. The effects of weight gain on outcomes of PD patients, thus, need further study.

Cardiovascular Disease

Vascular complications are the major cause of death in patients undergoing PD and include congestive heart failure, myocardial infarction, and cerebrovascular disease. While traditional risk factors like diabetes mellitus, hypertension, smoking, physical inactivity, obesity, and hyperlipidemia contribute substantially to cardiovascular disease in the general population, nontraditional risk factors like inflammation, anemia, and abnormal mineral metabolism are probably also important in dialysis patients [182]. These factors represent only some of the many nontraditional factors that may play a pathophysiologic role in the high cardiovascular burden in dialysis patients.

As discussed above, inflammation, indicated by elevated serum concentrations of acute phase proteins or cytokines, is associated with worse outcome in dialysis patients. Inflammation interacts with many pathophysiologic pathways that lead to vascular damage [183]. Emerging evidence indicates that loss of RRF may be associated with worsened inflammation and left ventricular hypertrophy and they may interact to increase mortality and cardiovascular death risk of PD patients [184].

There is substantial evidence that treatment of anemia in dialysis patients improves quality of life and objective markers of physical and cognitive performance [185, 186]. Furthermore, anemia has been shown to contribute to left ventricular hypertrophy [187]. Even though many epidemiological studies have consistently demonstrated an inverse relationship between hemoglobin levels and mortality, complete correction does not seem to lead to any improvement in survival over partial correction of anemia [188]. A randomized clinical trial of normalization of hemoglobin with erythropoietin in HD patients with cardiovascular disease was stopped prematurely as interim analyses suggested that continuation of the study was unlikely to prove the primary hypothesis [189]. There was a trend towards a higher mortality in the intervention group but this did not reach statistical significance. Thus, based on the current body of evidence, complete correction of anemia cannot be recommended for dialysis patients at this time.

Abnormal mineral metabolism is common in patients with chronic kidney disease and epidemiologic studies suggest that these abnormalities are associated with a higher cardiovascular risk [190]. It seems that hyperphosphatemia is a much stronger predictor of outcome in dialysis patients than hypercalcemia or hyperparathyroidism [190]. Most of the studies on mineral metabolism in dialysis patients have focused on HD but some recent studies demonstrate a similar risk in PD [191, 192]. There is currently no evidence that correction of abnormalities in mineral metabolism results in improvement in clinical outcomes of dialysis patients.

Table 2.4 Sources of infection of the peritoneal cavity in patients on peritoneal dialysis

Intraluminal
Touch contamination
Periluminal
Catheter-related infections (exit-site/tunnel infections)
Enteric
Iatrogenic (enteric, bacteremic, gynecologic)

Infectious Complications

Infectious complications, particularly peritonitis, have long been the proverbial "Achilles heel" of PD and have long accounted for technique failure [24, 106, 107] and catheter loss [23, 24, 193]. The pathophysiologic bases for peritonitis are summarized in Table 2.4.

As discussed earlier, refinements in connectology and use of the twin-bag systems have led to significant declines in the rates of peritonitis from touch contamination. Over the last decade, advances have been made in reducing catheter-related infections. The first step in preventing catheter-related infections is ensuring that the PD catheter is placed by an experienced operator under sterile conditions. The risk can be further reduced by using exit-site antibiotic prophylaxis by employing either mupirocin or gentamicin [194]. With these advances, the peritonitis rates have declined from about 1.4 episodes per patient-year to 0.5 episodes per patient-year in many centers [195, 196]. Guidelines for prevention, diagnosis, and treatment of infectious catheter-related complications were first published in 1983, have been revised several times, and are evidence based when evidence existed [196]. However, despite a bibliography of more than 9,000 publications on infections as a complication of peritoneal dialysis, the recommendations are hampered with insufficient randomized controlled trials to justify firm pronouncements on several topics being addressed. Therefore, they are not meant to be implemented in every situation. It is strongly advised that each center should examine its own pattern of infection, causative organisms, and sensitivities and adapt the protocols as necessary for local conditions. The guidelines can be considered as an important tool for quality improvement of peritoneal dialysis [197].

Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is a rare but life-threatening complication of peritoneal dialysis [198–201]. Most patients have undergone treatment at least 4 years, with the prevalence increasing with longer PD vintage [199]. The mortality rate is high, and in severe cases with complete intestinal obstruction, 60–93% of the patients die [199]. From experiences reported in the literature, optimal management requires a high index of suspicion for the diagnosis of the condition. Appropriate investigations include longitudinal peritoneal equilibration tests and regular measurement of CA125 in the dialysate. A sudden decrease in CA125 concentrations may indicate the development of EPS [202]. CT scanning of the abdomen for detecting fibrosis, thickening of the peritoneum, and calcifications may be helpful. There is no agreement about the therapy of choice for EPS, although it is generally agreed that total parenteral nutrition, steroids, and, sometimes, surgical enterolysis maybe important components [200]. Treatment of EPS with tamoxifen is still controversial [203]. The cause of EPS seems to be multifactorial. Given that only a small proportion of patients develop EPS, it is proposed that genetic factors may set up a predisposition for this life-threatening complication [204]. To address further research on this rare entity, international collaboration in the form of a global registry and DNA bank has recently been proposed [204].

Quality of Life

Studies on the outcome of dialysis treatment usually focus on mortality and morbidity. There is general consensus, however, that the quality of the remaining life is an important outcome parameter as well [205]. It is well known that quality of life (QoL) in new dialysis patients is substantially impaired, both in HD and PD patients [206–212]. In a study of 226 new dialysis patients (120 HD and 106 PD), it was observed that QoL is lower compared to the general population in all QoL dimensions [205]. Multivariate analysis showed that a higher number of co-morbid conditions, a lower hemoglobin level, and a lower RRF were the most important independent risk factors for a lower QoL.

However, these medical factors could explain only a small part of the variations in the observed QoL. Consistent with these observations, studies have shown that psychological and social issues have a significant impact on the QoL of PD patients [213–216]. Kutner et al. found limited evidence for an association between race and perceived health status and QoL in black and white patients starting dialysis (1,679 HD and 1,623 PD) enrolled in the DMMS Wave 2 cohort study [211].

It has been suggested that differences in QoL may become more apparent with increasing dialysis vintage. Longitudinal evaluation of the QoL was recently reported by Merkus et al. [206]. In 250 incident patients enrolled in the NECOSAD study, the physical QoL deteriorated during the first 18 months, both in HD and PD patients, but the deterioration was greater in PD patients. The mental QoL remained stable over time and did not differ between both dialysis modalities. These results are similar to the study by Wu et al. [212], but could not be confirmed by Kutner et al., who compared QoL in 455 HD and 413 PD patients [210]. PD patients' scores appeared to be higher than HD patients' scores with regards to the effects of kidney disease, burden of kidney disease, staff encouragement, and satisfaction with care.

When patients are confronted with the choice of dialysis modality, it is important to realize that there are distinct advantages and disadvantages to each of the modalities. Patients who initiate PD may be able to enjoy a period of time being largely independent of a dialysis facility, and they are more likely to be able to continue their jobs [217].

Future Directions

Over the past two decades, PD has established a niche for itself in the therapy of ESRD. Three different surveys – one each from United States, Canada, and the British Isles – concerning nephrologists' opinions about the optimal distribution of dialysis modalities reported that the optimal percentage of patients treated with PD should be around 30–40% [218–220]. When patients having no contraindication to PD are offered a free choice, 45–50% chose PD [69, 72]. These percentages are considerably higher than the 11% global PD penetration. Thus, much greater attention should be paid to optimal patient education. With the encouraging results with daily home HD, home therapies are likely to receive greater attention in the future. The effect of growth of home HD on the utilization of PD remains to be seen.

Economic Considerations

As discussed earlier, nonmedical factors are the most important determinant of choice of PD, and it is anticipated that these factors will continue to influence the use of this therapy. In the United States, annual costs for the HD patients are significantly higher than that for PD patients [57]. Greater utilization of self-care dialysis reduces overall costs: even after accounting for younger age and lower co-morbidity of the PD population; and annual per-capita Medicare expenditure is $12,000 lower than for in-center HD [221]. With increasing costs of the Medicare ESRD program, this issue is likely to receive greater attention, with a possible push towards greater use of home dialysis.

On the other hand, in developing countries, efforts are underway to reduce the costs associated with PD therapy, particularly by reducing the need to import PDS from the developed countries. The greater the success at outsourcing the production of dialysis solutions, the greater would be the potential to lower the cost of therapy and, hence, the higher the probability of use of PD.

Quality Considerations

Efforts to further improve the outcome of PD, particularly to reduce the cardiovascular disease burden, should continue in the future. To achieve this goal we need evidence-based best practice guidelines like those being released by the International Society for Peritoneal Dialysis, Dialysis Outcomes Quality Initiative (DOQI), European Best Practice Guidelines, and Caring for Australians with Renal Impairment (CARI). It has been shown that the release of guidelines has some effect on clinical practice. Renal replacement therapy is being started in the United States at progressively higher levels of glomerular filtration rate [57]. In the Netherlands, the introduction of the DOQI guidelines resulted in a tendency towards earlier introduction of renal replacement therapy and higher doses of dialysis [222]. The only way to ensure that guidelines actually improve medical outcomes is to emphasize implementation strategies. Furthermore, guidelines should be systematically re-evaluated on their effectiveness in clinical settings.

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Chapter 3
Comparing Survival Outcomes in Peritoneal Dialysis and Hemodialysis

K.E. Yeates and P.G. Blake

Since the emergence of peritoneal dialysis (PD) as a widely used, feasible, and successful home-based therapy in the 1980s, there has inevitably been interest in comparing outcomes on this modality with those on hemodialysis (HD). Many studies have been done comparing costs of treatment, quality of life, and hospitalization and results have been variable [1–12]. Most important and most controversial, however, have been the studies that have attempted to compare patient survival on PD to that on HD [13–27].

The background to this controversy is that in most developed countries, PD is less costly for payers and providers than HD [8–12]. Pressure from payers to use PD has therefore been significant and the question that arises is whether survival is equivalent or better and whether the therapy can consequently be deemed to be more cost effective.

Despite the positive attributes of PD, the proportion of incident patients treated with the modality has fallen in many countries over the last decade, most notably in the United States, where the PD prevalence has fallen from 14% in 1995 to 8% in 2002 [28]. This decline has many causes but may partly be driven by a series of U.S. studies suggesting higher mortality on PD, particularly for older patients and those with diabetes [13, 18, 19]. This trend towards a more expensive modality mix emphasizes the importance of resolving the relative benefits of the two modalities.

As this chapter will show, historically, most comparative survival studies have utilized renal registry data [13–23]. Head-to-head randomized controlled trials directly comparing PD to HD survival have never been successfully completed [24]. The literature is therefore imperfect and so is a source of ongoing controversy.

A striking feature of the literature comparing survival between PD and HD is that results seem to differ greatly between different countries or when different methods of analysis are used [13–27]. This confused situation is partly related to different study designs, and the variety of statistical methods that have been applied to compare overall patient survival.

There is some question as to whether it is even valid to compare survival rates in PD and HD or whether newer statistical methods can be used to overcome inherent differences between the two patient populations and modalities [29–32].

In this chapter we review historical and more contemporary survival outcomes between PD and HD. In addition, we will review changes in statistical methodology that have been utilized over time to compare survival between the two treatment modalities and discuss the merits and drawbacks of each study and its design. Lastly, we conclude with a summary of our findings and suggest ways to apply this knowledge to clinical practice.

Points to Consider When Interpreting Survival Analyses in Dialysis Therapy

Two key points need to be remembered when considering the design of studies comparing mortality on PD and HD. First, modality switches from PD to HD are much more frequent than those in the opposite direction [15–20]. Second, almost all studies indicate that PD compares best with HD in the early months and years after onset of end-stage kidney disease (ESKD) as compared to subsequently [15–20] (Fig. 3.1). The cause of this is unclear, though it may be related to better retention of residual renal function on PD or to unrecognized baseline case mix differences between patients on the two modalities. It is often referred to as an example of disproportionate hazards and it greatly complicates comparative survival analysis [20, 29, 31].

We will now consider a variety of factors that have to be taken into account in designing and evaluating studies done in this area.

P.G. Blake (✉)
Professor of Medicine, Division of Nephrology, Department of Medicine, London Health Sciences Centre and University of Western Ontario, London, Ontario
e-mail: peter.blake@lhsc.on.ca

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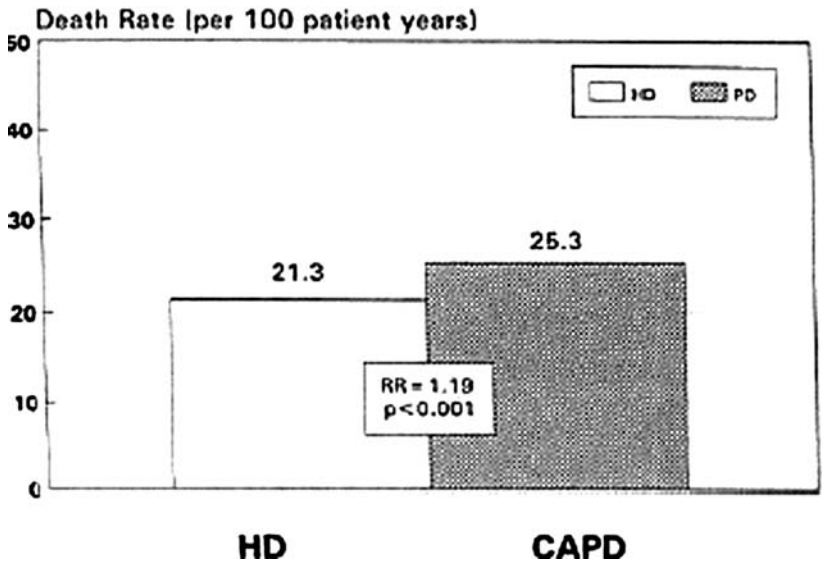

Fig. 3.1 Relative risks of mortality in Canadian PD versus HD patients from Fenton et al. [15]

The Use of Prevalent versus Incident Patients

Some studies that have compared survival between PD and HD have used prevalent patients, some have used incident only, and some have used both [13–20]. Incident studies are preferable, of course, because an early adverse effect will be missed in a purely prevalent study. Because of the disproportionate hazards phenomenon mentioned above, HD, the modality with the higher early mortality, will look misleadingly good in a purely prevalent study. Studies that use prevalent-only patients should therefore be interpreted with caution and likely will not be seen much in the future [13].

As-Treated (AT) versus Intent-to-Treat Analysis (ITT)

Careful consideration of each of these study design methods is important as the choice can have a significant impact on study outcomes in analyses that compare survival in PD and HD.

ITT attributes a patient's death to the treatment that the patient was originally placed on or "intended" to be receiving. AT attributes a patient's death to the therapy that the patient was receiving at the time of their death. ITT has been used in many of the survival analyses and does not allow the researcher to account for switches in therapy. It attributes a patient's death to the initial therapy they received without accounting for the "actual" therapy, or multiple therapies, the patient may have received during their course of treatment.

The different types of analyses try to answer subtly different questions. An ITT analysis asks the most clinically relevant question, which is whether initial modality assignment influences patient survival. This is what a physician needs to know when advising patient about modality choice prior to initiation of dialysis. An AT analysis tries to determine which modality is likely to be associated with better survival while a patient is receiving it. In a sense, the AT analysis compares the actual modalities while the ITT compares two strategies, "HD first" versus "PD first."

Often, the comparative studies use a modified ITT approach with censoring of patients either at the time of any modality switch, including transplantation, or at some designated time period after a switch [15–17].

Most statisticians would suggest that both ITT and AT analyses be performed when comparing outcomes, as each answers a distinct question and because differences in those answers can indicate that more detailed analyses are required. AT models require new complicated statistical models to deal appropriately with modality switches and are likely to yield more accurate results when large administrative datasets are being used.

When to Enter Patients in Comparative Studies

Most studies assign patients to the modality they are being treated with 90 days after initiation of dialysis and the period prior to that is omitted from the comparison [15–19]. Intuitively, it might appear more appropriate to use the

true initial modality to assign patients and to include all treatment time in the analysis. However, in most centers, patients presenting acutely or late are all treated with HD and, because these patients tend to be sicker and to have a worse prognosis, a survival comparison based on initial modality would be biased against HD. Also, deaths in the first 90 days are likely to be more affected by pre-existing co-morbidity than by dialysis modality per se. The notion is that by 90 days these patients will have stabilized or recovered renal function or died and that some will even have switched to PD and that, overall, the comparison will be fairer. It could even be argued that extending the assignation to 120 days might be even fairer in lessening the influence of pre dialysis co-morbid conditions.

In contrast, others argue that the 90-day approach removes from the analysis part of the time period where PD is most successful and this introduces a bias in favor of HD. Furthermore, this is a period when HD patients are most likely to be using venous catheters for blood access and these are associated with significant complications so that omitting this period might again leads to a bias against PD. The 90-day rule is probably a fair compromise. However, it is important that the large influence of this issue on the results of the analysis be clearly understood. Papers by Fenton et al. and by Murphy et al. particularly demonstrate this effect [15, 16, 25] (Fig. 3.2). One U.S. study by Winkelmayer surprisingly reports a bias in the opposite direction, with more deaths on PD in the first 90 days, but the cohort studied was small and comprised only elderly patients and the findings did not quite reach statistical significance and seem out of line with those in other studies [30].

Adjustment for Baseline Confounders

None of the comparative survival studies is randomized and so adjustment for baseline population differences is important. In most, though not all, developed countries, patients treated with PD tend to be younger and healthier than those on HD and so, in countries such as the United States and Canada, an unadjusted analysis will show misleadingly better results for PD [15, 26]. Conversely, in some European countries, PD tends to be used, particularly in older patients considered to be potentially less tolerant of the hemodynamic challenges of HD, and the bias might thus be in the opposite direction [23].

Clearly, adjustment of comparisons for age, sex, and baseline co-morbidity is crucial. However, co-morbidity information is often lacking or inaccurate in registry studies [20, 33]. Many analyses correct for age, sex, and diabetes only [17]. Others do a qualitative "yes/no" correction for conditions such as heart failure, ischemic heart disease, cancer, etc. [15, 16]. Prospective studies typically have more detail available and attempt to quantify co-morbidity by using scoring systems [25, 26, 27]. They may also adjust for functional characteristics, residual renal function, and laboratory measurements [27]. In general, in North American analyses, greater adjustments seem to result in findings that are more favorable to HD, but there are always concerns about the nature and accuracy of the adjustment [27, 31].

A key point about adjustment for co-morbidity is that only baseline data be used. It is completely inappropriate to adjust for data points or events occurring after initiation of dialysis as the modality may be influencing these. For example, outcomes should not be adjusted for residual renal function after initiation of dialysis as this may be better

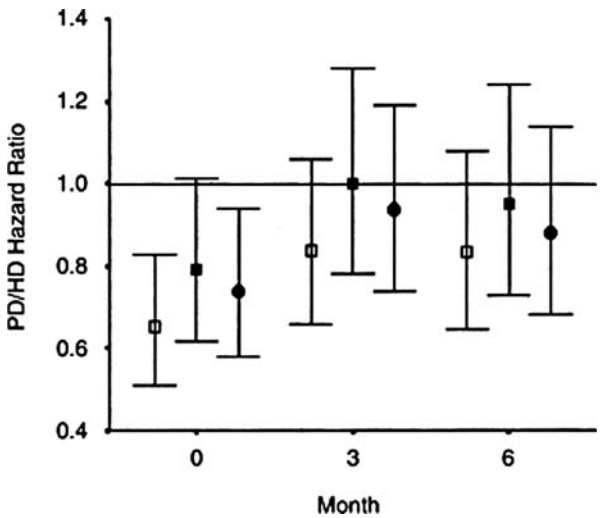

Fig. 3.2 Relative risks of mortality in Canadian PD versus HD patients before and after adjustment and with varying start points from Murphy et al. [25]

preserved on PD than HD and the adjustment may therefore take a key advantage of PD out of the analysis. Similarly, adjustment for serum albumin after initiation is inappropriate because it tends to be systematically lower on PD due to dialysate protein losses and the adjustment would introduce a bias against HD. The "Choices for Healthy Outcomes in Caring for End-stage renal disease" (CHOICE) study, for example, made the error of adjusting for serum C reactive protein levels measured after initiation of the treatments being compared [27, 31].

Adjustments will inevitably be incomplete, even in the most detailed of prospective cohort studies. Factors such as motivation and family support may be critical but are difficult to measure. Only a randomized trial could get around these concerns.

Adjustments are complicated and, recently, awareness has increased about complex interactions between modality and factors such as age, sex, and diabetic status and their effects on survival [20]. This has led to results of comparative studies being expressed separately for diabetics and nondiabetics, younger and older patients, men and women, and even for those with and without heart disease [17–20]. There is a realization that there is not one simple answer to the question of which modality is best and that the answer varies between the different subpopulations with ESKD.

The U.S registry-based and prospective cohort studies have all used the Medicare "Medical Evidence Form 2728" to identify co-morbid disease among study patients. Vonesh et al. found that 45% of patients had no co-morbidity data recorded [20]. This high proportion of patients likely includes those with missing data and those who truly are without co-morbid disease. Furthermore, in 2000, Longnecker et al. performed a validation of co-morbidity data from the CHOICE Study and found that co-morbid conditions are significantly underreported on Form 2728 but that wrongfully attributing a diagnosis to a patient did not frequently occur [33]. Missing co-morbidity data is less likely to be an issue in studies where the co-morbidity data is collected and validated from more than one source.

Time-Dependent Analyses

As already mentioned, the relative mortality risks between patients on HD and PD do not appear to be constant with time on dialysis. Almost all studies suggest PD is at its best in the initial 2 years after initiation of dialysis and that HD is at its best with longer-term patients. Indiscriminate application of the Cox proportional hazards model to such a "disproportionate" situation is clearly inappropriate. Recent studies have therefore done repeated analyses using different start points, i.e., redoing the analysis at 6 months, 12 months, 24 months, etc. (Fig. 3.2). Of course, the adjustments involved must still be based on predialysis baseline characteristics, as explained above. Time-dependent covariates have been used in other types of longitudinal dialysis outcome studies but would be inappropriate in comparative survival studies as adjustment would be made for a time-dependent covariate that is affected by the treatment that is being studied, potentially adjusting out the effect that is being measured.

The use of propensity scores can help to minimize the effects of case-mix differences and the potential for confounding in registry based and observational studies but requires substantial statistical expertise [30, 35]. It is most useful in dealing with situations where there are complex interactions between covariates that influence treatment assignment and also where there may be significant center effects influencing outcomes. This is clearly relevant in PD HD comparisons. Of course, propensity scores do not and cannot remove the biases associated with unidentified confounders. Only a randomized trial can do this.

Methodologic Issues in "Switching" Modalities

As already mentioned, modality switches from PD to HD are much more common than those in the opposite direction and this leads to problems in comparative AT studies. If a patient switches modality and then dies shortly thereafter, it would seem unfair to attribute the death to the new modality. Accordingly, most AT studies allow a "grace period," typically of 90 days' duration, during which deaths are attributed to the previous rather than the new modality. Longer grace periods might be considered but would seem excessive. In one study, the length of such periods did not appear to influence the final results substantially [15].

Other Clinical Points

Other issues that deserve consideration when comparing survival outcomes in PD and HD include within, and between, country differences in patient populations where PD is in high versus low use. For example, in Hong Kong, more than 80% of patients are receiving PD versus HD [36]; whereas the opposite is true in the United States

[37]. This raises the question as to how much one can extrapolate conclusions from comparative studies done in such countries to other jurisdictions. One has to presume that very "selected" populations are receiving the low-use modality in these settings. It also raises concerns about experience with the low-use modality in centers within such countries. There is significant literature suggesting improved outcomes with increased experience in many area of medicine including ESKD [38].

Significant changes that may impact on patient survival and technique failure have occurred in the way PD and HD have been delivered over the past two decades. For example, HD therapy has seen significant technologic advances with the introduction of volumetric HD machines and high flux dialyzers. PD therapy has also experienced similar trends with the introduction of cyclers, Y-set and double-bag systems, and novel dialysis solutions. Both modalities have also experienced a fluctuating emphasis on higher clearance prescriptions and more aggressive use of recombinant erythrocyte stimulating agents and higher hemoglobin targets. In other words, the modalities being compared are themselves in a state of flux and every comparative study may be considered out of date by the time it is published.

The Studies

To date, comparison of PD versus HD survival has occurred through retrospective analysis of registry-based data, prospective cohort studies, and two unsuccessful randomized controlled trials [13–27].

Randomized Trials

In the 1990s, Baxter attempted to enroll patients in a worldwide randomized trial comparing HD and PD. The study was abortive because once interested patients completed the prerandomization education session, the large majority had developed a preference and were no longer willing to undergo randomization. This has been a recurring problem and underlines the point that there is a limit to the types of therapies that patients will accept on a random basis [24].

More recently, the Dutch NECOSAD Study Group aimed to enroll in a randomized trial all new dialysis patients who had no contraindication to either HD or PD at 38 dialysis centers in The Netherlands [24]. The primary and secondary outcomes were quality-of-life adjusted life year (QALY) score and survival, respectively. The study was stopped early due to low enrollment, with only 38 patients agreeing to participate. In the first 2 years, there was only a slight difference in mean QALY score, which favored HD over PD. After 5 years of follow-up there was no persisting difference in quality of life but the hazard ratio for death with HD versus PD was significant at 3.8, suggesting that long-term survival favors PD. However, it could be argued that low study enrollment makes these results difficult to interpret and the small number of patients who agreed to participate in the study may have been "different" from the large number who chose not to be included [24].

Registry-Based Studies

A number of registry based studies have been published since the mid-1990 s reporting patient outcomes, particularly from the United States, Canada, Denmark and the Netherlands [13–23]. In 1995, Bloembergen et al. used Poisson regression to analyze a large sample of prevalent-only patients from the United States Renal Data System (USRDS) for the years 1987–1989 with adjustment for demographic characteristics and showed 19% higher all-cause mortality in prevalent PD patients in the United States as compared to HD [13] (Fig. 3.3). The excess risk of death was significant for patients aged over 55 years and was most pronounced in females and those with diabetes. The methodology used here was unusual. In addition to the prevalent based analysis method, the study only started analyzing patients who had completed 90 days of treatment on 1 January of each of the 3 years concerned and so systematically omitted the majority of the first 12 months of treatment in many patients. This introduced a substantial bias against PD. Vonesh, however, did a similar analysis with the USRDS dataset, but included both incident and prevalent patients from 1990 to 1993, and for these more contemporary cohorts reported no significant difference between PD and HD mortality although there was still a trend favoring HD in older diabetics and PD in younger diabetics [14].

In contradistinction, Fenton et al. published results of an analysis utilizing data from the Canadian Organ Replacement Register (CORR). This involved incident PD and HD patients who initiated therapy between 1990 and 1994, with follow-up for as long as 5 years [15, 16]. After adjustment for baseline differences including age, primary renal disease, center size, and co-morbidity at the initiation of dialysis, and using both an ITT and AT approach, the

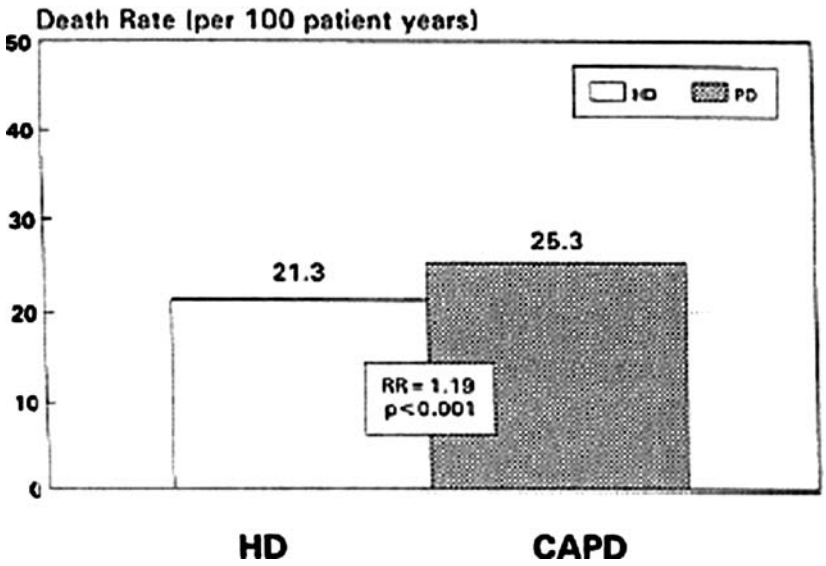

Fig. 3.3 Relative risks of mortality in U.S. PD versus HD patients from Bloembergen et al. [13]

Table 3.1 Relative risks of mortality using ITT and AT models in Canadian PD versus HD patients from Schaubel et al. [16]

	'As-treated' RR	'Intent-to-treat' RR
All patients	0.73 (0.69–0.77)	0.93 (0.87–0.99)
Nondiabetic		
<65 yrs	0.53 (0.46–0.60)	0.84 (0.73–0.96)
≥65 yrs	0.75 (0.65–0.86)	0.95 (0.86–1.05)
Diabetic		
<65 yrs	0.76 (0.65–0.83)	0.90 (0.82–1.10)
≥65 yrs	0.88 (0.75–1.04)	1.04 (0.87–1.24)

authors showed that, in Canada, there was a significant 27% survival advantage for PD patients compared to HD and that this advantage was greater in the first 2 years of dialysis and for younger patients [15, 16] (Table 3.1) (Fig. 3.1).

Comparable U.S results were reported by Collins et al. in 1999 in a study that comprised incident patients from 1994 to 1996 followed for the first 2 years of dialysis [17]. The authors used Poisson regression to compare death rates and adjusted for age, gender, race, and primary renal disease. A Cox model was utilized to evaluate cause-specific mortality with the issue of proportionality addressed through a separation of patients with and without diabetes. This study showed a significant survival advantage for PD over the first 2 years compared with HD in younger patients with and without diabetes and in older nondiabetic patients also (Fig. 3.4). The effect was most apparent, being almost 40%, in the younger nondiabetics. Only in older patients with diabetes did the authors report a survival advantage for HD [17].

These contrasting outcomes caused confusion but the studies did demonstrate a number of consistent findings. The U.S studies clearly showed how incident analyses, such as that by Collins et al., make PD look much better than prevalent ones, such as that by Bloembergen et al. [13, 17]. They also established that, for both countries, the relative

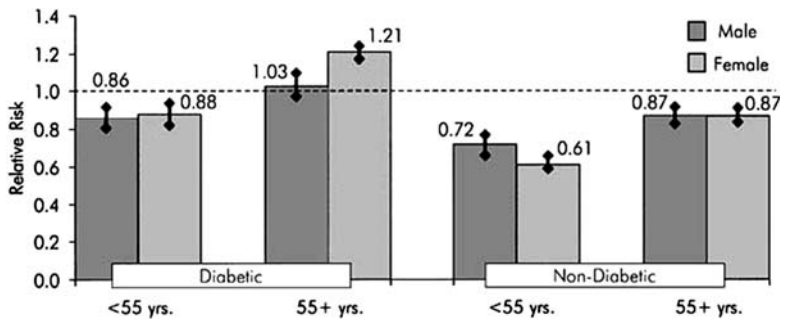

Fig. 3.4 Relative risks of mortality in incident U.S. PD versus HD patients by age and diabetic status from Collins et al. [17]

mortality favored PD initially but then, over 2–3 years, tended to move towards parity or even to favoring HD [13–16]. They also all showed the interaction between age and modality and between diabetic status and modality, when survival is being considered. It became clear that HD looked best in older patients and in diabetics, and that PD looked best in younger patients and in non-diabetics [13–17]. The studies also suggested a difference between outcomes in the United States and Canada and some corroborating evidence from the CANUSA study appeared to support the notion that Canadian patients did better on PD than their U.S. counterparts [39]. This led to extensive debate on whether this was a real finding. Some argued that it might reflect relatively greater experience with PD in the relatively larger PD centers in Canada [38]. However, it also had to be noted that overall ESKD treatment rates were higher in the United States, raising the possibility that U.S. patients might be on average a less healthy population and this might be confounding the analysis [39].

A conclusion from all these studies published between 1995 and 2001 was that PD survival was overall at least as good as that of HD and that the modality had a particular advantage in the early years of ESKD and especially in younger patients. Furthermore, a Danish registry study published in 2002 showed very similar results to those of Fenton et al. and Collins et al. (Table 3.2) [21]. All this gave support to the idea that PD was an excellent initial dialysis modality and the term "integrated dialysis care" was introduced to describe a frequently advocated policy of treating all suitable new ESKD patients with PD, recognizing that many will eventually switch to HD [40, 41].

Subsequent U.S. studies have, however, been less favorable to PD. In 2003, Ganesh et al. and Stack et al. from the same research group published two U.S. registry-based studies that compared mortality differences among PD and HD patients with ischemic heart disease and congestive cardiac failure, respectively [18, 19]. They used Center for Medicare and Medicaid Services Medical Evidence Forms to define co-morbidity data and they linked this to mortality data from the United States Renal Data System (USRDS). These studies were very similar and both were based on the same population of patients and compared outcomes over the first 2 years of dialysis. Given secular trends in the United States during the time period covered from 1995 to 1997, PD patients tended to be younger and healthier when compared to HD patients initiating dialysis. Both studies attempted extensive adjustment for baseline differences in demographic, clinical, and laboratory covariates and used nonproportional Cox regression models with ITT and AT models for comparison. Results were expressed separately for patients with and without diabetes. Ganesh et al. reported a 23% higher mortality in patients with diabetes and cardiac disease who received PD compared with HD [18]. Those patients with diabetes but without cardiac disease also had a higher mortality on PD by 17% when compared with HD. In those patients without diabetes and with cardiac disease, there was a 20% higher mortality on PD. However, for those without cardiac disease or diabetes there was no significant survival difference (Table 3.3). Similarly, Stack et al. reported that after 2 years, mortality was significantly higher for PD patients with congestive heart failure when compared to HD [19]. For patients without congestive heart failure but with diabetes there was also an 11% higher mortality among those who received PD compared with HD. These studies were noteworthy because they were the first to identify explicitly cardiac disease as an important characteristic to consider when determining the effect of dialysis modality on outcomes [18, 19].

Vonesh et al. subsequently published a U.S. registry based study in 2004 that expanded on the previous USRDS studies and adjusted for numerous clinical and demographic patient characteristics [20]. The effect of age was not reported in the previous studies and the Vonesh study therefore provided new data on the interaction of age on survival. The study was also designed to adjust for a cohort effect in order to account for changes in practice patterns in both PD and HD over the study time period of 1995–2000. The large study size with almost 400,000 incident U.S. Medicare dialysis patients also allowed for extensive subgroup analysis. The results showed that among the patients group with no baseline co-morbidity, the adjusted mortality rates for patients without diabetes was significantly higher for HD compared to PD for all age groups [20]. In those with diabetes but no other baseline co-morbidity, mortality

Table 3.2 Relative risks of mortality using ITT and AT models in Danish PD versus HD patients from Heaf et al. [21]

	'As-treated' RR	'Intent-to-treat' RR
All patients	0.65 (0.59–0.72)	0.86 (0.78–0.95)
Age < 55	0.57 (0.45–0.72)	0.90 (0.72–1.13)
Age > 55	0.66 (0.58–0.74)	0.85 (0.76–0.94)
Nondiabetics	0.61 (0.54–0.70)	0.84 (0.75–0.94)
Nondiabetics < 55	0.46 (0.32–0.65)	0.83 (0.59–1.15)
Nondiabetics > 55	0.64 (0.56–0.73)	0.84 (0.74–0.95)
Diabetics	0.69 (0.57–0.85)	0.93 (0.76–1.14)
Diabetics < 55	0.66 (0.48–0.90)	0.91 (0.70–1.19)
Diabetics > 55	0.75 (0.57–0.99)	1.04 (0.75–1.43)

Table 3.3 Relative risks of mortality in the United States for PD versus HD in patients with coronary artery disease by diabetic status from Ganesh et al. [18]

	With coronary disease		No coronary disease	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Diabetics				
0–6 months	0.89	1.03 (0.90–1.18)	0.77	1.04 (0.92–1.17)
18–24 months	1.27	1.39 (1.11–1.75)	1.11	1.31 (1.09–1.57)
0–24 months	1.07	1.23 (1.12–1.34)	0.92	1.17 (1.08–1.26)
Non-diabetics				
0–6 months	0.85	1.05 (0.91–1.20)	0.55	0.83 (0.75–0.91)
18–24 months	1.48	1.62 (1.30–2.02)	1.00	1.30 (1.12–1.50)
0–24 months	1.01	1.20 (1.10–1.32)	0.69	0.99 (0.93–1.05)

Table 3.4 Relative risks of mortality in U.S. PD versus HD patients by age and diabetic status from Vonesh et al. [20]

		Age	'Intent-to-treat' RR	'As-treated' RR
Non-diabetic	No co-morbidity			
		18–44	1.24 (1.07–1.44)	1.55 (1.30–1.84)
		45–64	1.13 (1.02–1.25)	1.23 (1.10–1.38)
		≥ 65	1.13 (1.05–1.21)	1.18 (1.09–1.28)
Diabetic	No co-morbidity			
		18–44	1.22 (1.05–1.42)	1.45 (1.21–1.74)
		45–64	0.92 (0.85–1.00)	0.98 (0.89–1.07)
		≥ 65	0.86 (0.79–0.93)	0.86 (0.79–0.94)
Non-diabetic	Co-morbidity			
		18–44	1.19 (0.94–1.50)	1.34 (1.03–1.76)
		45–64	1.01 (0.92–1.11)	1.10 (0.98–1.22)
		≥ 65	0.96 (0.91–1.01)	0.98 (0.93–1.04)
Diabetic	Co-morbidity			
		18–44	1.10 (0.92–1.32)	1.35 (1.09–1.68)
		45–64	0.82 (0.77–.0.87)	0.82 (0.78–0.91)
		≥ 65	0.80 (0.76–0.85)	0.82 (0.77–0.87)

was higher on HD among 18–44 year olds but the risk of death was significantly lower on HD for those over 65 years. For the group without diabetes and without baseline co-morbidity, there was no difference in adjusted mortality rates. For those with diabetes and co-morbidity at baseline there was higher mortality for PD among over 65 years but no difference for younger patients (Table 3.4) [20]. Both the Vonesh and Collins studies used an interval Poisson model whereas Ganesh and Stack et al. utilized Cox models. Both models should be considered acceptable and appropriate for survival analyses that compares PD and HD and, if used correctly, will not impact differently on survival outcomes.

The Ganesh and Stack study findings have not been reproduced outside the United States but have given rise to concern that PD is less effective in older and sicker patients, particularly when cardiac disease is involved. It is possible that some modality selection bias may underlie these findings but they have given rise to concern about PD use in cardiac patients in the United States, and to a lesser extent elsewhere. There are theoretical concerns that the systemic absorption of the hypertonic glucose in PD solutions may have adverse metabolic consequences in patients with cardiac disease. It is possible that this effect might be more pronounced and apparent in a U.S. ESKD population, where obesity and diabetes are particularly prevalent.

Prospective Cohort Studies

Three noteworthy prospective cohort studies have been done comparing survival between PD and HD [25–27]. A Canadian study by Murphy et al., published in 2000, enrolled 822 incident patients from 11 dialysis centers across Canada with almost half on PD and half on HD in the period of March 1993 to November 1994 [25]. The study was well designed with a long follow-up period to January 1998, using a Cox model for ITT and Poisson regression for their AT model. Using time-dependent covariates with adjustment for case-mix, including demographic characteristics such

as age, race and gender and clinical characteristics including diabetes status, heart failure, peripheral vascular disease, myocardial infarction, malignancy, and late referral. A validated total co-morbidity score was used to classify levels of disease severity. Patients' modality was classified by the therapy they were receiving after 90 days. The uncorrected data showed the usual survival advantage for PD study but once full adjustments were performed there was no significant overall survival difference between the modalities (Fig. 3.2). Subgroup analyses were not performed due to sample size issues [25].

The Netherlands Cooperative Study on the Adequacy of Dialysis 2 (NECOSAD 2) was published in 2003 [32] and enrolled 1222 incident patients (61% HD and 39% PD) during the period from January 1997 to September 2002 [26]. The authors applied proportional and nonproportional Cox models for both ITT and AT models. Adjustment for case-mix was carried including baseline demographic (age and gender) and clinical characteristics such as primary renal disease, cardiovascular disease, Davies co-morbidity index, and Subjective Global Assessment of nutrition as well as baseline glomerular filtration rate, serum albumin, and hemoglobin measurements. As with the Canadian study, there was no overall difference between PD and HD patient survival during the first 2 years of follow-up. Beyond the second year, the Dutch study showed a significantly lower mortality in the HD cohort, however.

The CHOICE Study, published in 2005 by Jaar et al., enrolled 1041 incident U.S. patients (74% HD and 26% PD) from 81 dialysis centers in 19 states. Patients were enrolled during the period 1995–1998 with follow-up for 5–7 years. Compared to the previously described prospective cohort studies, the CHOICE Study was designed to capture an even wider variety of demographic and clinical patient variables and adjustment for case-mix included a wide variety of characteristics. Demographic factors included age, sex, education level, race, employment status, marital status, and geographic distance from the dialysis clinic. Clinical covariates included body mass index, primary renal disease, cardiovascular disease, glomerular filtration rate, index of co-existent disease, and late referral. Laboratory variables included serum levels of C-reactive protein, albumin, hemoglobin, creatinine, cholesterol, and calcium phosphate product. Both Cox proportional and nonproportional models were applied and showed that, overall, before adjustment for covariates, there was no difference between PD and HD survival. However, after adjustment for clinical and laboratory covariates, there was a significant survival advantage for HD that became very marked after the first year (Table 3.5).

One criticism of the CHOICE Study is that many of the laboratory parameters were not measured at baseline and were treated as continuous variables rather than analyzed as categories [26, 42]. Results of the CHOICE subgroup analysis showed HD as having a more significant survival advantage over PD for patients without diabetes and showed very little age interaction; all of which is widely dissimilar from the previously published registry based studies of U.S patients [13, 14]. These differences in outcomes have been postulated as being due to small subgroup sample size and potential bias from dialysis center selection in the CHOICE Study [26, 32, 42]. As patients in the CHOICE Study were recruited almost entirely from one dialysis provider (90%), less than half of whose centers provided both PD and HD, and given the low PD

Table 3.5 Relative risks of mortality in U.S. PD versus HD patients before and after adjustment and by vintage in Choice Study [26]

	Multivariate model RR	Propensity score model RR
All patients:		
Unadjusted	1.10 (0.80–1.51)	1.10 (0.80–1.51)
Adjusted:		
Demographics	1.25 (0.91–1.73)	1.33 (0.96–1.84)
Plus clinical	1.35 (0.97–1.87)	1.57 (1.12–2.18)
Plus laboratory	1.61 (1.13–2.30)	1.74 (1.23–2.46)
First year only:		
Unadjusted	0.75 (0.37–1.54)	0.75 (0.37–1.54)
Adjusted:		
Demographics	0.92 (0.45–1.89)	0.97 (0.47–2.00)
Plus clinical	1.06 (0.51–2.19)	1.33 (0.64–2.77)
Plus laboratory	1.39 (0.64–3.06)	1.47 (0.69–3.15)
Second year only:		
Unadjusted	1.06 (0.59–1.90)	1.06 (0.59–1.90)
Adjusted:		
Demographics	0.77 (0.31–1.88)	1.23 (0.67–2.27)
Plus clinical	0.84 (0.33–2.14)	1.47 (0.80–2.72)
Plus laboratory	2.34 (1.19–4.59)	2.05 (1.07–3.92)

utilization rate in the United States, a rather contrived method of oversampling of PD patients was required and may have contributed to the discrepancy in the subgroup analysis results when compared to previously published studies.

There was also criticism of this study because of the enormous effect of adjustment for baseline laboratory findings that appeared to convert an advantage for PD into one for HD [34, 42]. This coupled with concerns about laboratory measurements made after initiation of dialysis has led to controversy about the results of this study [32].

Where to from Here?

How should all these data be interpreted? More importantly, should the results of these comparative studies be used to change practice patterns? It is possible that the differences in nephrologists' levels of PD training and expertise explain the between-country differences that have been reported in studies reviewed from Canada and Denmark; as compared to the United States [13–21, 39]. If this is the case, then perhaps comparing survival between PD and HD in countries where PD penetration has historically been low is potentially misleading. Caring for PD patients and managing complications requires training that may be lacking among physicians who have completed their nephrology training in the last decade in many parts of North America and Europe [38]. The concept that high PD penetration within a center, region, or country may impact on PD outcomes has been suggested in the past and has recently been further postulated [38]. Lo cites examples of locales with high PD penetration such as Mexico and Hong Kong [43]. Furthermore, where Mexico has experienced high PD penetration due to significant economic constraints [44], the publicly funded Hong Kong medical system has insisted on an economically driven "PD First" policy since the late 1980 s [36]. Survival comparisons between PD and HD patients in Hong Kong or Mexico would be equally difficult to assess due to the low HD rates in those countries.

What Conclusions Can Be Made Regarding Patient Survival in PD Compared with HD?

We have attempted to provide a review of study methodologies and various study designs that are meant to highlight features that should be considered when comparing studies on dialysis survival. Certainly the results reported by the most current prospective cohort studies should be taken into account with careful consideration given to the difference in study methodologies.

At this time there is no consistent evidence that PD or HD provide an overall survival advantage. Subgroup analyses would suggest that certain patient groups, namely older patients with diabetes or those with established cardiac disease, may have a survival advantage with HD, but it is neither large enough nor sufficiently convincing to override the individual patient-specific factors that drive modality selection in many centers. Furthermore, until the data is reproduced outside the United States, there will be concerns that it may reflect specific socioeconomic and other factors peculiar to the dialysis delivery model and the patient population in that country. Conversely, the survival advantage for PD that is seen in younger patients in many of these studies is impressive but not sufficient to mandate treating all such patients with PD, though clearly the modality is particular attractive and cost effective in this age group.

It would, however, be wise for PD researchers to pay attention to the possibility that adverse interactions between diabetes, cardiac disease, PD utilization, and survival may reflect real biological causation. The potential negative effects of glucose based PD solutions and their tendency to induce hyperglycemia and hyperlipidemia, and perhaps hyperinsulinemia and obesity, highlight the need for further research and development of effective non-glucose based dialysis solutions [45].

It is possible that, given the apparent nonfeasibility of carrying out a good quality randomized trial and given the inherent difficulties in comparing two very different modalities, we may never have a conclusive answer about overall comparative survival [24, 31, 32]. Some argue that the debate has become sterile and that the therapies are better seen as complementary and not competitive [40, 41]. There is a need to improve the practice of both and to address the particular complications of each. The survival debate has, however, been helpful in that it has assisted in our understanding of the two modalities and their potential strengths and weaknesses. It has also given unique insights into statistical analyses for comparing mortality in ESKD populations. Knowledge, however imperfect, is worth having as long as it is not overinterpreted.

These authors, at least, would argue that individual patient circumstances and center characteristics and, in particular, informed patient choice after predialysis education should have the maximum weight in modality selection processes. The data is simply not sufficiently strong to justify a blanket approach of, for example, putting all young patients on PD and all older diabetics or those with heart disease on HD.

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Chapter 4
The Peritoneal Microcirculation in Peritoneal Dialysis

A.S. De Vriese, R. White, D.N. Granger, and N.H. Lameire

The peritoneal microcirculation is an intricate microvascular network through which physiological interactions occur between the systemic vasculature and the peritoneal cavity. In peritoneal dialysis these dynamic interactions are of paramount importance in maintaining effective dialysis. The peritoneal microcirculation participates in numerous physiological functions including solute transfer and exchange, regulation of fluid dynamics and ultrafiltration, delivery of nutrients and hormones, delivery of leukocytes to areas of inflammation, and distribution of drugs. Physiological and pathophysiological changes, as well as the process of peritoneal dialysis, may affect many of these microvascular functions. The emphasis of this chapter will be to review available information regarding the peritoneal microcirculation and to integrate this information into a general functional knowledge as it relates to peritoneal dialysis. The chapter will examine: 1) the functional anatomy and blood supply of the peritoneum, 2) components of the peritoneal microvascular network, 3) peritoneal microvascular hemodynamics and the effects of vasoactive agents on the microcirculation, and 4) inflammation in the peritoneal microcirculation with emphasis on leukocyte-endothelial interactions.

Overview of the Functional Anatomy and Blood Supply of the Peritoneum

Functional Anatomy of the Parietal and Visceral Peritoneum

The peritoneum is a large, intricately arranged serous membrane that lines the abdominal wall (parietal peritoneum) and visceral organs of the abdominal cavity (visceral peritoneum). The peritoneal cavity is the potential space between the parietal and visceral layers of peritoneum [1]. The primary purpose of the peritoneum is to provide a smooth surface over which the abdominal viscera may easily move [2]. Normally, the peritoneal cavity contains less than 100 mL of fluid but can accommodate a more than 20-fold increase without patient discomfort [3]. The peritoneal cavity is lined by a layer of mesothelial cells on a connective tissue base that is perfused with blood and lymphatic vessels. Specialized regions of peritoneum, the omenta and mesenteries, are double-layer folds of peritoneum that connect certain viscera to the posterior abdominal wall or to each other. For example, the greater omentum extends from the greater curvature of the stomach to attach to the transverse colon. Specific double-layered peritoneal folds attach solid viscera to the abdominal wall (e.g., the falciform ligament of the liver). The total surface area of the peritoneum in adults approximates the surface area of skin (1–2 m^2) [4]. However, the effective surface of the peritoneal membrane may be below 1 m^2, and can be further reduced as a result of adhesions or prior abdominal surgery [5, 6]. The visceral peritoneum accounts for the majority of the total peritoneal membrane surface area [7, 8]. About 60% of the peritoneal surface can be ascribed to the mesentery of the esophageal-rectal viscera, 15% covers the liver, and 15% is parietal [8]. Considering that most of the surface area is composed of visceral peritoneum, one might intuitively suspect that the contribution of the visceral peritoneum to total peritoneal membrane exchange would predominate over that contribution made by the parietal peritoneum. However, animal studies have suggested that the contribution of the visceral peritoneum to peritoneal exchange is less than would be predicted from the relative anatomical surface area. For example, eviscerated rats exhibit only slight reductions in peritoneal absorption rates for urea, creatinine, glucose, and inulin relative to control animals [9]. Studies in other evisceration animal models have shown similar findings with reductions in peritoneal mass transport of small solutes by only 10–30% [10–14]. In these eviscerated animal models, contact between the dialysate and the parietal peritoneal membrane may be improved, thus

A.S. De Vriese (✉)
AZ Sint-Jan AV, Dept. of Internal Medicine, Brugge, Belgium
e-mail: An.DeVriese@azbrugge.be

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contributing to these findings. Other conditions may improve transport across the visceral peritoneum. Small solute mass transfer is significantly enhanced with vibration in the intact rat (i.e., with the visceral peritoneum intact), but only marginally improved in the eviscerated animal. With vibration, improved dialysate to visceral membrane contact is thought to occur. Based on these animal studies it has been proposed that the parietal peritoneum can significantly contribute to small solute transport, and that visceral peritoneal transport may be improved when contact is enhanced between visceral peritoneal surfaces and dialysis solutions [15]. The correlation of these animal findings to clinical peritoneal dialysis currently remains speculative, but these results suggest that the relative contribution of the visceral and parietal peritoneum to small solute mass transport may not necessarily correlate to anatomical surface area.

Blood Supply to the Peritoneum

The vascular and lymphatic systems supplying the peritoneal membrane and intraperitoneal organs constitute a complex and efficient system for fluid and solute delivery to the peritoneum. The arterial blood supply to the visceral peritoneum and intraperitoneal organs arises from the coeliac, superior mesenteric, and inferior mesenteric arteries. The arterial blood supply to the parietal peritoneum and underlying musculature arises from the circumflex, iliac, lumbar, intercostal, and epigastric arteries. The veins draining the visceral peritoneum and intraperitoneal organs empty into the portal vein, while the venous system of the parietal peritoneum empties into the systemic veins. A potentially important consequence of this venous vascular arrangement is that drugs and other solutes that are absorbed across the visceral peritoneum are subject to hepatic metabolism. Pharmacological studies have shown intraperitoneal administration of compounds such as atropine, caffeine, glucose, glycine, and progesterone and some intraperitoneally administered vasoactive drugs are subject to metabolism by the liver [16, 17]. Another important example is insulin, which may be absorbed through the portal circulation and a significant portion degraded through first-pass metabolism by the liver [18, 19]. Thus, the pharmacokinetic effects of hepatic first-pass metabolism may play an important role in the systemic availability of some intraperitoneally administered substances.

Summary

In summary, animal studies suggest that the contribution of the visceral and parietal peritoneal membrane to total solute transport may not necessary correlate to anatomical surface area. The importance of contact between peritoneal tissue and dialysis solutions was suggested both in the eviscerated animal model and in studies of the effect of vibration on solute transport in the intact animal model. The general vascular supply to the peritoneum was reviewed and the potential importance of the portal venous drainage was presented.

The Peritoneal Microvascular Network

Peritoneal Microvascular Architecture

The large vessels supplying blood to the visceral peritoneum function primarily as conduits to supply blood to the visceral organs. As the large vessels course through the mesentery they divide and reflect over the bowel surface forming capillary beds, which can presumably participate in transperitoneal solute and fluid exchange. Over 50 years ago, Chambers and Zweifach described the topography of the mesenteric microcirculation [20]. The typical capillary network consists of arterioles, terminal arterioles, precapillary sphincters, arteriovenous anastomoses, throughfare channels, capillaries, postcapillary venules, and venules (Fig. 4.1) [21]. Arterioles and throughfare channels modulate blood flow into the network, while precapillary sphincters regulate blood flow to single capillaries. Arteriovenous anastomoses can divert blood flow from arterioles directly into venules, thereby bypassing capillary networks. The flow through a capillary network can be extremely variable with individual capillary flow starting, stopping, and sometimes reversing direction [22, 23]. In baseline circumstances, only 25–50% of capillaries are perfused. Capillary recruitment increases perfused capillary density and increases surface area for potential exchange processes. Capillary recruitment may occur to meet metabolic demands, as a result of certain vasoactive agents or in response to exposure to peritoneal dialysate [24]. The architecture of the peritoneal microvasculature in animal models has been previously reviewed by Miller [25]. The visceral microvasculature may be visualized on the mesenteric surface and includes abundant arterial and venular arcades that may function to equalize flow during periods of bowel compression. The

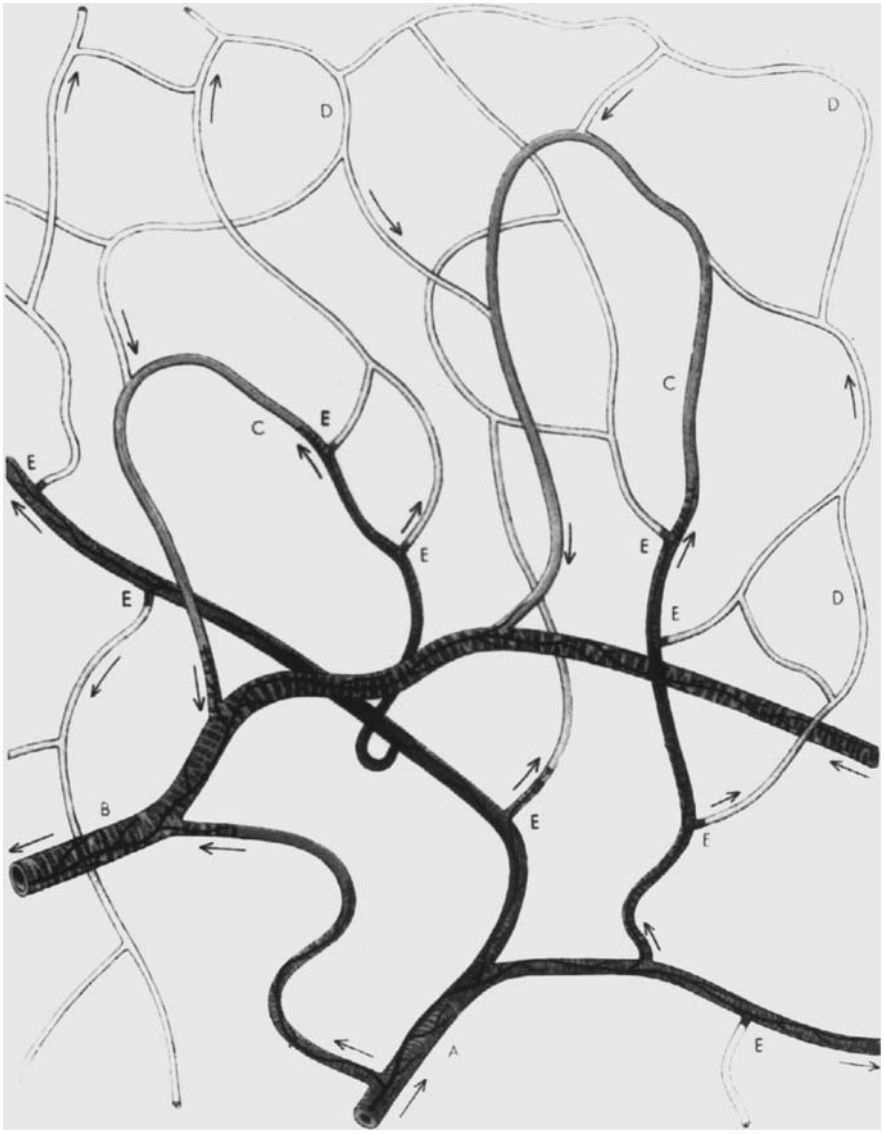

Fig. 4.1 Structural elements of a typical mesenteric microcirculatory bed. A = arteriole, B = venule, C = thoroughfare channel, D = capillary, E = capillary sphincter [21]

parietal microvasculature may be represented by the vascular supply to the cremaster muscle, since this muscle extends from the abdominal wall musculature. Features of the cremaster microcirculation include the absence of short artery to vein anastomoses and the formation of arteriolar and venular arcades from which capillaries may arise [25–27].

Arterioles

The arterioles are the major site of microvascular resistance and regulate flow to capillary beds. Arterioles are lined by endothelial cells resting on a basal lamina surrounded by a layer of smooth muscle cells. Terminal arterioles may participate in the exchange process as they have a discontinuous muscle layer and portions of these vessels are lined only by endothelium and basement membrane. However, the relative contribution to overall peritoneal transport is minimal since the surface area and permeability of these vessels are much less than in capillaries and postcapillary venules. The distal smooth muscle layer of an arteriole may extend to form a ring around the site of capillary origin. This area is termed a precapillary sphincter and regulates flow to single capillaries. Marked arteriolar vasoconstriction can completely close the vascular lumen, resulting in no flow to its capillary distribution [28]. Figure 4.2 illustrates the hemodynamic pressure profiles and demonstrates that the greatest slope for microvascular pressure change occurs in

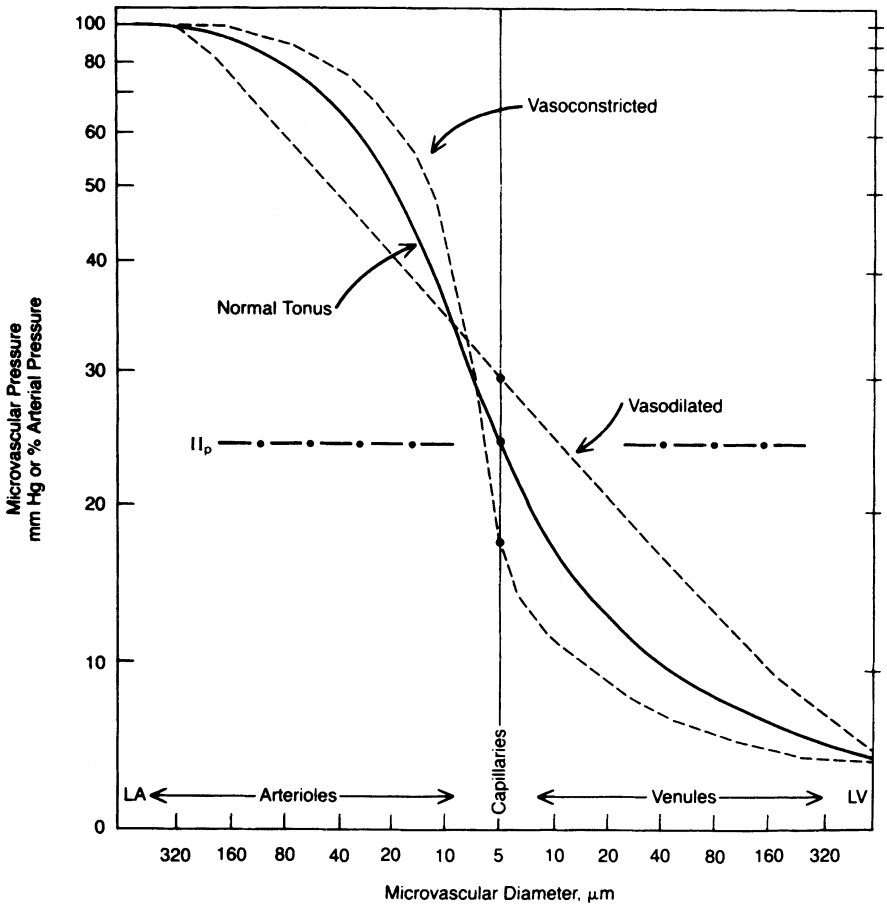

Fig. 4.2 Microvascular pressure profiles as related to microvascular diameter. The dotted lines represent changes in microvascular pressure that occur with vasoconstriction and vasodilation [29]

arterioles 8–40 μm in diameter [29]. This figure also illustrates the pressure changes associated with vasoconstriction and vasodilation and the typical microvessel size gradations for arterioles, capillaries, and venules.

Capillaries

In the peritoneal microvascular network capillaries are the principal sites for solute and fluid exchange [30, 31]. The wall of the capillary is composed of an endothelium and a basal lamina. Capillary size is approximately 5–8 μm, which is large enough to let red blood cells (average diameter 7.5 μm) through, usually one at a time and with some deformity [28]. The capillaries have no smooth muscle and do not vasoactively participate in blood flow regulation. There are three types of capillary endothelium present in the mesenteric area: 1) continuous endothelium as in the peritoneal vessels, 2) fenestrated endothelium as in the intestinal villi, and 3) discontinuous endothelium as found in the liver sinusoids [25]. The properties of peritoneal capillary transport will be reviewed in the following chapter.

Postcapillary Venules

The postcapillary venules participate in fluid and solute exchange, are an important site for microvascular leukocyte adhesion, and may demonstrate dramatic changes in permeability during inflammatory conditions. Small venules that are located just distal to the capillaries are often termed postcapillary venules. Postcapillary venules are generally 10–40 μm in diameter and are composed of endothelial cells resting on a basal lamina surrounded by pericytes with larger venules enclosed by muscular media [32].

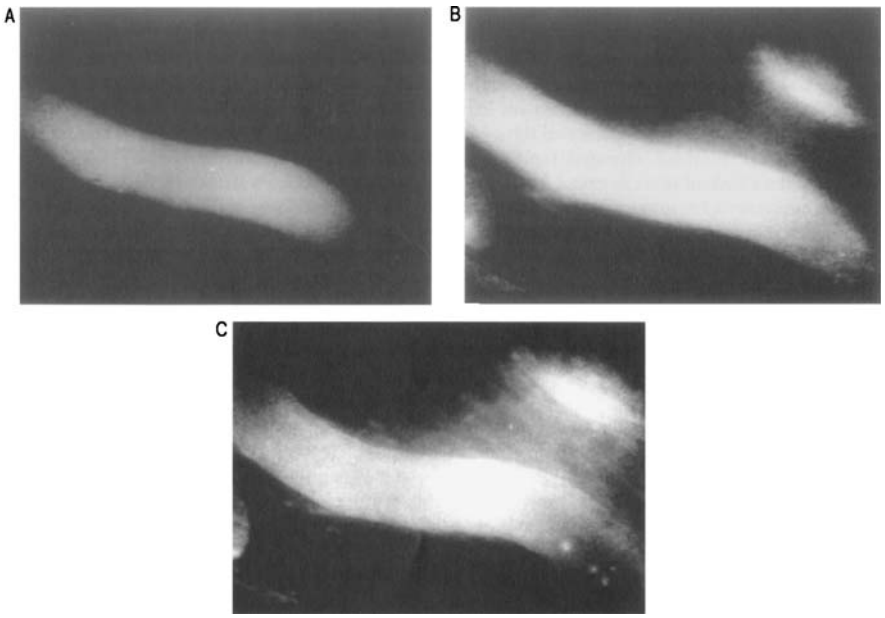

Fig. 4.3 Fluorescence photomicrograph of the mesenteric microcirculation demonstrating the effects of vascular endothelial growth factor (VEGF) on permeability in the rat mesentery. (**a**) No significant leakage of FITC-labeled albumin during basal conditions. (**b**) Superfusion of VEGF (660 pm) induces albumin leakage from the microcirculation after only 10 min of exposure. (**c**) Albumin leakage into the interstitium continues to progress after 20 min of exposure to VEGF. Photomicrograph courtesy of N. Yount, S. Ram, and R. White

Significant changes in microvascular permeability can occur in postcapillary venules. Numerous vasoactive agents, cytokines, and drugs may induce changes in permeability. Histamine, bradykinin, platelet-activating factor, vascular endothelial growth factor (VEGF), certain components of the complement cascade, and drugs such as nitroprusside are examples of agents that can affect mesenteric microvascular permeability [33–40]. For example, Fig. 4.3 demonstrates the effects of vascular permeability factor on albumin permeability in a mesenteric postcapillary venule.

Intravital microscopic studies have demonstrated that the attachment and migration of leukocytes from the vascular space to the extravascular space is localized primarily to postcapillary venules [41–45]. The mechanisms and determinants of intraperitoneal leukocyte migration will be discussed in detail later in this chapter.

Endothelium

The microvascular endothelium has a central regulatory role in microvascular physiology [46–48]. Endothelial-derived substances regulate microvascular hemodynamics, thrombogenesis, fibrinolysis, and leukocyte adhesion. Endothelial cells actively regulate basal vascular tone and vascular reactivity in physiological and pathological conditions, by responding to mechanical forces and neurohumoral mediators with the release of a variety of relaxing and contracting factors. The endothelium-derived relaxing factors include nitric oxide (NO), prostacyclin, and an, as yet elusive, endothelium-derived hyperpolarizing factor (EDHF) [49]. NO is a diffusible, labile gas with a short biological half-life (seconds) [46, 50]. NO is synthesized from L-arginine by a family of enzymes known as nitric oxide synthases (NOS), namely neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3). The eNOS is a constitutive, calcium–calmodulin dependent enzyme [50–52]. Once NO is produced in the endothelium it diffuses to the smooth muscle cells and produces smooth muscle relaxation via a cGMP-dependent mechanism [53]. All three NOS isoforms are present in the peritoneal membrane and can be upregulated in response to specific pathophysiologic circumstances [54]. NO production can be inhibited by several exogenous L-arginine analogues such as N^G-monomethyl-L-argine (L-NMMA), N^G-nitro-L-arginine methyl ester (L-NAME), and endogenous arginine analogues such as N^G, N^G-dimethylarginine (ADMA or asymmetrical dimethylarginine) [55–57]. Interestingly, ADMA and other guanidino compounds that inhibit NO production have been shown to accumulate in renal failure [56], although this cannot entirely explain the endothelial dysfunction observed in uremia [58]. Inhibition of NO synthesis produces mesenteric arteriolar vasoconstriction (Fig. 4.4) [59, 60]. This demonstrates that basal levels of NO are important in maintaining normal microvascular tone in the mesenteric microcirculation.

Although NO has generally been considered to be the principal mediator of endothelium-dependent relaxations, evidence is mounting that EDHF is a major determinant of vascular tone, especially in small resistance vessels, like the mesenteric arteries. These vessels control tissue perfusion and thus may be of larger physiological relevance than conductance arteries. The nature of EDHF is still not entirely elucidated [61]. Current evidence suggests that

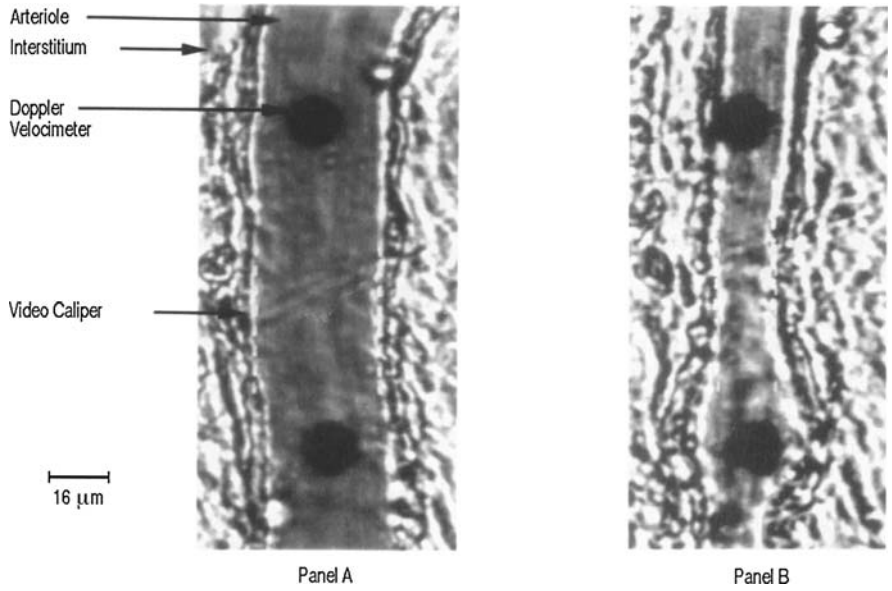

Fig. 4.4 Hemodynamic effect of a nitric oxide synthesis inhibitor (ADMA) on an arteriole in the mesenteric microcirculation in the rat. (**a**) The arteriole during basal conditions with superfusion of a buffer solution. (**b**) ADMA (100 μm) added to the buffer solution induces marked arteriolar vasoconstriction. This demonstrates that basal levels of NO are important in maintaining normal microvascular tone in the mesenteric microcirculation [60]

EDHF-mediated responses are initiated by activation of endothelial K^+ channels with resultant hyperpolarization of endothelial cells. This endothelial hyperpolarization spreads to the underlying smooth muscle layer through myoendothelial gap junctions, or the efflux of K^+ from the endothelial cells elicits hyperpolarization of the adjacent smooth muscle cells. Epoxyeicosatrienoic acids likely have a regulatory role in this pathway. The contribution of EDHF to relaxation is dependent on vessel size, being more prominent in smaller arteries than in larger ones. Although the effect of peritoneal dialysis on the EDHF-mediated responses has not been directly studied, both the uremic state [62] as well as exposure to high glucose concentrations [63] are known to affect EDHF-mediated relaxations. Disturbance of this pathway may thus contribute to altered vascular reactivity in the peritoneal circulation of patients undergoing peritoneal dialysis.

An important constricting factor produced by the endothelium is the potent vasoconstrictor endothelin. The endothelins (ET) are a family of amino acid peptides with diverse and overlapping biological activity. Three isoforms exist: ET-1, ET-2, ET-3 [62–66]. Two human ET receptors have been cloned: ET_A and ET_B. ET_A receptors bind ET-1 > ET-2 > ET-3, whereas ET_B receptors bind these three ET with approximate equal affinity [67–69]. ET-1 is the most potent vasoconstrictor produced by the endothelium and induces sustained, intense vasoconstriction. ET-1 has a short circulating half-life, but the effects may be sustained due to the slow dissociation of the bound peptide from its receptor [66]. In general, ET activates phospholipase C and increases the production of inositol trisphosphate, which mobilizes calcium from the endoplasmic reticulum. ET can also activate calcium channels that allow for the influx of calcium into the cytosol [70]. ET-1 produces vasoconstriction in both mesenteric arterioles and venules [71, 72]. Intravital microscopic observations of mesenteric arterioles have shown that ET-1 can completely arrest blood flow in the microcirculation. ET-1 in small concentrations attached to ET_B may produce mild vasodilation through the release of NO and prostacyclin from endothelial cells, thus forming a potential feedback mechanism [46, 73]. Levels of ET have been shown to be elevated in ESRD, and ET-1 is present in the peritoneal dialysis effluent of PD patients [74]. The relevance of some of these findings as it relates to peritoneal dialysis will be discussed in the next section.

NO and ET also have effects in modulating inflammatory processes. Inhibition of NO production is proinflammatory, as evidenced by an increase in the number of adherent leukocytes in postcapillary venules [75]. ET-1 is a proinflammatory cytokine and in cell culture, ET-1 stimulates neutrophil adhesion to endothelial cell monolayers [76]. ET-1 increases the in vitro endothelial expression of E-selectin [77]. In vivo observations in the mesenteric microcirculation have shown that ET-1 increases leukocyte rolling in postcapillary venules [78].

The endothelium produces both growth promoters and growth inhibitors. An intact endothelium protects the microvascular wall from processes such as intimal hyperplasia, which can occur when the endothelium is disrupted and smooth muscle growth factors are released. NO, heparin sulphates, and transforming growth factor $\beta_1$are inhibitors of vascular smooth muscle proliferation; while angiotensin II, epidermal growth factor, and platelet-derived growth factor contribute to smooth muscle proliferation [46]. ET-1 is known to exert significant proliferative activities on a variety of cell types leading to an accumulation of extracellular matrix. A prospective study in PD patients found that increasing the dwell volume from 1500 to 2500 mL per dwell induced an increase in peritoneal ET-1 synthesis [79]. This volume-induced ET-1 release may contribute to long-term structural alterations in the peritoneal membrane.

Junctional Adhesion Proteins

The tight junction forms an apical intercellular semi-permeable diffusion barrier between endothelial cells [80, 81]. A number of proteins have been described which participate in the formation of the tight junction. Zonula occludens-1 (ZO-1) was the first tight junction protein described and is a peripheral membrane protein located near the plasma membrane [80, 82]. Occludin is another important junctional protein and is transmembrane in location at membrane–membrane sites [83–86]. Occludin appears to be bound near the cytoplasmic membrane to ZO-1. A possible molecular model has ZO-1 bound to spectrin, which is bound to actin [82]. Regulation of occludin has been suggested as a possible mechanism for controlling paracellular permeability [87]. Occludin is more concentrated in arterial junctions than in venous junctions. Kevil and colleagues have shown that arterial endothelial cells express 18-fold more occludin protein than venous endothelial cells. These authors suggest that the arterial and venous endothelial barriers reflect the level of expression of different junctional molecules [88].

In addition to ZO-1 and occludin, many other junctional proteins have been identified. Another cell-to-cell junctional structure is the adherens junction. Adherens junctions are formed by the transmembrane cadherins bound intercellularly to catenins anchored to actin [89–92]. For example, VE-cadherin is a junctional protein localized to the borders between endothelial cells [93]. Kevil et al. have shown that VEGF increases permeability in endothelial monolayers through disorganization of endothelial junctional proteins. The increase in permeability has been related to the rearrangement of endothelial junctional proteins occludin and VE-cadherin [94]. The permeability-enhancing effect of VEGF may also involve the induction of endothelial fenestrations and the functional activation of vesicular-vacuolar organelles in the cytoplasm of endothelial cells. It has been proposed that the increase in microvascular permeability induced by VEGF is an essential step in angiogenesis, allowing the extravasation of blood-borne proteins and the formation of matrix to support the growth of the endothelial cells and the formation of tubes [95]. The relevance of this mechanism for peritoneal dialysis was demonstrated by the observation that VEGF mediates the development of hyperpermeability and angiogenesis in the peritoneal membrane induced by exposure to high glucose concentrations [96].

Basement Membrane

The basement membrane functions as a substratum that acts as a solid support to anchor cells and limits the domain of connective tissue, thus producing distinct cellular compartments [97]. With the exception of large molecules such as plasma proteins, the basement membrane appears to be freely permeable to most solutes [98–102]. This concept is supported by the fact that the restrictive properties of the intestinal capillaries to endogenous macro-molecules are similar to the capillaries found in the mesentery, skin, and skeletal muscle, despite the fact that numerous large fenestrations are present in the intestinal capillary endothelium [103]. It has also been shown that colloidal carbon penetrates the intercellular clefts of continuous capillaries after exposure to histamine, but the transport of the colloidal carbon into the interstitial space is impeded at the basement membrane [104, 105]. These observations imply that the basement membrane may constitute a component of the barrier in the blood to lymph transport of large macromolecules. In addition, the proteoglycans in the basement membrane and interstitial gel matrix create an electrostatic barrier that retards the movement of anionic solutes [106]. These findings suggest that, although the basement membrane is permeable to small solutes, it may provide a significant transport barrier for large macromolecules under conditions of endothelial contraction and/or injury.

Summary

The general architecture of the microvascular network and some important physiological processes occurring in arterioles, capillaries, and postcapillary venules have been reviewed. Arterioles are the major site of microvascular resistance and regulate blood flow to the capillaries. Capillaries are the principal location of solute and fluid exchange. Postcapillary venules are important sites for leukocyte adherence and may show marked changes in permeability under inflammatory conditions. The endothelium is active in the physiological regulation of numerous microvascular processes including microvascular hemodynamics, leukocyte adhesion, and production of growth factors and growth inhibitors. Endothelial adhesion molecules have been described and appear to have important roles in maintenance of tight junctions. The basement membrane appears to be freely permeable to small solutes, but restricts the transport of macromolecules.

Peritoneal Microvascular Hemodynamics

In this section we will first consider the regulation of mesenteric blood flow. Subsequently, the effect of peritoneal microvascular blood flow on solute clearance and ultrafiltration will be discussed. The effect of vasoactive agents on the peritoneal microcirculation will then be considered. Finally, the effect of peritoneal dialysis fluid (PDF) and certain agents with elevated concentrations in renal failure on the microcirculation will be examined.

Regulation of the Mesenteric Circulation (See Also Chapter 9)

The extrinsic control of the mesenteric circulation is mediated by the sympathethic and parasympathethic nervous system and by circulating vasoactive agents, including catecholamines, vasopressin, and angiotensin [107, 108]. There are also intrinsic vascular control mechanisms, that are evidenced by pressure-flow autoregulation, reactive hyperemia, vascular responses to acute venous hypertension, and functional hyperemia [109]. Although myogenic factors have long been considered to be solely responsible for the intrinsic ability of the mesentery to regulate its blood flow, more recent developments indicate that metabolic mechanisms may be of equal importance in this regard. The functional hyperemia after ingestion of a meal is mediated by hormones such as gastrin and cholecystokinin. The purine nucleoside adenosine is a powerful intestinal vasodilator and may be an important metabolic regulator of intestinal autoregulation, although the evidence is controversial [110].

The Impact of Effective Peritoneal Blood Flow on Clearance and Ultrafiltration

Approximately 25% of cardiac output is directed to the splanchnic vascular bed in normal, resting individuals [111]. Excluding the parietal peritoneum, the total abdominal splanchnic blood flow usually exceeds 1200 mL/min at rest [112]. Granger et al. have measured superior mesenteric and peritoneal blood flow during intraperitoneal administration of a commercial peritoneal dialysis fluid (PDF) in anesthetized cats. The PDF significantly increased blood flow to the mesentery, omentum, intestinal serosa, and parietal peritoneum [113]. When considering the overall effective capillary blood flow in the peritoneum, an important question arises. Is the effective blood flow adequate to deliver solutes and fluid such that solute clearance is not primarily blood flow limited?

Due to the heterogeneous nature of peritoneal tissue and its vasculature, it is difficult to precisely measure the effective blood flow in the peritoneal capillary bed. Indirect measures of effective peritoneal blood flow have been made using inert gas (H_2, Xe) washout techniques. Estimates of peritoneal blood flow range between 2.5 and 6.2 mL/min per kg body weight in rabbits to 7.5 mL/min per 100 g body weight in rats [114, 115]. Despite the difficulties in direct measurement of effective blood flow, Nolph et al. have presented indirect evidence that maximum clearance is not primarily blood flow limited [116]. This evidence relies on the interpretation of urea clearance data under conditions of decreased mesenteric blood flow as well as data derived from kinetic modeling. Maximum urea clearances obtained with rapid cycling and predicted clearances at infinite dialysis flow are in the range of 30–40 mL/min. If urea clearances were blood flow limited, a severe restriction in mesenteric blood flow would be expected to reduce urea clearance. However, the results of studies in dogs subjected to circulatory shock have shown that urea clearances remain at 74% of control values despite a 38% reduction in mean arterial pressure [117]. In rabbits, urea clearances are affected when blood flow is reduced to 20% of normal [114, 118]. These findings demonstrate that, despite marked reductions in mesenteric blood flow, only modest decreases in urea clearance occur, suggesting that urea clearance is not primarily blood flow limited. Estimates of effective capillary blood flow have been made using gas diffusion techniques and range between 68 and 82 mL/min. Peritoneal clearances of carbon dioxide are approximately two to three times the maximum urea clearance. Using the ratio of urea clearance to peritoneal blood flow, Aune predicted that a doubling in blood flow would produce less than a 10% increase in urea clearance [114]. However, results obtained using gas diffusion techniques should be viewed with caution since they are based on the assumption that peritoneal gas clearance is equal to effective blood flow. Further studies using intraperitoneal vasodilators and kinetic modeling have also suggested clearance is not blood flow limited [17, 106, 116, 119–123]. However, some authors have suggested that blood flow may be a limiting factor with rapid peritoneal exchanges such as with high flux automated peritoneal dialysis [124].

Kim and colleagues have performed experiments using diffusion chambers attached to the serosal side of the abdominal wall, stomach, caecum, and liver in conjunction with laser Doppler flowmetry to directly evaluate the effect of decreased blood flow on mass transfer of solutes [125, 126]. In these experiments local blood flow beneath a

diffusion chamber was monitored by Doppler flowmetry with simultaneous measurements of the disappearance of a tracer during conditions of baseline control blood flow, 30% of control, and zero blood flow. No significant difference in the rate of mass transfer for mannitol or urea was demonstrated between control blood flow and 30% of control in the abdominal wall. There was a significant reduction in rates of mass transfer with no blood flow. In similar experiments involving the stomach, caecum, and liver there was no difference in the urea mass transfer coefficient for the stomach and caecum when blood flow was reduced to 30% of control. There was a significant decrease in the urea mass transfer coefficient in the liver with reduction of flow to 30% of control. Significant reductions in mass transfer were again demonstrated with zero blood flow. These data demonstrate that reductions of blood flow by approximately 70% do not significantly reduce mass transfer in the parietal and visceral peritoneal areas tested, except in the liver. As noted previously, the relative contribution of a tissue to total transport must take into account the actual tissue surface area available for dialysis solution contact. Since the liver has only a relatively small effective exchange area available, it was concluded that total solute transport in peritoneal dialysis should not be greatly affected during conditions of decreased blood flow.

Rosengren and Rippe studied the effect of peritoneal blood flow on small solute transport in the rat [127]. Peritoneal blood flow reductions were achieved by bleeding the rats to 25% of their blood volume. The resultant reductions in blood pressure and peritoneal blood flow were associated with a significant decrease in the permeability-surface area product for ^{51}Cr-EDTA and glucose. The clearance of albumin fell largely in proportion to the estimated capillary hydrostatic pressure drop. It was concluded that the transperitoneal clearance of small solutes is blood flow limited when peritoneal perfusion is markedly reduced, but to a lower than expected extent, while albumin transport is not blood flow limited [127].

In 20 stable PD patients, effective peritoneal blood flow did not affect peritoneal transfer of small solutes in the first 25 min of the dwell, but appeared to affect transfer rates later in the dwell [128].

Current opinion thus prevails that under physiological conditions, peritoneal blood flow does not limit the transfer of solutes. However, the effective peritoneal blood flow available for transport is only a fraction of the total blood flow through the tissues surrounding the peritoneal cavity, because most of the capillaries are too far from the cavity to be active in the exchange process or they are contained in tissues not in contact with the solution in the cavity. In this respect, it was shown that the use of a surfactant (dioctyl sodium sulfosuccinate) increased the mass transfer rates of mannitol and protein by augmenting the contact area between the peritoneum and the dialysis solution [129].

To evaluate whether ultrafiltration may be limited by effective peritoneal blood flow, Grzegorzewska et al. studied the effects of ultrafiltration and effective peritoneal blood flow during peritoneal dialysis in the rat [130]. When maximum net ultrafiltration rate was obtained with hypertonic solutions, effective peritoneal blood flow was approximately five times greater than net ultrafiltration rate; and under isosmotic conditions effective peritoneal blood flow exceeded net ultrafiltration rate by 57 times. Since there is a great difference between effective peritoneal blood flow and net ultrafiltration rate, it is unlikely that normal peritoneal blood flow significantly limits ultrafiltration during peritoneal dialysis.

Using the same technique of diffusion chambers and laser Doppler flowmetry, the group of Flessner evaluated the effect of blood flow on the hypertonic water flux during periods of control, reduced (50–80%) or no blood flow [131]. With the exception of the liver, marked blood flow reductions had small but insignificant effects on osmotic water transport.

The Effects of Vasoactive Agents on the Peritoneal Microcirculation (See Also Chapter 9)

Numerous endogenous and exogenous vasoactive agents have been shown to modify blood flow in the peritoneal microcirculation. A wide variety of drugs, hormones, neurotransmitters, and mediators of inflammation alter mesenteric vascular resistance. In addition to altering blood flow, some of these agents can also simultaneously affect perfused capillary density and microvascular permeability. For example, bradykinin, glucagon, and histamine increase both blood flow and permeability [33–35]. In contrast, secretin and cholecystokinin infusions increase blood flow but do not alter microvascular permeability to macromolecules [132]. Despite the lack of effect of secretin and cholecystokinin on macromolecular permeability, these agents increase the capillary filtration coefficient. The latter observation suggests that changes in capillary surface area, secondary to capillary recruitment, primarily account for the ability of these agents to increase peritoneal clearances. Using intravital microscopy, the effect of a number of vasodilators on several components of the peritoneal circulation was evaluated [24]. Local application of acetylcholine (10^{-7} to 10^{-5} M), nitroglycerin (10^{-6} to 10^{-4} M), verapamil (10^{-6} to 10^{-4} M), and papaverine (10^{-6} to 10^{-4} M) resulted in

a vasodilation of the mesenteric arteries (diameter 250–350 μm). The diameter of the arterioles (15–25 μm) did not change, however, while the blood flow rate (calculated als $V_{RBC} \times \pi D^2/4$ with V_{RBC} indicating the red blood cell velocity and D indicating the luminal diameter) increased, indicating that the arterioles are passively conducting the rise in flow caused by the upstream vasodilation. The vasodilators also caused capillary recruitment, resulting in a rise of the perfused capillary length [24]. In this study, nitroglycerin was found to be the most powerful vasodilator [24].

Many vasoactive drugs and hormones are known to affect peritoneal clearance (Table 4.1). Nitroprusside and isoproterenol are the best studied agents known to augment clearances in peritoneal dialysis [17, 119, 121, 122, 133–135]. Nitroprusside increases the clearance of urea, creatinine, inulin, and protein in a dose-dependent fashion. Small solute clearance appears to be most affected at lower doses, while large solute clearances are significantly increased at higher doses [136]. The maximum effect of intraperitoneally administered nitroprusside appears to occur after three to five consecutive exchanges with the drug, and the effects of nitroprusside are reversed when the drug is removed from the dialysis solution. With nitroprusside, mass transfer coefficients increase proportionately more for inulin than for urea, suggesting that alterations in permeability occur with exposure to the drug [17]. Nitroprusside also enhances the leakage of fluorescein-tagged albumin across the mesenteric microvessels [25, 39].

Studies by Grzegorzewska et al. using gas diffusion techniques in patients receiving intermittent peritoneal dialysis showed that the intraperitoneal administration of nitroprusside produced no significant differences in the peritoneal transfer of CO_2 [137, 138]. Nitroprusside did enhance the removal of certain solutes such as urea and total protein. Thus, the effect of nitroprusside on solute clearance did not appear to be attributable to changes in effective peritoneal blood flow. Studies by Douma et al. in CAPD patients also demonstrated that the mass area transfer coefficient of CO_2 was not significantly different after the intraperitoneal administration of nitroprusside in a glucose dialysate [133]. Since nitroprusside appears to have no significant effects on effective peritoneal blood flow in the setting of peritoneal dialysis (based on gas diffusion of CO_2), the effects of nitroprusside on other parameters such as capillary permeability and perfused capillary density need to be defined in order to explain the increase in solute clearance.

In the same study of CAPD patients, Douma et al. demonstrated that nitroprusside increased the mass transfer area coefficient of low molecular weight solutes and serum proteins. Using kinetic modeling and concepts of the pore theory, they related the effects of nitroprusside to an increase in the radius of both large and small pores and an increase in the effective peritoneal surface area. An increase in the number of perfused capillaries would increase the total number of pores available for exchange but theoretically should not alter the distribution of the sizes of the pores. Nitroprusside had a greater relative increase in the clearance of larger molecular proteins, suggesting a greater relative effect on the large pore radius. In this study the dialysate to plasma concentration of cGMP was greater with the addition of nitroprusside, suggesting a local generation of NO produced by nitroprusside. There was no difference in the dialysate concentrations of PGE_2, 6-keto-$PGF_2\alpha$, or thromboxane B_2 with the addition of nitroprusside. These workers also demonstrated that the ultrafiltration rate was increased with nitroprusside during the initial phase of dwell but the effect on net ultrafiltration was not significantly different for nitroprusside and control after 4 h. This information suggests that the effect of nitroprusside in improving clearance in the setting of peritoneal dialysis is not due to arteriolar vasodilation but to changes in perfused capillary density and alterations in microvascular pore diameter.

Table 4.1 Drugs and hormones that modify peritoneal clearance

Agents that may increase clearance
Albumin, Aminoproprionate, Anthranilic acid, Arachidonic acid
Calcium channel blockers, Cetyl trimethyl NH_4Cl, Cholecystokinin, Cytochalasin D
Desferrioxamine, Dialysate alkalinization, Diazoxide, Dioctyl sodium sulphosuccinate, Dipyridamole, Dopamine
Edetate calcium disodium, Ethacrynic acid
Furosemide
Glucagon
Histamine, Hydralazine, Hypertonic glucose
Indomethacin, Insulin, Isoproterenol
Lipid in dialysate
Nitroprusside, N-myristyl alanine
Procaine hydrochloride, Prostaglandin A1, Prostaglandin E1, Prostaglandin E2, Phentolamine, Protamine, Puromycin
Salicylate, Secretin, Serotonin, Streptokinase
Tris hydroxymethyl aminomethane (THAM)
Agents that may decrease clearance
Calcium, Dopamine, Norepinephrine, Prostaglandin F2, Vasopressin

Isoproterenol administered intraperitoneally increases peritoneal transport. The route of administration is important in determining isoproterenol's effects on clearance. Intravenous isoproterenol increases superior mesenteric blood flow by 88%, but does not alter peritoneal clearances of creatinine and inulin. In contrast, intraperitoneally administered isoproterenol increases superior mesenteric blood flow and increases solute clearance [139]. In animal studies it has been suggested that the vasoactive effects of isoproterenol increase capillary surface area through the recruitment of capillaries. Isoproterenol increases the mass transfer area coefficients of small solutes, especially in the early phases of the dialysis dwell [140].

A possible and major disadvantage for clinical use of nitroprusside is the potential for systemic vasodilation. Some studies indicate the peripheral vasodilatory effects may be limited with appropriate intraperitoneal dosing [122]. In the study of CAPD patients by Douma et al. no marked blood pressure decreases were noted [133]. Intraperitoneal isoproterenol has been used in certain clinical situations [140]. Patients with vascular diseases such as scleroderma may experience decreased clearances during peritoneal dialysis. In a patient with scleroderma, addition of isoproterenol to the dialysis fluid appeared to improve clearance [140]. However, the clinical use of isoproterenol is hindered by its potential cardiac stimulatory actions [139].

The Effects of Peritoneal Dialysis Solutions on the Peritoneal Microcirculation

Peritoneal dialysis markedly affects the mesenteric microcirculation [24, 25, 60, 120, 141–145]. Topical application of a conventional PDF reversibly dilated mesenteric arteries by more than 20%. The extent of the PDF-induced vasodilation was similar to that of nitroglycerin 10^{-4} M, and no additive effects were observed when PDF and nitroglycerin were applied simultaneously [24]. In another study, no further vasodilation was observed after addition of nitroprusside 10^{-4} M, indicating that PDF induces a maximal vasodilation [144]. In contrast, the small arterioles in the peritoneal membrane did not appear to respond directly to the local application of PDF, because their luminal diameters remained unchanged. However, the flow in these arterioles nearly doubled, indicating that they are passively conducting the increased flow caused by the vasodilation of the mesenteric arteries. This PDF-induced increase in peritoneal blood flow resulted in capillary recruitment, increasing the number of perfused capillaries with more than 20% [24]. Conventional PDF have a high osmolality as a result of elevated glucose concentrations and contain lactate as the buffer system. The pH is approximately 5.5 to limit caramelization of glucose during heat-sterilization process with the formation of a variety of toxic glucose degradation products (GDPs). Even at this low pH, considerable formation of GDPs occurs. The vasodilatory effects of low pH, lactate, and hyperosmolarity are well recognized. However, adjustment of the pH of the PDF to 7.4 did not decrease the vasoactive effects [24, 120, 144], indicating that although low pH *per se* may cause vasodilation, it is not essential for the observed dialysate-induced hemodynamic effects. These observations are important because acidity is rapidly corrected after infusion of standard PDF in the abdominal cavity. Conventional PDF may thus maintain its vasodilatory potential during the entire dwell time.

Novel techniques to prepare PDF have been developed in order to decrease GDP content. A substantial reduction in GDP formation can be achieved by sterilizing glucose separately at a pH of approximately 3. The electrolytes and buffer are kept in another bag compartment at a pH of approximately 8. The contents of both chambers are mixed immediately before use, yielding a solution with neutral pH [146]. A similar double-chamber system has been applied to allow use of bicarbonate as the buffer system. Since bicarbonate and the divalent ions are kept in separate chambers and mixed immediately before use, the precipitation of calcium and magnesium carbonate is avoided [147]. Because glucose is also sterilized separately at a low pH, formation of GDPs is in addition markedly reduced [146]. Local application to the mesenteric microcirculation of a PDF with low GDP content and high lactate concentrations induced only a transient vasodilation and capillary recruitment despite ongoing exposure. Exposure of the peritoneal membrane to a PDF with low GDP content and use of bicarbonate as the buffer was found to be entirely neutral with respect to hemodynamic parameters. Resterilization of the PDF with low GDP content and bicarbonate as the buffer increased GDP levels without otherwise altering the composition of the solution. The resterilized solution caused similar increases in blood flow and capillary recruitment in the peritoneal microcirculation as the conventional solution [24]. Taken together, these results indicate that lactate is only in part responsible for the PDF-induced vasoreactivity, whereas GDPs exert major hemodynamic effects [24]. The results do not support a role for hyperosmolarity in PDF-induced vascular reactivity, because the bicarbonate solutions were hemodynamically inert, even though their osmolality is identical to that of conventional PDF. In addition, the neutral effect of the bicarbonate solutions demonstrates that high glucose concentrations *per se* do not have hemodynamic effects [24].

Superfusion of the peritoneal membrane with conventional PDF rapidly reverses the vasoconstrictive effects of NO synthesis inhibitors [60]. When L-NAME and PDF are simultaneously superfused, the arteriole remained significantly

vasodilated throughout a 1-h superfusion period. Thus, PDF remain vasoactive despite arteriolar exposure to NO synthesis inhibitors, suggesting that the vasoactive properties are largely NO-independent. In studies of CAPD patients using amino acid-based peritoneal dialysis solutions, amino acid solutions increased estimated peritoneal blood flow. Based on nitrate and cGMP mass transfer area coefficients, this effect was not attributable to NO [148]. The exact mechanism through which PDF are vasoactive remains imprecisely defined, but it does not appear to be attributable to NO.

Summary

Animal studies and other evidence suggest that peritoneal clearance is not blood flow limited as long as effective peritoneal blood flow is greater than 30% of normal (with the exception of the liver). Ultrafiltration does not appear to be significantly limited by blood flow under usual conditions. Numerous vasoactive agents can affect peritoneal clearance and one of the most studied vasoactive agents is nitroprusside. Conventional PDF are vasoactive and have pronounced vasodilatory effects on mesenteric arteries. They increase microcirculatory blood flow and cause capillary recruitment. PDF with a low GDP content and lactate as buffer induce only a transient vasodilation, while PDF with low GDP content and bicarbonate as the buffer do not cause hemodynamic effects. Lactate may thus be in part responsible for the PDF-induced increase in peritoneal blood flow, whereas GDPs exert major hemodynamic effects.

The Peritoneal Microcirculation in Inflammation

The microcirculation plays a critical role in inflammatory responses associated with peritoneal dialysis. An important aspect of this response is the interaction of leukocytes with the vascular endothelium during inflammation. In pathophysiological states such as peritonitis the intraperitoneal leukocyte cell count may rapidly increase from a few cells to thousands of cells per mm^3. This rapid rise in the number of peritoneal leukocytes is dependent on factors that govern adhesive interactions between leukocytes and the microvascular endothelium. This section will focus on leukocyte-endothelial interactions in the peritoneal microcirculation.

General Principles of Leukocyte–Endothelial Interactions

Leukocyte recruitment from the vascular to the extravascular compartment follows a multistep process, directed by adhesive interactions. Leukocyte adhesion is localized primarily to postcapillary venules [41–44]. In order for a leukocyte to establish an adhesive interaction with the endothelium it must first be displaced from the center stream to the vessel wall. This appears to be related to microvascular network topography and radial dispersive forces. As the blood vessel diameter increases from the capillary to the postcapillary venules, the more flexible erythrocytes begin to pass the leukocytes and deflect them towards the vessel wall [149]. Once displaced to the vessel wall, the leukocyte can begin to adhere. Adhesion begins as a rolling movement along the postcapillary endothelium. As the inflammatory process proceeds, the number of rolling neutrophils increases and the velocity of the rolling decreases. This exposes the leukocyte to chemotactic agents released from parenchymal cells and/or the endothelium. Leukocyte activation allows the establishment of firm (stationary) adhesive interactions. The firmly adherent leukocyte may then migrate across the endothelial barrier and enter the interstitium (Fig. 4.5) [150].

The adhesive interaction between the leukocyte and the endothelium is mediated by a complex, highly coordinated, dynamic interplay between adhesion glycoproteins expressed on the surface of both the leukocyte and the endothelium [151]. The selectin family of adhesion molecules and their carbohydrate-containing ligands mediate the leukocyte rolling. At flow conditions typical of postcapillary venules, selectins are capable of interacting with their ligands within a fraction of a second. The rates of bond formation and dissociation are very high, but the bonds have a high tensile strength [152]. These qualities give rise to the rolling phenomenon, which brings the leukocyte into transient but close contact with the endothelial cells. If the appropriate stimuli are present, the leukocyte undergoes juxtacrine activation and prepares for firm adhesion and transendothelial migration. The firm adherence and transendothelial migration are mediated by the interaction of integrins with Ig-like molecules.

The integrins are heterodimers composed of a common beta subunit (CD18) and a specific alpha subunit (CD11a, CD11b, or CD11c). The superimmunoglobulin family is represented by intercellular adhesion molecules known as ICAM. The selectins are represented by L-selectin, E-selectin, and P-selectin. The integrins and L-selectin are

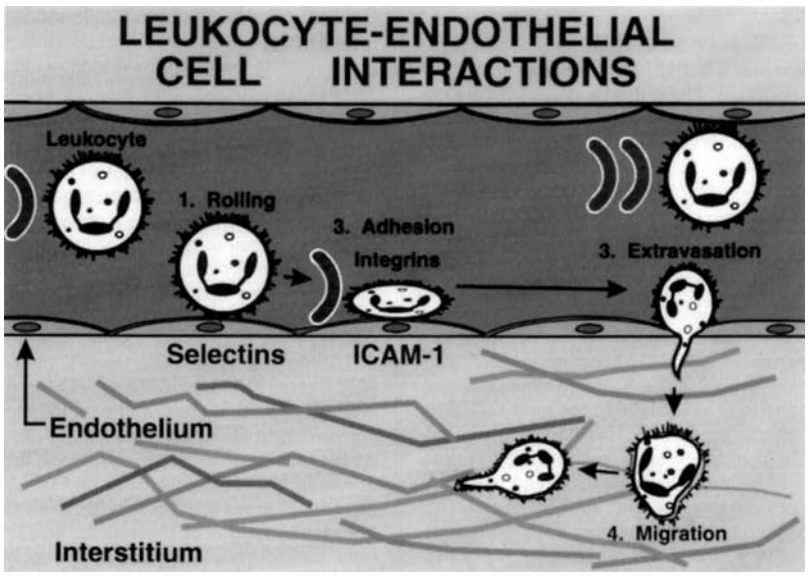

Fig. 4.5 The sequence of events involved in leukocyte adherence and migration to sites of inflammation requires coordination of the adhesive interaction between the leukocyte and vascular endothelium. (1) The initial leukocyte rolling appears to involve interaction between l-selectin on the neutrophil and E-selectin and P-selectin on the vascular endothelium. (2) This interaction allows for the up-regulation of the leukocyte integrin CD11b/CD18, which can bind to ICAM-1 and strengthen neutrophil adhesion. (3) The firmly adherent leukocyte may then extravasate by a process that is dependent on CD11a/CD18, CD11b/CD18, and ICAM-1. (4) The leukocyte may then migrate into the interstial tissue. Figure courtesy of Kristine Bienvenu

expressed on the surface of neutrophils. ICAM-1 is present on endothelial cells and its expression may be increased by endotoxin and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). Cytokines can also activate endothelial cells to express E-selectin. P-selectin is present on platelets and vascular endothelial cells [153–158].

The sequence of events involved in neutrophil adherence and migration to sites of inflammation requires coordination of the adhesive interactions between the neutrophil and the vascular endothelium. The initial leukocyte rolling appears to involve interactions between L-selectin on the surface of leukocytes and E-selectin and P-selectin on the vascular endothelium with their carbohydrate-containing ligands. These interactions allow for the up-regulation of CD11b/CD18 which can bind to ICAM-1 and strengthen neutrophil adhesion (Fig. 4.6). L-selectin is then

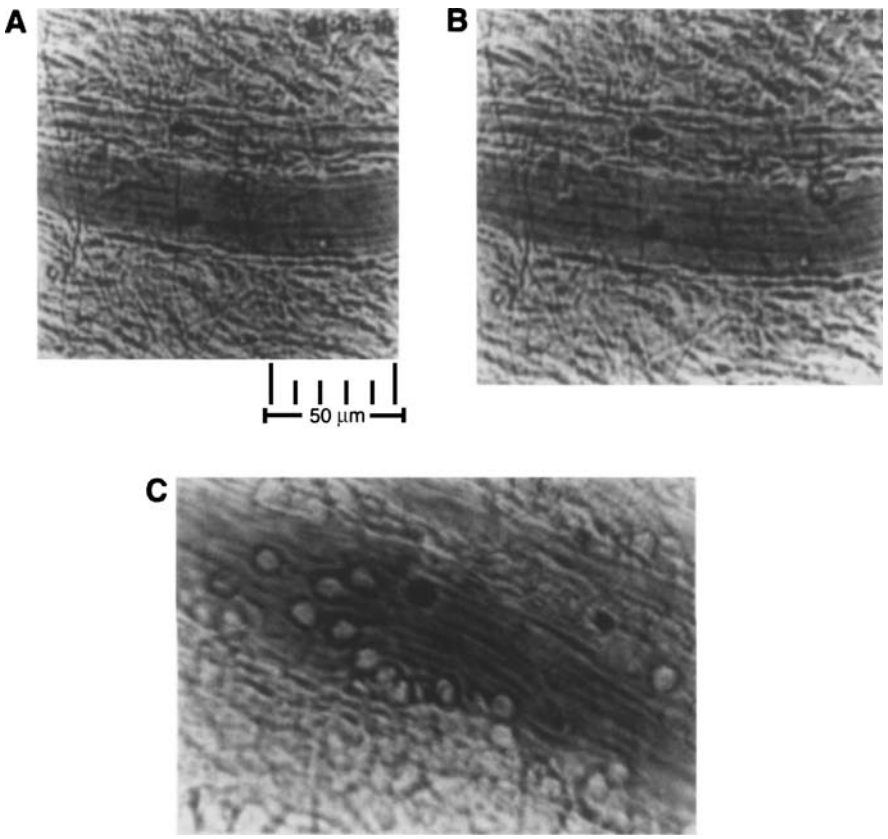

Fig. 4.6 (**a**) A mesenteric venule with a leukocyte (arrow) rolling along the length of the venule. (**b**) This micrograph was taken 2 s after the micrograph depicted in **A** to demonstrate that the leukocyte moved approximately 40 μm downstream in the venule. (**c**) A mesenteric venule during 2 ng/min platelet-activating factor (PAF) infusion. Note the numerous white blood cells adhering to the endothelial wall after PAF infusion [170]

down-regulated (shed) from the cell surface. The firmly adherent neutrophil may then migrate across the vessel wall by a process that is dependent on CD11a/CD18, CD11b/CD18, and ICAM-1.

Inflammatory Mediators and the Microcirculation

The physiological interaction between leukocytes and the endothelium may be influenced by several factors. Intravital videomicroscopic approaches have provided a wealth of information regarding the influence of intravascular hydrodynamic dispersal forces [41, 159, 160], leukocyte capillary plugging [161–163], electrostatic charge [164], and chemical mediators on leukocyte–endothelial cell interactions during inflammation. Table 4.2 lists several agents that affect leukocyte rolling and adherence in postcapillary venules.

As examples, platelet-activating factor (PAF), leukotriene B_4 (LTB_4), and nitric oxide synthesis inhibitors (such as L-NAME and ADMA) and superoxide have been shown to increase microvascular leukocyte adherence. The presence of adherent leukocytes and inflammatory agents may also promote changes in permeability. As an example, adherent leukocytes mediate PAF-induced vascular leakage. Pretreatment with monoclonal antibodies directed against the common beta subunit of the leukocyte integrin CD11/CD18 largely prevents the increased vascular protein leakage caused by infusion of PAF [165]. In the cat mesentery, local intra-arterial infusion of either LTB_4 or PAF promotes leukocyte adherence, but only PAF alters microvascular permeability. This indicates that leukocyte adhesion alone does not always result in increased microvascular permeability. When LTB_4 and PAF are infused simultaneously, LTB_4 causes a further increase in microvascular permeability than is observed with PAF alone. While PAF *per se* may increase microvascular permeability in the presence of adherent leukocytes, it may also serve as a "priming agent" that sensitizes neutrophils and/or the endothelium to other stimuli such as LTB_4 [166]. Reactive oxygen metabolites such as superoxide and hydrogen peroxide may be produced by neutrophils and endothelial cells [167–169]. Hydrogen peroxide appears to promote leukocyte adhesion to vascular endothelium by a PAF-mediated up-regulation or activation of CD11/CD18. Superoxide-induced increases in leukocyte adherence may be related to inactivation of nitric oxide by superoxide [170]. The inhibition of nitric oxide production by the vascular endothelium can produce an increase in microvascular protein efflux that is mediated in part by leukocyte-dependent mechanisms in the mesentery [171].

Thus, several agents promote leukocyte rolling and adherence in mesenteric postcapillary venules. Leukocyte adherence in the presence of an appropriate chemical stimulus may affect microvascular permeability. Since leukocyte adhesion has been associated with changes in permeability, the question arises as to whether leukocyte adhesion could modify endothelial junctional elements. Recent in vitro studies have shown that PMN adhesion to endothelial cells activated by tumor necrosis factor results in VE-cadherin/catenin disorganization [172]. This effect could be blocked by an anti-integrin beta 2 antibody. PMN adhesion also resulted in increased endothelial cell permeability. In vivo animal studies have shown that a monoclonal antibody against VE-cadherin increases vascular permeability and accelerates the entry of neutrophils into inflamed mouse peritoneum [173]. Thus, it appears that some agents which promote leukocyte adhesion may affect microvascular permeability through modulation of some junctional adhesion proteins.

The Effect of Peritoneal Dialysis Fluids (PDF) on Microvascular Leukocyte Adhesion

A large body of evidence indicates that conventional PDF cause a functional impairment of peritoneal host defense mechanisms [174]. The viability and production of inflammatory cytokines and chemoattractants by polymorphonuclear

Table 4.2 Substances or conditions that affect leukoctye adherence to postcapillary venules

A. Stimulants for leukocyte rolling
Superoxide, Histamine, Interleukin-1, Hydrogen peroxide, Indomethacin, Ischemia–reperfusion, Endothelin
Stimulants for adherence
C5a, PAF, Leukotriene B4, N-formylmethionyl-leucyl-phenylalanine, Hydrogen peroxide, Indomethacin, Nitric oxide synthesis inhibitors, Ischemia–reperfusion, Endotoxin, Superoxide
Substances which reduce leukocyte adherence
Adenosine, PGI_2, Iloprost (PGI_2 analogue), NO donors, 8-Bromo-cGMP (cGMP analogue), Superoxide dismutase, Catalase, Quinacrine (phosopholipase A_2 inhibitor), WEB2086 (PAF antagonist), Misoprostol (PGE_2 analogue), Colchicine, Methotrexate, Cromolyn (mast cell stabilizer), Salicylate

leukocytes, monocytes, and peritoneal macrophages is markedly affected by standard PDF. Phagocytosis, respiratory burst, and bacterial killing are lower when polymorphonuclear leukocytes, monocytes, and peritoneal macrophages are exposed to conventional PDF [174].

This section will focus on the effects of PDF on leukocyte recruitment in the peritoneal microcirculation. Intravital microscopy studies allow a direct visualization of the acute effects of PDF on leukocyte recruitment in mesenteric postcapillary venules [175–177]. Exposure of the rat peritoneal membrane to either LPS derived from *Escherichia coli* or a supernatant of a strain of coagulase-negative staphylococci previously isolated from a peritoneal dialysis patient with peritonitis resulted in an impressive increase in the number of rolling, adhering, and extravasated leukocytes in the postcapillary venules and a decrease in leukocyte rolling velocity [176]. The leukocyte response to these inflammatory stimuli was, however, dramatically suppressed by concomitant exposure to conventional PDF [176, 177] (Fig. 4.7). In contrast, superfusion with a pH-neutral, exclusively bicarbonate buffered PDF with low GDP content [176] and a pH-neutral bicarbonate/lactate-buffered PDF with low GDP content [177] had minimal suppressive effects. A lactate-buffered icodextrin solution partially blocked leukocyte-endothelial interactions and a lactate-buffered amino acid–based or amino acid/glycerol–based PDF abolished leukocyte recruitment in a similar manner as conventional PDF [177]. The differences between the responses to the various PDFs could not be attributed to variability of systemic blood pressure, circulating leukocyte numbers, or baseline levels of rolling, adhesion, extravasation, leukocyte rolling velocity, or venular shear rate, as these parameters did not vary between the groups. In addition, no correlation was found between the number of rolling leukocytes and venular wall shear rate at any time point, indicating that potential dialysate-induced variations in blood flow [24] were not responsible for the observed effects. The impairment of leukocyte recruitment by conventional PDF persisted after pH-adjustment to 7.4, indicating that, although low pH has well-documented inhibitory effects on various leukocyte effector functions in vitro [174], it does not appear to be essential for the observed inhibition in vivo. In order to identify the causative PDF-components in greater detail, additional experiments were performed. While superfusion with a pH-neutral solution containing high lactate concentrations and physiologic glucose levels caused a partial inhibition of leukocyte recruitment, a pH-neutral solution with both high lactate and high glucose concentrations abolished the leukocyte response similarly to conventional PDF [176], suggesting additive effects of lactate and hyperosmolarity on leukocyte kinetics.

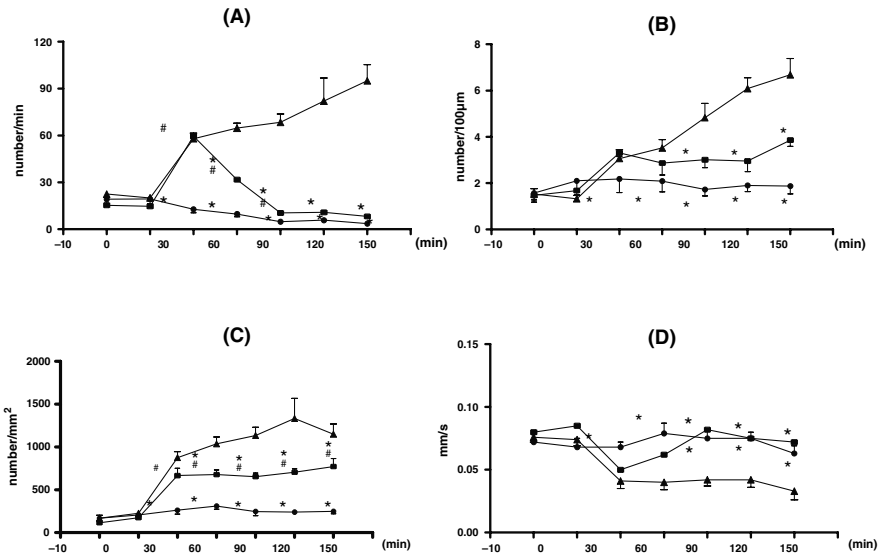

Fig. 4.7 The different aspects of leukocyte recruitment in peritoneal postcapillary venules after stimulation with LPS were evaluated with intravital microscopy, during superfusion with a pH-neutral buffer solution with physiological glucose and bicarbonate concentrations (EBSS) (triangles), a standard peritoneal dialysate fluid (PDF) (circles) and a pH-neutral bicabonate-buffered PDF with low glucose degradation product content (squares). (**a**) The number of rolling leukcytes rises progressively after an inflammatory stimulus, but not when the peritoneal membrane is superfused with a standard PDF. The suppressive effect of the pH-neutral bicarbonate-buffered PDF is less pronounced. *$p < 0.005$ versus EBSS, #$p < 0.01$ versus standard PDF. (**b**) The number of firmly adherent leukocytes in response to LPS increases after superfusion with EBSS, but not with standard PDF. During exposure to pH-neutral bicarbonate-buffered PDF, the response is intermediary. *$p < 0.05$ versus EBSS. (**c**) Extravasation of the leukocyte is the final step in leukocyte recruitment. The number of extravasated leukocytes rises sharply after LPS and reaches a plateau after 60 min. No recruitment occurs during standard PDF exposure, while a somewhat lower plateau is reached after pH-neutral bicarbonate-buffered PDF. *$p < 0.05$ versus EBSS, #$p < 0.005$ versus standard PDF. (**d**) Leukocyte rolling velocity decreases during EBSS, but not during standard PDF and only transiently during pH-neutral bicarbonate-buffered PDF. *$p < 0.05$ versus EBSS [176]

After resterilization, in order to increase GDP levels without otherwise altering the composition of the solution, the pH-neutral bicarbonate-buffered PDF suppressed leukocyte recruitment to a similar extent as the standard solution. These results thus support the inhibitory effects of GDPs on leukocyte recruitment, as suggested by in vitro experiments [174]. However, as the combination of lactate and hyperosmolarity already caused a maximal suppression of leukocyte recruitment, lowering the GDP content of a PDF alone may not be sufficient to improve host defense. The subordinate effect of GDPs on leukocyte recruitment is supported by observations of a lower influx of neutrophils in the peritoneal cavity of rats infected with *Staphylococcus aureus* after previous exposure to both a pH-neutral lactate-buffered PDF with low GDP content and a conventional PDF [178]. The pivotal role of lactate in the inhibition of leukocyte recruitment is further corroborated by the previously mentioned suppressive effects of the nonglucose lactate-buffered PDFs (icodextrin, amino acids, and amino-acid glycerol), that all have a low GDP content [177]. The low lactate concentrations in the combined bicarbonate/lactate-buffered PDF, however, do not appear to exert an adverse effect on leukocyte recruitment. These observations are in line with the finding that the migration distance of polymorphonuclear cells was not adversely affected unless lactate concentrations rose above 15 mmol/L [179].

The nonphysiologic composition of PDF disappears progressively during the dwell time. Osmolarity decreases due to glucose absorption and water ultra-filtration, although it never reaches physiologic values. Lactate concentration also diminishes rapidly during the dwell. Spent dialysate obtained from a patient after a 6-h dwell, however, affected leukocyte kinetics to a similar extent as fresh PDF [176], suggesting that osmolarity and lactate concentration remain sufficiently elevated to profoundly inhibit leukocyte recruitment. Alternatively, uremic toxins and reactive carbonyl compounds that accumulate in the dialysate during the dwell [180, 181] may affect peritoneal leukocyte behavior. Taken together, the results indicate that inhibition of leukocyte recruitment by conventional dialysate will persist throughout the entire PD cycle.

The underlying molecular mechanisms of the inhibition of leukocyte recruitment by PDF is unknown, but it likely involves effects on the adhesion molecules. Superfusion of the peritoneal membrane with L-NAME increased the number of firmly adherent leukocytes in the postcapillary venules. A standard PDF attenuated L-NAME-induced leukocyte adhesion, returning it to baseline conditions [182]. This suggests a possible effect on either the integrins or ICAM. In vitro studies have demonstrated that hyperosmolar solutions affect integrin expression. Kaupke and colleagues have demonstrated that incubation of blood with PDF resulted in depressed basal neutrophil expression of CD11b and CD18 and monocyte expression of CD14 [183]. In addition, the glucose-containing PDF decrease the LPS-induced upregulation of CD11b and CD18. PDF in which sodium chloride was substituted for glucose to obtain similar osmolalities as the glucose-based PDF also show a reduction in basal and LPS-stimulated expression of CD11b.

It is important to note that these in vitro and in vivo studies have been performed with acute exposure to PDF. Chronic exposure to conventional PDF resulted in neoangiogenesis and an increase in the baseline rolling of the leukocytes, while baseline leukocyte adhesion was unchanged [184]. These results possibly indicate changes in adhesion molecule expression in newly formed blood vessels in response to exposure to conventional PDF.

Summary

Several inflammatory mediators promote leukocyte rolling and adhesion in the mesenteric microcirculation. In the presence of some inflammatory agents, leukocyte adherence may affect microvascular permeability, possibly through modulation of junctional adhesion proteins. Animal models have demonstrated that PDF acutely affect leukocyte-endothelial interactions. Conventional PDF decrease leukocyte recruitment, most likely owing to a combination of high lactate concentrations, hyperosmolarity, and presence of GDPs. In contrast, bicarbonate-buffered PDF with low GDP content have only minimal effects on leukocyte kinetics.

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Chapter 5
Functional Structure of the Peritoneum as a Dialyzing Membrane

L. Gotloib

Not everything that can be counted counts; and not everything that counts can be counted.

Albert Einstein

More than a century ago, Robinson [1], after summarizing more than two centuries of research, defined the diverse natural functions of the peritoneum as follows: a) to regulate fluid for nutrient and mechanical purposes: b) to facilitate motion; c) to minimize friction, and d) to conduct vessels and nerves to the viscera.

Several medical and scientific developments that occurred during the 20th century originated a new approach for the peritoneum being used as a dialysing membrane for long-term life support [2–6]. These same developments created the need for a deeper understanding of peritoneal structure and function.

The peritoneum is a serous membrane embryologically derived from mesenchyma and composed of thin layers of connective tissue covered by a sheet of mesothelium [7]. When the membrane is folded, forming the omentum and the mesentery, both luminal surfaces are covered by mesothelium.

The *anatomical* peritoneal surface area for the human adult is considered to range between 2.08 [8] and 1.72 m^2 [9], with a ratio of area/body weight of 0.284. The intestinal mesothelium, together with that of mesentery, makes up to 49% of the total mesothelial area [10]. For infants having a body weight of 2,700–2,900 g, the total peritoneal surface was found to oscillate between 0.106 [10] and 0.151 m^2 [8], with an area to body weight ratio that fluctuates between 0.383 [10] and 0.522. In infants the contribution of intestine and mesentery to the total surface area is 67.5% [10].

However, from the functional point of view, vis-à-vis peritoneal dialysis, it may well be that the peritoneal area of contact with the dialysis solutions were substantially lower than the anatomical one. This concept, postulated by Krediet et al., was defined as the effective surface area [11]. This hypothesis finds strong support in the elegant study performed by Chagnac et al. [12] showing that the peritoneal surface actively involved in the dialytic process, estimated in six CAPD patients, was 0.55∼0.04 m^2, about one third of the area measured in anatomical studies. Interestingly, other investigators reached similar conclusions in experiments performed in rats [13].

Peritoneal thickness is not uniform and varies according to the area examined. Measurements are quite problematic in parietal and diaphragmatic peritoneum due to the considerable amount of connective tissue, and at times fat, intervening between the peritoneum itself and the underlying tissue (Fig. 5.1). The submesothelial connective tissue layer of visceral peritoneum is firmly bound to the fibrous tissue of the viscus. Therefore, the mesentery, having mesothelial lining on both surfaces and including its trabecular connective framework, appears to be the most appropriate peritoneal portion for estimation of membrane thickness which, in the rabbit, ranges between 30 and 38 μm [14, 15] (Figs. 5.2 and 5.3).

Normal Mesothelium

Electron microscopic studies performed on mouse embryo disclosed that the mesothelium is derived from mesenchymal cells that become flattened, form their own basement membrane, and develop tight junctions as well as desmosomes [16] (Fig. 5.4, inset). Both pinocytotic vesicles and rough endoplasmic reticulum were present. Yolk sac of human embryos at the 5th–7th week of gestation also exhibit flattened mesothelial cells lying on a hyaline, homogeneous basement membrane [17, 18].

L. Gotloib (✉)
Ha'Emek Medical Center, Department of Nephrology, Afula, Israel
e-mail: gotloib@012.net.il

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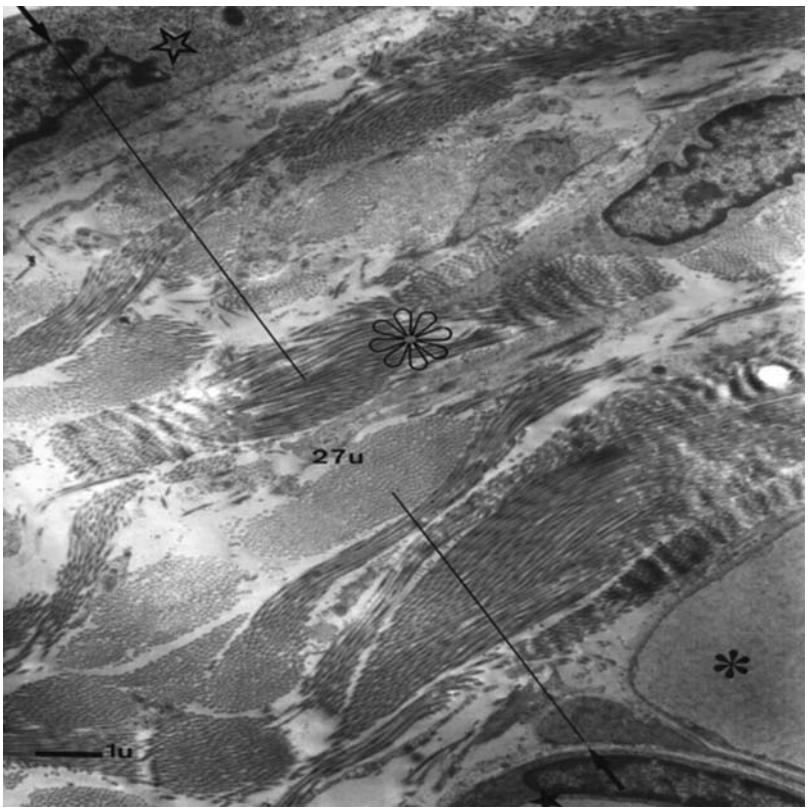

Fig. 5.1 Sample of diaphragmatic rabbit peritoneum. The distance (straight line) between the peritoneal space (upper arrow) and the lumen of the blood capillary (black star) is around 27 μm. The actual pathway through the collagen fibers (open asterisk) is longer (open star: mesothelial cell; black asterisk: fenestrated capillary (× 14,250))

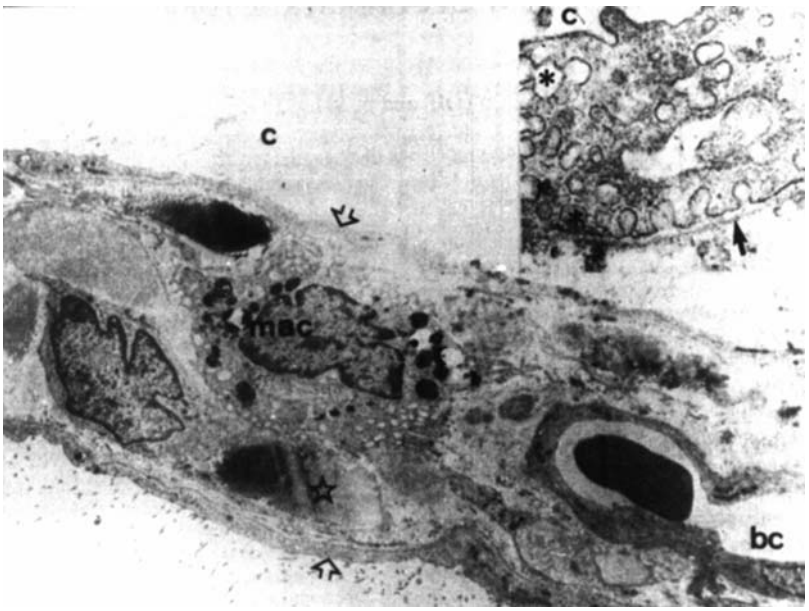

Fig. 5.2 Section of normal rabbit mesentery showing the mesothelial layer (open arrows) covering both aspects of the mesenteric surface area facing the abdominal cavity (c). The interstitium contains a continuous blood capillaty (bc), bundles of collagen (open star), as well as a macrophage (mac). Numerous microvilli can be seen at the lower mesothelial surface (original magnification × 4,750).

Upper right inset. Parietal peritoneum of normal mice. Note the presence of numerous pinocytotic vesicles (*) which, on the left side of the electron micrograph, form a chain between the luminal aspect of the mesothelial cell facing the abdominal cavity (c) and the abluminal one, lying on the continuous basement membrane (arrow) (× 41,500)

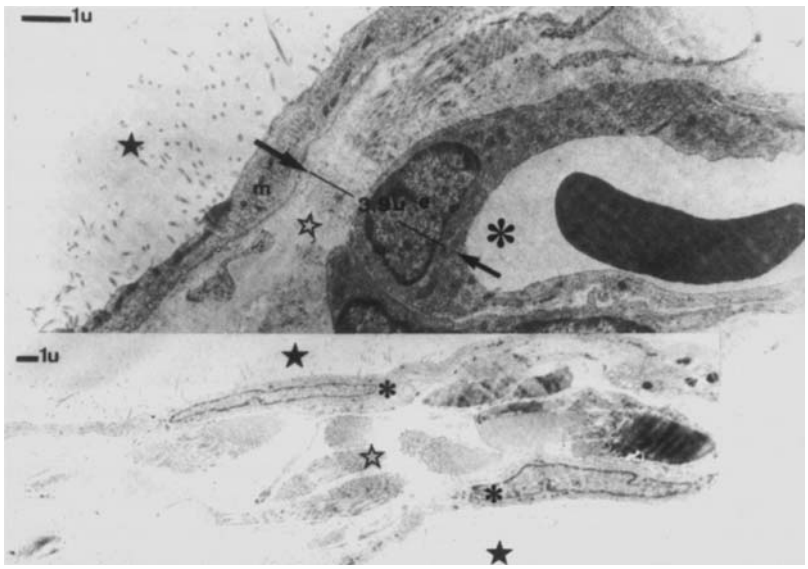

Fig. 5.3 The main photograph shows a sample of rabbit mesenteric peritoneum where the distance (straight line) between the peritoneal space (upper black star) and the microvascular lumen (*) is 3.9 µm (open star: interstitial connective tissue) (× 14,250).

Lower inset. Section of a 42.1 µm length avascular rabbit mesenteric peritoneum sample (black star: peritoneal space; asterisk: mesothelial cell; open star: interstitial connective tissue) (× 4,750)

The cell plasmalemma, when stained specifically, shows the typical trilaminar structure observed in all biological cell membranes [19]. The normal mesothelium occasionally shows macrophages implanted on the luminal peritoneal surface instead of mesothelial cells (Fig. 5.5).

The luminal aspect of the mesothelial cell plasmalemma has numerous cytoplasmic extensions: the microvilli (Figs. 5.2, 5.3, and 5.4), whose existence was originally reported by Kolossow [20] and many years later confirmed by electron microscopy on the serosa covering the rat oviduct [21, 22]. Even though microvilli are more frequently observed in visceral than in parietal peritoneum [23, 24], their distribution is variable and fluctuates from very numerous to completely absent [24, 25]. It should be taken into account, however, that microvilli are extremely sensitive to minor injury or even to dryness, and can therefore be lost from the cell surface if removal and handling of samples are not done with extremely careful techniques. On the other hand, loss of microvilli, as described in continuous ambulatory peritoneal dialysis (CAPD)patients [26] (Fig. 5.6), represent an early sign of impending apoptosis [27–29] that can be easily identified in mesothelial cell imprints (Fig. 5.7).

Light microscopy applied to the observation of resting mesothelium imprints [30] shows a continuous monolayer made up mostly of polygonal mononuclear cells (Fig. 5.8), showing, in mice visceral peritoneum, a density of about 300,000 cells/cm^2 [31]. The number of mesothelial cells per unit area seems higher on the visceral than on the parietal peritoneal surface. Of those cells, 1–2% are binucleated (Fig. 5.8, lower left inset), whereas cells showing three nuclei can be observed (Fig. 5.8).

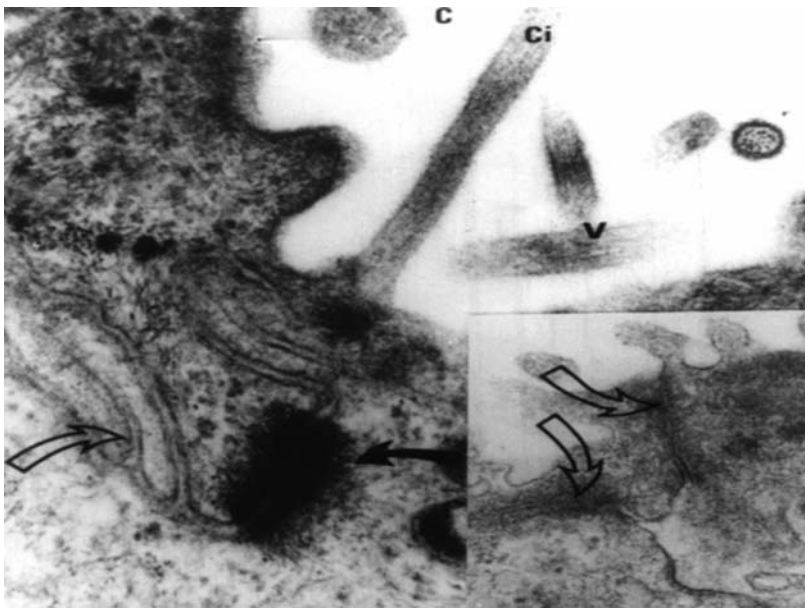

Fig. 5.4 Biopsy of parietal peritoneum taken from a chronic uremic patient on maintenance peritoneal dialysis. Note the presence of an oligocilium (Ci) showing the deviated axial microtubule (open arrow) and the attached basal body (black arrow). Their function is unknown (C: abdominal cavity; V: microvilli) (× 42,900).

Inset. (Lower right). Rabbit mesentery: the open arrows show tight junctions between adjoining mesothelial cells (× 62,500)

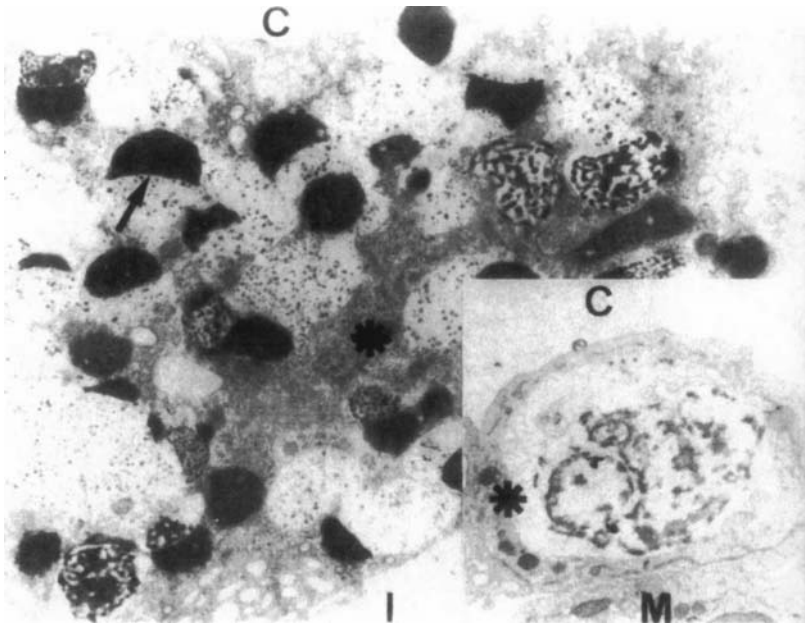

Fig. 5.5 Mesentery of normal rabbit. A macrophage (*) is covering a denuded area of peritoneum (C: abdominal cavity; black arrow: lysosome; I: interstitium). Original magnification × 27,500.

Inset. (Lower right). Mouse mesenteric mesothelium: a signet-ring macrophage (*) is covering a recently implanted mesothelial cell (M) (original magnification × 15,400)

Under normal circumstances the cell population of the monolayer is not stained by vital dyes such as Trypan Blue (Fig. 5.9). This is an indication of their viability. In perpendicular cuts observed under light microscopy, the resting normal mesothelium appears as a continuous layer formed by flattened cells that are apparently elongated, as a result of the angle of section (Fig. 5.10). The mesothelial sheet lies on a layer of connective interstitial tissue (Fig. 5.10), the thickness of which varies in the different portions of the peritoneum (Figs 5.1 and 5.3). The relevance of this point on peritoneal permeability will be discussed later.

Thickness of mesothelial cells in the rabbit ranges between 0.6 and 2 μm [14, 15] (Fig. 5.11).

The human omentum has not yet been studied in great depth. However, some ultrastructural investigations performed in mice and rats [22, 32] seem to indicate that there is little variation between species [33] and that, in mice, omental mesothelial cells can transiently increase their population of microvilli up to seven-fold, suggesting that their concentration in any given area could reflect functional adaptation rather than static structural variation [34].

The presence of pinocytotic vesicles in microvilli has been both reported [21, 23, 35] and denied [34].

Experimental studies done in mice and rats [35–37] using cationic tracers such as ruthenium red (MW 551 da) and cationized ferritin (MW 445 da) revealed the existence of anionic fixed charges on the luminal surface of the microvilli

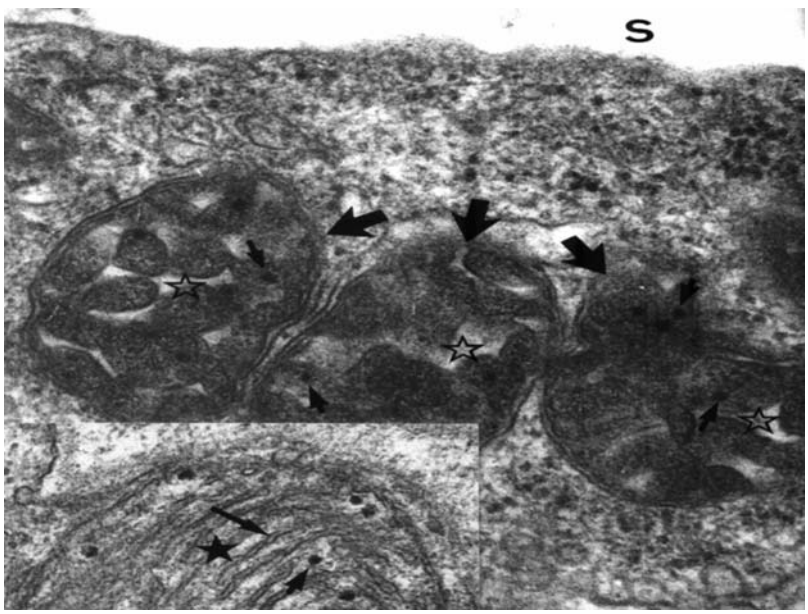

Fig. 5.6 Section of a mesothelial cell seen in a biopsy of parietal peritoneum taken from a patient on CAPD. Mitochondria (open stars) assumed a condensed configuration with increased density of the matrix, blurring of cristae as well as fusions and adhesions of the inner membrane (thick arrows). The matrical granules are still visible (short arrows). These signs of cell injury, in addition to the absence of microvilli, are early signs of impending apoptosis (S: peritoneal space) (× 54,600).

Inset. Intact mitochondrion (short star) showing normal cristae (long arrow) and matrical granules (short arrow) (× 64,550)

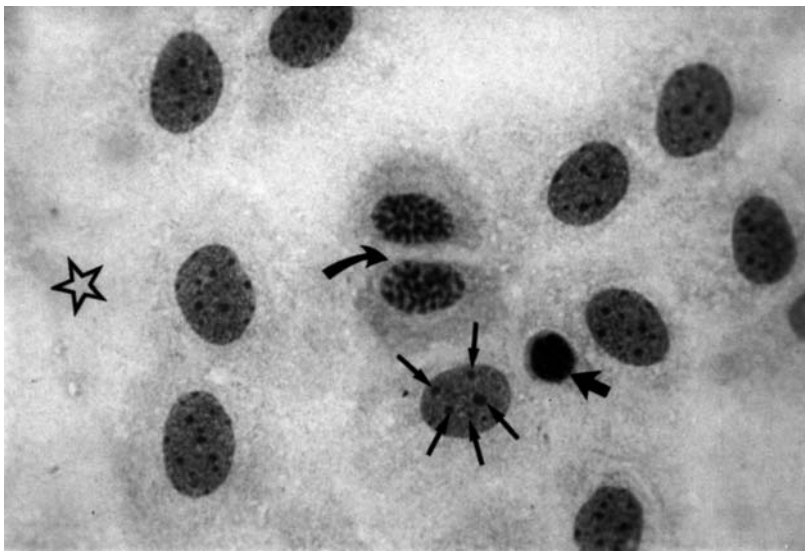

Fig. 5.7 Sample from a mouse injected for 30 consecutive days with 4.25% glucose-enriched dialysis solution. The material was taken 7 days after interruption of the exposure to the dialysis solution (7 days of recovery). This photograph shows the two most critical moments in the life cycle of a mesothelial cell: mitosis (curved arrow), and apoptosis (short thick arrow). Open star shows an area of peritoneum where the mesothelial monolayer is absent (desertic peritoneum). Note the substantially reduced density distribution of cells (small arrows: nucleoii) (hematoxylin-eosin; × 1,000)

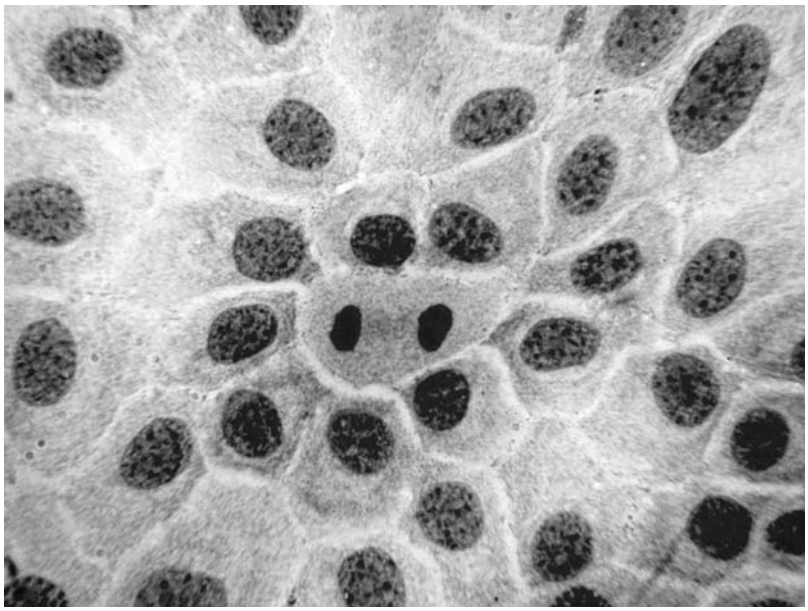

Fig. 5.8 Normal density distribution of mesothelial cells observed in intact, unexposed animals. Unstimulated mesothelium shows a quite low proportion of cells undergoing mitosis at any given time. (Center of microphotograph: cell in mitosis.) (× 1,000)

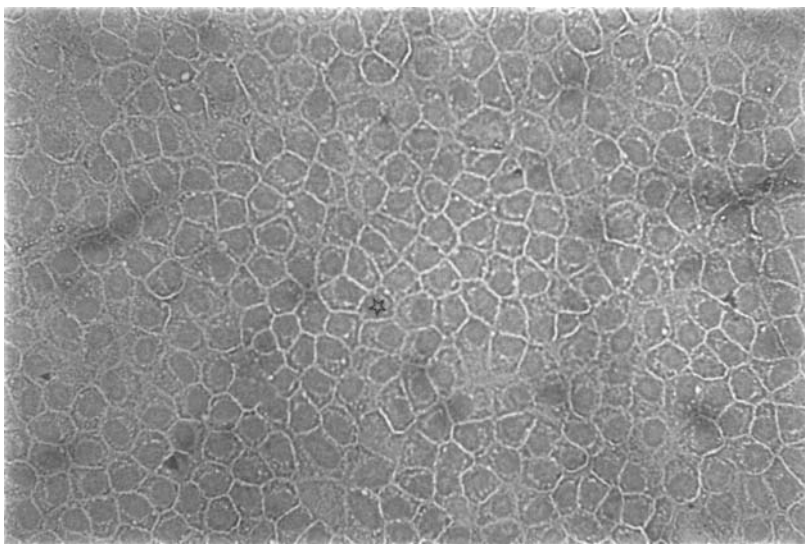

Fig. 5.9 Cell viability evaluated on visceral mesothelium by Trypan-blue exclusion in an intact unexposed mouse. The stain did not permeate the cell membrane (open star: mesothelial cell) (× 400)

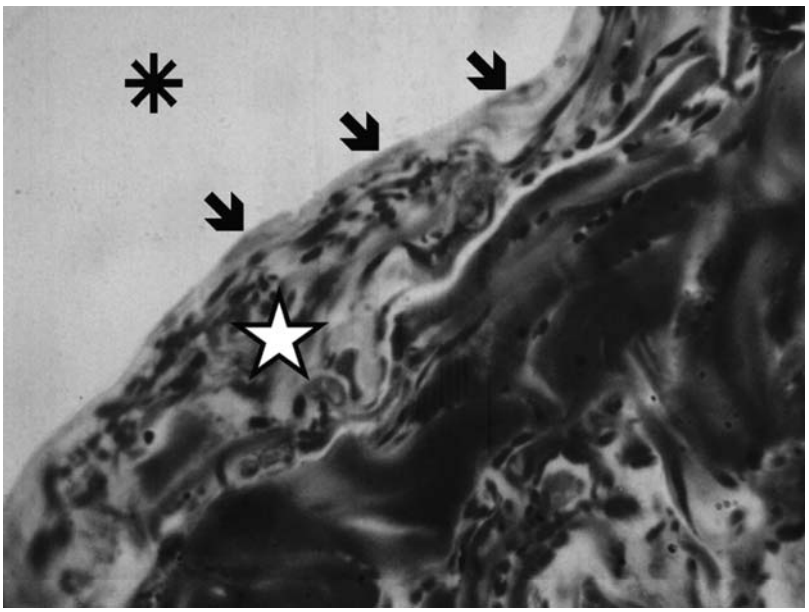

Fig. 5.10 Biopsy of parietal peritoneum taken from a uremic patient at the time of implanting the first dialysis catheter. Arrows point at nuclei of mesothelial cells. Open star was placed on the submesothelial interstitial tissue, the thickness of which ranges between 37 and 62 μm (*: peritoneal cavity) (toluidin blue; × 400)

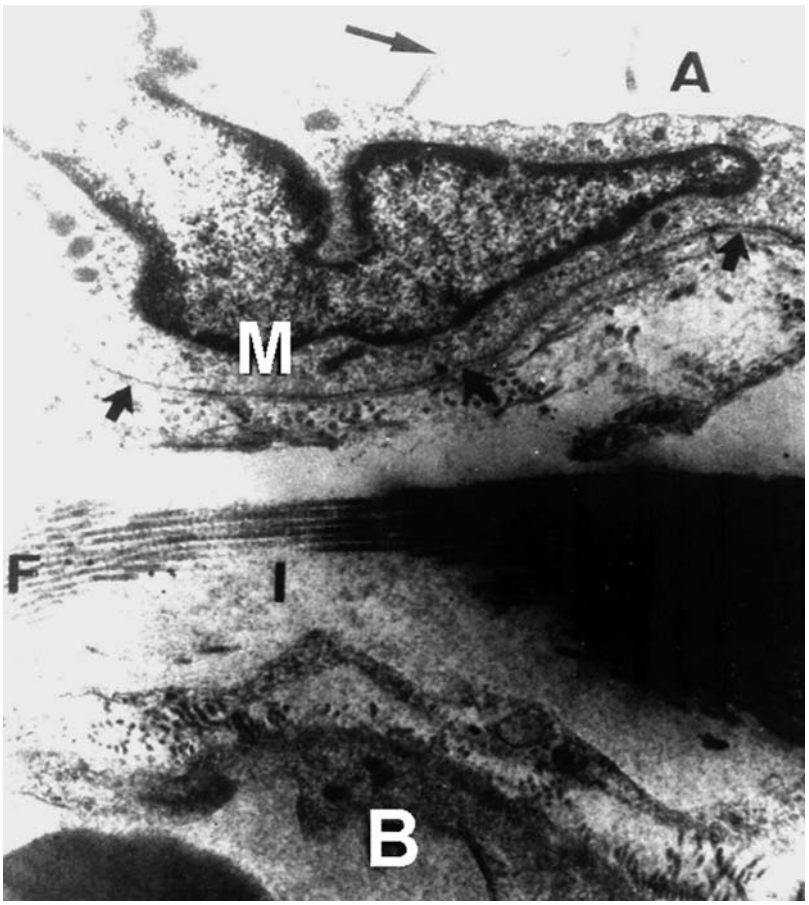

Fig. 5.11 Rabbit mesentery: normal resting mesothelial cell (M) lying on a continuous basement membrane (short arrows) (A: abdominal cavity; long arrow: microvilli; I: interstitium; F: collagen fibers; B: blood capillary; E: erythrocyte) (original magnification × 27,500)

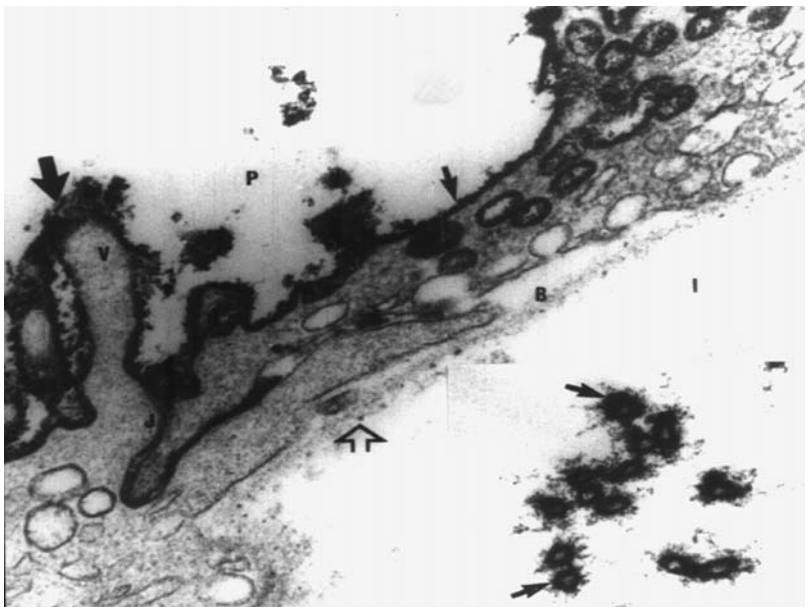

Fig. 5.12 Section of rat mesentery showing microvilli (V) with heavily ruthenium-red decorated glycocalyx (large arrow), also evident on the mesothelial cell plasmalemma (small arrow). The cationic dye also stains a long portion of the intercellular junction (J). The basement membrane (B) shows quite regularly distributed anionic sites (open arrow) (P: abdominal cavity; I: interstitium). Original magnification × 50,720.

Inset. Rat mesentery: transversal section of microvilli showing the fibrilar ruthenium red-stained glycocalyx (arrows) (× 50,720)

cytoplasmic membrane (Fig. 5.12, inset). This cell membrane coating, or glycocalyx, composed of fine fibers that are continuous with the membrane itself [38], furnishes the microvilli surface with electronegative charge, which most probably plays a significant role in the transperitoneal transfer of anionic macromolecules such as plasma proteins [36, 39], as well as in that of charged small molecules, as suggested by Curry and Michel [40] in their fiber matrix model of capillary permeability. This surface charge is substantially reduced in cells undergoing apoptosis [41]. The relevance of these charges upon peritoneal permeability will be discussed later.

Length of microvilli in rodents ranges between 0.42 and 2.7 μm, and their average diameter is 0.1 μm [14, 21, 23, 32]. We have observed a similar range in adult humans. However, mesothelial cells of human embryos (5th–7th week of gestation) showed microvilli up to 3.5 μm long [17].

It has been estimated that microvilli present in the striated border of intestinal epithelium increase the surface area of the intestine by a factor of 20 [42]. Consequently, it has been speculated that mesothelial microvilli could increase the actual peritoneal surface up to 40 m^2 [43].

Plasmalemma of mesothelial cells, like that of microvilli, shows electronegatively charged glycocalyx (Fig. 5.12) [35–37, 44].

Plasmalemmal vesicles, or caveolae, originally described by Lewis [45] in macrophages of rat omentum, are conspicuously present in mesothelial cells at both the basal and luminal borders, as well as in the paranuclear cytoplasm [21–23, 32, 46–48] (Fig. 5.2, inset). Their average diameter is approximately 0.717 μm [14]. At times, pinocytotic vesicles appear clustered together and communicating with each other (Fig. 5.2, inset). Occasionally they appear forming transcellular channels similar to those described in endothelial cells of blood capillaries [49, 50] (Fig. 5.13, inset), apparently communicating both aspects, luminal and abluminal, of the mesothelial cell. These channels can be formed by a chain of several vesicles (Fig. 5.13, inset) or just by two adjoining vesicles. Often pinocytotic vesicles appear to open through the plasma membrane into the luminal or abluminal aspect of the cell (Fig. 5.2, inset; Fig. 5.12), as well as into the intercellular space (Fig. 5.12), exhibiting a neck and a mouth whose respective average diameters are 0.176 and 0.028 μm [14]. With respect to the density distribution of these caveolae, it has been suggested that the parietal mesothelium is less well endowed than the visceral [47].

Palade [51] first proposed that a large part of the macromolecular transport across capillary walls could be attributed to exchange of pinocytotic vesicles between the internal and external surfaces of endothelial cells. This concept was repeatedly applied to the mesothelium. Several electron-dense tracers such as native ferritin [48], iron dextran [14, 32], and melanin [22] were found randomly distributed within pinocytotic vesicles of mesothelial cells after being injected intraperitoneally. Casley-Smith and Chin [47] calculated that the median transit time of vesicles through mesothelial cells ranges between 3 and 5 s, and that approximately 40% of the released vesicles reach the cytoplasmic membrane on the opposite side of the cell. It was even observed that metabolic inhibitors such as dinitrophenol, poisons (cyanide), or slow cooling to 0°C did not completely preclude the uptake of electrondense macromolecules by pinocytosis [48, 52]. This information, supporting Palade's prediction [51] that vesicles could be the structural

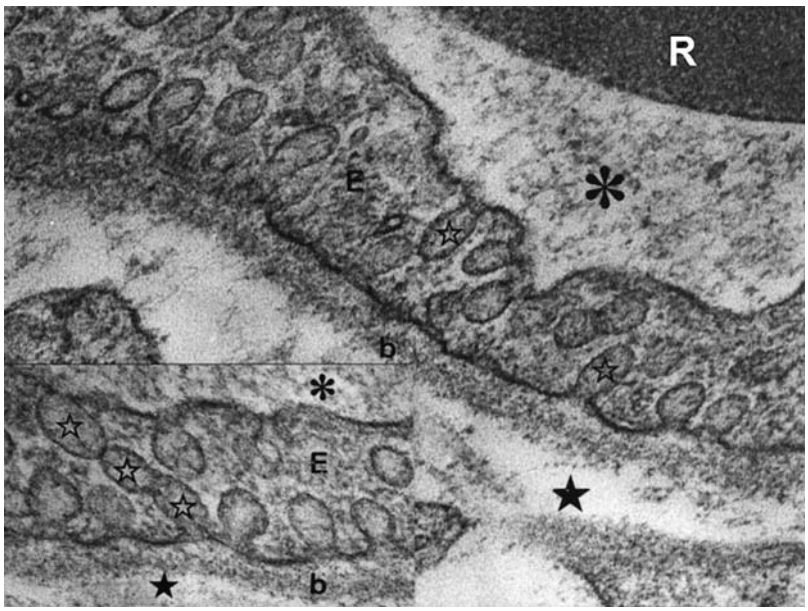

Fig. 5.13 Continuous blood capillary of rat mesenteric peritoneum. Plasmalemmal vesicles (open stars) are open to both aspects of the endothelial cell (E) (R: red blood cell; *: microvascular lumen; b: subendothelial basement membrane; black star: interstitial space) (× 87,000).

Inset. Another capillary from the same sample, showing a transcellular channel made up by a chain of three plasmalemmal vesicles (open stars), connecting both aspects of the endothelial cell (E) (*: microvascular lumen; b: subendothelial basement membrane; black star: subendothelial interstitial space) (× 87,000)

equivalent of the large pore [53], was challenged by stereological analysis of plasmalemmal vesicles. This study apparently showed that vesicles represent merely invaginations of the plasmalemma from both sides of the capillary wall in frog mesentery [54]. It was suggested that this organization of the vesicular system is incompatible with the concept that macromolecules could be transferred across cells by vesicular transport. The methodology followed in this study has been reviewed and criticized, and its conclusions have been refuted [55].

Furthermore, a huge body of scientifically based evidence indicates that endocytosis, transcytosis, as well as potocytosis (an endocytic pathway that utilizes phosphatylinositol anchored membrane proteins and plasmalemmal vesicles or caveolae to concentrate and internalize small molecules) are basic mechanisms used by cells to carry in, out, and through the cytoplasm a variety of substances [56]. The following part of our description applies to both mesothelium and endothelium.

Work done basically during the past decade shed new light on the intimal structure of pinocytotic vesicles. Even though their morphometric parameters are more or less homogeneous, differences in nature, function, and biochemical structure identified at least two kinds of vesicles showing distinctive characteristics.

Caveolae or plasmalemmal vesicles are membrane domains that represent a subcompartment of the plasma membrane [57], characteristic of all vascular endothelium [58]. In capillary endothelial cells, morphological studies indicate that caveolae are effectors of transcytosis of certain macromolecules across the microvascular endothelium: native as well as modified albumins [59–67], low-density lipoprotein (LDL) [68–71], protein hormones [72, 73], AGE [74], as well as orosomucoid [75], a 41 kDa glycoprotein that qualifies as a probe for the postulated large pore [76–78]. Furthermore, endocytosis and transcytosis of albumin–gold complexes have been observed in mice peritoneal mesothelium [79] (Fig. 5.14, inset; Fig. 5.15, inset).

Schnitzer and Oh have demonstrated that transendothelial transport of native albumin through caveolae in both experimental situations (in vivo as well as in the in vitro set-up) is dependent on the interactions of the probe with the endothelial cell surface protein albondin, a 60 kDa albumin binding protein formerly called gp60 [63]. Other binding proteins, gp30 and gp18, appear to mediate the attachment, endocytosis, and degradation of modified albumin. These vesicular carriers require key intracellular components that are sensitive to alkylation with N-ethylmaleimide. Indeed, this substance has been shown to substantially inhibit native albumin (MW: 67 kDa, $r = 36$ Å) and ferritin (MW $\sim$ 500 kDa, $r = 100$–110 Å) uptake, both transcytosed by caveolae [80]. Additional experiments have shown that transcytosis and capillary permeability of insulin and albumin are selectively inhibited by filipin, a complex of polyene antibiotics obtained from *Streptomyces filipenensis*, but does not affect endocytosis mediated by the clathrin-coated vesicles [81]. This concept that identifies two different vesicular pathways is completed with the recent discovery of caveolin, the major structural caveolar protein [82]. This substance is a 22 kDa integral protein that represents a subcompartment of the plasma membrane [57, 83]. Basically, it is a component of the coating covering the luminal aspect of caveolae [84] that, when specifically stained by immunocytochemical methods, serves as a useful marker to draw the diagnostic line between caveolae and other pinocytotic related structures, e.g., coated vesicles [85–87].

Coated pits and coated vesicles (Fig. 5.14, left and right insets) remain the most extensively characterized transport vesicles. They are involved in the intracellular transport of membrane proteins between a variety of membrane

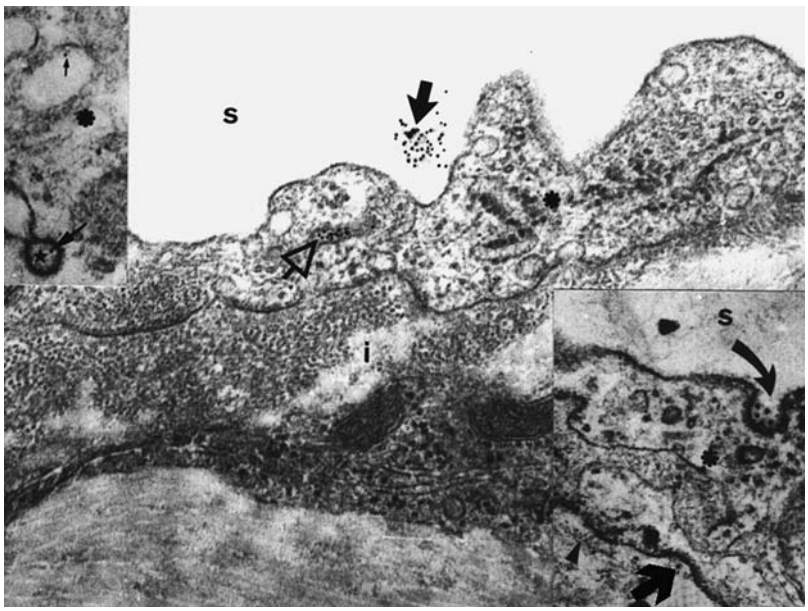

Fig. 5.14 Diaphragmatic peritoneum of a mouse taken 10 min after intra-arterial perfusion with gold-labeled albumin. Some particles (black arrow) can be seen in the peritoneal space (s). The mesothelial cell (*) shows a multivesicular body (open arrow) containing particles of the tracer (I: interstitial space) (× 41,500).

Upper left inset. Cytoplasmic compartment of a mesothelial cell (*) showing albu min–gold complexes decorating the membrane luminal aspect of a pynocytotic vesicle (small arrow), as well as that of coated vesicle (big arrow) (× 64,550).

Lower right inset. Particles of the tracer decorating the luminal glycocalyx of a coated pit (curved arrow) of a mesothelial cell (*), seen in the same sample. The tracer is also present in the abluminal aspect of the mesothelial cell (straight arrow), between the plasmalemma and the submesothelial basement membrane (arrowhead) (× 64,550)

components, mediate endocytosis of transmembrane receptors, and transport newly synthesized lysosomal hydrolases from the trans-Golgi network to lysosomes [88]. The luminal coat contains at least six polypeptides, in addition to the above-mentioned 180 kDa polypeptide clathrin [89, 90]. This type of vesicle is also involved in receptor-mediated endocytosis. Cell surface mediators operate endocytosis clusters into clathrin-coated pits, which pinch off to form vesicles that transport the receptors and their ligand [91]. The complex process of invagination, constriction and budding of clathrin-coated vesicles employs the coordinated actions of several proteins. The best characterized of them is the expanding family of dynamin guanosine triphosphate phosphatases (GTPase), essential for receptor-mediated endocytosis [92, 93]. This enzyme appears to be assembled around the necks of clathrin-coated pits, and assists in

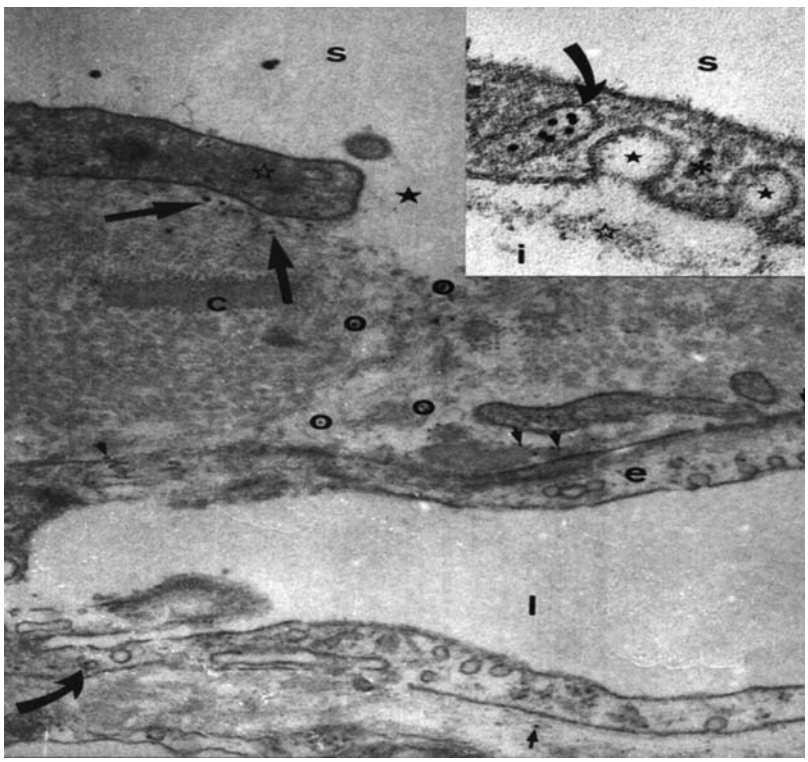

Fig. 5.15 Diaphragmatic peritoneum of a mouse, taken 10 min after intraperitoneal injection of albumin–gold complexes. The black star points at stomata communicating the peritoneal space(s), and the submesothelial connective tissue (c). Albu min–gold complexes (large straight arrow) are present immediately under the mesothelial cell (open star), between collagen fibers (open circles), as well as in the submesothelial interstitial space, near the lymphatic lacuna (short straight arrows). The curved arrow points at a particle of the tracer included in an endothelial pinocytotic vesicle (I: lymphatic lacuna; c: interstitial space) (× 30,740).

Inset. Mouse diaphragmatic mesothelium taken 10 min after intraperitoneal injection of albumin–gold complexes. Arrow indicates an endosome containing particles of the tracer (S: peritoneal space; *: mesothelial cell cytoplasm; black star: plasmalemmal vesicles; open star: submesothelial basement membrane; I: interstitial space) (× 64,550).

Used with permission from [79]

pinching vesicles from the plasma membrane [93]. Recently published information suggests that dynamins mediate both clathrin-dependent endocytosis and the internalization of caveolae in microvascular endothelial cells [94, 95].

Some 70 years ago [96], it was suggested that junctions between capillary endothelial cells should be considered the main pathway for exchanges across the microvascular wall. This concept was later extended to the peritoneal blood microvessels and mesothelium, and extensively analyzed within the frame of the two [77, 78], and lately, the three [97] pore size model of capillary and/or peritoneal permeability. (Assumed pores size: large pore: > 150 Å; small pore: up to 40–45 Å; ultra-small pore: 2–5 Å.) To date, physiological studies and mathematical models have failed to convincingly identify the morphological equivalents of the hypothetical cylindrical water-filled pores [76]. On the other hand, however, this short review of the topic testifies that, at least for protein traffic, the vesicular carried hypothesis has been largely proven and accepted in the last few years [80]. Basically, that caveolae and transcellular channels function as a continuous operating conveyor belt, fusing with each other [49, 50, 98, 99], and moving through the cell [98, 99]. The source of energy fuelling vesicular movement remains one of the many questions still open [98–104].

Furthermore, the demonstrated presence of glucose transporters in mesothelial cells [105] furnish further support regarding the active role of the monolayer in solute's transport from and to the peritoneal cavity. Specialized transporter proteins, which are the products of two closely related genes, UT-A (Sic 14a2) and UT-B (Sic 14a1), modulate the movement of urea across cell membranes. Up to date, five UT-A isoforms have been identified in most tissues [106]. It may be speculated that UT-A transporters are also present in the mesothelium. This hypothesis deserves to be explored.

Additionally, recently published evidence demonstrated not only the presence of aquaporin channels in mesothelial cells, but also that their expression can be modulated by both osmotic and non-osmotic stimulation [107]. The relevance of these channels for peritoneal permeability will be analyzed in the section dealing with peritoneal microvasculature. Their presence in mesothelial cells is one more indication giving support to Henle's prediction that the essential anatomy and physiology of the peritoneum are located in its "endothelia" [108].

Simionescu et al. [109] showed the existence of differentiated microdomains on the luminal surface of capillary endothelium where they found a distinct and preferential distribution of electronegative fixed charges, also called anionic sites. Cationic tracers, which did not bind to caveolae or to transcellular channels, decorated the luminal glycocalyx, coated pits, and coated vesicles [98, 103, 109]. Recent studies applying cationic tracers such as ruthenium red and cationized ferritin in rat and mouse peritoneum also showed a preferential distribution of negative charges at the level of the mesothelial cells luminal surface [36, 37, 44] (Figs. 5.12 and 5.16). Density of these surface plasmalemmal charges is substantially reduced in cells undergoing apoptosis [41].

Mesothelial cell boundaries are tortuous, with adjacent cells often tending to overlap (Fig. 5.4, inset; Fig. 5.12). Tight junctions close the luminal side of the intercellular boundaries [14, 21, 32] (Figs. 5.4 and 5.12). When studied in the horizontal plane by using the freeze-fracture technique, these junctional contact areas were defined as cell extensions and finger-like processes, overlapping into the adjacent cell body. Cell processes were wedge-shaped and numerous, and the cell periphery appeared serrated [110]. Desmosomes have also been observed near the cellular

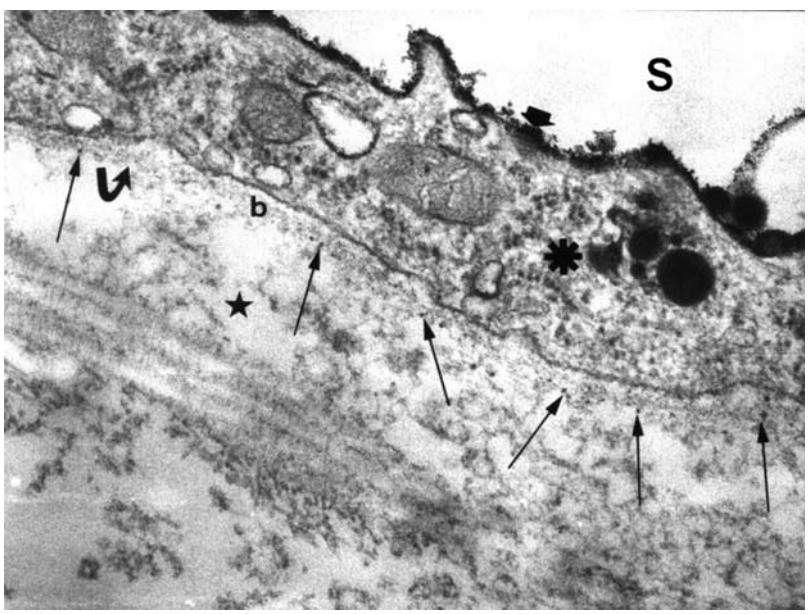

Fig. 5.16 Mesenteric mesothelial cell of a diabetic rat (*). The animal was perfused with ruthenium-red 6 months after induction of the disease, with streptozotocin (glucose blood levels were higher than 500 mg/dL; glycated hemoglobin: $16.38 \pm 0.57\%$). Glycocalyx covering the cavitary aspect of the mesothelial cell is heavily decorated by the cationic tracer (thick arrow). The submesothelial basement membrane (b) shows few dispersed anionic sites (long arrows), as well as areas where they are completely absent (curved arrow) (s: peritoneal cavity; black star: interstitial space) ($\times$ 41,500)

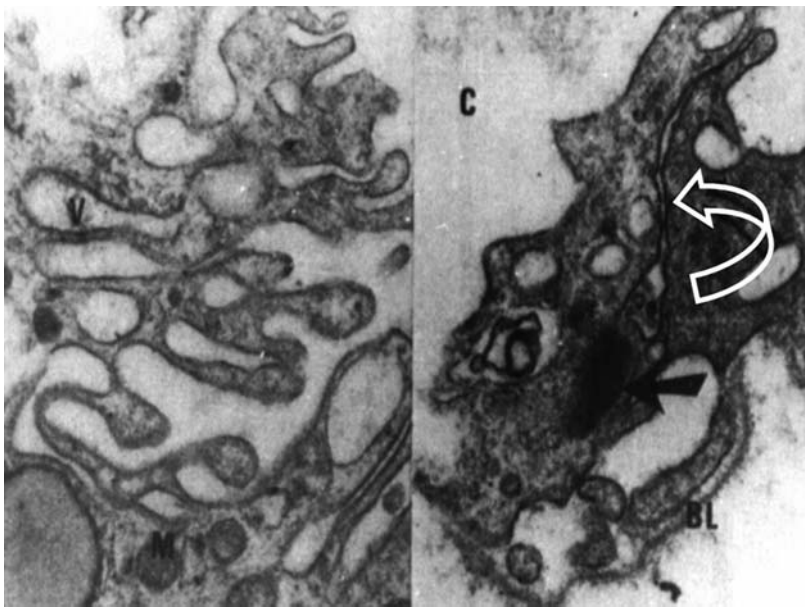

Fig. 5.17 Biopsy of parietal peritoneum taken from a 67-years-old chronic uremic patient, who was on IPD for a period of almost 2 years. A young mesothelial cell shows numerous vacuoles (V) giving a worm-like appearance, which is why this structure is called micropinocytosis vermiformis. The abluminal aspect of the mesothelial cell is lying on a hyaline basement membrane (open arrow) (C: abdominal cavity; M: mitochondrion) (× 26,000).

Right inset. Another area of the same biopsy. This electron micrograph shows the vacuolized cytoplasm of two adjacent mesothelial cells developing a new intercellular junction (open arrow). Note the presence of a typical desmosome (black arrow). The basement membrane (BL) is still discontinuous (original magnification × 30,740)

luminal front [14, 23, 25, 32] (Fig. 5.17) and so have gap junctions [25]. The abluminal portions of cell interfaces usually show an open intercellular infundibulum. Completely open intercellular interphases have not been observed in normal, resting mesothelium [14, 21, 32]. Even desquamated mesothelial cells showing severe degenerative changes can keep their junctional system almost intact (Fig. 5.18). These junctional morphological features are, however, different from those observed between mesothelial cells covering the diaphragmatic lymphatic lacunae, which are more cuboidal and prominent than mesothelial cells observed in other areas of the peritoneal surface.

The existence of stomata (open intermesothelial communications between the abdominal cavity and the submesothelial diaphragmatic lymphatics), predicted by William Hewson [1] 100 years before being discovered by Von Recklinghausen [111], have been the subject of a long and rich controversy along the years. Accepted by some [112–114] and denied by others [115–117], it was not until the advent of electron microscopy that their existence was demonstrated [44, 118, 119]. Scanning electron microscopy disclosed the patent intermesothelial junctions forming gaps whose average diameter ranged between 4 and 12 μm [118, 119] and circumscribed by cuboidal mesothelial cells. These gaps open into submesothelial lymphatics [44] and have not been observed in diaphragmatic mesothelium covering nonlacunar areas [119]. Additional studies have shown the passage of particles from the abdominal cavity into the submesothelial diaphragmatic lymphatics [114, 120]. These studies also confirm the results of experiments

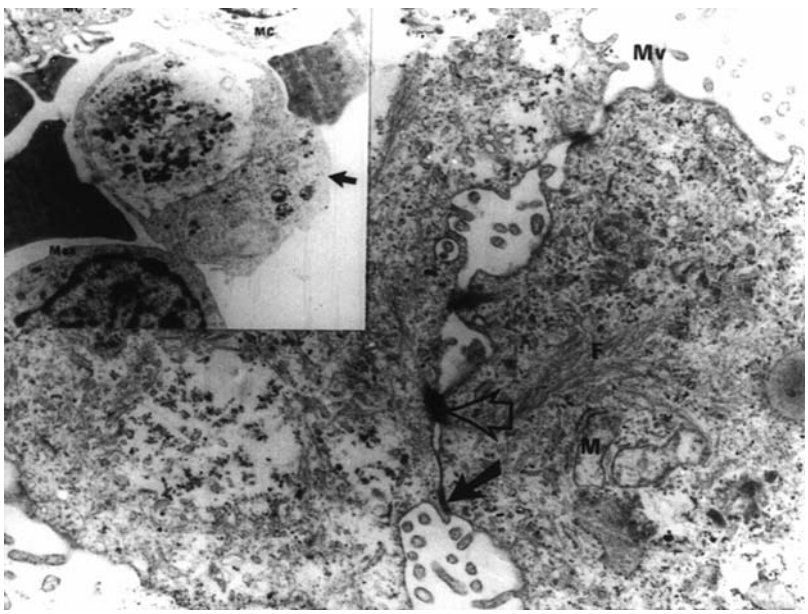

Fig. 5.18 Effluent dialysate obtained from a noninfected patient on peritoneal dialysis. Two desquamated mesothelial cells show severe degenerative changes: swollen mitochondria (M) with broken membranes, sheaves of filaments (F), and swollen cytoplasm. Part of the tight junction is still present (black arrow), as well as a desmosome (open arrow) (M: microvilli) (original magnification × 15,400).

Upper left inset. Effluent dialysate obtained from the same patient. Note the presence of a signet-ring macrophage (arrow), as well as part of two floating mesothelial cells (Mc) (mac: macrophage) (original magnification × 8,600)

performed by Allen [113], who demonstrated the passage of frog erythrocytes through stomata of the mouse diaphragmatic peritoneum, and their appearance within submesothelial lymphatics. This pathway paved the way for intraperitoneal blood transfusions that have been successfully performed in fetuses [121, 122], human adults [123], rats, mice, dogs, and lambs [124, 125]. On the other hand, intraperitoneal malignant cells [126] and bacteria [127] also leave the abdominal cavity on their way to the central venous circulation, through diaphragmatic stomata. The same pathway applies for absorption of albumin–gold complexes injected into the peritoneal cavity (Fig. 5.15) [79]. These structures can be found only between mesothelial cells overlying lacunae.

At the sites of stomata and their channels, mesothelial and lymphatic endothelial cells contain actin-like filaments [128] assumed to induce cell contraction, opening the stomatal pathway for the passage of macromolecules and cells. Cationized ferritin has been observed decorating the glycocalyx of mesothelial and lymphatic endothelial cells located along the stomata, as well as the coated pits and coated vesicles of both types of cells [44, 129]. It should be noted that the presence of stomata has been recently detected in mouse mesenteric mesothelium [130], in omental, ovaric, and pelvic peritoneum, as well as in that covering the anterior liver surface and the anterior abdominal wall [131, 132]. Therefore, it may be assumed that all these extradiaphragmatic openings contribute to the absorptive capacity of the entire peritoneal membrane. Albumin–gold complexes appear to be absorbed also from the peritoneal space through stomata [79] (Fig. 5.15), even though the capability of this pathway for the uptake of the probe did not seem to be much higher than that shown by nonstomatal mesothelial infundibular junctions that contained only 1% of the injected tracer.

Stomata have been ascribed the role of a preferential pathway for the output of fluids, cells, particles, and bacteria from the abdominal cavity [133]. However, the luminal surface of mesothelial cells (which limits the gaps), after staining with cationized ferritin, displayed dense labeling of their cytoplasmic plasmalemma as well as coated pits and coated vesicles. The same cationic tracer also decorated the lymphatic endothelial plasmalemma, which circumscribed the stomatal openings [44]. If this is so, the passage of solutes through stomata is most likely dependent not only on molecular weight, size, and shape, but also on electric charge [44].

Studies in rat and mouse perfused with ruthenium red revealed that intermesothelial cell junctions were, in general, stained just at the level of their infundibulum, even though the dye now and then decorated the junctional complex, staining approximately 50% of its length [37] (Fig. 5.12).

Nuclei are generally located in the central region of mesothelial cells, showing an elongated, oval, or reniform appearance with occasional irregularities in their outlines and sometimes protrusions and indentations (Fig. 5.11). The chromatin is fine, evenly distributed and forms a dense rim around the nuclear membrane (Fig. 5.11). In normal unexposed mesothelium, around 2% of cells are binucleated [31] (Fig. 5.8). Nucleoli have been reported both as present and absent [21, 32]. However, studies performed in imprints [31] showed that they are present and that their number ranges between 6 and 8 (Fig. 5.7). Rough endoplasmic reticulum and ribosomes are dispersed in the cytoplasm. Mitochondria and the Golgi complex are evident mainly in perinuclear areas (Fig. 5.6). Although seldom observed, isolated cilia may emerge from the luminal aspect of mesothelial cells, showing in their cytoplasmic part the axial microtubule as well as the attached basal body (Fig. 5.4). More frequently observed in splenic mesothelium [134], their functional significance is still unknown [135].

The submesothelial basement membrane, originally described by Todd and Bowman [136], and later reported as hyaline, homogeneous, one-layered, and continuous [112, 128], with an average thickness of approximately 40 nm for mouse and rabbit peritoneum [14, 22], normally appears lying under the mesothelial layer of visceral, parietal, and diaphragmatic peritoneum [137] (Figs. 5.11 and 5.17). As an exception, the functional significance of which is still unknown, the omental mesothelium of mice and humans lacks basement membrane [22, 138].

Submesothelial basement membrane of visceral, parietal, and diaphragmatic peritoneum of rat and mouse, perfused with the cationic tracer ruthenium red, consistently showed anionic charges periodically distributed along the lamina rara externa and interna, most of the time, forming double rows [36, 37] (Fig. 5.12).

The reported average diameter of ruthenium red–stained particles in the basement membrane was 2.7 nm, whereas the average distance measured between the one-row oriented basal lamina dye particles ranged between 65 and 90 nm, not far from the interval value of 60 nm observed using the same tracer in rats [139] and human kidney glomeruli [140].

The fact that these charges are, as stated above, distributed along both aspects of the basement membrane implies that the charge-free interval is actually smaller than the mean distance calculated for each membrane layer. The electric field of each particle of ruthenium is around 8–10 nm, and charge discrimination for negative tracers is effective for substances with a molecular radius around 1 nm, corresponding approximately to a globular molecule showing a molecular weight of 2 kDa [141]. In this sense it should be taken into account that the radius of macromolecular anionic albumin is 3.6 nm, whereas its molecular weight is 67 kDa.

It should be noted that the density distribution of these anionic fixed charges of the basement membrane almost disappears during the acute inflammatory reaction secondary to septic peritonitis [142] (Fig. 5.19), and is substantially reduced in rats, soon after 4 months of streptozotocin-induced, uncontrolled diabetes [143] (Fig. 5.16).

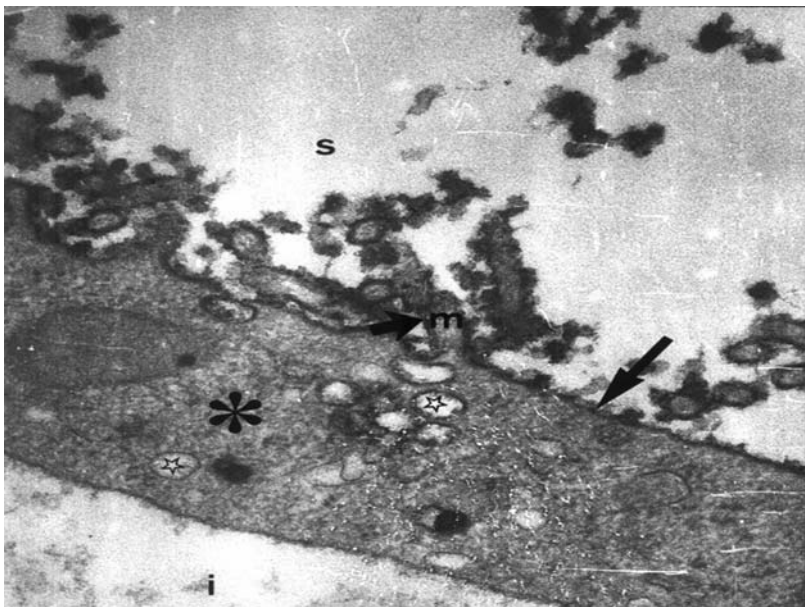

Fig. 5.19 Rat mesenteric mesothelium. The animal was perfused with ruthenium-red, 24 h after experimental induction of *E. coli* peritonitis. Plasmalemmal vesicles or caveolae (open stars) can be seen in the cytoplasm of the mesothelial cell (*). The submesothelial basement membrane is absent, as well as the normally present anionic sites. The luminal aspect of microvilli (m) and that of the cellular membrane are decorated by the cationic tracer (short and long arrows, respectively) (S: peritoneal space; I: edematous interstitial space) (× 41,500)

The relevance of the electronegative charge of the mesothelial monolayer upon the peritoneal permeability to anionic plasma proteins will be discussed in the section dealing with microvascular permeability.

Reduplicated submesothelial basement membrane has been observed in diabetic and nondiabetic chronic uremic patients treated by maintenance peritoneal dialysis [144, 145] (Fig. 5.20). It has been shown that perivascular basement membrane thickness increases with age [146, 147] as well as in the direction of head to foot [147, 148]. This same ultrastructural alteration has been observed in diabetics [147, 149]. It has been suggested that diabetes alone is not responsible for excessive accumulation of basement membrane associated with aging [150]. Therefore, it could be claimed that the reduplication of basement membrane observed in human mesothelium is a by-product of cell renewal regardless of the cause of cell death that triggers the process of repopulation [144, 151]. However, the fact that this phenomenon was also detected in the submesothelial basement membrane of diabetic rats suggests that a high glucose content in the extracellular fluid appears to be related to the mechanism(s) leading to these changes [143].

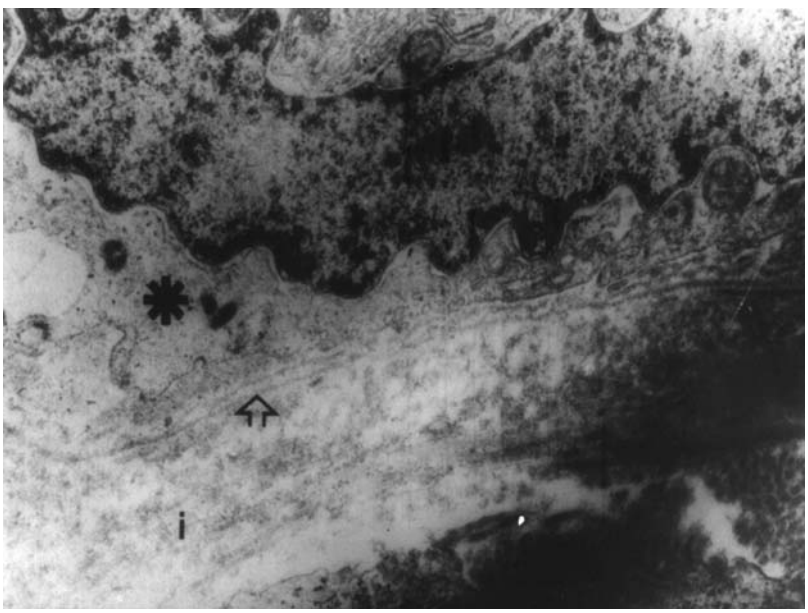

Fig. 5.20 Parietal peritoneum taken from a 67-year-old patient on IPD. The open arrow shows the reduplicated submesothelial basement membrane (*: mesothelial cell; i: submesothelial interstitium) (original magnification × 24,600)

Interstitium

Connective tissue, which originates from mesenchyma, is composed of cells and fibers embedded in an amorphous substance. The main connective tissue cell is the fibroblast and the main fiber is collagen [152].

The submesothelial connective tissue normally has a low cell population surrounded by high-molecular-weight intercellular material. Fibroblasts, mast cells in the proximity of blood microvessels (Fig. 5.21), occasional monocytes and macrophages (Fig. 5.2) are frequently observed.

Substantial amounts of quite compact bundles of collagen are usually interposed between the blood microvessels and the mesothelial layer (Figs. 5.1, 5.2, and 5.3). The collagen density distribution in the different regions of visceral peritoneum is quite variable [146].

The macromolecular common denomination of connective tissues is a broad molecular class of polyanions: the tissue polysaccharides. They form a gel-like structure with the collagen fibers [153], which, when stained with ruthenium red, shows the presence of anionic fixed charges [37].

Thickness of the interstitial layer is extremely variable in the different portions of the peritoneum. This heterogeneity can also be applied to the distances separating the submesothelial blood vessels from the peritoneal cavity, ranging between 1–2 μm to $\geq$ 30 μm (Fig. 5.1). It should be noted that restriction of molecular movement through the interstitial tissue and its progression from or to the microvasculature is affected not only by their molecular weight, shape, and electric charge, but also by the length of the pathway. According to Fick's law of diffusion, it is the difference in concentration per unit of distance (the concentration gradient) that determines the rate of movement of the solute. If we double the distance over which the same concentration difference occurred, the gradient and, therefore, the rate of transfer, would be cut in half. Therefore, the relevance of the interstitial compartment thickness in the transperitoneal transfer of solutes may well be critical [78, 154], and diffusion of solutes coming out from capillaries far from the abdominal cavity could be rendered useful only in long-dwell exchanges, like those performed in CAPD.

The question of the interstitium in terms of plasma to lymph traffic of macromolecules has been basically investigated in lung interstitial tissue [155], which, at physiological pH, has the properties of a negatively charged membrane [156]. Therefore, the polyanionic glycosaminoglycans (mainly hyaluronan) and glycoproteins located in the interstitial ground substance have the capability of influencing the interstitial distribution of volumes of plasma proteins coming out from the intravascular compartment, according to their molecular charge [157]. It has been suggested that these glycosaminoglycans restrict free diffusion through the interstitium [158] and can both reduce the interstitial distribution volume of anionic plasma proteins, and retard the plasma-lymph traffic of cationic macromolecules [155]. Anyway, the effect of protein charge on the interstitial hydraulic conductivity has been only partly clarified.

Fig. 5.21 Interstitial tissue of human parietal peritoneum. Bundles of collagen (c) and fibroblasts (f) are interposed between the blood microvessels (open stars) and the mesothelial cells (not included in the electron micrograph). Mast cells (*) are frequently observed near blood microvessels (original magnification × 42,900)

The extremely low and, at times, negative interstitial pressure (0 to –4 mm Hg) [159–161] represents, together with the capillary permselectivity and the lymphatic drainage, one of the three key factors modulating the plasma-to-lymph fluid traffic, therefore, preventing the formation of interstitial edema [162, 163]. Specifically, during peritoneal dialysis, studies by Flessner [164] have shown that transfer of small solutes through the tortuous interstitial pathways is primarily by diffusion, and that convection may contribute to overall transport in parietal tissue. As stated above, in normal conditions the interstitium has a hydrostatic pressure near 0 [159, 164]. During clinical peritoneal dialysis the intra-abdominal pressure ranges between 4 and 10 cm H_2O [165, 166], thus creating a pressure gradient that drives fluid as well as solutes out of the peritoneal cavity to the interstitium. Thus, fluid loss from the abdominal cavity to the periperitoneal interstitial space is directly proportional to intra-abdominal pressures higher than 2 cm H_2O [166].

Blood Microvessels

Capillaries of human and rodent parietal [167] and visceral peritoneum [43, 168] have been reported to be of the continuous type (Figs. 5.1, 5.3, 5.22–5.24), according to the classification of Majno [169]. However, the existence of fenestrated capillaries in human parietal and rabbit diaphragmatic peritoneum (Figs. 5.1 and 5.25), as well as in mouse mesentery [170–172] has been reported. The incidence of fenestrated capillaries in human parietal peritoneum (Fig. 5.22, inset) appears to be low (1.7% of the total number of capillaries) [172]. The reported density of fenestrated microvessels in mouse mesentery and rabbit diaphragmatic peritoneum ranged between 26 and 29% of the observed capillaries, whereas their presence in parietal peritoneum of nondialyzed uremic patients was only 1.7%. It should be noted, however, that the anterior abdominal wall of humans comprises less than 4% of the peritoneal surface area [10]. Diameter of fenestrae, which ranged between 60 and 90 nm, is well within the range of fenestrae observed in other capillary beds: 40–70 nm in renal peritubular capillaries [173], glomerular capillaries [169], and rabbit submandibular gland [174]. The reported density of fenestrae counted along the capillary circumference of mice mesenteric microvessels is 3.4 fenestrae/micron [175]. This value is quite close to that of 3 fenestrae/micron of capillary circumference observed in renal glomerular capillaries [169]. Density of fenestrae per square micron of endothelial surface is 45–60/μm^2 in renal peritubular capillaries [176] and 20/μm^2 in renal glomerular capillaries [169], whereas their frequency in mouse mesenteric capillaries is approximately 12/μm^2 [171].

The density distribution of submesothelial microvessels along the different portions of the peritoneum is variable. In the rabbit the mesentery appears to be the most vascularized peritoneal segment (contributing 71.1% of the total number of observed capillaries). The reported diaphragmatic and parietal contributions to the total microvascular bed examined were 17.9 and 10.9%, respectively [177].

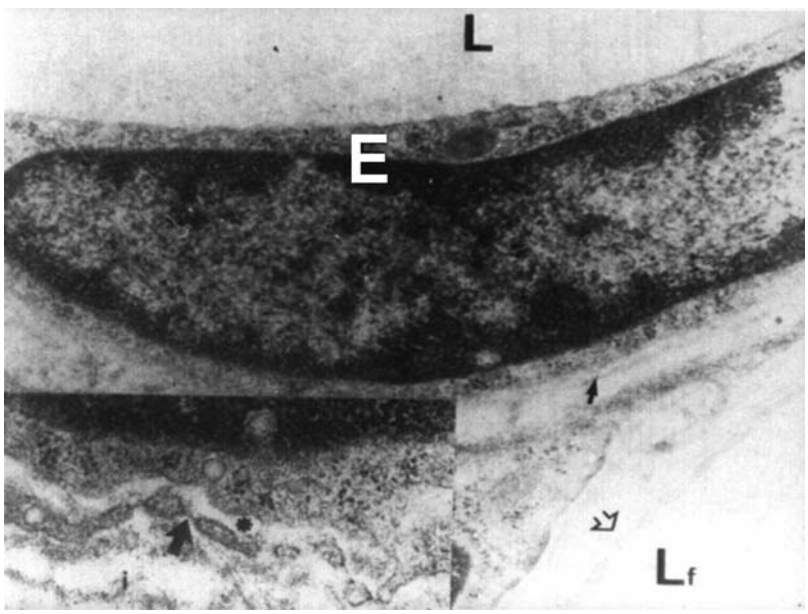

Fig. 5.22 Continuous capillary of a blood mesenteric rabbit capillary whose endothelial layer (E) is lying on the basement membrane (black arrow). (open arrow) (L: lumen of continuous capillary. (Original magnification × 47,400).

Lower left inset. Fenestrated capillary of human parietal peritoneum. The arrow points to a fenestral diaphragm (i: interstitium; *: lumen of fenestrated capillary) (original magnification × 42,900).

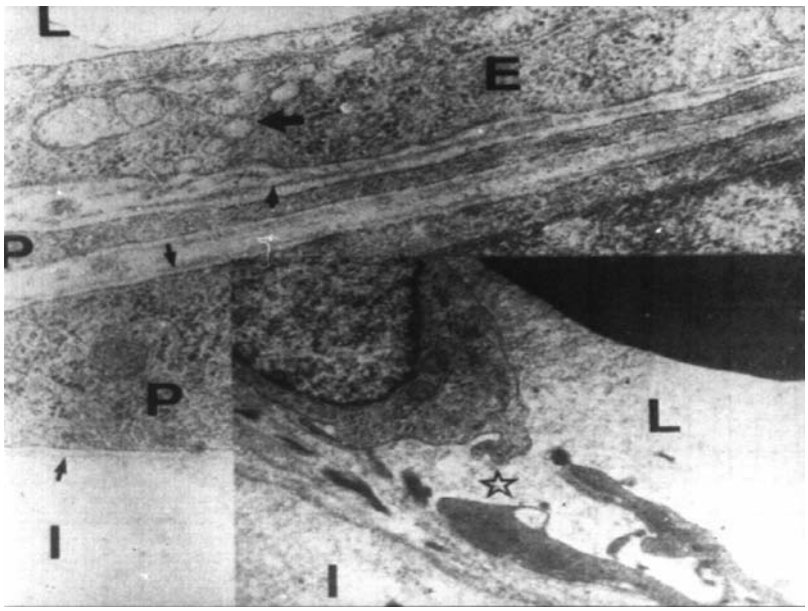

Fig. 5.23 Postcapillary venule of rabbit mesentery. The large arrow shows a transcellular channel (L: microvascular lumen; E: endothelial cell; short arrow: subendothelial basement membrane; P: pericyte; small arrows: subperithelial basement membrane; I: interstitium) (× 62,500).

Lower right inset. Human parietal peritoneum taken from a 21-year-old patient with *E. coli* peritonitis. The star shows an open interendothelial junction of a blood capillary. Note part of an erythrocyte in the upper right quadrant (L: capillary lumen; I: interstitium) (original magnification ×41,500)

In rabbit mesentery the main population of continuous blood microvessels is represented by:

1. True capillaries (without perithelial cells), the mean luminal diameter of which is 7.2 μm and whose mean wall thickness is 0.4 μm (Figs. 5.11, 5.22, 5.23, and 5.24).
2. Venous capillaries usually formed by the confluence of two or three capillaries. These show a thin endothelial layer, occasional peripheral perithelial cells, and have a mean luminal diameter of 9.2 μm.
3. Postcapillary venules whose luminal diameter ranges between 9.4 and 20.6 μm [43].

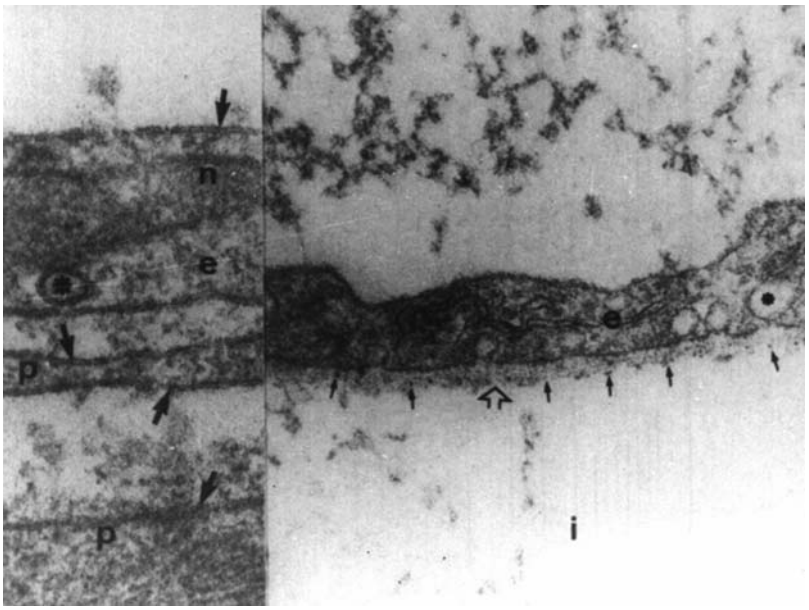

Fig. 5.24 The right part of the figure shows part of a blood capillary wall observed in a sample of diaphragmatic peritoneum obtained from a normal rat. The luminal aspect (upper cell border) of the endothelial cell (e) shows a fine reticular glycocalyx stained by ruthenium red which, on the other hand, does not decorate pynocytotic vesicles (*). The subendothelial basement membrane (open arrow) is continuous and shows quite regularly distributed ruthenium-red stained anionic sites (small arrows) along both the lamina rara externa and the lamina rara interna (original magnification × 50,720).

Inset. Left part of the figure. Part of a postcapillary venule observed in mesentery of rat, 5 days after induction of peritonitis. The trilaminar structure of the endothelial (e) and perithelial cell plasmalemma is clearly observed (arrows), as well as that of the limiting membrane of the pinocytotic vesicle (*). Glycocalyx, basement membrane and anionic sites are absent (n: nucleus of endothelial cell) (original magnification × 84,530)

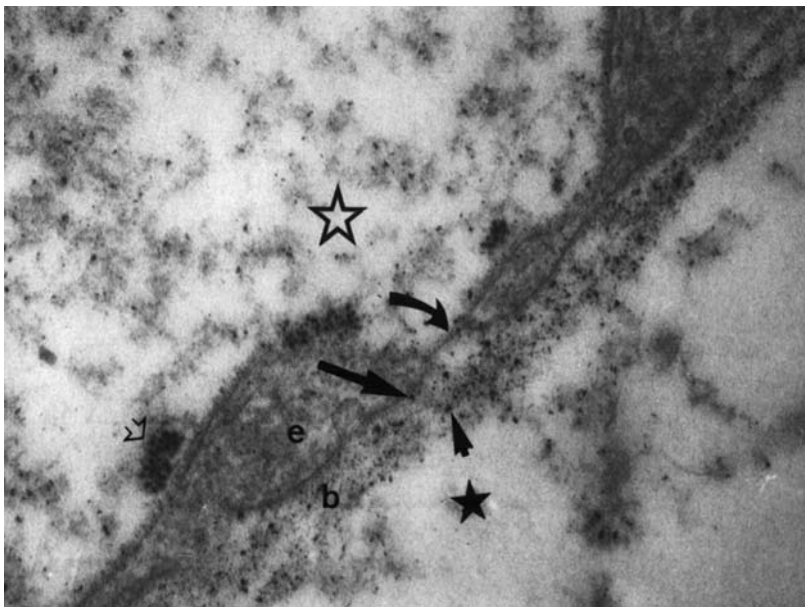

Fig. 5.25 Fenestrated capillary of mouse mesenteric peritoneum. The animal was perfused with cationized ferritin. Particles of the tracer decorate the luminal (long straight arrow) and the abluminal (short black arrow) aspects of the basement membrane (b) laying under the endothelial cells (e). A fenestral diaphragm is also decorated on its luminal aspect by particles of cationized ferritin (curved arrow). Clumps of the tracer appear located on the luminal endothelial cell plasmalemma (open arrow) (open star: microvascular lumen; black star: subendothelial interstitial space) (× 41,500)

With increasing luminal diameter there is a proportional increase in wall thickness due to the presence of more perithelial cells encircling the endothelial layer [178] (Fig. 5.23). The average ratio of luminal diameter to wall thickness is approximately 10/1 [178]. All aforementioned exchange vessels present at their luminal aspect a limiting area that separates the endothelial cell from the circulating blood and is formed by the plasmalemma with its trilaminar structure [19] (Fig. 5.24) and the glycocalyx (Fig. 5.24). The latter, originally described by Luft [38] in other vascular beds, has also been observed at the luminal aspect of peritoneal microvessels [39, 179] The presence of sialoconjugates, proteoglycans, and acidic glycoproteins organized as a fibrous network provides the plasmalemmal glycocalyx with electronegative charge [180] (Fig. 5.26).

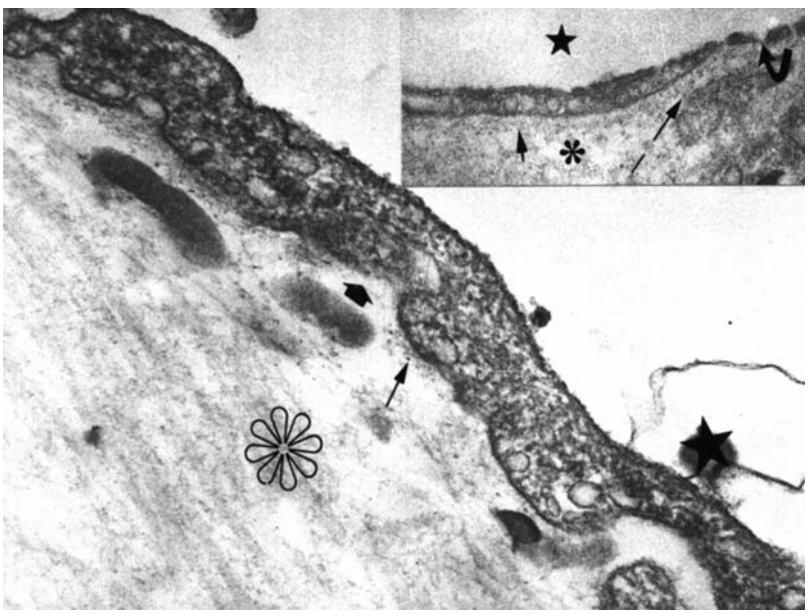

Fig. 5.26 Continuous capillary of rat mesentery. The sample of tissue was recovered 24 h after induction of abdominal sepsis. Distribution of subendothelial anionic sites is irregular; at times they are totally absent (thick arrow), whereas in other portions of the basement membrane they can be seen, but showing an extremely low density (small thin arrow). The luminal aspect of the endothelial cell shows a black rim decorated by ruthenium red, indicating the still-present negative charges of the endothelial glycocalyx (star: microvascular lumen; *: edematous interstitial tissue) (ruthenium red; × 41,500).

Inset. Mesenteric fenestrated capillary taken from the same animal. Occasional anionic sites (long arrow) can be seen along the basement membrane. Most of its length is free from ruthenium-red decorated negative charges (short arrow) (*: structureless interstitial space; star: capillary lumen; curved arrow: fenestra) (ruthenium-red; × 30,740)

There is evidence that anionic plasma proteins (albumin and IgG) are adsorbed to the glycocalyx of microvascular endothelial cells [181]. The fiber-matrix model of capillary permeability envisages the glycocalyx as a meshwork of glycoprotein fibers that, after adsorbing circulating proteins, would tighten its mesh, thereby rendering the underlying endothelium less accessible to water and other water-soluble molecules [40]. Furthermore, it has been shown that the adsorption of circulating anionic plasma proteins to the glycocalyx renders the underlying endothelium relatively impermeable to large, electron-dense, anionic tracers such as native ferritin (MW $\sim$ 450 kDa) [181].

The mean endothelial cell width of rabbit mesenteric capillaries is 0.4 μm, unless the cytoplasm bulges up to more than 1 μm at the site of the nucleus (compare Figs. 5.3 and 5.22 with Fig. 5.24). The cytoplasm includes the usual cell organelles: mitochondria, rough endoplasmic reticulum and free ribosomes [14, 169].

The mitochondrial content of vascular endothelial cells in frog mesentery decreases gradually from arterioles towards venous capillaries and subsequently increases toward venules [182].

The Golgi complex displays variable degrees of development in biopsies taken from different patients. This same variability was observed when comparing different peritoneal microvascular endothelial cells present in a single sample.

The cytoplasmic matrix of endothelial cells shows long filaments, parallel to the longitudinal cellular axis. Their diameter ranges between 20 and 100 Å [169], and at times they appear in bundles. These intermediate-size filaments seem to be a common component of the cytoplasmic matrix of vascular endothelial cells showing, however, a lower density distribution than that observed in other cell types [135].

Nuclei are generally oval, elongated (Fig. 5.22), or occasionally kidney-shaped with focal surface irregularities (Fig. 5.11). Their mean short-axis width in rabbit mesentery is 0.957 ± 0.417 μm [14].

Plasmalemmal vesicles, which can be found in most cell types, are particularly common in capillary endothelia [183], where they occupy approximately 7% of the cell volume [101] (Fig. 5.23). Their outer diameter is approximately 700 Å (it ranges between 500 and 900 Å) [14, 36, 50] and they have a round or oval shape surrounded by a three-layered membrane of 80 Å thickness (Fig. 5.24, inset).

According to their location in the cytoplasmic matrix, vesicles can be classified into three groups: a) vesicles attached to the plasmalemma limiting the blood front of the endothelial cell; b) free vesicles within the cytoplasmic matrix; and c) attached vesicles, but this time to the tissue front of the endothelial cell plasmalemma [50] (Fig. 5.23). The density population of plasmalemmal vesicles varies considerably from one vascular segment to another, even within the same microvascular territory [49, 50]. In the mouse diaphragm, arterioles show 200 vesicles/μm^2, true capillaries 900 μm^2, venular segments of capillaries 1,200 μm^2, and postcapillary venules 600 μm^2 [49].

Most vesicles that open to the extracellular medium have necks whose diameter can be as small as 100 Å [50]. Transendothelial channels formed by a chain of vesicles opening simultaneously on both fronts of the endothelium have been described in capillaries of mouse diaphragmatic muscle [49] as well as in postcapillary venules of rabbit and rat mesentery (Figs. 5.23 and 5.27) [14]. The relative frequency of transendothelial channels has been found to be higher in true capillaries than in arterioles and venules, with the highest density in the venular segment of capillaries [103]. Microvessels of frog mesentery showed a density distribution of three transendothelial channels for every

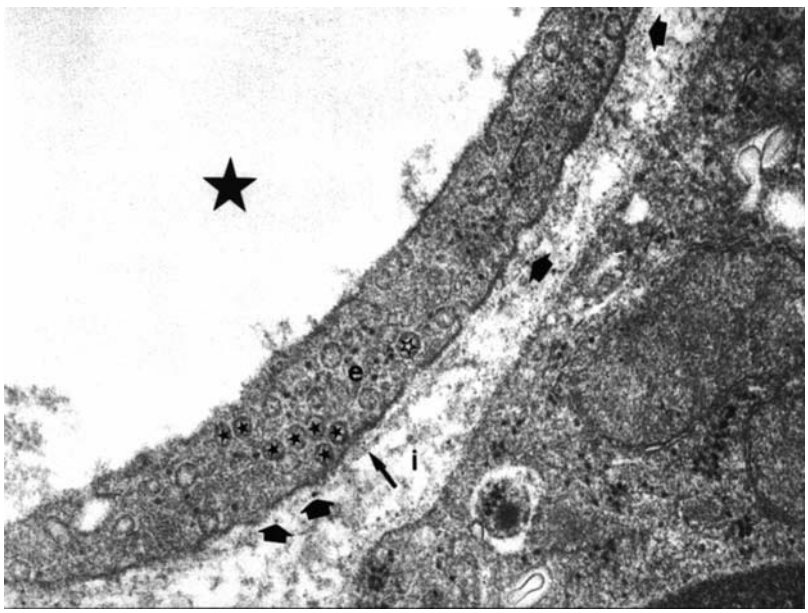

Fig. 5.27 Mesenteric capillary of a rat 6 months after induction of diabetes with streptozotocin (glucose blood levels were higher than 500 mg/dL; glycated hemoglobin $16.38 \pm 0.57\%$). The animal was perfused with ruthenium red. The basement membrane (long arrow), lying under the endothelial cell (e), shows few and occasional anionic sites (thick arrows) (large black star: capillary lumen; open star: pinocytotic vesicle; small black stars: transendothelial channel; i: interstitial space) ($\times$ 41,500)

400 vascular profiles examined [182]. Just as in observations made on mesothelial cells, plasmalemmal vesicles and transendothelial channels do not bind cationic electron-dense tracers that, on the other hand, decorate the luminal aspect of coated pits and coated vesicles [98, 109] in the peritoneal microvasculature [37].

The functional significance of plasmalemmal vesicles or caveolae, vesicles, transendothelial channels, coated pits, and coated vesicles has been discussed in the section on normal mesothelium.

As stated above, in fenestrated capillaries, endothelial cells are pierced by fenestrae closed by a diaphram [184] (Fig. 5.22, inset; Figs. 5.25 and 5.28). Fenestrae are not static structures. It has been shown that their prevalence can be increased under the effect of vitamin A metabolites [185], the influence of sexual hormones [168], thrombocytopenia [186], and by the acute inflammatory reaction [169]. In this sense a microvascular bed (capillaries and postcapillary venules), supplied with a continuous endothelium, can rapidly develop endothelial fenestrations under the influence of vascular endothelial growth factor (VEGF), a 34–42 kDa cytokine, released by different cell types (eosinophils, neutrophils, and others) during the acute inflammatory reaction [187–190]. This effect has been demonstrated in vivo [191, 192], after acute and chronic exposure of different microvascular beds.

High concentrations of negative fixed charges (heparin and heparan sulfate) have been found on the blood front of fenestral diaphragms in several microvascular beds [98, 109, 184, 193–196]. They are expected to discriminate against anionic macromolecules, essentially anionic plasma protein. Similarly, mesenteric fenestrated capillaries of mice perfused with the cationic tracer ferritin showed densely packed anionic fixed charges on the endothelial cell glycocalyx, on the luminal aspect of fenestral diaphragms, as well as along both sides of the subendothelial basement membrane [175] (Fig. 5.25).

What is the role of fenestrae and intercellular junctions in the still ill-defined mechanisms related to capillary permeability? For more than 25 years the fenestral pathway was ascribed a major role in the permeability capabilities of fenestrated capillaries [197]. Some investigators suggested that, while open fenestrae could represent the ultrastructural equivalent of the large pore [77], fenestrae, closed by diaphragms (Fig. 5.25), could also provide a diffusive pathway for water- and lipid-soluble substances [198]. However, fenestral openings of 60–90 nm diameter are too large to be considered the structural equivalent of the hypothetical large pores, the radii of which range between 11 and 35 nm [77, 199]. Furthermore, the density of these pores, estimated at one every 20 μm^2 [50], is substantially lower than the density of fenestrae per square micron observed in microvascular beds.

At least from a theoretical point of view, the presence of anionic fixed charges at the level of fenestral diaphragms, as well as in the subendothelial basement membrane (Fig. 5.25), is a strong argument against the transfenestral passage of macromolecular anionic proteins [139, 200]. Indeed, previously reported physiological studies have demonstrated the selectivity and restriction of the fenestrated microvascular wall to the passage of electronegatively charged

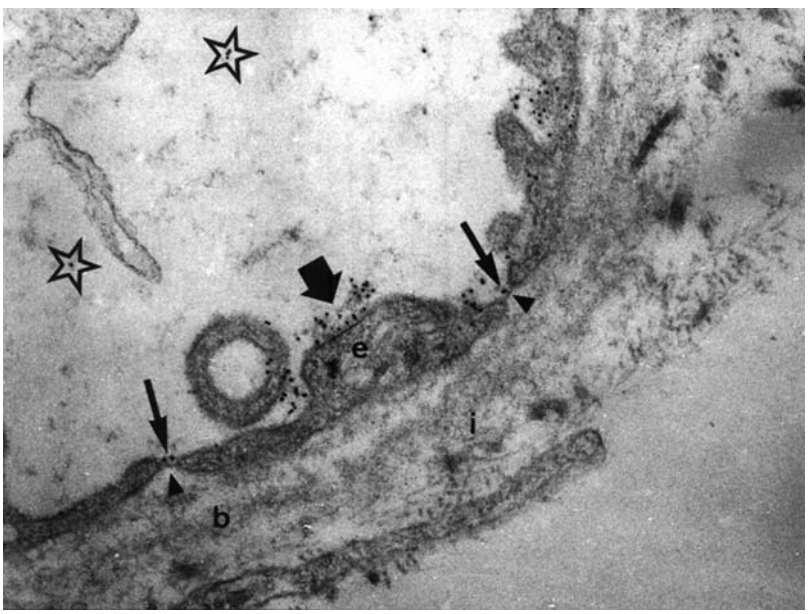

Fig. 5.28 Fenestrated capillary of mouse mesentery taken 30 min after intra-arterial perfusion of the tissue with albumin–gold complexes. Particles of the tracer can be seen in the microvascular lumen (open stars), on the glycocalyx of the endothelial plasmalemma (short thick arrow), as well as on the luminal aspect (long arrows) of fenestral diaphragms (arrowheads). The tracer did not reach the subendothelial interstitial space (i) (b: subendothelial basement membrane) (× 50,720)

macromolecules [201–203]. Moreover, the permeability of fenestrated capillaries to anionic macromolecules is not higher than that of capillaries of the continuous type [204]. In this context Fig. 5.28 offers a descriptive account of the problem, observed in our laboratory (Gotloib L, unpublished observations). Rat mesentery was perfused (in vivo) through the arterial tree with negatively charged albumin–gold complexes for a period of 30 min. As can be seen, substantial amounts of albumin–gold particles appear contacting the luminal aspect of the endothelial cell plasmalemma, as well as free into the capillary lumen. Particles of the tracer can be observed in close apposition to the luminal front of fenestral diaphragms. However, albumin–gold particles were not seen in the subendothelial space, even 30 min after perfusion. These observations support the hypothesis that fenestrae are not permeable to anionic plasma proteins. Consequently, it appears that fenestral openings are unrelated to the theoretically predicted large pore system [197, 200, 204, 205]. On the other hand, fenestrated endothelia have higher hydraulic conductivity, and are more permeable to small ions and molecules than continuous endothelia [206].

Capillary endothelial cells are linked to each other by tight junctions (zonula occludens), originally described by Farquhar and Palade [207–209] (Fig. 5.29). Communicating or gap junctions have been observed in arteriolar endothelium [208]. Postcapillary venules have loosely organized junctions with discontinuous ridges and grooves of which 25–30% appear to be open with a gap of 20–60 Å [50]. The presence of gap junctions has also been documented [14].

Cytoplasmic plasmalemma bordering both sides of junctions also shows anionic fixed charges [37]. Their functional significance in relation to the passage of charged molecules will be discussed later.

Research performed during the past 10–15 years revealed that interendothelial tight junctions appear as a set of long, parallel, linear fibrils that circumscribe the cell, with short fibrillar fragments interconnecting the main parallel array. The number of fibers correlates with junctional permeability: the more densely packed the fibrillar mesh, the lower the junctional permeability [210]. Therefore, the tight junction is not a simple fusion between the outer plasmalemmal leaflets of neighboring cells [211]; rather, it consists of protein molecules such as occludins and cadherins in tight junctions, desmoleins and desmocolins in desmosomes, and connexins in gap juctions [212, 213].

Occludin is an integral membrane protein, exclusively localized at tight junctions in both epithelial and endothelial cells [212], and is directly involved in sealing the cleft, creating the primary barrier to the diffusion of solutes through the paracellular pathway as well as regulating, according to the modulation of occludin expression, the permeability properties of different microvascular beds [214]. Occludin is bound on the endothelial cytoplasmic surface to ZO-1, a 220 kDa membrane-associated protein likely to have both structural and signaling roles [215, 216].

Vascular endothelial cadherin, in turn, is an endothelial-specific cadherin that regulates cell to cell junction organization in this cell type, and provides strength and cohesion to the junction [217]. Cadherins are also implicated

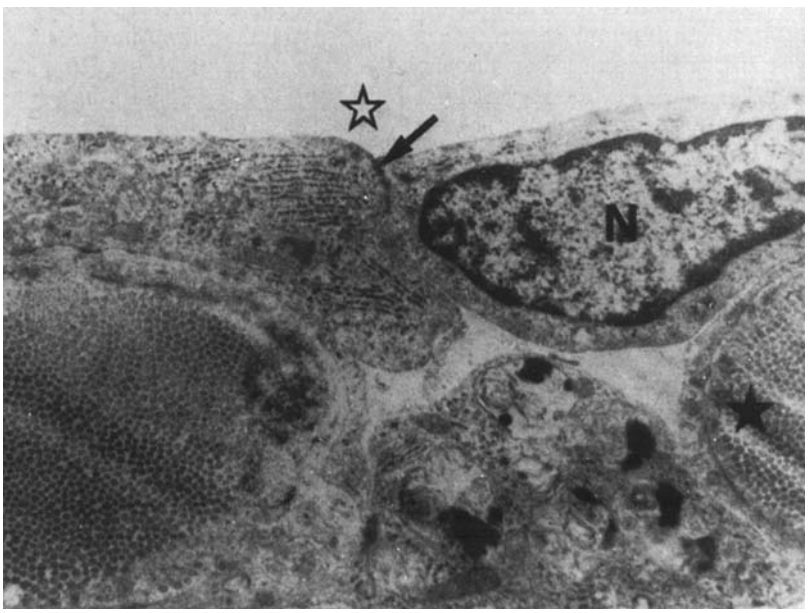

Fig. 5.29 Blood capillary of rabbit mesentery. The black arrow points at a tight junction formed by two adjoining endothelial cells. A macrophage can be observed lying under the endothelial cells interposed between two bundles of collagen (black stars) (open star: capillary lumen; N: nucleus of endothelial cell) (original magnification × 85,000)

in junctional permeability, basically under the effect of inflammatory mediators such as tumor necrosis factor and histamine, which have been shown to induce a redistribution of these adhesion molecules to nonjunctional regions and junctional disassembly [218, 219].

The role of tight junctions in the permeability capabilities of the microvasculature, during the situation of normal physiology, has been a topic for intensive research and controversy through the years. Whereas some groups considered the intercellular cleft as the main pathway for water, as well as for small and large solutes and electrolytes [220, 221], other groups developed the concept that tight junctions create a regulated paracellular barrier to the movement of water, solutes, and immune cells between the microvascular compartment and the interstitial space, enabling the endothelial monolayer to create compositionally different fluid compartments [210, 222–224]. Recently published information indicates that the presence of tight junctions does not imply a foolproof seal of the intercellular cleft. Instead, this structure contains discrete ion-selective pathways through the extracellular portion of the junction, regulated, at least in part, by the activity of the cytoskeleton [210, 225]. As stated above, the transmembrane protein occludin is an excellent candidate for the sealing protein. Understanding the mechanisms involved in junction permeability will require both a more detailed molecular characterization of tight junction proteins and the regulation by the endothelial cells of their attachment to the perijunctional cytoskeleton [222]. As stated by Renkin [204] in 1977, identification of the tight junction with the diffusional pathway for macromolecular plasma proteins, in a situation of normal physiology, still remains questionable. Their role in capillary permeability is still debated.

As for blood cells, recent investigations showed that neutrophils preferentially migrate by crossing at tricellular corners, rather than passing through tight junctions that lie between two adjacent endothelial cells [226].

The basement membrane of true capillaries is normally a thin sheet at the interface between the abluminal aspect of the endothelial cell and the connective tissue (Figs. 5.13 and 5.22). In postcapillary venules it is interposed between the endothelial and the periendothelial cell (Fig. 5.23). Generally uniform for a given structure, its thickness varies among the different parts of the body. True capillaries of normal rabbit mesentery have a mean basal membrane thickness of 0.234 ± 0.095 μm [14]. As described for the submesothelial basement membrane, that of human capillaries also exhibits a significantly increasing thickness in the direction of head to foot [147]. It has been suggested that these regional variations are secondary to differences in venous hydrostatic pressure effective on the capillary bed [147]. Diabetic and nondiabetic patients on long-term peritoneal dialysis, showing reduplicated submesothelial basement membrane, had similar alterations on the capillary basement membrane of parietal peritoneum [144]. These changes were also observed in postcapillary venules and small arterioles of parietal peritoneum taken from diabetic uremics on CAPD (Figs. 5.30 and 5.31), as well as in skin capillaries (Fig. 5.32). Additionally, reduplication of mesenteric subendothelial capillary basement membrane has been recently reported in streptozotocin-induced diabetic rats, as early as after 4 months of uncontrolled hyperglycemia [144], whereas thickening was seen in the same animals 6 months after induction of the disease. These structural alterations of diabetic basement membranes seem to be derived from a substantial increased presence of collagen IV [149, 227–231] which, according to in vitro studies, appears to derive from extended exposure of cells to high concentrations of glucose [232, 233].

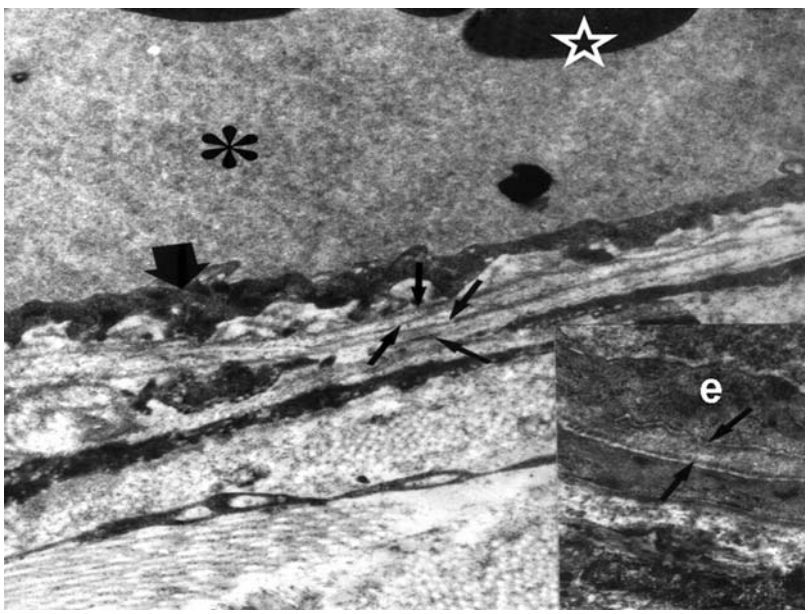

Fig. 5.30 Subendothelial reduplicated basement membrane (small arrows) observed in a small venule of parietal peritoneum taken from a diabetic patient on CAPD (open star: red blood cells; *: vascular lumen; thick arrow: endothelial cell) (× 15,400).

Inset. One arteriole from the same biopsy shows splitting of the subendothelial basement membrane (arrows) (e: endothelial cell) (× 12,600)

Fig. 5.31 Blood capillary of parietal peritoneum taken from a 69-year-old uraemic patient on IPD for almost 3 years. The endothelial cell (e) is lying on a reduplicated basement membrane (arrow) (i: interstitium) (× 24,600)

In rats, both thickening and layering of microvascular basement membrane can also develop as a consequence of aging [151, 234], but not before completing the first year of life [234].

So far, it may be speculated that reduplication or layering of submesothelial and peritoneal microvascular basement membranes in nondiabetics on CAPD could result from their continuous and long exposure to high glucose concentrations.

Subendothelial basement membranes of both continuous and fenestrated capillaries (Figs. 5.24 and 5.25), have regularly distributed anionic fixed charges along both aspects of the membrane [39, 175]. Their density distribution in continuous capillaries ranges between 31 and 34 μm of basement membrane [39, 143]. These values, shown in the section devoted to the mesothelial basement membrane, are not far from those detected in other microvascular basement membranes.

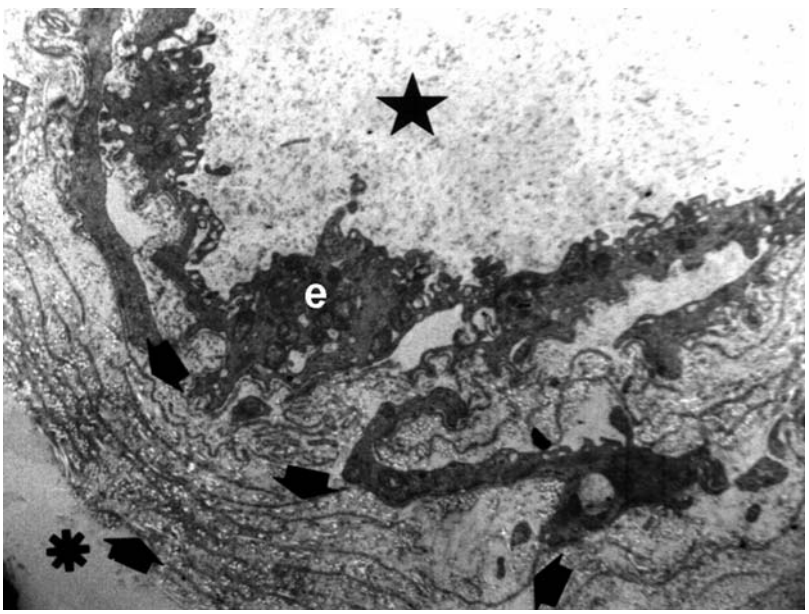

Fig. 5.32 Blood capillary observed in a skin biopsy taken from the same diabetic chronic uraemic patient, whose parietal peritoneum was shown in Fig. 5.31. Arrows point at the multiple layers of basement membrane (star: microvascular lumen; e: endothelial cell; *: interstitial space) (× 5,850)

The chemical composition of the fixed electronegative charges linked to the subendothelial basement membrane has been explored in several microvascular beds. Studies have shown that their main structural components are glycosaminoglycans such as heparan sulfate and chondroitin sulfate [109, 235–237]. This is at variance with the biochemical and histochemical observations made on the glycocalyx cell surface charges, the main component of which is sialic acid and sialo conjugate. This pattern has been detected in microvascular endothelium [238–242], pleural, pericardial, and peritoneal mesothelial cells [243], as well as in macrophages [244], erythrocytes [245], and platelets [246].

What is the functional significance of these electronegative charges? A strong body of literature supports the concept that the permselectivity of capillary walls to anionic macromolecules is basically dependent on molecular charge, besides size and shape [139, 141, 167, 205, 236, 247–253]. Investigations performed in in vivo, whole organ studies [155], in isolated perfused frog capillaries [254], and in isolated rat hindquarters [248] have demonstrated their presence evaluating permeability of different endogenous proteins in a variety of microvascular beds. Indeed, similar results were observed in patients on CAPD comparing dialysate to plasma concentrations of amino acids, having almost the same molecular weight but quite different charge [255], as well as in rat peritoneum, using charged dextrans [256]. The fact that endogenous proteins of graded size are heterogeneous with respect to their molecular charge [257] lead to some conflicting results [258]. The key to this problem was found investigating clinical and experimental situations, where the permselectivity was substantially reduced or neutralized, enabling the observer to evaluate changes in permeability, derived from the absence of the normally present fixed electronegative charges. In the clinical set-up, type I diabetes [259], congenital [260, 261], and acquired nephrotic syndrome [262, 263] have been shown to expose the association of depleted glomerular negative charges and loss of the permselectivity of the capillary wall, leading to massive proteinuria. Experimental interventions performed in laboratory animals confirmed, in turn, the aforementioned findings. Enzymatic removal of sulfated (heparan sulfate) or nonsulfated (hyaluronic acid) glycosaminoglycans from the glomerular basement membrane resulted in a substantially increased permeability to bovine serum albumin [264]. Rats with streptozotocin-induced diabetic nephropathy showed reduced glycosaminoglycan contents in the glomerular basement membrane [265], decreased presence of their heparan sulfate-associated anionic sites [266], as well as significantly increased proteinuria [143]. Further observations made in the streptozotocin diabetic rat have shown a substantial reduction in the submesothelial and capillary subendothelial density distribution of anionic fixed charges (from 31 ± 2 to 12 ± 2 ruthenium red-decorated anionic sites/μm of basement membrane) and, at the same time, a significant increase of albumin losses in the peritoneal dialysis effluent, indicating a marked decrease of the permselective capabilities of the charged components of the peritoneal membrane (Fig. 5.16) [143]. Similar observations were made in intact rats after neutralization of the peritoneal negative charges with protamine sulfate [267].

The acute inflammatory reaction is the most spectacular experimental set-up to demonstrate the permeability changes derived from an acute reduction of the microvascular negative charge. This situation has been classically defined by the development of acute low hydrostatic pressure, high capillary permeability, and albumin-rich interstitial edema [163, 268]. In this sense the generalized acute inflammatory reaction derived from abdominal sepsis promotes a major erosion of the density distribution of the anionic fixed charges in several microvascular beds, diaphragmatic and mesenteric peritoneum (showing values as low as six anionic sites/micron of basement membrane) [269], myocardium [270], skeletal muscle, pancreas, renal peritubular capillaries [271], as well as in the submesothelial basement membrane of rat diaphragmatic and mesenteric peritoneum [142] (Figs. 5.19 and 5.26). Additional studies in the same experimental model of abdominal sepsis in rats demonstrated abnormally increased albumin content in mesenteric, diaphragmatic, and pancreatic interstitial fluid [272]. This drastic loss of the permselectivity of the capillary wall derives from a massive liberation and reduced inactivation of a host of mediators of inflammation triggered by acute inflammation [273–275], including tumor necrosis factor alpha, interleukins, platelet-activating factor, leukotrienes, thromboxane A2, activators of the complement cascade, kinins, transforming growth factor B, vascular endothelial growth factor, as well as many others already known, or still waiting to be identified [185, 276–279].

The role of intercellular junctions in macromolecular leakage during acute inflammation is still controversial. Some groups pointed to the endothelial tight junction as the main pathway for extravasation of macromolecular plasma protein. It was postulated that inflammatory mediators such as histamine, serotonin, bradykinin and leukotriene E4 induced junctional openings (Fig. 5.23, inset), by means of endothelial cells contraction [280–283] or by a loss of occludin and cadherin from the junctional complex [284, 285]. Unpublished observations from our laboratory (Gotloib L.) made in intact rats, as well as in rats with *E. coli* peritonitis, by means of intra-arterial injection of albumin–gold complexes, showed that most particles of the tracer cross the endothelial barrier transcellularly, via plasmalemmal vesicles. In both experimental situations, intact and infected rats, the tracer was not seen beyond the junctional infundibulum (Figs. 5.33 and 5.34); just the opposite: the tracer was present in plasmalemmal vesicles (Fig. 5.34, inset), and reached the subendothelial space in areas far from intercellular junctions (Figs. 5.33 and 5.34). This concept of transcellular transport of albumin through the capillary wall, also during acute inflammation, is

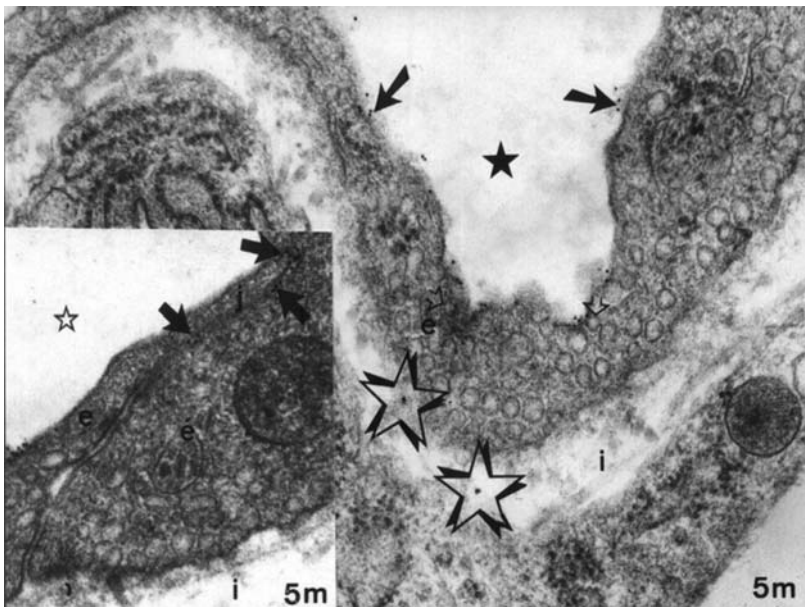

Fig. 5.33 Blood continuous capillary of mouse diaphragmatic peritoneum. The material was taken 5 min after intra-arterial perfusion of the tissue with albumin–gold. Particles of the tracer decorate the luminal aspect (black arrows) of the endothelial cell, as well as that of pynocytotic vesicles (open arrows). Note the presence of albumin–gold complexes (open stars) in the subendothelial interstitial space (i), in an area free of intercellular junctions (× 41,500).

Inset. Another aspect of the same sample shows particles of the tracer (arrows) in the luminal side of the intercellular junction, whereas the interstitial space (i) is devoid of albumin–gold complexes (open star: microvascular lumen; b: subendothelial basement membrane; e and é: adjacent endothelial cells) (× 41,500)

supported by recently published evidence postulating a significant role for plasmalemmal vesicles and even for fenestrations induced by vascular endothelial growth factor [286–288].

Water transport across endothelium of continuous capillaries was classically thought to occur almost completely via the paracellular pathway through intercellular junctions. Transcellular transport was considered to be nil.

However, the relevance of the transcellular pathway also for water has recently been brought to the forefront by the immunohistochemical identification of aquaporin-1 channels in peritoneal microvascular endothelium [289, 290], as well as in rat peritoneal mesothelium [107]. Expression of this transmembrane water channel protein in the endothelial cell surface of continuous capillaries appeared to be basically localized in plasmalemmal vesicles, and its concentration is quantitatively comparable to that seen in erythrocyte plasma membrane [291]. The presence of aquaporin-1 in microvascular endothelium provides a molecular explanation for the water permeability of some capillary beds [292], as well as a low-energy cost pathway [293] for almost 70% of the transmembrane transport of water [289]. Furthermore, this evidence confirms the predicted concept that, also during peritoneal dialysis, not less than 50% of the transperitoneal water flow occurs through postulated ultra-small transcellular pores [97] that appear to be metabolically driven pathways rather than just holes located in the microvascular wall.

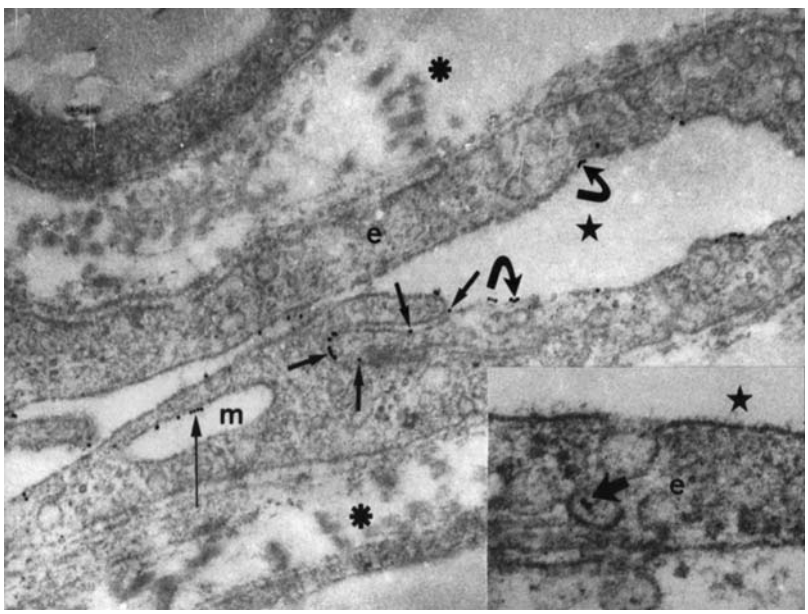

Fig. 5.34 Mesenteric capillary of a rat with experimentally induced *E. coli* peritonitis. Intraarterial perfusion with albumin–gold was performed 24 h after provoking the disease. Particles of the tracer can be seen adsorbed to the luminal aspect of the endothelial cell membrane (curved arrows), as well as within the infundibulum of the interendothelial cell junction (short arrows). Some particles of the tracer (long thin arrow) are also present in a cytoplasmic multivesicular body (m) (*: interstitial space; e: endothelial cell; black star: capillary lumen) (× 41,500).

Inset: Another aspect of the sample taken from the same animal. Albumin–gold complexes are also present in a pinocytotic vesicle (arrow) (star: capillary lumen; e: endothelial cell) (× 84,530)

Summarizing the information obtained from ultrastructural and physiological studies, it can be stated that the microvascular endothelial cell should be considered a highly active structure, serving not only as a permeability barrier and an effective thromboresistant surface, but also as the location of important synthetic and other metabolic activities [182, 209].

Continuous capillaries are more permeable to larger molecules than are fenestrated capillaries [199]. Coated pits and coated vesicles are involved in receptor-mediated endocytosis, whereas the uncharged pinocytotic vesicles and transcellular channels are involved in the transfer of proteins and fluid-phase pinocytosis. The transcellular pathway plays a relevant role in the transmembrane transport of water and macromolecular plasma proteins. Additionally, all the resistances described by Predescu et al. [75] along the pathway leading from the microvascular lumen to the abdominal cavity, are negatively charged [37, 39].

Lymphatics

The lymphatic system serves to drain, from the interstitial compartment, a range of materials such as water, proteins, colloid materials and cells [294], all elements included in the interstitial fluid. Under normal conditions fluid crosses the microvascular endothelial membrane at a rate whose magnitude depends on the Starling forces acting at each aspect of the capillary membrane, as well as on the permeability properties of the endothelial microvascular monolayer. The local autoregulation of interstitial volume is provided by automatic adjustment of the transcapillary Starling forces and lymphatic drainage [161]. Therefore, an alteration in the aforementioned forces results in interstitial accumulation of fluid that will eventually be removed by the lymphatic flow that, in situations of high capillary permeability edema occurring during acute inflammation, can increase by a factor of ten [295]. In the abdominal cavity, lymphatics have a relevant role in the prevention of ascites [296].

Work during the last 20 years has revealed relevant evidence characterizing lymphatic structure and organization. The first stage of lymph collection occurs through a system of interstitial nonendothelial channels, or low-resistance pathways known as pre-initial lymphatics [297, 298], which have been seen in the cat and the rabbit mesentery [299].

This most peripheral part of the lymph vessel system is a completely open net of tissue channels which drain, at least in the cat mesentery, mainly along the paravascular area of the venous microvasculature, into a network of 0.5 mm long, irregularly shaped endothelial tubes, approximately 20–30 μm width [300]. By the time these tubes are completely filled they can reach a maximal diameter of up to 75 μm [301]. A single endothelial layer (Fig. 5.35, inset) forms these endothelial tubes defined as initial lymphatics or lymphatic capillaries [299, 301, 302].

The subendothelial area is most of the time devoid from basement membrane, as well as from a smooth muscle layer present in larger lymphatic collectors [303]. The sporadically observed patches of basement membrane have, as in blood capillaries, anionic fixed charges that can be decorated by cationic tracers [304]. Due to the absence of muscular layer, lymphatic capillaries lack the capability for spontaneous contractility [305]. However, the fact that lymphatic

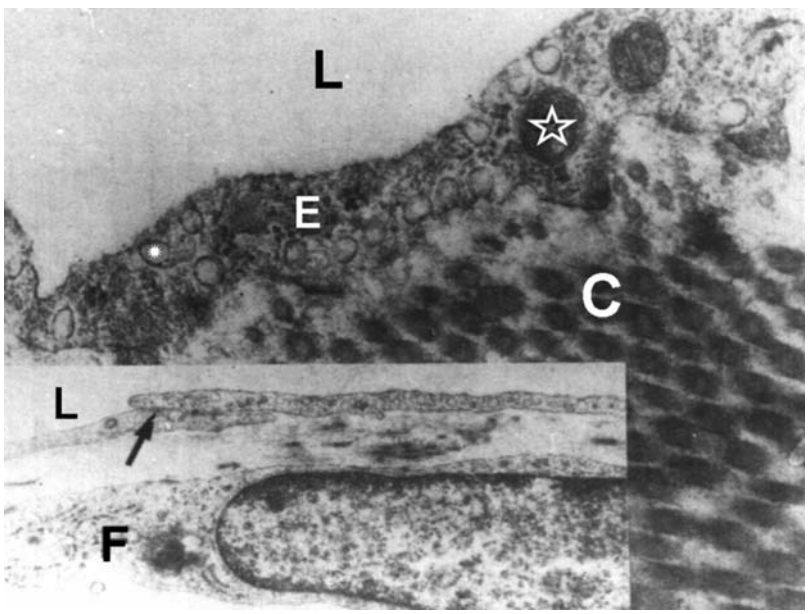

Fig. 5.35 Partial view of a lymphatic lacuna observed in a sample of rabbit diaphragmatic peritoneum. The thin endothelial cell (E) shows numerous pinocytotic vesicles (*) and occasional mitochondria (star). Note the absence of subendothelial basement membrane (L: lacunar lumen; C: collagen fibres) (original magnification × 85,000).

Lower left inset. Lymphatic capillary of rabbit diaphragmatic peritoneum. Two adjoining endothelial cells, forming a tight junction (arrow), appear lying on the interstitial tissue. Basement membrane, as well as anchoring filaments, are not observed (L: capillary lumen; F: fibroblasts) (original magnification × 62,500)

endothelial cells contain an abundant supply of fine actin-like filaments, 40–60 Å in diameter, arranged in bundles parallel to the long axis of the cell, led some investigators to postulate that these filaments could function as a contractile element of the lymphatic capillary wall [306, 307].

Anchoring filaments, having histochemical and ultrastructural characteristics similar to those observed in elastin-associated microfibrils, form a uniform population of fibrous elements, leading to the development of structural and functional continuity between the abluminal aspect of the lymphatic capillary endothelial cell and the elastic network of the adjacent connective tissue [308]. The main role of these anchoring filaments is the prevention of capillary collapse, when the interstitial pressure gains strength as a consequence of expanded fluid content of the interstitial compartment [309]. This simple element enables the lymphatic system to launch a mechanism of fluid drainage that accounts for 25% of the safety factors that can prevent formation of interstitial edema [308]. In this context it has been proposed that initial lymphatics directly sense and regulate the interstitial fluid volume [310].

The total surface area of pre-initial and initial lymphatics seems to be smaller than the total exchange area of blood microvessels [198]. Other studies on cat and rabbit mesentery showed the additional presence of flat, blind saccular structures up to 40 μm wide, with a wall made up of a simple layer of thin endothelial cells, devoid of basement membrane [198, 300].

Lymphatic endothelial cells are flat and elongated, showing an average thickness of 0.3 μm in non-nuclear areas [46, 306]. The luminal aspect of lymphatic endothelium, when exposed to cationic tracers such as cationized ferritin or ruthenium red, shows a high density of anionic fixed charges that, at times, can also be detected labeling the luminal aspect of the intercellular cleft (Fig. 5.36) [307, 44]. These charges prevent the adhesion of electronegatively charged blood cells to the endothelial luminal surface and may play a significant role in the movement of charged solutes from the interstitial compartment to the capillary lumen [44]. Furthermore, the absence of subendothelial and negatively charged basement membrane (Fig. 5.36) points at the asymmetry of the lymphatic capillary wall that is at variance with the electric symmetry characteristic of blood capillaries.

Nuclei of endothelial cells are flattened and, on electron microscopy, appear elongated. Their irregular outline shows a thin peripheral rim of dense chromatin. Plasmalemmal vesicles [46, 311] and transendothelial channels, similar to those described for blood microvessels, are commonly observed [307]. Plasmalemmal vesicles have been shown to participate in the transcellular movement of albumin–gold complexes, from the submesothelial interstitial space to the lumen of capillary lymphatics [79] (Fig. 5.37). Furthermore, the endocytotic pathway has been shown up by the presence of the same tracer into cytoplasmic endosomes (Fig. 5.38).

Several types of interendothelial junctions have been described. Approximately 2% of the whole junctional system consists of open junctions, showing gaps up to 100 nm width, that can, at times, be as wide as 1,000 nm [307, 312]. These openings serve as a way in for macromolecular solutes such as gold-labeled albumin (Fig. 5.38) or cationized ferritin (Fig. 5.39). At times two adjoining endothelial cells overlap each other, forming a kind of valvular junction that can be easily opened by an eventual increase of interstitial pressure (Fig. 5.36, inset). Junctional infundibuli show anionic fixed charges similar to those observed in the luminal endothelial glycocalyx (Fig. 5.36). Around 10% of junctions are

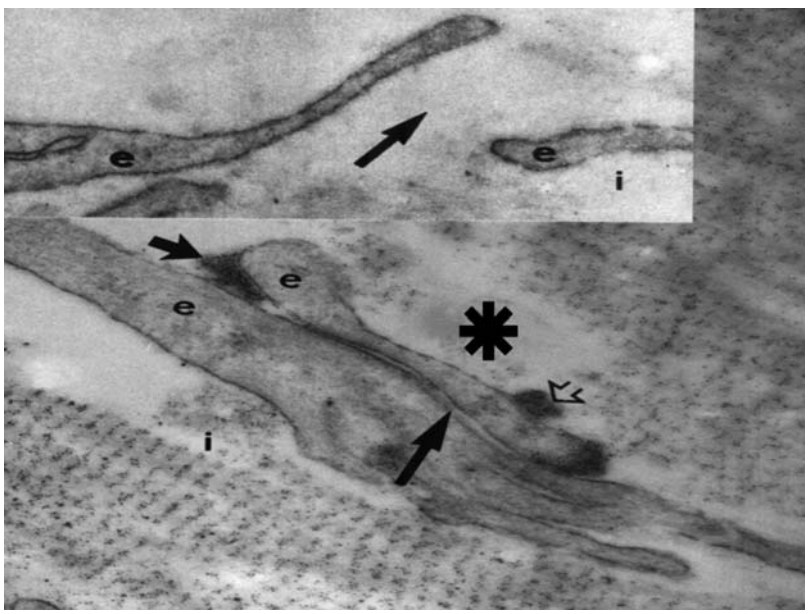

Fig. 5.36 Mesenteric lymphatic capillary of a mouse perfused with cationized ferritin. The long arrow points at the intercellular junction formed by two adjacent endothelial cells (e). The short black arrow indicates the presence of the electropositive tracer on the luminal aspect of the intercellular junction, whereas the open arrow shows particles of ferritin decorating the endothelial luminal plasmalemma. Note the absence of subendothelial basement membrane (*: microvascular lumen. i: subendothelial interstitial space) (× 41,500).

Inset. Mesenteric lymphatic capillary of an intact mouse. The arrow points at an open intercellular cleft formed by two adjacent endothelial cells (e). The junction serves as a valvular structure sensitive to the hydrostatic gradient between the interstitial space (i) and the microvascular lumen (open star) (× 41,500)

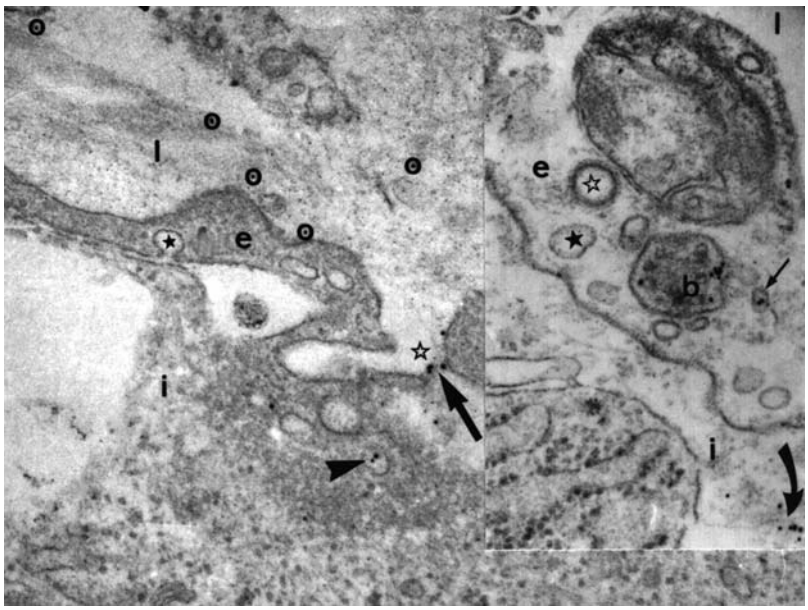

Fig. 5.37 Diaphragmatic submesothelial lymphatic capillary taken from a mouse 10 min after intraperitoneal injection of albumin–gold complexes.

Left inset. Albumin–gold complexes (long arrow) can be observed in their pathway through an open interendothelial cell junction (open star). More particles of the tracer are seen (open circles) within the luminal space (I) of the microvessel. Arrowhead points at albumin–gold included into a pinocytotic vesicle (i: subendothelial interstitial space; black star: plasmalemmal vesicle) (× 41,500).

Right inset. Lymphatic capillary endothelial cell (e). Albumin–gold complexes appear in an endosome (b) as well as in a pinocytotic vesicle (straight arrow). Curved arrow points at albumin–gold complexes present in the interstitium (i). Notice the absence of subendothelial basement membrane (black star: plasmalemmal vesicle; open star: coated vesicle) (× 64,450).

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zonula adherens, whereas the rest are tight junctions [301, 313]. It has been proposed that, in addition to the organized prelymphatic system [314], a small percentage of open junctions (1–6%) can account for a substantial proportion of the lymphatic pathway for fluid as well as small and large molecule drainage [301].

The diaphragmatic lymphatic capillary net is organized as a plexus along the submesothelial surface [315], which drains, through an intercommunicating microvascular system, into a plexus on the pleural side of the diaphragm [133]. The distribution of the whole diaphragmatic network is irregular, and varies in different species.

A prominent feature of diaphragmatic lymphatics is the presence of flattened, elongated cisternae or lacunae, approximately 0.3–0.6 cm length, with a long axis that is parallel to the long axis of the muscle fibres [315–317] (Fig. 5.40). The monolayer endothelial lining of the lymphatic lacunae is thin and shows no tight junctions. Adjacent cells usually overlap, forming valve-like processes, leaving an open interface that can be as wide as 12 μm. The cytoplasm of endothelial cells, basement membrane, and anchoring filaments of lymphatic lacunae are similar to those structures described for lymphatic capillaries. While anionic sites have not been observed, the glycocalyx of cisternal endothelium, when exposed to ferritin, is heavily decorated by the cationized tracer, which also appears along the open intercellular clefts [44, 318].

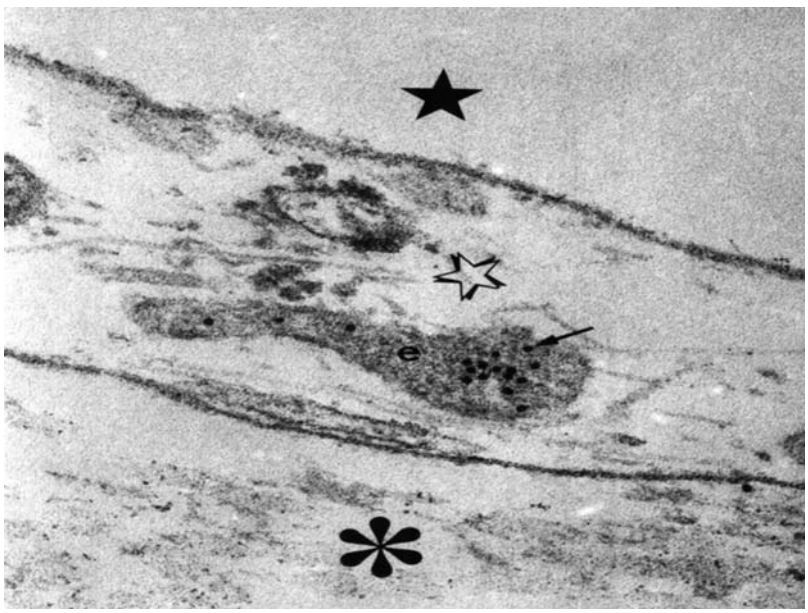

Fig. 5.38 Diaphragmatic lymphatic capillary of a rat. The sample was taken 15 min after starting intraarterial perfusion with albumin–gold complexes. Endosome (e) present in the cytoplasm of the endothelial cell (open star) shows particles of the tracer. This may well represent the endocytotic pathway for degradation of the complex. Note the absence of subendothelial basement membrane (black star: microvascular lumen; *: interstitial tissue) (× 87,000)

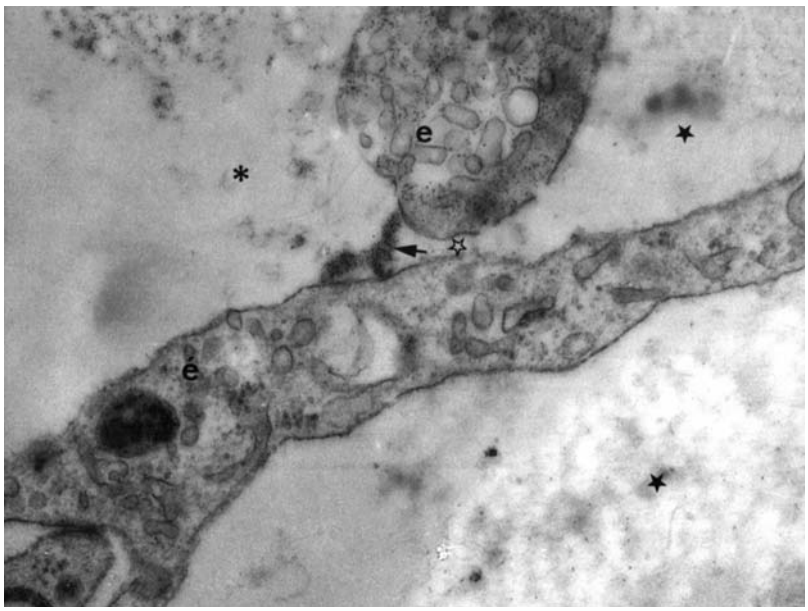

Fig. 5.39 Mesenteric lymphatic capillary obtained from a mouse intraperitoneally injected with cationized ferritin. Particles of the tracer (arrow) can be seen entering the microvascular lumen (*) through the open interendothelial cell junction (open star). Again, note the absence of subendothelial basement membrane and anionic sites (e and é: lymphatic endothelial cells; black stars: interstitial space) (× 41,500)

Diaphragmatic lymphatic lacunae, regularly connected by transverse anastomosis [114], and capillaries from the whole peritoneal lymphatic network, including the rich omental plexus [319], drain into a system of precollector, small-caliber lymph vessels that have a poorly developed smooth muscle layer underlying the endothelium. These vessels, which have semilunar valves [1, 320], drain, in turn, into the larger collecting vessels, whose diameter ranges between 40 and 200 μm [321]. The luminal aspect of the endothelial layer shows a sequence of valvular segments, with a semilunar bicuspidal valve at the distal end of each [133, 321]. The smooth muscle layer underlying the subendothelial basement membrane shows a spiral arrangement around the endothelial tube that becomes more pronounced towards the downstream end of the intervalvular segment [305, 322, 323]. Distances between adjacent valves range between 0.1 and 0.6 mm [323]. Thereby, the anatomical and functional unit (lymphangion) is established, consisting of one valve and the following intervalvular segment, which measures 2–3 mm in length [324]. This collecting segment, limited by two one-way valves and an intrinsic smooth muscle layer, compresses the lymphatic lumen driving the intravascular fluid centrally into the next compartment, making up an escalated system of drainage that has, in the proximal part of each lymphangion, a valve that prevents retrograde flow [305]. The presence of valves also enables this part of the system to reach differential intraluminal pressures around 1–2 cm of water [325].

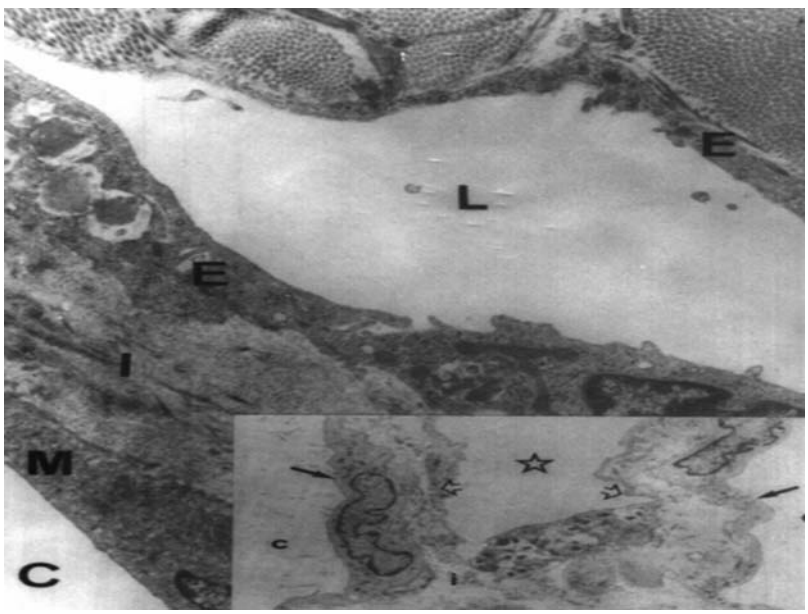

Fig. 5.40 Lymphatic lacuna of rabbit diaphragmatic peritoneum. The wide lacunar lumen (L) is surrounded by the lymphatic endothelium (E). Connective tissue (I) is interposed between the lacuna and the mesothelial cell layer (M) (C: abdominal cavity) (original magnification × 17,750).

Lower right inset. Lymphatic lacuna of rabbit mesentery. The open star shows the lacunar lumen surrounded by a thin endothelial layer (open arrows). Mesothelial cells (black arrows) are covering both aspects of the mesenteric peritoneal surface (i: interstitium. C: abdominal cavity) (original magnification × 4,750)

Capillary lymph that flows from the interstitium slowly moves downstream (average velocity for particles with diameter up to 5 μm = 1 μm/min) [303], drains into large collecting channels (40–200 μm diameter), and proceeds in the direction of the central venous circulation, propelled by peristaltic and rhythmic contractions of consecutive lymphangions [292, 303, 321, 326], with frequencies ranging between 4 and 12 contractions/minute [321, 326]. Within each lymphangion, hydrostatic pressure increases to a threshold of approximately 12 cm of water, after which the proximal valve is closed, and the downstream valve is opened. The cycle is repeated in the following segment. Contractility of lymphangions is modulated by a pacemaker site of spontaneous activity, apparently located, at least in bovine mesenteric lymphatics, in the vessel wall near the inlet valve of the unit. Activity propagates at a speed of 4 mm/s, and the ejection fraction was evaluated at 45–65% [327].

Contractions are generated by myogenic stimuli (hydrostatic pressure of 5–7 cm water) [327], and influenced by activation of α- and β-adrenoreceptors [328–330], histamine, leukotriene C4 and D4, platelet-activating factor [331, 332], PGF2 alpha, PGA2, PGB2 [333], bradykinin [334], and vasoactive intestinal peptide [335]. It should be noted that all the aforementioned vasoactive substances are mediators of inflammation present in high concentrations in blood and tissues during the localized or the generalized acute defense reaction [276].

Lymph flows from collectors to the thoracic duct and the right lymph duct, and finally drains into the subclavian veins. Lymphangions join larger collecting lymphatic vessels, forming a dichotomous tree that drains entire tissue regions. This arrangement has been described in the diaphragm as well as in mesentery [305, 325, 336].

Innervation of lymph vessels has been studied in the dog and cat mesentery, by means of silver stains [320]. It was shown that large lymphatic collectors have myelinated nerves that remain on the adventitial area, and nonmyelinated nerve fibers that penetrate into the region of valve attachment and are considered to be the motor supply to the smooth muscle. Bovine mesenteric lymphatics show adrenergic nerve fibers in the media, as well as in the adventitia. Human mesenteric lymph collector neurotransmitters are both adrenergic and cholinergic, the former being prevalent. Lymphatic capillaries are devoid of innervation [337].

Since Starling [338, 339], it has been accepted that, besides the removal of excess interstitial tissue, the lymphatic system has the special function of absorbing protein. Normally, blood capillaries leak protein, which will not re-enter the blood vessels unless delivered by the lymphatic system [340]. It is generally accepted that the rate of lymph formation is equal to the net capillary efflux under normal physiological conditions, in order for the interstitial fluid volume to remain constant [310]. However, the mechanisms involved in the formation of lymph, at the level of the most peripheral part of the lymphatic system, are still controversial. According to Allen and Vogt [341], who formulated the hydraulic theory, lymph formation is the end-result of hydraulic forces acting across initial lymphatics. Assuming that the interstitial hydrostatic pressure is zero, or even negative [159, 342], any rise will also increase the initial lymphatic flow, and edema will eventually develop if and when the lymphatic drainage capabilities are exceeded [343–345]. This concept of increased hydrostatic pressure as the main factor in the process of lymph formation was extrapolated to the lymphatic absorption from the peritoneal cavity [346, 347]. In this context it was postulated that, during peritoneal dialysis, the intra-abdominal pressures [348, 349] modulated lymphatic drainage from the abdominal cavity well within the range of values observed in dialyzed patients [166, 350]. This concept has been substantially challenged by a series of elegant studies performed by Flessner et al. [166, 351], who showed that a significant proportion of the intra-abdominal fluid is lost to the abdominal wall, the rate of which is also dependent on the intra-abdominal pressure. This fluid, after being incorporated to the tissues surrounding the abdominal cavity, will be drained through the lymphatic circulation [352]. The eventual influence of the intrathoracic negative pressure upon the lymphatic downstream circulation [353] may well be an additional component of the hydrostatic forces involved in lymph progression to the venous-blood compartment.

The osmotic theory of lymph formation [354] postulates the existence of a protein-concentrating mechanism at the level of the initial lymphatics, the main result of which would be that only 10–40% of the fluid initially entering within the lymphatic network would flow downstream, back to the blood compartment, and the remaining fluid would be filtered out from the lymphatics as a protein-free solution. This process would eventually cause a high protein concentration, and an oncotic gradient between the contents of the initial lymphatics and the surrounding interstitial fluid. Other investigators have proposed a vesicular theory of lymph formation, which holds that plasmalemmal vesicles provide the major route for transendothelial transport of protein, thereby creating the oncotic gradient needed for further fluid flow between adjacent cells or through transendothelial channels [355, 356]. This hypothesis is supported by recent studies that have shown active transendothelial transport of albumin in plasmalemmal vesicles [60, 357]. Figure 5.37 shows gold-labeled albumin transported by plasmalemmal vesicles of a mouse diaphragmatic lymphatic capillary.

On the other hand, it has been suggested that the postulated mechanisms may not necessarily be exclusive in the sense that some or all could function simultaneously. However, the relative influence of each one could vary in different areas of the initial lymphatic network [358].

The relevance of peritoneal lymphatics, as well as their impact upon ultrafiltration during peritoneal dialysis, is addressed in Chapter 6. Omental milky spots have, relatively recently, attracted the attention of investigators working in

the field of peritoneal dialysis. First described by Von Recklinghausen in pleura of rabbits [359], and later on in humans [360], these structures are part of the peritoneal lymphatic system [361]. Been described as submesothelial lymphoid structures essential for the maturation of resident peritoneal macrophages, they are actively involved in peritoneal defense reactions under a diversity of inflammatory conditions [362]. Macroscopically, milky spots appear as small (up to 1 mm diameter), white bodies, most commonly detected in perivascular areas of the greater omentum. Their structure, as seen under light microscopy, has been thoroughly reviewed by Di Paolo et al. [362, 363] in rats, rabbits as well as in patients on long-term peritoneal dialysis. In all the abovementioned species, they are located in the submesothelial tissue, showing blood capillaries surrounded by lymphocytes and macrophages and, at times, even lymphatic microvessels that can be identified within the frame of the same structure. The cell population of milky spots is made up by 400–600 cells, including macrophages (45–70%), lymphocytes (14–29%), and a low number of plasma cells (around 6%). Occasionally, megakariocytes and adipocytes can also be detected. Work done in experimental animals showed that number and size of milky spots, as well as their cell population, substantially increase after introduction of a peritoneal catheter, at the time of infection and inflammation, or after repeated exposure of the peritoneum to dialysis solutions containing 1.5 or 4.25% glucose [363]. Observations made in patients depicted changes not far from those seen in experimental animals, since both, size and cellularity of milky spots increased with the time-span of maintenance term peritoneal dialysis [363].

Peritoneal Innervation

The first report announcing the presence of nerves in the peritoneal interstitium was made by Haller in 1751 [364] and confirmed during the 19th century by Ranvier and Robin who, using osmic acid and silver nitrate, described nerve trunks, branches, and nerve endings accompanying arteries and veins. Robinson [1] described the peritoneum as being richly supplied with myelinated and nonmyelinated nerves (Fig. 5.41).

In rat mesentery, networks of adrenergic axons innervate the principal and small arteries and arterioles. Precapillary arterioles, collecting venules and small veins are not innervated, and are most likely under the influence of humoral vasoactive substances [365]. Lymphatic innervation was described in the previous section.

In 1741, Vater observed that the submesothelial connective tissue of cat mesentery contained oval corpuscles with a diameter of approximately 1–2 mm. In 1830, Paccini rediscovered and gave a systemic description of this corpuscle, known as the Vater–Paccini corpuscle [1]; it takes the form of a nonmyelinated nerve ending, which, in transverse section, appears as a sliced onion. In humans it has been observed in the peritoneum of mesentery and visceral ligaments, functioning as the main receptor for perception of pressure.

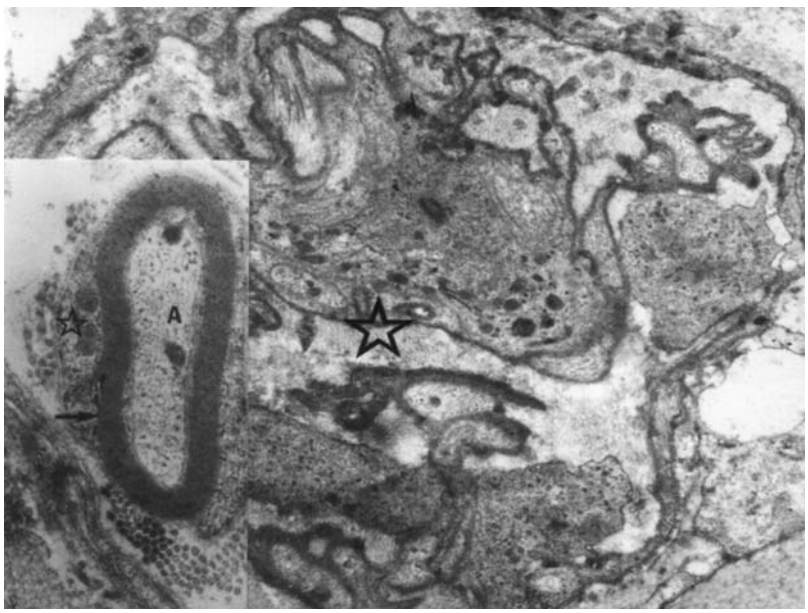

Fig. 5.41 Parietal peritoneum taken from a 67-year-old chronic uraemic patient on IPD, showing a transversal section of an unmyelinated nerve (star) (× 12,600).

Inset. Rabbit mesentery showing a myelinated nerve fiber (star: Schwann cell cytoplasma; arrow: myelin; A: axon) (original magnification × 47,400)

Cytology of the Peritoneal Fluid

The peritoneal fluid of laboratory animals has classically been a favored site for experiments dealing with the inflammatory response [366], as well as for those designed to analyse the biological reaction to infection [367].

More than 50 years ago, Josey and Webb realized that fluid shifts into and out of the peritoneal cavity could change the concentration of cells without affecting their absolute number [368–371]. The methodological answer to this question was given by Seeley and colleagues, who weighed peritoneal fluid and measured the cellular concentrations, and so were able to estimate the absolute number of cells [372]. Padawer and Gordon [370], after analyzing the cellular elements present in peritoneal fluid of eight different normal mammals, concluded that the most frequently observed cells were eosinophils, mast cells and mononuclears (including lymphocytic and macrophagic elements). Total cell numbers, as well as percentages of the different cells, varied greatly among the species examined. Neutrophils were never observed in normal animals. Total absolute counts were higher for females than for males, as well as for older animals compared with younger ones. In the individual animal, under normal conditions, the number of cells present within the abdominal cavity was constant [370].

Observation of peritoneal fluid obtained from healthy women showed that macrophages and mesothelial cells contributed more than 70% of the whole cell population, whereas lymphocytes and polymorphonuclears contributed to a lesser extent (18 and 7%, respectively) [373]. Other investigators observed that at the midphase of the menstrual cycle, macrophages, which comprised 82–98% of the peritoneal cells, showed morphological as well as biochemical heterogeneity and were seen to be involved in phagocytosis of erythrocytes [374] (Fig. 5.42). However, other studies showed up to four different types of cytological patterns in peritoneal fluid of women during the course of the menstrual cycle, in all of which mesothelial cells contributed substantially to the total cell counts. The paramenstrual type was in most cases hemorrhagic and highly cellular [375]. Ciliocytophtoria, anucleated remnants of ciliated mesothelial cells, can be occasionally observed in effluent dialysate, basically in young women. Inability to identify

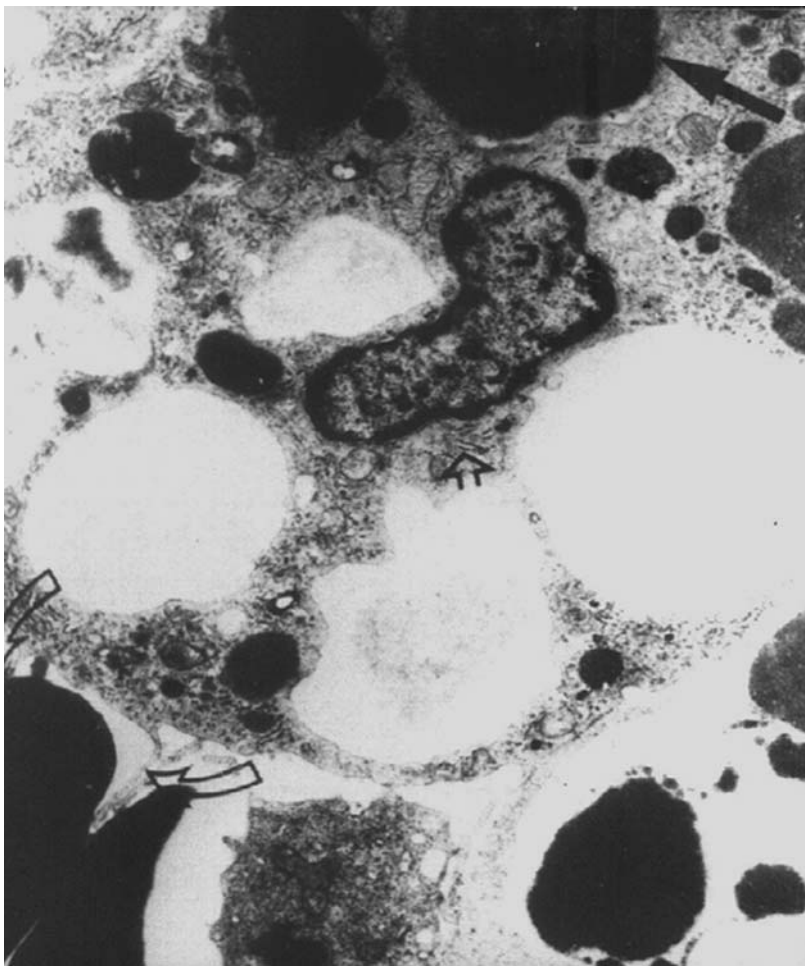

Fig. 5.42 Peritoneal effluent obtained from a chronic uraemic patient on peritoneal dialysis. The macrophages depicted in the figure show phagolysosomes digesting erythrocytes (black arrow). Note the presence of rough endoplasmic reticulum (short open arrow) near the nucleus (n). The former normally appears in macrophages when the cells are involved in phagocytic activity. The curved open arrows are pointing to cell processes engulfing red blood cells (× 8,600)

these structures can mislead the laboratory team as well as the physician to search for parasitic or fungal contamination [376].

The apparently puzzling effect of intraperitoneal saline inducing substantial influx of neutrophils into the abdominal cavity, which was observed long ago [367], was not confirmed when the experiments were carried out using sterile techniques. Bacterial lipopolysaccharides proved to be very effective in producing intraperitoneal exudate rich in cells [371]. This phenomenon was inhibited by prior intraperitoneal injection of cortisone [377].

In humans, sterile inflammatory effusions are characterized by a rich cellular content including neutrophils, lymphocytes, macrophages, mesothelial cells, eosinophils, and basophils, usually in that order of frequency [378]. The presence of macrophages, mesothelial cells, lymphocytes, eosinophils, and even plasma cells has been confirmed by electron microscope studies [379–381].

Peritoneal eosinophilia (eosinophils >10–50%) has been experimentally induced by intraperitoneal injection of iodine, chalk, nucleic acids, pilocarpine, hemoglobin or red blood cells, egg albumin, gold salts, mineral and vegetable oils, hydatidic fluid, and saline [378, 382]. On the other hand, intraperitoneal injection of bacteria and/or bacterial endotoxins induces a massive migration of neutrophils and monocytes into the peritoneal cavity [370, 383, 384].

The information presented above suggests that the cell content of effluent peritoneal dialysate is likely to be modified by so many factors that a concise description of a standardized cytological pattern becomes extremely difficult. There are, however, a few aspects of peritoneal effluent dialysate that have been defined: a) Patients on CAPD have total cell counts up to 50 cells/mL [383]. (b) The population of resident peritoneal cells observed in patients on long-term peritoneal dialysis is basically made up by macrophages (around 50% of the population), and lower

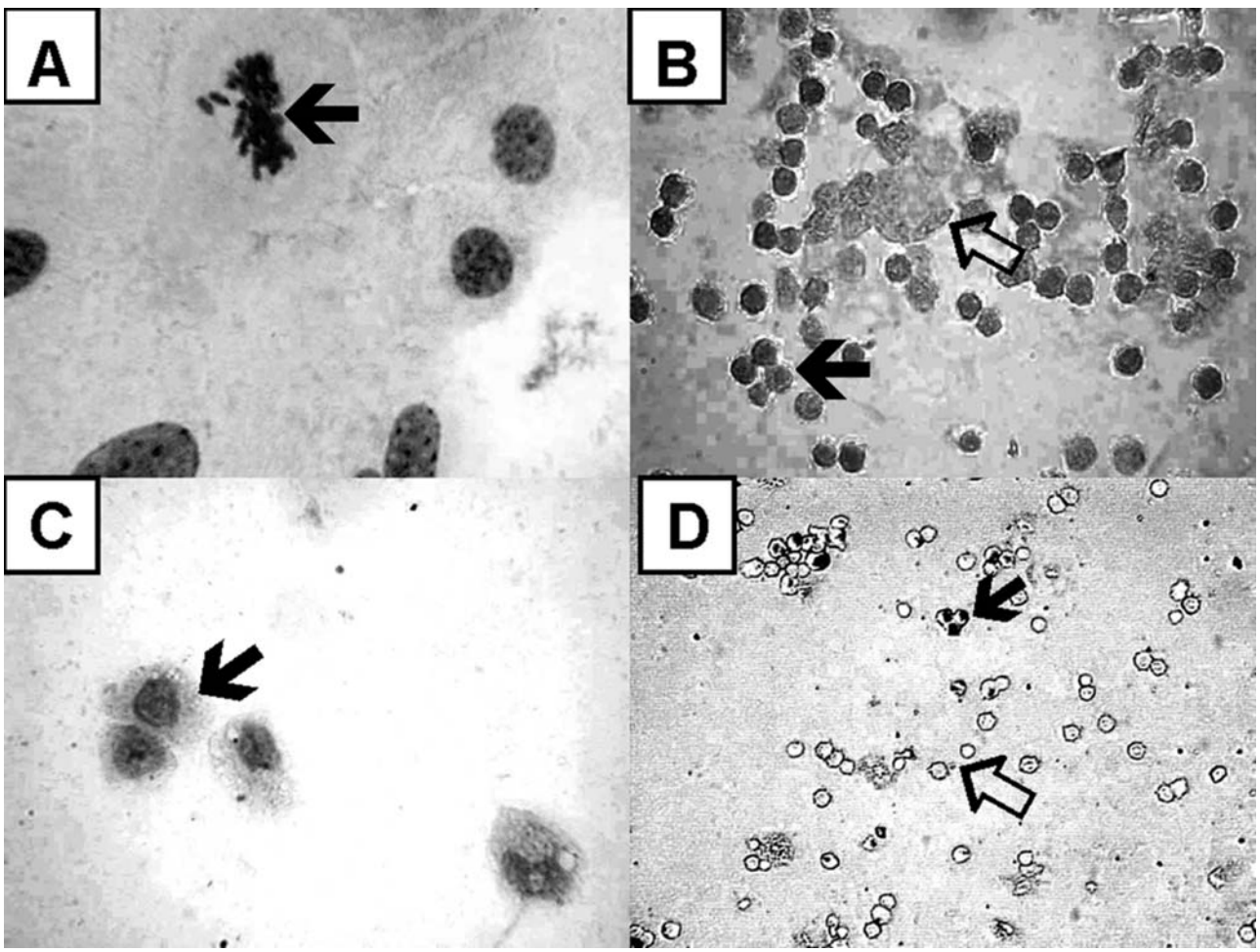

Fig. 5.43 Samples of the first dialysate effluent recovered from a new chronic uremic patient starting renal replacement therapy by means of PD. **(A)** Wandering mesothelial cell undergoing mitosis. (Black arrow: methaphase:). (Hematoxylin-eosin; × 1,000). **(B)** A high proportion of cells show positive immunostaining for PCNA (black arrow), indicating remarkable mitotic activity. (Open arrow: unstained free floating mesothelial cells). (PCNA immunostaining; × 400). **(C)** Occasionally, small groups of nonviable mesothelial cells can be detected (black arrow). (Trypan Blue staining; × 1,000). **(D)** Few mesothelial cells express β-galactosidase. (β-Galactosidase staining at pH 6; × 160)

prevalence of lymphocytes, mast cells, and mesothelial cells [385–388]. (c) During infection there is a substantial increase in total cell number [389], as well as in the proportion of neutrophils [385–388]. (d) Fluid eosinophilia is a basic component of the still ill-defined eosinophilic peritonitis [390–392].

Besides, the unphysiological situation of PD derives in substantial micro environmental changes that significantly affect the life cycle of the exposed and still attached monolayer. As a result, the population of cells recovered from dialysate effluent from a new patient is considerably different from that of patients on long-term PD. As shown in Fig. 5.43, cells detected in the first effluent of a new patient show remarkable mitotic activity (Figs 5.43a and 5.43b), a quite modest proportion of non viable cells (Fig. 5.43c) as well as a low prevalence of cells demonstrating positive expression to beta galactosidase, denoting the low prevalence of cells undergoing terminal replicative senescence (Fig. 5.43d). On the other hand, mesothelial cells isolated from effluent of patients on long-term PD (Fig. 5.44) show a quite different phenotype: they appear mostly as nonviable (Fig. 5.44a), the mitotic activity is nil (Fig. 5.44b), the vast majority are positively stained by beta galactosidase (Figs 5.44c and 5.45d), whereas a high proportion are undergoing apoptosis (Fig. 5.46). As it will be discussed later, this senescent phenotype of mesothelium was also detected in the monolayer of experimental animals exposed to high glucose concentration dialysis fluids. So, it may be hypothesized that careful and sequential observation of mesothelial cells recovered from patients' effluent, using the aforementioned staining technique, may well give quite representative information regarding the regenerative capabilities of the mesothelial monolayer still dressing the cavitary aspect of the peritoneal membrane of patients undergoing long-term PD.

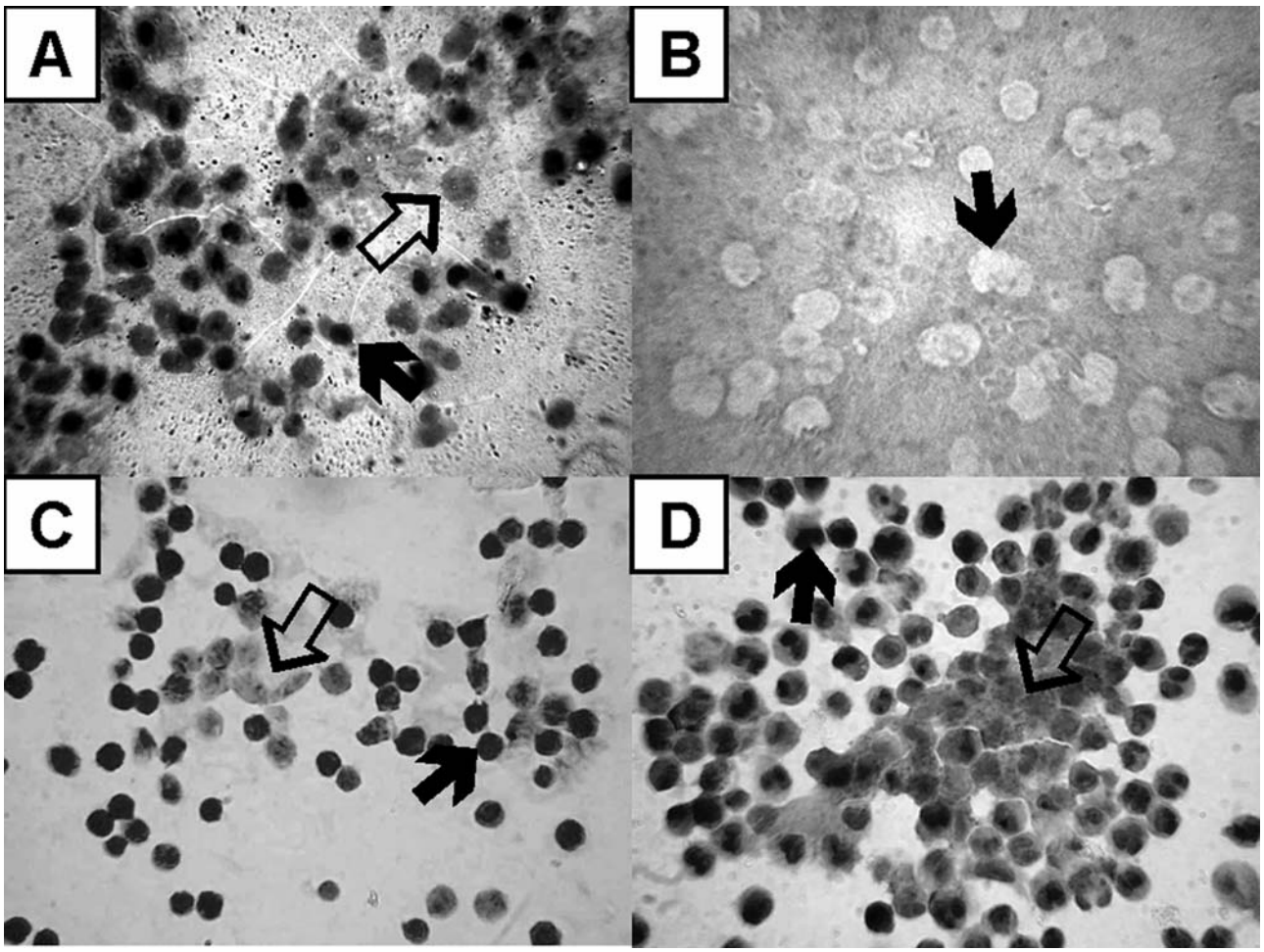

Fig. 5.44 Samples of fluid taken from effluent of a patient treated by means of CAPD for a period of seven months. **(A)** Most cells appear as nonviable, as indicated by positive staining with Trypan Blue (black arrow). (Open arrow: nonstained viable cells). (Trypan Blue; × 400). **(B)** There are no cells expressing PCNA positive immunostaining (black arrow), indicating that the mitotic activity is nil. (PCNA immunostaining; × 1,000). **(C)** Most cells show β-galactosidase expression (black arrow), pointing at the fact that they have reached a situation of terminal replicative senescence. (Open arrow: unstained cells). (β-Galactosidase expression at pH 6; × 400). **(D)** A substantial proportion of cells show P53 activity (black arrow), indicating that they are undergoing apoptosis. (Open arrow: unstained cells). (P53 immunostaining; × 400)

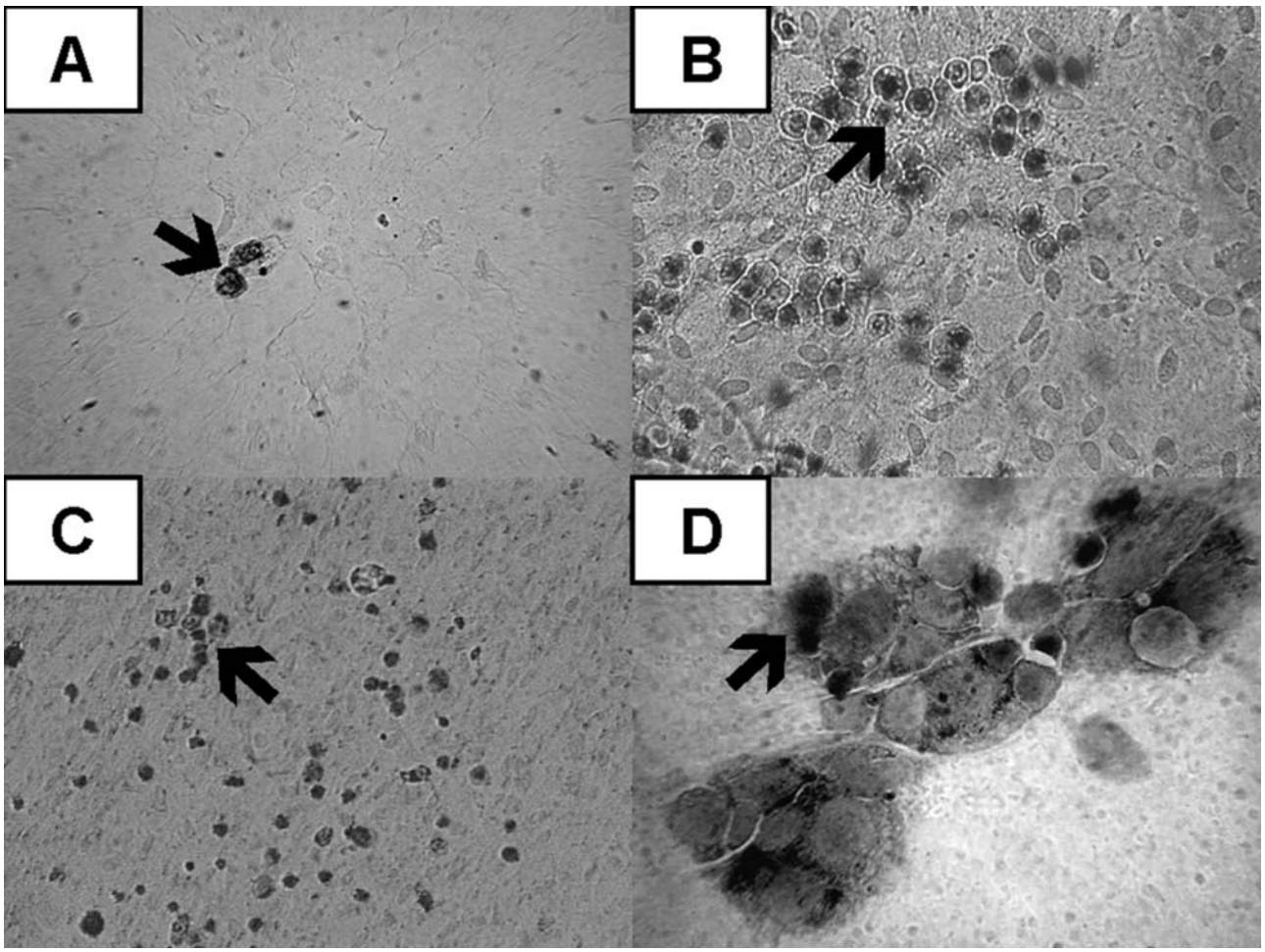

Fig. 5.45 (A) Sample of intact, unexposed mice mesothelium. Notice the low proportion of cells expressing β-galactosidase (arrow). (β-Galactosidase staining at pH 6; × 400). **(B)** Imprint recovered from a mouse after 30 days exposure to one daily intraperitoneal injection of 4.25% glucose, lactated dialysis solution. Arrow calls attention to the high prevalence of senescent cells, as indicated by positive staining to β-galactosidase. (β-Galactosidase staining at pH 6; × 400). **(C)** This imprint was recovered from a rat treated during 30 days with one daily intraperitoneal injection of 7.5% icodextrin. The prevalence of senescent cells is substantially higher than that detected in intact, unexposed animals. (β-Galactosidase staining at pH 6; × 160). **(D)** Mesothelial cells recovered from dialysate effluent of a patient on long term (7 months) peritoneal dialysis. Most cells express β-galactosidase activity. (β-Galactosidase staining at pH 6; × 1,000)

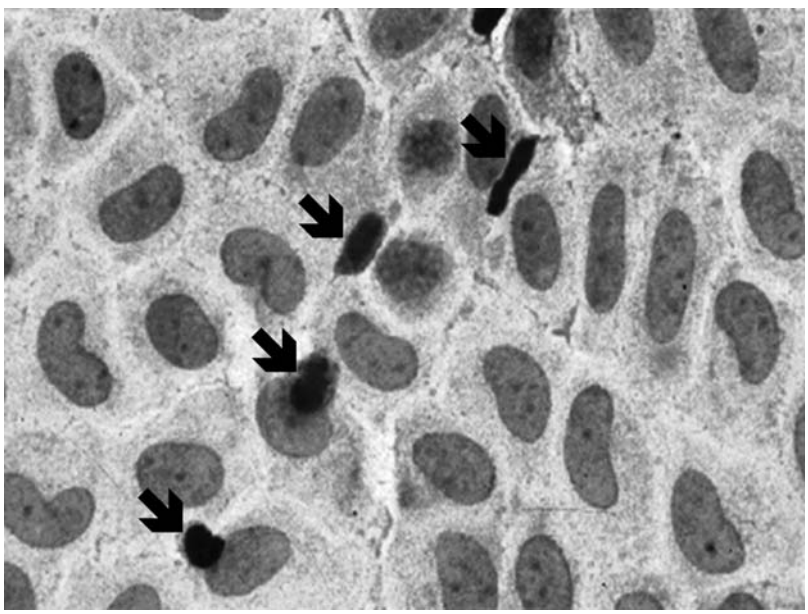

Fig. 5.46 Sample of a mesothelial imprint exfoliated from a rat after a 30 days exposure (one daily intraperitoneal injection) of 7.5% icodextrin dialysis solution. Notice the increased prevalenve of cells undergoing apoptosis (black arrow). (Hematoxylin-eosin; × 1,000)

Ultrastructure of Peritoneal Fluid Cells

Free-floating mesothelial cells are round or oval in shape and show a central, round nucleus (Fig. 5.47). Occasionally, binucleated mesothelial cells can be observed (Fig. 5.48). Nuclear chromatin is quite evenly distributed (Fig. 5.49, inset) and a small nucleolus may be observed. Numerous slender and sometimes branching microvilli emerge from the cytoplasmic membrane [379, 381, 393–395]. Branching microvilli, similar to those observed in human embryos [14], can be quite crowded in some cells, whereas in others they are scarce [381] (Fig. 5.49, inset). The glycocalyx covering the luminal aspect of the plasmalemma is endowed with electronegative fixed charges as shown in preparations exposed to the cationic tracer ruthenium red. Mitochondria, numerous cisternae of rough endoplasmic reticulum, and free ribosomes are mainly located in the outer part of the cytoplasm, and so are pinocytotic vesicles [379, 395]. The presence of intermediate-size filaments, perinuclear or irregularly scattered along the cytoplasm, has been documented in young free-floating mesothelial cells

Fig. 5.47 Effluent dialysate obtained from a non-infected uraemic patient, showing a floating mesothelial cell (star), as well as one macrophage. (*) (× 6,900)

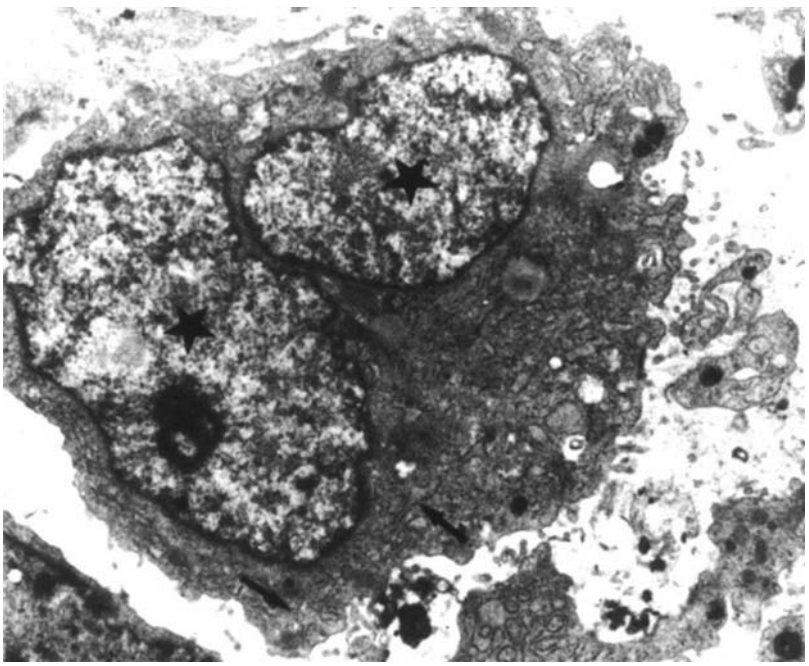

Fig. 5.48 Binucleated mesothelial cell observed in effluent fluid from a patient on CAPD. Note the abundance of rough endoplasmic reticulum (arrows) (stars: nuclei of mesothelial cell) (× 8,600)

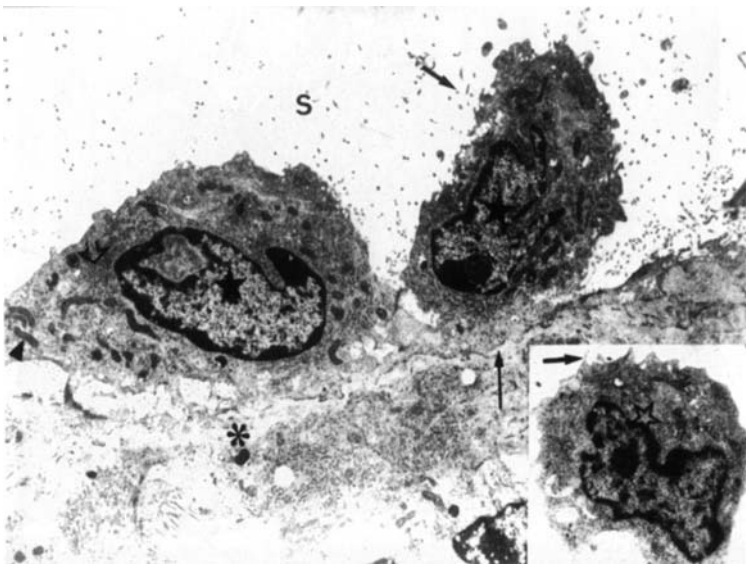

Fig. 5.49 Sample taken from the parietal peritoneum of a patient on CAPD. Two recently implanted young and active mesothelial cells (black stars), showing numerous mitochondria (arrowhead), rough endoplasmic reticulum (open arrow) and microvilli (short arrow). The cell on the right is forming its own basement membrane (long arrow) (*: submesothelial connective tissue; S: peritoneal space) (× 6,900).

Inset. Free-floating mesothelial cell (open star), seen in effluent dialysate of a CAPD patient (arrow: microvilli) (× 5,600)

[378, 380], as well as in those recently implanted on the peritoneal surface. These free-floating mesothelial cells should be distinguished from desquamated, degenerating mesothelial cells wandering in the peritoneal fluid (Fig. 5.48) [396].

Macrophages, which can be observed in large numbers, usually show an irregular and, at times, kidney-shaped nucleus with distorted masses of chromatin concentrated along the nuclear membrane (Figs. 5.42 and 5.47). The cytoplasmic outline of macrophages is irregular, with thin processes of variable length which, at times, engulf degenerated cells (Fig. 5.42) or take the form of signet-ring macrophages (Fig. 5.5, inset). Mitochondria, a small Golgi complex and phagolysosomes are more evident when the cell is involved in phagocytic activity (Fig. 5.42).

The ultrastructural aspect of inflammatory cells that eventually appear in the peritoneal fluid is similar to that classically described for other tissues.

The Origin of the New Mesothelial Cells

It has been experimentally shown that small and large mesothelial wounds heal at the same rate within 7–10 days after injury [397]. The basal, normally observed mitotic rate of mesothelial cells, as measured in the rat by ^{3}H-thymidine incorporation, ranges between 1 and 2% day (Fig. 5.50). This concept is supported by the fact that the steady state of the cell population is clearly defined by the following parameters: the proportion of cells passing through the G1 checkpoint, indicated by PCNA expression (proliferative cell nuclear antigen) that is also around 1–2%, as well as prevalence of non viable (Trypan Blue stained) senescent (positively stained with beta galactosidase at pH 6) (Fig. 5.45) and apoptotic mesothelial cells (Figs 5.46 and 5.51) that are within the same range [398, 399]. This rate of renewal is significantly increased during peritonitis, reaching maximal values of up to 19% between 1 and 3 days after injury, and returning to the basal activity on the 4th or 5th day [400]. It should be noted, however, that proliferations of fibroblasts, as well as mesothelial cell regeneration, are substantially inhibited in experimental uremic animals [400–402].

The origin of the new mesothelial cells repopulating denuded areas of injury is still controversial. Four different hypotheses have been proposed:

1. The repopulating cells originate from the bone marrow [102]. Other experimental studies showed, however, that whole-body irradiation sufficient to depress peripheral white blood cell count as well as cell replacement by the bone marrow did not prevent mesothelial healing [403]. Therefore, the existence of a circulating mesothelial precursor originating from the bone marrow seems unlikely.
2. Free-floating cells of the serosal cavity settle on the injured areas and gradually differentiate into new mesothelial cells [283, 404–406], (Fig. 5.49). Research done in order to settle this proposal, exposed evidence indicating that, after injury, free floating mesothelial cells, exfoliated from noninjured areas or from omental milky spots (12), settle on the injured areas, being instrumental to the healing of the monolayer [399, 407, 408]. Even though some investigators have not accepted this hypothesis [401, 406, 409], this approach finds support in other studies demonstrating the feasibility of mesothelial cells transplantation in humans, rabbits and rats as reported by several investigators [410, 411], as well as by our group (Fig. 5.52a).

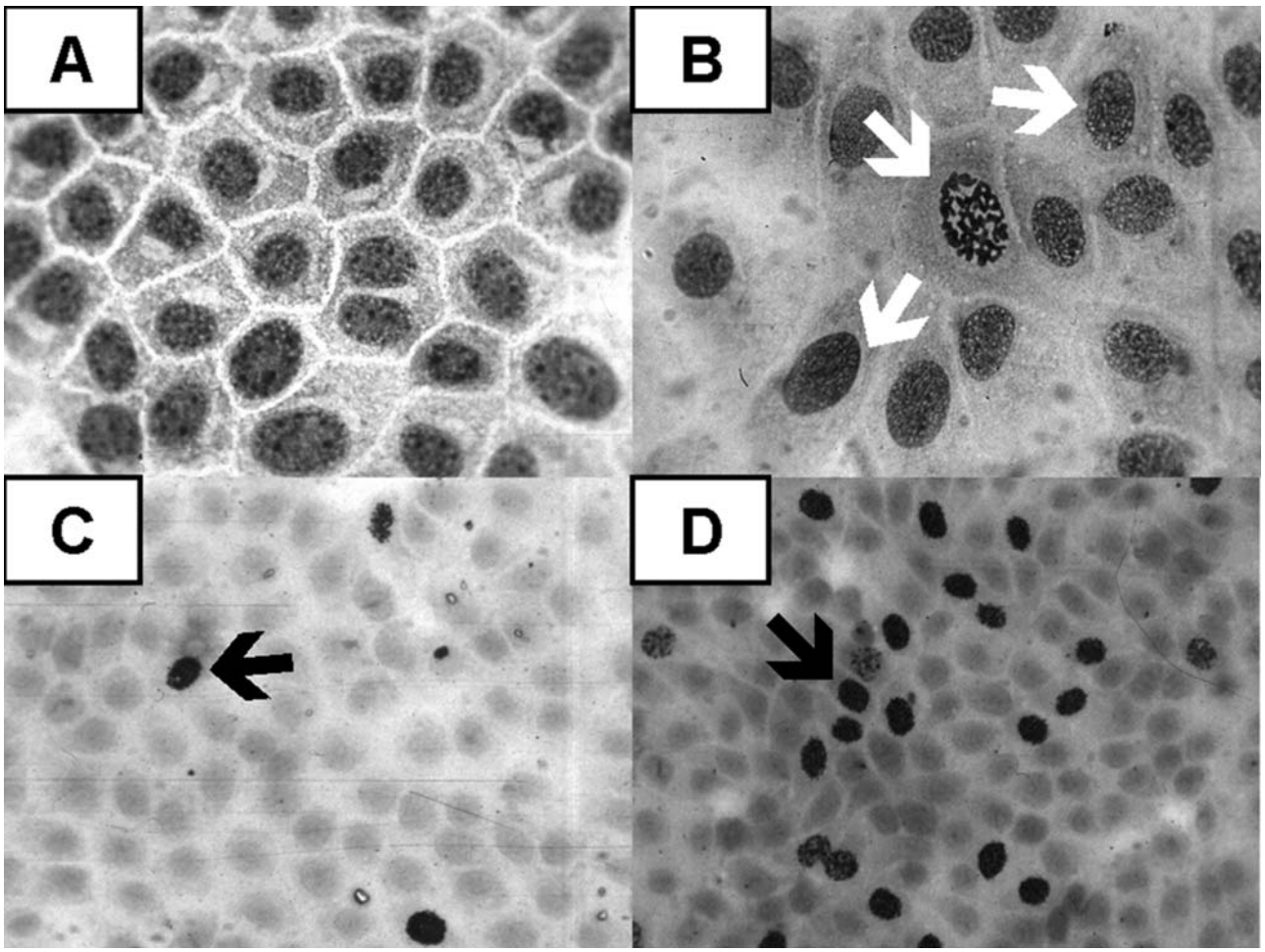

Fig. 5.50 **(A)** Intact unexposed mesothelium. Notice the normal density distribution of the cell population. (Hematoxylin-eosin; × 1,000). **(B)** Sample of the monolayer recovered from a mouse after a 2 h exposure to a 4.25% glucose, lactated dialysis solution. Notice the increased prevalence of cells undergoing mitosis (white arrows). Compare with precedent microphotograph. (Hematoxylin-eosin. × 1,000). **(C)** Again, intact unexposed mesothelium showing a few cells in S phase, incorporating tritriated thymidin (black arrows). (Autoradiography with tritriated thymidin and hematoxylin-eosin; × 400). **(D)** Imprint taken from a mouse after a 2 h exposure to the same high glucose concentration dialysis solution used in Inset B. Many cells are incorporating thymidin (black arrows), testifying for a remarkable acceleration of the cell cycle. In addition, this micro photograph, indicates that counts of cells in mitosis underestimate the mitotic activity, if compared with the information obtained by evaluation of cells incorporating thymidin. (Autoradiography with tritriated thymidin and hematoxylin-eosin; × 400)

3. Other studies [393, 401, 412] suggested the sequence of a two-stage process; during the first 24 h, macrophages forming the first line of defense [413] and coming from the peritoneal fluid, repopulate the wound surface (Fig. 5.5, inset). Later, during the second stage, new mesothelial cells, arising from metaplasia of mesenchymal precursors located in the interstitial tissue well below the site of injury, migrate to the surface and differentiate into mature mesothelial cells (Fig. 5.53). This hypothesis has not been universally accepted [25, 283, 399, 404, 414]. It has also been suggested that the early implanted macrophages are gradually transformed into mesothelial cells [414]. However, Raftery [415], after labeling peritoneal macrophages with polystyrene spheres, presented strong evidence against the hypothesis that peritoneal macrophages could be transformed into mesothelial cells.

   On the other hand, elongated, fish-like mesothelial cell precursors coming up from the submesothelial connective tissue were also observed under the damaged areas. The nuclear and cytoplasmic aspects of these cells were identical to that shown by new mesothelial cells already implanted on the peritoneal surface (Fig. 5.52b).
4. Mature mesothelial cells from adjacent areas migrate and proliferate to repopulate a depopulated area [407, 416]. This approach is supported by in vitro studies [417, 418] showing early migration and increased bromodeoxyuridine (BrdU) incorporation 24 h after injury, the latter showing values ranging between 20 and 26% of the observed cells. It should be noticed that these figures, representing the proportion of cells in S phase, imply an underestimation

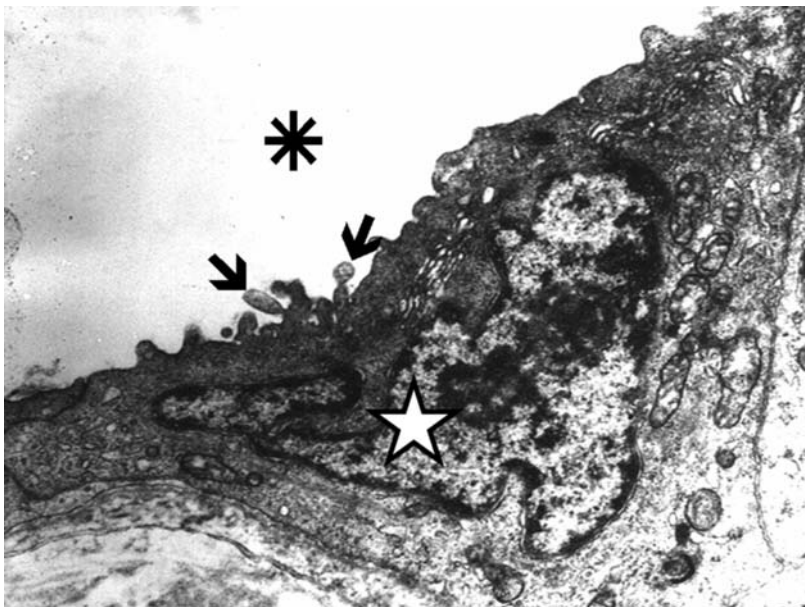

Fig. 5.51 Sample of parietal peritoneum taken from a patient undergoing peritoneal dialysis during a period of 16 months. Arrows point at areas of blebbing in the plasma membrane. Notice the absence of microvilli. Both elements define the situation of a cell at a relatively early stage of apoptosis. (Asterisk: peritoneal space; white arrow: nucleous of mesothelial cell; × 41,500).

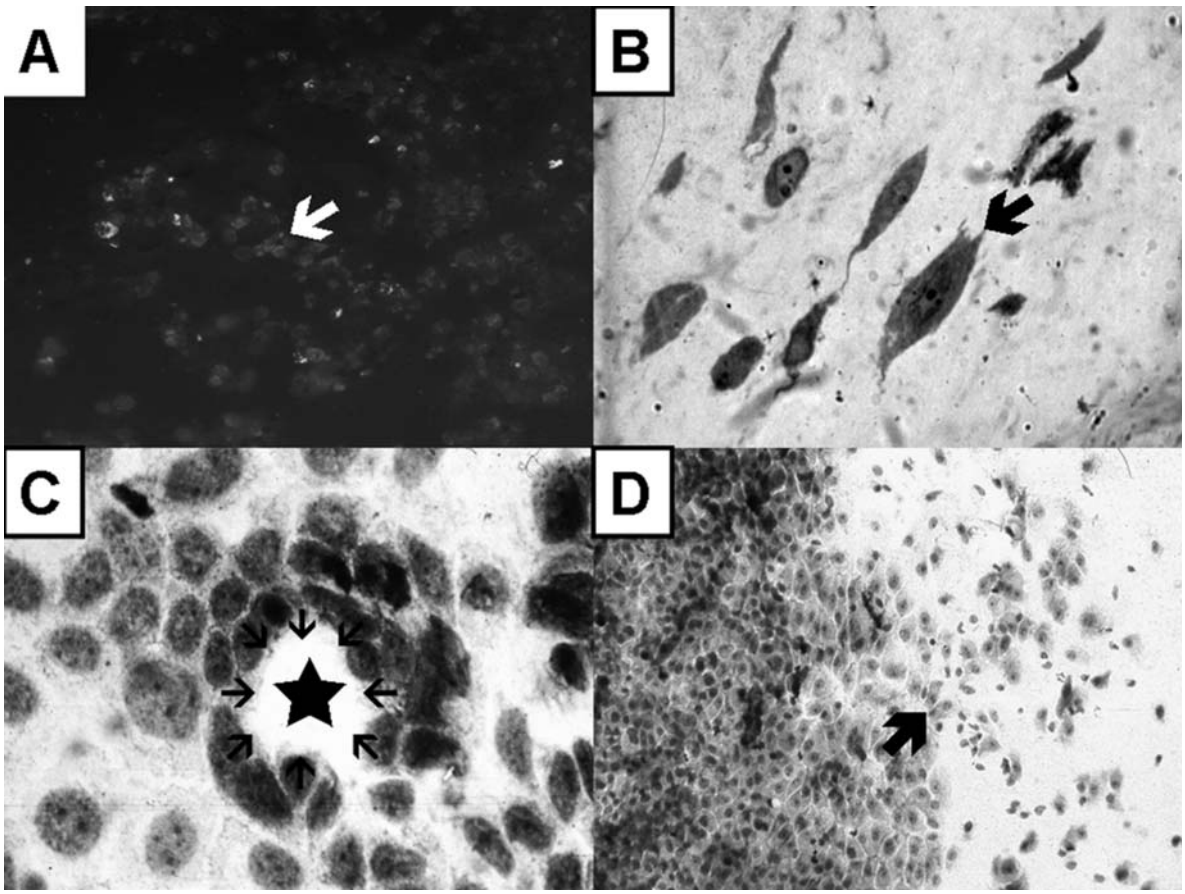

Fig. 5.52 (a) Imprint taken from a rat 24 h after autologous transplantation of mesothelial cells. White arrow points at cells already engrafted on the peritoneal surface. (PKH 26; × 400). **(b)** Peritoneal biopsy taken from a patient on peritoneal dialysis. Microphotograph shows elongated, fish like mesothelial cells migrating towards the cavitary aspect of the peritoneal membrane (arrow). (Toluidine blue; × 1,000). **(c)** Sample of the monolayer recovered 5 days after experimental, localized exfoliation of the mesothelial dressing. Young mesothelial cells that circumscribe an area of depopulated mesothelium (star), appear as moving centripetally in order to fill the gap in the monolayer. (Hematoxylin-eosin; × 1,000). **(d)** This imprint was taken from a rat 5 days after the experimental exfoliation. New mesothelial (arrow) redress the denude area through replication and centripetal migration. (Hematoxylin-eosin; × 160)

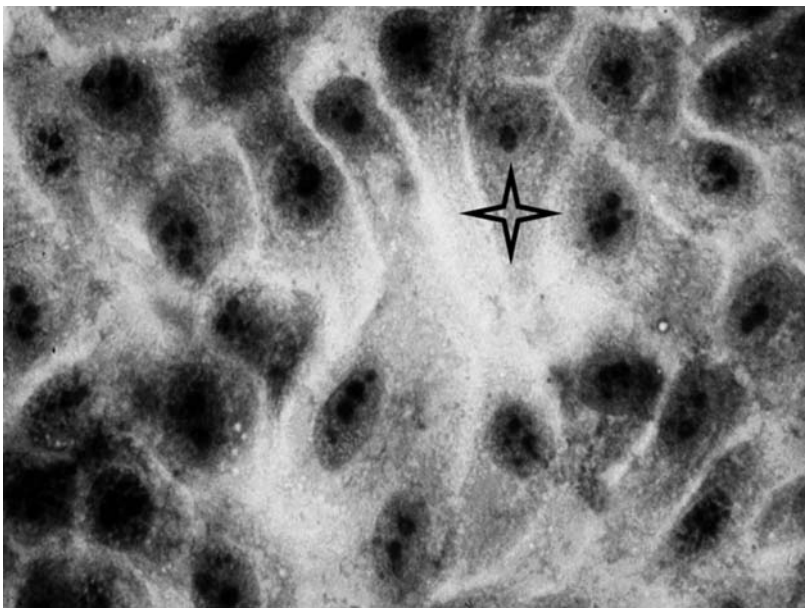

Fig. 5.53 Sample of mesothelium taken from a control animal, 10 days after the experimental exfoliation. Most of the peritoneal cavitary surface area has been repopulated. Yet, some elongated, fish like cells (four pointed star) are present, indicating that the regenerative process is still going on. (Hematoxylin-eosin. × 1,000)

of the actual number of cells undergoing mitosis. Indeed, the proportion of cells that passed the G1 checkpoint and supposed to reach S phase after some 10 h may well be similar, or even higher, than that observed during incorporation of BrdU. In addition, in vivo studies have been performed evaluating sequentially the dynamics of mesothelial repopulation, after a local mechanical exfoliation creating a doughnut-like area of undressed peritoneal surface [419]. This study demonstrated that repopulation also takes place by replication and centripetal migration of mature mesothelial cells located in in the monolayer bordering the injured area. (Figs 5.52c and 5.52d, Figs 5.53 and 5.54). Here again, the prevalence of cells undergoing mitosis is several times higher than that observed in intact, unexposed mesothelium.

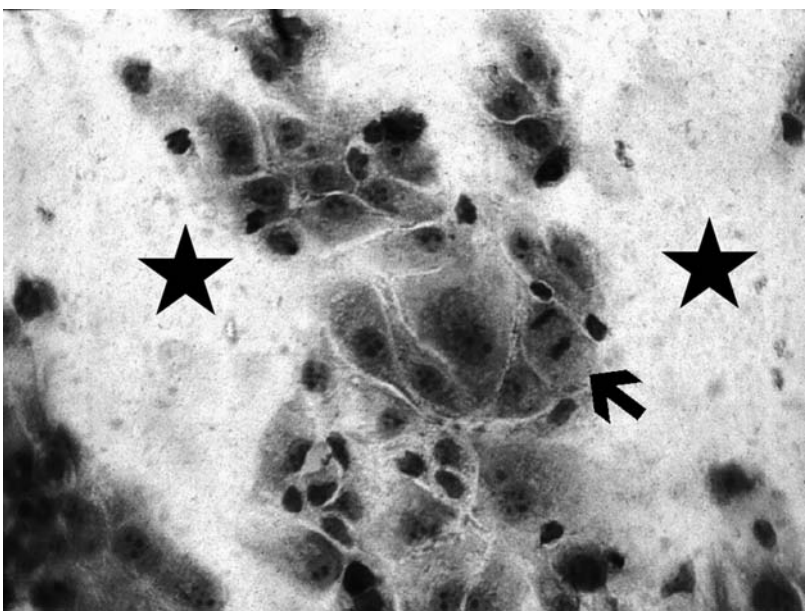

Fig. 5.54 Specimen obtained from a rat 2 days after experimental, localized, exfoliation of the monolayer. Mesothelial cells appear migrating, building up a bridge in order to repopulate undressed domains of the peritoneal cavitary surface of the liver (stars). Some cells are undergoing mitosis (arrow). (Hematoxylin-eosin; × 400)

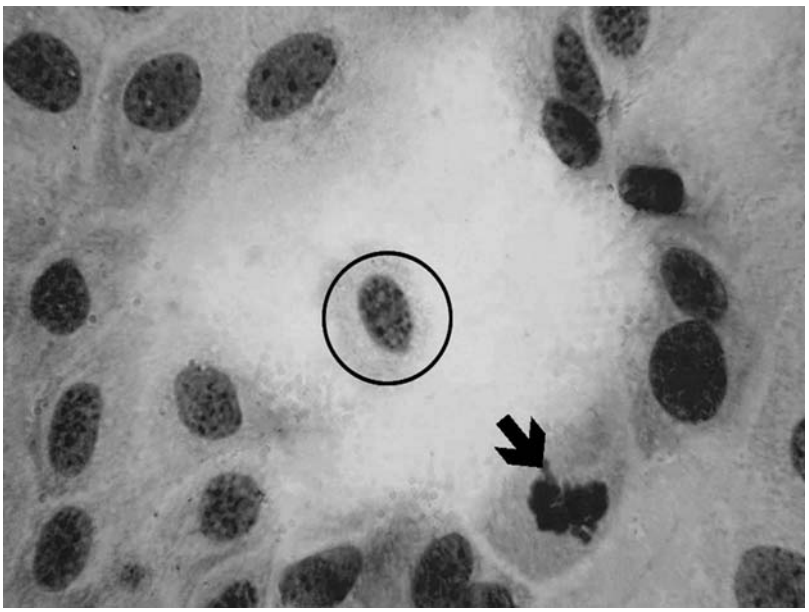

Fig. 5.55 Another sample of the monolayer recovered from a rat 5 days after the experimental exfoliation. One mesothelial cell is located in the middle of a depopulated area. (black circle), surrounded by young cells, one of them undergoing midosis (arrow). This image illustrates about the complexity of identifying the origin of new, repopulating cells. This specific cell could have reached the peritoneal surface migrating from the bordering area or from the submesothelial tisuue, or just be a free-floating mesothelial cell, recently implanted on the cavitary aspect of the peritoneum. (Hematoxylin-eosin; × 1,000)

All this evidence suggests that, most likely, mesothelial cell regeneration takes place through three different processes occurring simultaneously: implantation of young wandering mesothelial cells, migration of mesothelial cell precursors coming from the underlying connective tissue, and mitosis and migration of mature mesothelial cells bordering the injured area. The individual contribution of each mechanism cannot still be evaluated, as suggested by the presence of isolated new mesothelial cells repopulating denuded areas of the peritoneal surface (Fig. 5.55). These cells could eventually derive from by any of the already mentioned pathways of regeneration. According to studies done using the doughnut model of mesothelial regeneration, complete repopulation of the monolayer occurs after a recovery period of 15 days (Fig. 5.56).

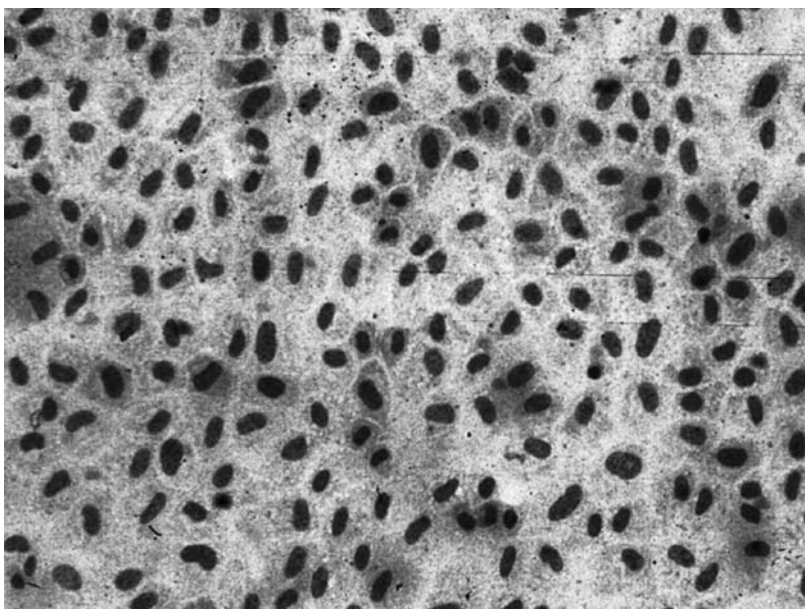

Fig. 5.56 Imprint recovered from a control rat, 15 days after performing a localized, doughnut shaped exfoliation of the monolayer dressing the anterior liver surface. The injured area appears completely repopulated. (Hematoxylin-eosin; × 400)

The Price of a Failing Regeneration

The normal density population of mesothelial cells dressing the cavitary aspect of the peritoneum is around 300,000/cm^2 in mice and rats [31, 420].

This number remains basically unchanged in the intact, unexposed animal, showing a minimal and non significant variability between samples of the same animal, as well as between those obtained from different mice or rats. This situation of no numerical change results from a continuous replacement of dying cells by means of cell replication. This mechanism has also been detected in peritoneal biopsies taken from human patients on long-term peritoneal dialysis [421], suggesting that the therapeutic procedure induced a situation of continuous mesothelial injury, coupled to an also continuous process of regeneration. This working hypothesis found support in the original observation of Di Paolo et al. [26] regarding the absence of mesothelial microvilli in peritoneal biopsies taken from patients on CAPD, later on identified as a sign of impending apoptosis [422] (Fig. 5.51).

A tight regulation of the rates of cell growth and cell death is critical for maintaining a normally populated monolayer. In this sense, a decreased rate of mesothelial cells growth, an increased proportion of dying cells, or both could eventually lead to a depopulated monolayer that, in turn, would result in repair by means of connective tissue [399, 423, 424], the thickness of which can be as high as 100 μ.

So far, during the situation of steady state, new mesothelial cells continuously replace the dying ones [425]. This steady state is broken when: a) the magnitude of cell injury overwhelms the regenerating capabilities of the monolayer; b) the cell cycle of the mesothelial cells is blocked or departs from its normal course; and c) both developments occurring simultaneously. When the balance between regeneration and injury is broken, proliferative mechanisms are required to relieve the structural alterations represented by a depopulated monolayer. This process of repopulation and regeneration is dependent on the presence of a resilient cell population that has retained the potential for proliferation and differentiation. Failure of this mechanism leads to repair by means of connective tissue, which, in turn, becomes the first step toward peritoneal fibrosis and sclerosis [425] (Fig. 5.57). At this point it is pertinent to remind that submesothelial peritoneal sclerosis is an extremely frequent complication of long term peritoneal dialysis. It has been detected in about one half of dialyzed patients during the first year on peritoneal dialysis [426], whereas its prevalence reaches an 80% level after only 2 years on the aforementioned technique of renal replacement therapy [427, 428]. Actually, a variable degree of diffuse peritoneal fibrosis has been documented in all patients who have been on long-term peritoneal dialysis [429]. And, in turn, this development paves the way to membrane failure [430], a situation in which, at least from the point of view of its dialytic capabilities, the peritoneum is no more peritoneum.

Mesothelial cells are extremely vulnerable to minor injury. Mild drying or wetting of rat cecal peritoneum for 5 min induced mesothelial cell degeneration and detachment, and severe interstitial edema [393, 394]. This fragility of the monolayer is somehow compensated by the remarkable regenerative capabilities mentioned before. Evidence of this property is brought to light by the almost complete repopulation of the mesothelium 15 days after its massive exfoliation resulting from exposure to a 0.125 mg% Trypsin solution during a period of 10 min [431] (Fig. 5.58). This enzyme is commonly used in order to harvest mesothelial cells from human omentum or from experimental animals [432].

However, as stated in the title of this section, exfoliation always demands a price. Meticulous observation of peritoneal biopsies showed, in the same animals, small domains were depopulation was repaired by connective tissue, launching at the local level the mechanisms involved in peritoneal sclerosis (Fig. 5.58). Recently published investigations have shown that new fibroblastic cells can develop from native mesothelial cells by a mechanism of epithelial-to-mesenchymal transition, launched by injury resulting from the use of poorly biocompatible dialysis solutions [433]. So far, these findings coincide with previously reported observations [420, 425] postulating that the mesothelial cell plays a key role in the preservation of the peritoneum as an effective dialysis membrane, as well as in its structural break down and final functional failure. In addition, it has been postulated that submesothelial myofibroblasts, actively involved in the reaction to the persistent tissue injury derived from exposure to PD solutions, take part in the inflammatory response leading to extracellular matrix accumulation and angiogenesis. Probably, these cells may also arise from mesothelial cells through epithelial to mesenchymal transition [433].

Peritoneal sclerosis goes along with a marked increase in the density of microvessels of neoformation. This phenomenon of neoangiogenesis has been detected in peritoneal biopsies of patients in long term peritoneal dialysis [433–436], as well as in rats after experimental induction of the fibrous reaction [431]. Those studies showed that the thicker the peritoneal tissue, the higher the number of vessels/surface area unit.

Besides, analysis of the microvascular alterations seen in humans on long-term peritoneal dialysis led Williams et al. [436] to systemize and define four sequential degrees of pathology, that go from presence of subendothelial hyaline material with thickness lower than 7 μm (degree 1); same changes but with thickness over 7 μm (degree 2); additional

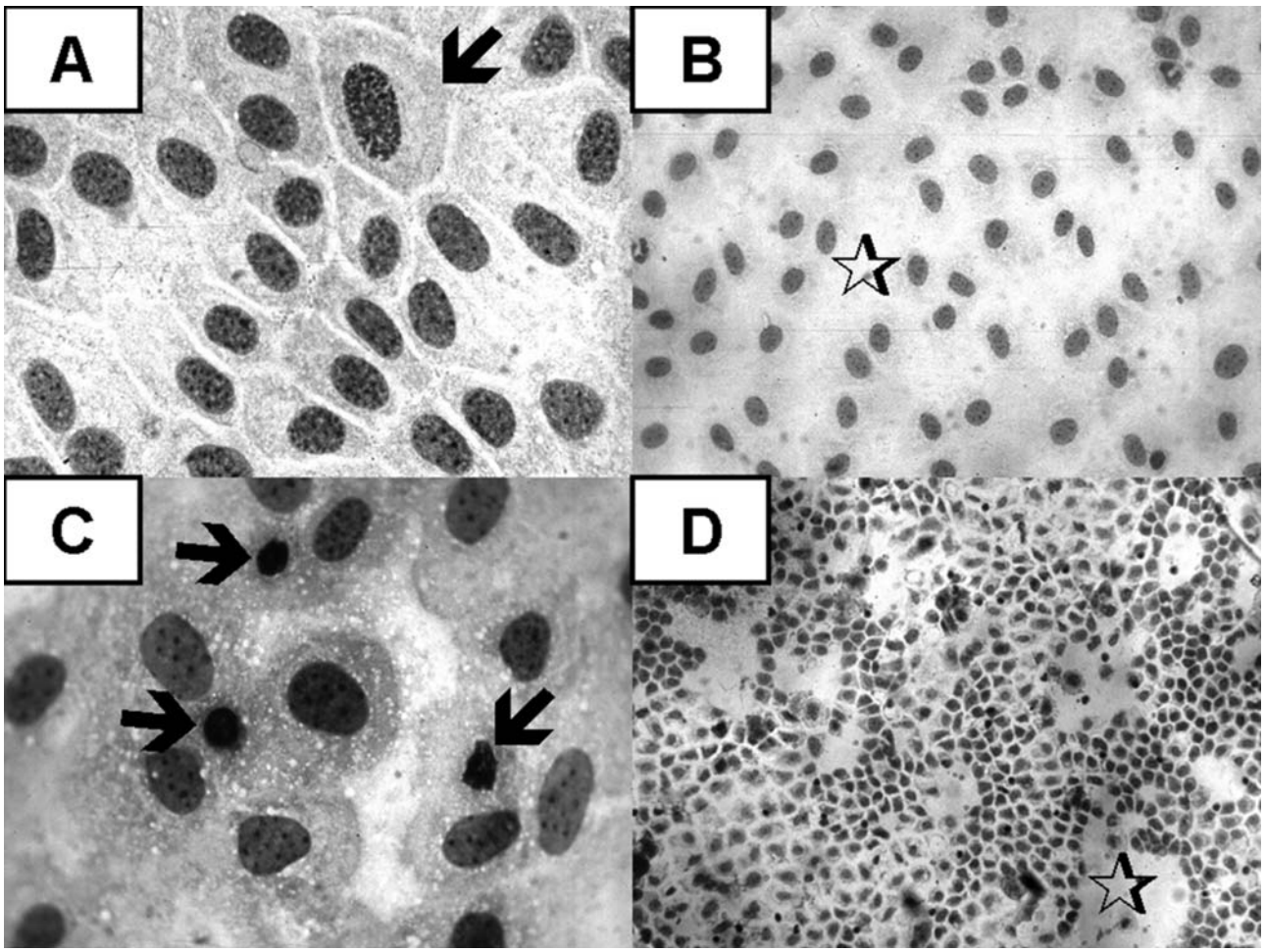

Fig. 5.57 **(a)** Mesothelial sample exfoliated from an intact, unexposed mouse. Arrow points at one cell in methaphase, (Hematoxylin-eosin; × 1,000). **(b)** Imprint obtained from a rat after being treated with one daily intraperitoneal injection of a 4.25% glucose, lactated dialysis solution. Open star denotes one of the many undressed domains of the liver surface. (Hematoxylin-eosin; × 400). **(c)** Same sample of Inset B at larger magnification. Notice the presence of unusual number of phagocytized apoptotic bodies (arrows). (Hematoxylin-eosin; ×1,000). **(d)** Specimen recovered from a rat treated during 30 days with one daily injection of 7.5% icodextrin dialysis fluid. Open star calls attention to the presence of large domains of undressed peritoneal liver surface. (Hematoxylin-eosin; × 160)

luminal distortion or narrowing (degree 3); and luminal obliteration (degree 4). It is interesting to remark that in this same study [436], 87% of patients treated with PD for periods of 6 years, exhibited clear signs of microvasculopathy, and that in 66% of them, changes reached degree 4. Therefore, two thirds of microvessels appeared closed. From this information it may be deduced that, in the long range, development of neovascularization does not automatically imply increase of blood flow. Indeed, having such a high proportion of occluded microvessels, not few areas of the peritoneal tissue become, with time, underperfused. This point should be taken into consideration in order to analyze the pathophysiology of permeability changes commonly detected in cases of membrane failure. This, in addition to the increased thickness of the peritoneal membrane that, per se, will substantially affect the transit time of solute's molecules between the still permeable capillaries and the peritoneal cavity.

All osmotic agents present in commercially available solutions for peritoneal dialysis share, regarding the long-term exposed monolayer, at least three basic effects: a substantial reduction of the cell population density of around 50%, a mitotic index near zero, and a significantly increased prevalence of nonviable cells [423].

This information suggested that the monolayer became depopulated under the influence of dialysis solutions (Figs. 5.59 and 5.60). But, going from bad to worse, the regenerative capabilities of the mesothelial cells still dressing the cavitary surface of the peritoneum appeared substantially reduced. In addition, the mechanisms leading to regeneration are substantially restrained, at least in experimental grounds, by the continuous exposure to the commonly used osmotic agents. This concept finds support in experimental observations done in rats using the "Doughnut" model of mesothelial regeneration in the rat [419]. After a ring of the monolayer was exfoliated, animals were exposed to either

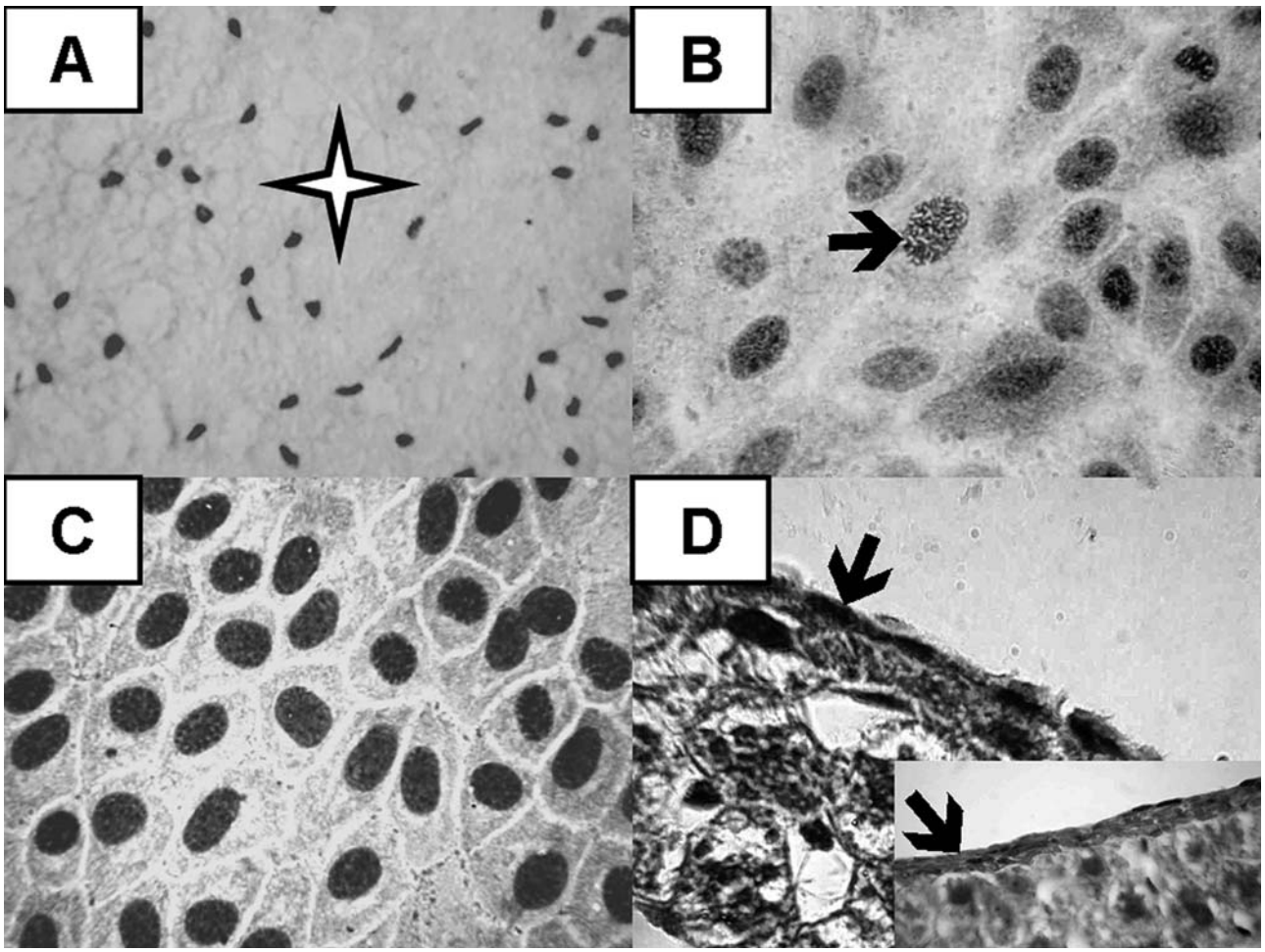

Fig. 5.58 **(a)** This sample was taken from a mouse after a 15-min exposure to 0.125% Trypsin solution. Notice the substantially decreased density of the cell population and the consequent presence of large depopulated areas (four-pointed star). (Hematoxylin-eosin; × 160). **(b)** Imprint exfoliated from a mouse 2 days after the 15-min exposure to the 0.125% Trypsin solution. Increased density as well as mitosis (arrow), point at the undergoing process of repopulation. (Hematoxylin-eosin; × 400). **(c)** Repopulated, normal monolayer seen after a recovery period of 30 days after the experimental intervention. (Hematoxylin-eosin; × 400). **(d)** Liver biopsy taken at the end of the 15-day recovery period. A normal monolayer is dressing the cavitary aspect of the liver surface (arrow). (Hematoxylin-eosin; × 400).

Inset. Other sector of the same biopsy showing that in spite of the repopulation, occasional areas of repair by means of fibrous tissue can be detected (arrow). (Hematoxilin–eosin; × 160)

4.25% glucose or 7.5 icodextrin dialysis solution for a period of 30 consecutive days. Macroscopic observation of the abdominal cavity at the end of the observation period showed that most animals developed scarring and fibrous adhesions at the level of the injured areas. Imprints and biopsies taken from the affected domains confirmed that not only repopulation failed, but that the missing mesothelial dressing was replaced by a thick layer of fibrous tissue, containing numerous microvessels of neoformation (Fig. 5.61). Consequently, these observations support the contention that both osmotic agents, 4.25% glucose and 7.5 icodextrin, substantially restrain the normal process of mesothelial repopulation expected to take place during and after the experimental exfoliation. This development launched the repair mechanisms leading to peritoneal sclerosis.

Several studies have shown evidence indicating that different cell types exposed to hydrogen peroxide display a reduced rate of proliferation, premature senescence, and, consequently, higher prevalence of apoptosis [437]. Within this context, additional experiments exposed to view the existence of a dose-related effect. Indeed, low levels of oxidants potentiate growth signals and enhance proliferation as long as the specific cell type can initiate new rounds of mitosis (Fig. 5.50), whereas higher concentrations of oxidants can block cell proliferation, which, in turn, derives in premature senescence and the consequent activation of the mechanisms leading to apoptotic cell death [438] (Figs. 5.45 and 5.46).

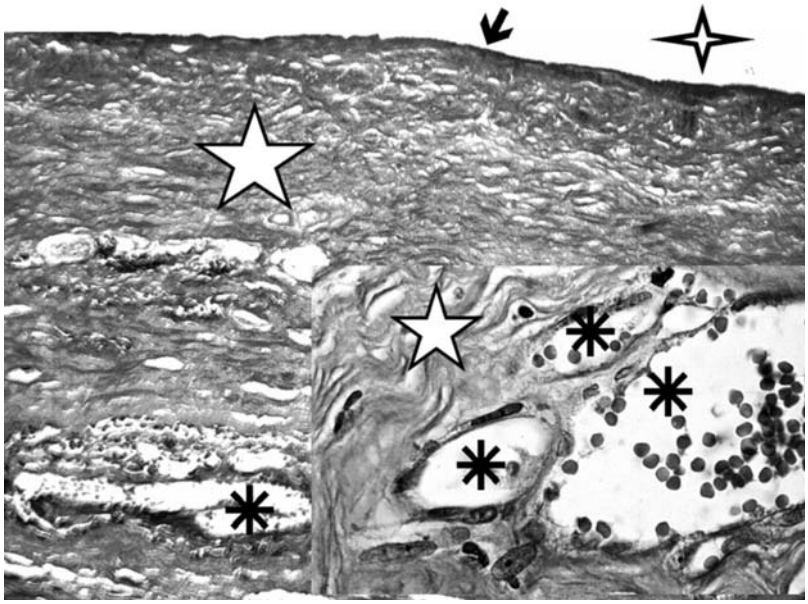

Fig. 5.59 Biopsy of parietal peritoneum taken from a patient with total membrane failure developed after being treated with CAPD for a period of 44 months. Notice the absence of mesothelial dressing (Arrow) on the peritoneal surface facing the abdominal cavity (four-pointed star). A thick layer of fibrous tissue (white star) replaced the missing monolayer. These images define the the situation of peritoneal sclerosis. (Asterisk: venule of neoformation). (Masson × 160).

Inset: Other section of the same biopsy showing a group of microvessels (asterisks) indicating the magnitude of neovascularization. (White star: fibrous tissue). (Masson × 400)

Higher degrees of oxidative injury lead to cell death by nonphysiological, necrotic pathways that, in turn, put in motion the local inflammatory reaction derived from extravasation of the cytoplasmic contents into the interstitial tissue [439] (Fig. 5.62). Both glucose-enriched solutions and icodextrin have the intrinsic capabilities of inducing different degrees of oxidative stress upon the exposed mesothelium. Glucose acts through products derived from its nonenzymatic degradation [440] and the irreversible formation of AGE products [441] by glucose autoxidation [442] and/or by oxidative mitochondrial DNA damage [443]. Icodextrin, in turn, induces substantial lipid peroxidation of mesothelial cell's membrane almost immediately after being infused into the abdominal cavity [444, 445].

This injury derives, at least in part, from the intra-abdominal formation of carbonyl compounds during the dwell time [446]. This phenomenon of carbonyl compounds liberation during the dwell time has been shown by the same group of investigators, using amino acid–based dialysis solutions.

Development of oxidative injury is facilitated by the demonstrated capability of mesothelial cells in culture to generate hydrogen peroxide [447]. This interpretation of the above-mentioned chain of events has been substantiated by a recent study, showing that acute and severe in vivo oxidative stress applied to the mesothelial monolayer results in

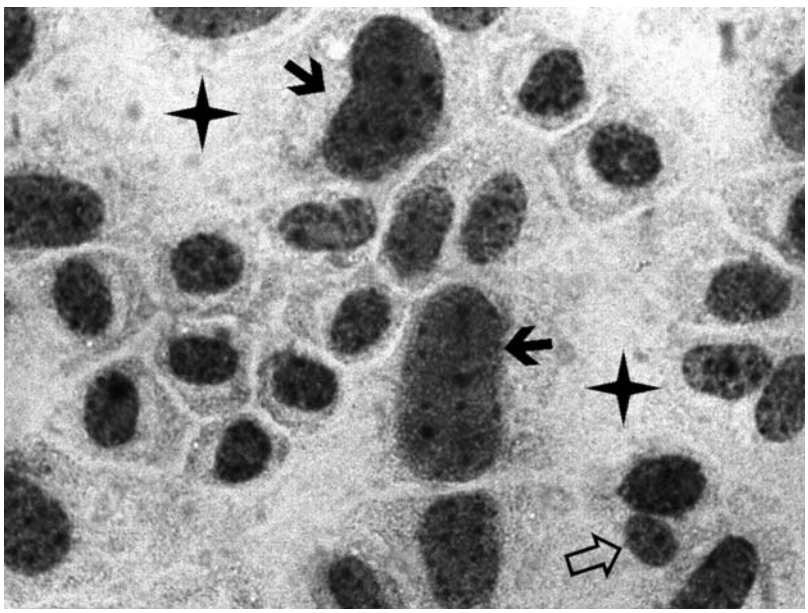

Fig. 5.60 Imprint of the mesothelial monolayer recovered from a mouse after being injected once a day, during 30 consecutive days with a 1.1% Aminoacids solution for peritoneal dialysis. Density of the mesothelium looks reduced as shown by the presence of depopulated areas (four-pointed stars). Black arrows indicate large, senescent cells. (Open arrow: Binucleated mesothelial cell with one micronucleus, the presence of which is suggestive of DNA damage). (Hematoxylin -eosin; × 1,000).

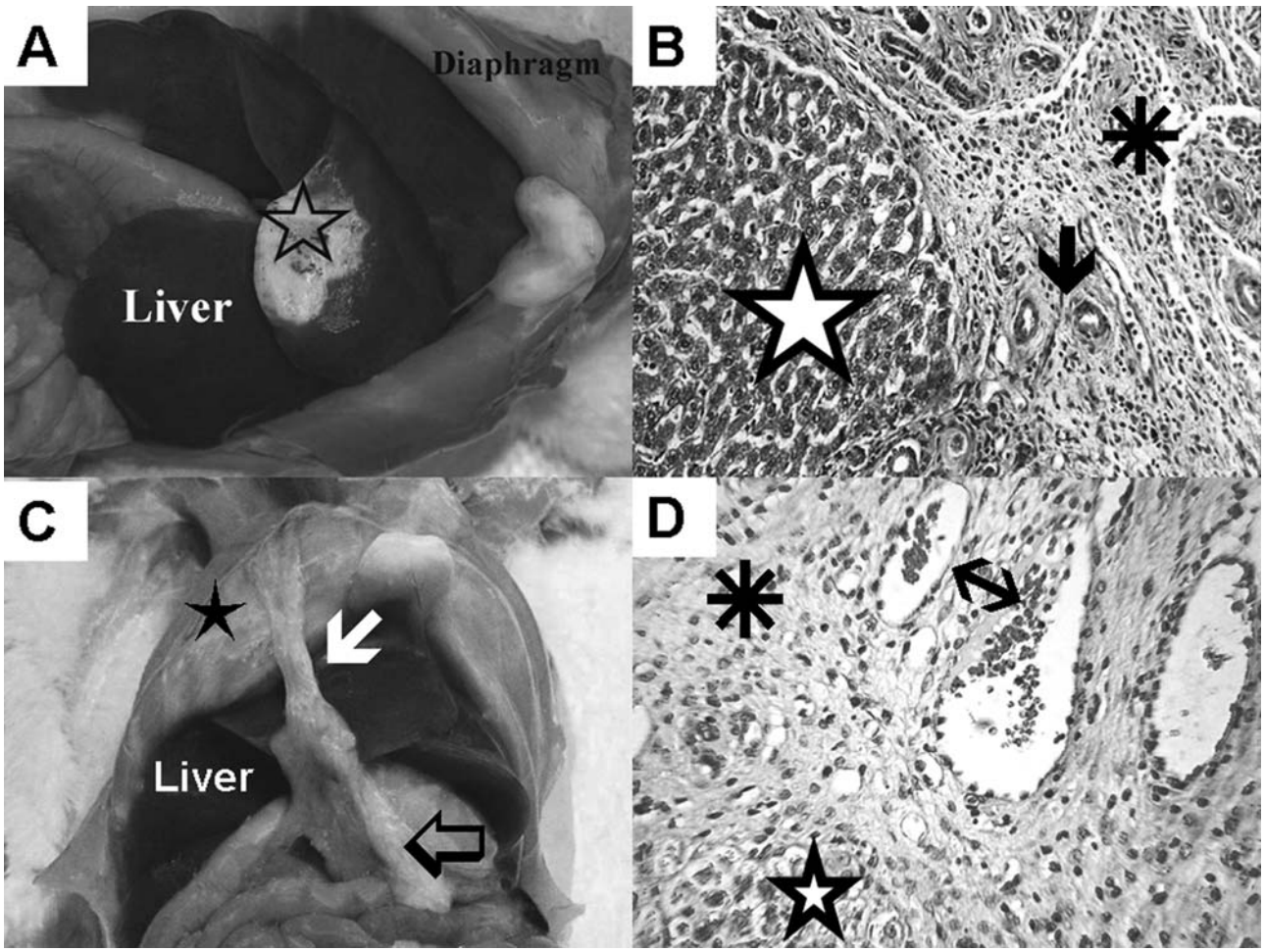

Fig. 5.61 **(A)** Photograph taken 15 days after focal exfoliation of an 8-mm diameter, doughnut-shaped area of mesothelium. The intervention was performed on the anterior liver surface of a rat that, after the procedure, was treated with one daily intraperitoneal injection of a 4.25% glucose, lactated dialysis solution. A failing repopulation derived in fibrous scarring of the exfoliated area (open star). **(B)** Sample of the liver taken from the same rat showing a thick layer of fibrous tissue (asterisk) that replaced the absent mesothelial dressing. (White star: liver tissue; black arrow: microvessels of neoformation). (Hematoxylin-eosin; × 160). **(C)** Open abdominal cavity of a rat that, after creation of a doughnut-like local exfoliation on the anterior liver surface, received one daily intraperitoneal injection of 7.5% icodextrin dialysis fluid, during 15 consecutive days. Notice the fibrous adhesion (white arrow) between an intestinal loop (open arrow), the experimentally injured liver surface and the diaphragm (black star). **(D)** This specimen belongs to the same rat of Inset C. A dense layer of fibrous tissue (asterisk) appears covering the subjacent liver tissue (five-pointed star). Double arrow points at two venules of neoformation. (Hematoxylin-eosin; × 160)

extensive fibrosis, adhesions, and permeability changes similar to those observed in clinical ultrafiltration failure [448] (Fig. 5.63).

Peritoneal sclerosis has been induced in rodents by in vivo exposing the membrane to a variety of experimental interventions: asbestos [449], 0.1% chlorexidine [450], iron dextran [451], glucose degradation products [452], AGE deposits derived from uremia per se [453], sodium hypochlorite [454], lipopolysaccharide [455], low pH of around 3.8 [456], pure water combining low pH and hypo-osmolarity [457], silica [458], and zymosan [459].

It should be noticed at this point of the analysis that, with a few exceptions (pure water, chloroxidine, and low pH), the other substances quoted as used to experimentally induce peritoneal sclerosis operate setting out different degrees of oxidative stress [460–471]. So far, after evaluating the aforementioned offered evidence, it may be concluded that addition of antioxidant agents to the currently used peritoneal dialysis solutions seems to be a quite rational and wanted development [472, 473].

We cannot complete this review without mentioning the enigmatic problem of sclerosing encapsulating peritonitis (SEP), currently also named encapsulating peritoneal sclerosis (EPS). This fearful syndrome leads to a situation in

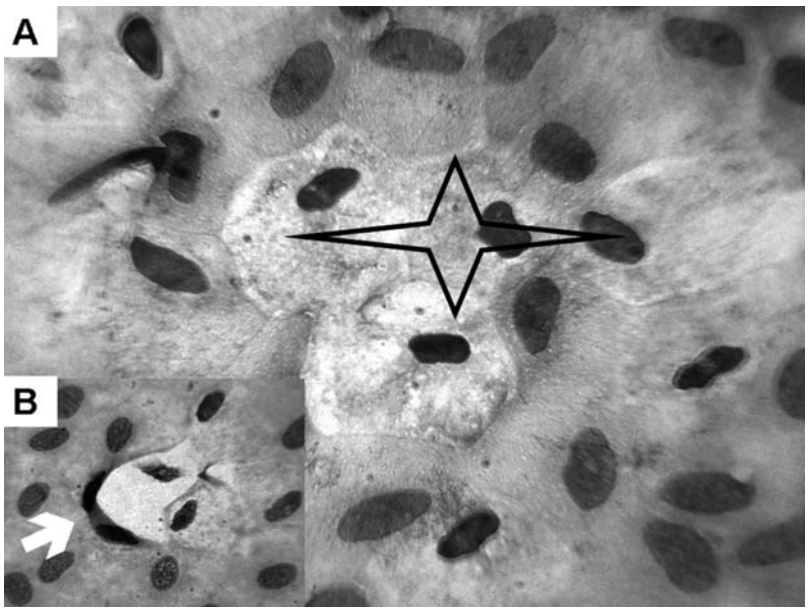

Fig. 5.62 **(A)** Imprint recovered from a rat 10 min after acute oxidative injury. Group of mesothelial cells undergoing picnotic changes (4 points star). (Hematoxylin-eosin; × 1,000). **(B)** Other aspect of the same specimen showing picnotic mesothelial cells exfoliating from the peritoneum dressing the anterior liver surface. (Hematoxylin-eosin; × 160)

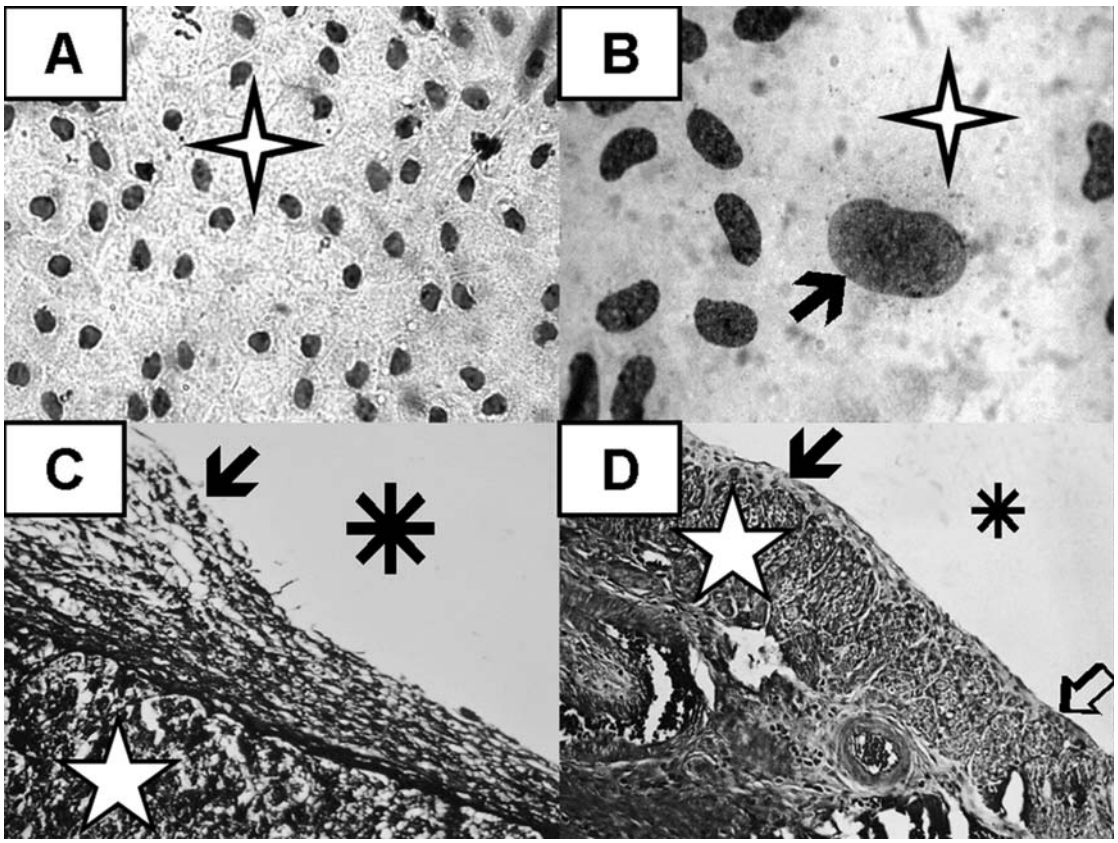

Fig. 5.63 **(A)** Imprint taken from the liver surface 10 min after experimental exfoliation by means of 5 mM/L deoxycholate solution. It is evident that most of the peritoneal surface is devoid of the normally seen mesothelial dressing (open star). (Hematoxylin-eosin; × 160). **(B)** After a recovery period of 15 days, mesothelial cells are still absent in large domains of the peritoneal surface (open star), suggesting that fibrous repair took place, instead of regeneration of the monolayer. Arrow points at a large senescent mesothelial cell. **(c)** Sample of a liver biopsy obtained from a rat, 15 days after the experimental intervention using deoxycholate. A thick layer (arrow) of fibrous tissue replaced the missing mesothelial monolayer. (Asterisk: peritoneal cavity; white star: liver tissue). (Hematoxylin-eosin; × 400). **(d)** Section of small intestine recovered from the same rat mentioned in Inset C. Some areas of the intestinal wall are covered by a wide coat of fibrous tissue (black arrow), whereas neighboring domains show a normal mesothelial dressing (open arrow). (Asterisk: peritoneal cavity; five-pointed white star: intestinal wall). (Hematoxylin-eosin; × 160)

which a thickened, fibrous sheet of tissue envelops the small intestine [474–477], liver, and stomach, as well as pelvic organs. This complication covers a wide range of morphological alterations starting from peritoneal opacification, passing through the tanned peritoneum syndrome, and finally reaching replacement of the serosal layer by fibrous tissue. Fibrous bands may be present compromising mesentery, gallbladder, spleen, liver, and stomach, as well as pelvic organs and even the cavitary aspect of the peritoneal tissue. The most affected areas configure, at times, a mass of fibrous tissue packaging abdominal viscera, conforming the cocoon that usually includes loops of small intestine as well as pockets of encapsulated ascites. Light microscopy reveals serosal fibrosis and total absence of the mesothelial monolayer, replaced by a thick layer of connective fibrous tissue, the thickness of which can reach 4 cm [478, 479] (Fig. 5.64). Neovascularization is also seen, even though these blood vessels show major structural alterations: sclerosis of the whole vascular wall, at times occlusion of the lumen, and even hyaline changes of the blocked microvessels (Fig. 5.65). Peritoneal calcifications and formation of bone and even bone marrow have been detected. All this may be combined with wide areas of inflammatory infiltrates [480, 481].

Changes detected in patients with SEP/EPS appear far away from those described in the commonly observed peritoneal sclerosis. Besides, its prevalence in patients on peritoneal dialysis is, fortunately, extremely low, whereas the impact of each condition is absolutely different. SEP/EPS carries a quite poor prognosis, with a mortality rate ranging between 26 and 93% [480], whereas simple peritoneal sclerosis basically leads patients to switch to other ways of renal replacement therapy, usually hemodialysis. These differences support the concept postulated by Di Paolo and Garosi [478, 479], who concluded that both conditions represent different nosological entities. In patients on peritoneal dialysis, the origin of this complication is still ill-defined. Many possible factors have been invoked (acetate, hyperosmolarity, recurrent peritonitis, glucose, antiseptics, intraperitoneal antibiotics, bacterial endotoxins), even though there is no available evidence clearly demonstrating specific relevance for any of them [474, 482]. Besides, at least one case has been reported on a chronic uremic patient having renal replacement therapy by means of only hemodialysis [483].

It should be noticed that sclerosing peritonitis has been reported in not few clinical situations unrelated to both, chronic uremia and peritoneal dialysis as: idiopathic [484, 485], associated with the use of some β-blockers such as practolol [486], propranolol [487], or timolol [488], as well as to metoprolol [489], oxprenolol [490], and intraperitoneally administered antibiotics such as tetracycline [491]. Besides, the literature mentions cases of sclerosing peritonitis associated to intra-abdominal tumors like gastric carcinoma, carcinoma of pancreas, familial polyposis of colon, renal carcinoma, lymphoma, ovarian teratoma or thecoma, and even in patients affected by liver cirrhosis as well as after liver transplantation [492–502]. So far, our understanding of SEP/EPS is still blurred as a result of the complexity of the problem, and namely, by its multiple ethiopathogenesis.

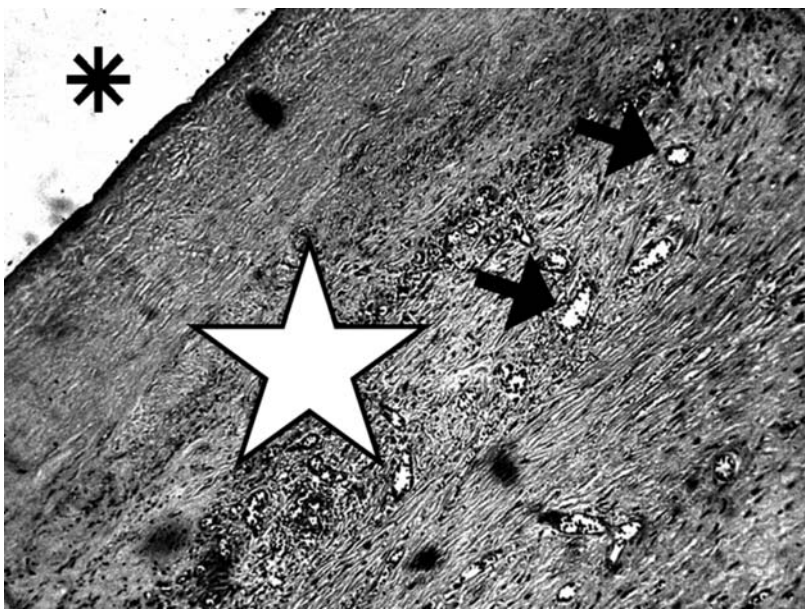

Fig. 5.64 Biopsy of parietal peritoneum recovered from a patient with sclerosing peritonitis. A thick layer of around 2,500 microns (white star) is covering the peritoneal surface. (Asterisk: peritoneal space; arrows: blood vessels of neoformation). (Hematoxylin-eosin; × 100)

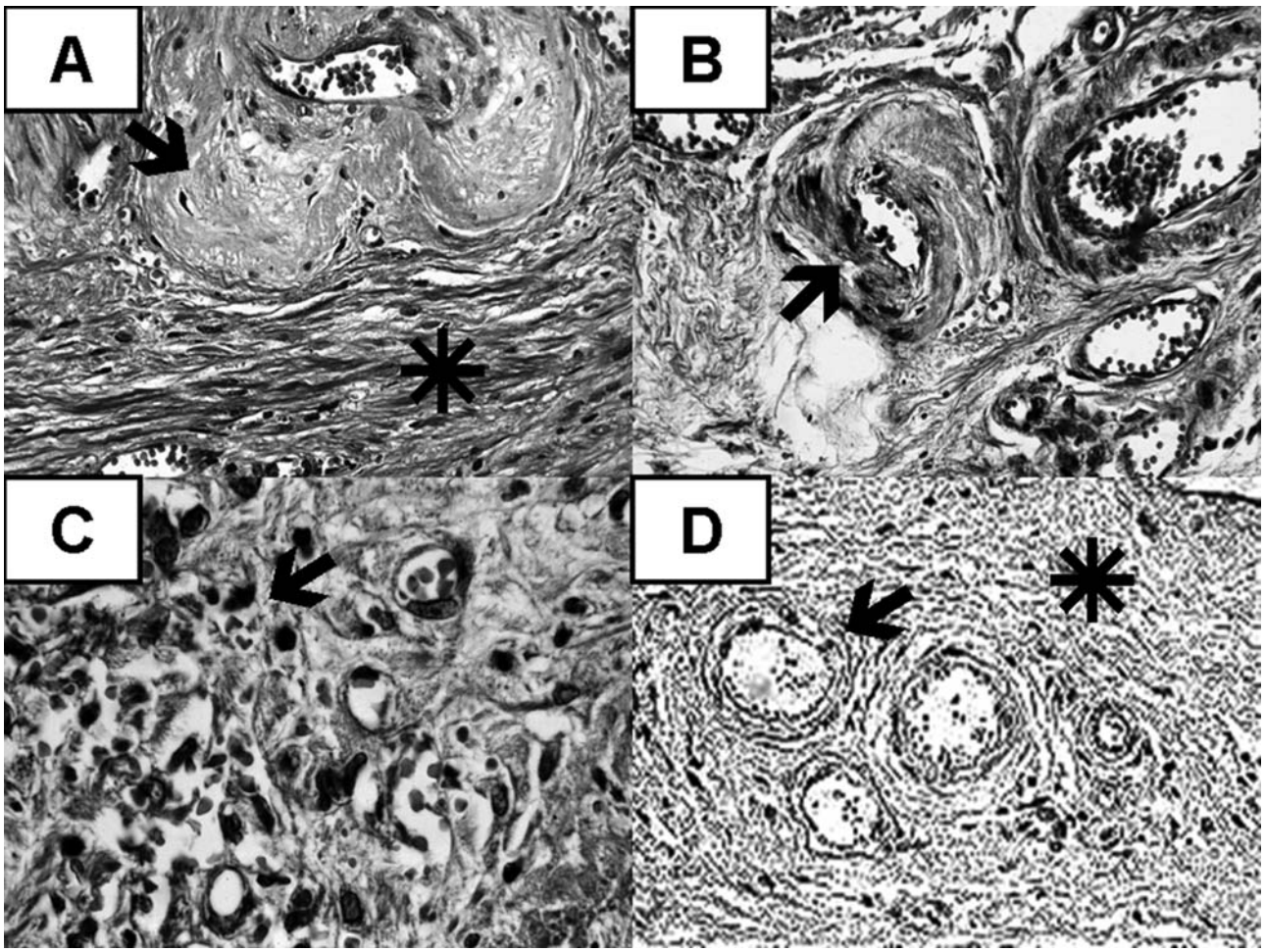

Fig. 5.65 **(A)** Dense hyaline deposits (arrow) located in the thickened wall of an almost obstructed blood vessel of neoformation, embedded in a mass of fibrous tissue (asterisk). (Masson; × 160). **(B)** Microvessels of neoformation showing thickened sclerotic wall (arrow). (Masson; × 160). **(C)** Mononuclear cells (black arrow) infiltrating the fibrous tissue surrounding blood vessels of neoformation (open arrow). (Masson; × 400). **(D)** Perivascular fibrosis in blood vessels (arrow) embedded into a densely packed interstitial mass of fibrous tissue. (Hematoxylin-eosin; × 400)

The Potential Use of the Mesothelium as a Source of Mesenchymal Stem Cells

As stated in the previous paragraphs, the existence of pluripotent mesenchymal cells as precursors of the mesothelium has been already proposed. Even though a mesothelial stem cell has not yet been definitely identified, the existence of pluripotent mesenchymal cells in the mesothelial monolayer as well as in the submesothelial connective tissue, has been repeatedly considered in the literature [401], opening the way in order to consider their use, as an actual option, in regenerating therapies [503].

Some observations performed in human pathology as well as in animal experimentally induced tissue reactions lend strong support to this contention. As a living proof, it may be mentioned that differentiation towards cartilage and bone has been described in a primary tumour of pleura, suggesting that mesothelial cells are pluripotent. In this sense, being mesenchyma, they may well retain the potential to differentiate along embryonic developmental lines, including cartilage and bone [504, 505].

Besides, cartilaginous differentiation of the peritoneum not associated with intra-abdominal malignancy has been already detected [506], whereas bone and cartilaginous formation has been reported in both, human patients and experimentally induced mesothelioma [507, 508]. Bone formation was also seen in four cases of sclerosing peritonitis observed in patients treated by means of peritoneal dialysis, whereas in two of them, islands of bone marrow were also detected [481].

Interestingly, glomerular-like structures in fibrous tissue of biopsies of visceral peritoneum have been detected in biopsies taken from rats with experimentally induced peritoneal sclerosis [505] (Fig. 5.66). This information emphasizes the capability of the mesothelium to differentiate in other cell lines in response to injury [504].

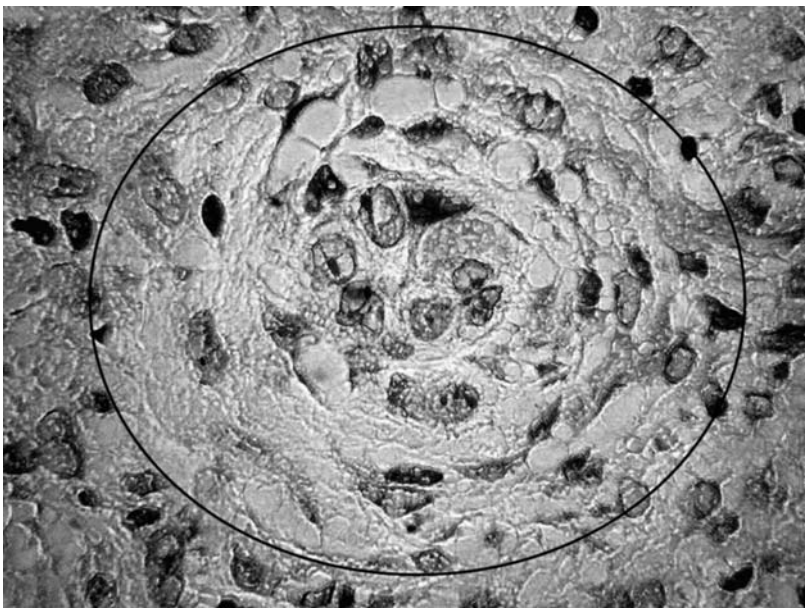

Fig. 5.66 Glomerular-like structure detected in fibrous tissue covering the cavitary aspect of the liver. The specimen was taken from a rat with experimentally induced peritoneal sclerosis. (Hematoxylin-eosin; × 400).

Additional research identified mesenchymal cells in the adult human synovial membrane. These cells showed the capability to differentiate in chondrocytes and osteocytes [509, 510]. Synovium, also of mesenchymal origin, is considered one more type of serous membrane like peritoneum, pericardium and pleura [511]. Therefore, this common embryological origin opens the possibility of eventual therapeutic interventions in the course of joint diseases that could be performed using peritoneal mesothelial cells [505].

Recent published evidence exposed to view the fact that, when placed under the appropriate biophysical and/or biochemical conditions mesothelial cells demonstrate a remarkable degree of plasticity. This property supports the concept, that mesothelial cell progenitors are endowed with the capability to switch between different cell types, according to the conditions of their microenvironment [504]. Within this context, it is illustrating to remind the observed myofibroblastic conversion of human adult mesothelial cells in culture, under the influence of transforming growth factor (TGF)-β-1 [512, 513].

The relationship between blood cells and mesothelium represents one more exciting aspect of this topic. As mentioned before, a proposed mechanism of mesothelial healing postulated that progenitor cells, originally located in the bone marrow, migrate and convert into mesothelial cells [380]. Although additional research concluded that this hypothesis looks unlikely [403], a link between both cell lines seems to be possible. A quite strong point is that hemangioblasts, a proposed progenitor of the endothelial and hematopoietic cell lineages, derive from the embryonic splanchnic mesothelium. This structure, in turn, has been proposed as the embryonic source of the endothelium-lined vascular system, pointing at a specialization of the phylogenetically older celomic cavities. Within this context, the origin of the hematopoietic cells might be related to differentiation of celomocytes derived from the celomic epithelium. So far, endothelial and blood cells appear to derive from a common mesothelial-derived progenitor [514].

In addition, morphological and immunohistochemical evidence for a translocation of cells from the celomic mesothelium to the ventral wall has been observed during development of the quail embryos. Consequently, the concurrence of translocation of mesothelial cells and the appearance of aortic smooth muscle cell progenitors point at a link between the former and the latter cells lineages [515].

This ontogenetic relationship between mesothelium, blood, and blood vessels is substantiated by two excellent studies performed applying the tools of tissue bioengineering. Donna et al. [516] presented evidence demonstrating that cultured adult human mesothelial cells have the capabilities to generate hematopoietic cells, similar to those of the bone marrow. This conversion was confirmed by morphological analysis as well as by cell immunoreactivity toward specific antibodies directed to antigens of the hematopoietic cell lines, at various stages of differentiation. The experiment was performed culturing mesothelial cells in collagen sponges. This is one more suggestion of the remarkable plasticity of the mesothelium, as well as of the relevance of the microenvironment hosting the cultured cells. Regarding blood vessels, a key study is that reported by Campbell et al. [517], who succeeded in creating an artificial blood conduct by inserting a Silastic tubing into the peritoneal cavity of rats. Two weeks after the surgical intervention, a new laparotomy showed that the implanted

silicon rubber tubing was covered by several layers of fibroblasts, collagen matrix, and a single layer of mesothelium. This new "blood vessel" was everted and successfully grafted by end-to-end anastomosis, in arteries of the same animal in which it was grown. These observations have been confirmed by Moldovan and Haveman [518], as well as by our group [505].

So far, it seems evident that peritoneal mesothelial cells are endowed with a degree of plasticity that shapes their capability of generating other cell lines, if placed in the appropriate micro-environment. Investigative steps will have to define the best conditions that will eventually lead to the use of mesothelium in stem cell therapy as well as in tissue engineering, taking also in account that harvesting of large numbers of cells from patients having an unexposed monolayer, may well be unlimited.

Final Remarks

It was not the purpose of the author merely to deliver a cold and tedious description of anatomical structures. On the contrary, the goal has been to offer the reader a comprehensive and balanced analytical approach of structure and function covering, at least in part, their interactions. It is evident that the function of the peritoneum as a dialysis membrane cannot be evaluated only within the frame of passive diffusion through water-filled, cylindrical pores [204] and/or mathematical models [519], based on assumptions that, at times, lose sight of the formidable barrier of the living cell membrane as well as the structural organization of the tissues.

Research during the last two decades provided enough evidence to characterize the peritoneum not as an inert dialyzing sheet, but as a living and reusable membrane for dialysis [271], as predicted more than 25 years ago [520].

It becomes evident that the mesothelial monolayer continuously exposed to dialysis solutions in vivo is structurally and functionally different, at least from the histochemical point of view, from that observed in unexposed–intact cells, or in those growing in the in vitro set-up of culture and later exposed to experimental incubation [521]. Therefore, I have the feeling that a good deal of creative thinking is required to integrate data obtained during 50 years of physiological studies and mathematical models, with the realities of tissue structure and cell biology.

Introduction of peritoneal dialysis as a therapeutic tool to fight chronic uremia shaped a kind of chain reaction that went well beyond the expectations of the early years. Actually, observations made in clinical settings showed the way to a new window open to the fascinating world of cell biology. Within this specific field, there are still more questions than answers.

It is the author's hope that this chapter will serve to stimulate the imagination of young scientists as a catalytic element for further research.

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Chapter 6
The Physiology of Peritoneal Solute, Water, and Lymphatic Transport

R.T. Krediet

The Surface Area of the Peritoneum

Few studies have been published on the magnitude of the surface area of the peritoneum. Wegener mentioned a surface area of 1.72 m^2 in one adult woman [1] and Putiloff a value of 2.07 m^2 in one adult male [2]. More recent autopsy studies reported lower values [3–5]; the average peritoneal surface area in adults ranged from 1.0 m^2 [3] to 1.3 m^2 [5]. Using CT scanning in continuous ambulatory peritoneal dialysis (CAPD) patients a value of 0.55 m^2 has been found [6]. Some studies reported relationships between peritoneal surface area and body weight and/or body surface area, while others did not. The ratio between peritoneal surface area and body weight in adults is about half of that found in newborn infants [3]. A difference between adults and infants is barely present when peritoneal surface area is related to body surface area [3]. The peritoneal/body surface area averaged 0.6–0.8 in adults and 0.5–0.6 in infants. About 60% of the peritoneum consists of visceral peritoneum, 10% of which covers the liver, 30% of mesenterium and omentum, and 10% is parietal peritoneum [3–5]. The latter includes the diaphragmatic peritoneum, which comprises 3–8% of the total peritoneal surface area. Species differences are present, especially with regard to the contribution of diaphragmatic peritoneum, which is larger in humans than in rodents [5]. The contribution of the various parts of the peritoneum to solute transport during peritoneal dialysis may vary. Evisceration was found to cause a marked reduction in the transport of creatinine in rabbits [7] but not in rats [8, 9]. Effective peritoneal dialysis has been described in a neonate with extensive resection of the small intestine [10]. It has been hypothesized that the peritoneum covering the liver might be especially important in solute transport during peritoneal dialysis because of the close proximity with the liver sinusoids, but this could not be confirmed in experimental studies in rats [11, 12]. The diaphragmatic part of the peritoneum is especially involved in the absorption of solutes and fluid from the peritoneal cavity into the lymphatic system [13]. Observations in rats have shown that the peritoneal surface area increases with the age of the animals, with a proportional increase in dialysate/plasma (D/P) ratios of urea and creatinine [14].

The proportion of the peritoneum that is involved in transport during peritoneal dialysis is not known. The above-mentioned evisceration experiments suggest that the relative contribution of the parietal peritoneum may be more important than that of the visceral peritoneum. Although similar diffusion rates were found during experiments in rats undergoing peritoneal dialysis using a diffusion chamber, placed at various parts of the peritoneum, it appeared that only 25–30% of the visceral peritoneum was in contact with the dialysis solution [11]. Furthermore, it has been shown in cats that commercial dialysis solutions increase blood flow to the mesentery, omentum, intestinal serosa, and parietal peritoneum without altering total splanchnic blood flow [15]. This study, using microspheres, points to hyperemia of these tissues, thereby increasing the peritoneal capillary surface area.

It appears from the above data that the surface area of the peritoneal membrane involved in peritoneal dialysis is not a static property but should be defined in a functional way. The functional surface area of the peritoneal membrane cannot be measured directly, but the functional cross-sectional exchange pore area divided by the effective diffusion path length can be estimated. This parameter takes not only the capillary surface area into account, but also the distance to the dialysate/mesothelial contact. Using kinetic modeling, values of 117–250 m have been reported [16–19]. When the surface area of the peritoneum that is involved in transport is 0.6 m^2 and the unrestricted area over diffusion distance is set at 190 m, it can be calculated that the length from the capillary wall to the peritoneal cavity would be 3 mm in case of unrestricted diffusion in water. As the peritoneum is much thinner, this means that the resistance to diffusion of interstitial tissue must greatly exceed that of water. This will be discussed further in the following section.

R.T. Krediet (✉)
Academic Medical Center University of Amsterdam, Amsterdam, Netherlands
e-mail: c.n.deboer@amc.uva.nl

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Pathways and Barriers

Solutes passing from the blood in the peritoneal capillaries to the dialysate-filled peritoneal cavity have to pass at least three structures that can offer resistance: the capillary wall, the interstitial tissue, and the mesothelial cell layer (Fig. 6.1). Stagnant fluid layers at the mesothelial site have also been proposed as sites of resistance [20]. However, it has been calculated by Flessner that these are only a minor barrier to solute transport compared to the interstitial tissue [21]. The mesenterium is an important layer in the prevention of friction between abdominal organs, and is also involved in host defense. It is, however, not a main barrier to peritoneal transport of solutes and water. In vitro studies on the diffusion properties of an isolated avascular part of mesentery, thus representing transport in a diffusion chamber across two layers of mesothelium divided by interstitial tissue, have shown that the diffusion of particles with a molecular weight up to 500 kDa was similar to the expected values on the basis of their molecular weights [22, 23]. A pore radius of 0.7 μm could be calculated [22]. In vivo studies have shown that, although permeability coefficients were lower than in vitro [24], intraperitoneally administered macromolecules could easily pass the mesothelial layer [25, 26]. The mesothelium of the parietal peritoneum was also no osmotic barrier [27].

The interstitial tissue in general consists of bundles of collagen within a mucopolysaccharide hydrogel. It has been described as a two-phase system, in which a colloid-rich, water-poor phase is in equilibrium with a water-rich, colloid-poor phase [28]. The mucopolysaccharides of the colloid-rich phase are mainly composed of glycosaminoglycans, either hyaluronan or proteoglycans fixed to their core proteins. The free fluid phase is interspaced between areas of the colloid-rich phase. It is assumed that water transports throughout the interstitial space, while small solutes are partly excluded from the colloid phase and protein transport is restricted to the tortuous, water-rich phase. The thickness of the peritoneum is variable depending on its localization. In the mesentery the average thickness from mesothelium to mesothelium is 30 μm, with exceptions up to 110 μm [29]. The parietal peritoneum is loosely attached to the abdominal wall and easily stripped. Its thickness is estimated to be 2 mm [30]. The visceral peritoneum is more dense and firmly attached to the underlying tissues [30]. Examining cross-sections of the gut reveals that the thickness of the serosa varies from 30 to 250 μm [31]. Assuming a contribution of the visceral peritoneum to solute transport of 30% [11], an average thickness of the peritoneal interstitium of 500 μm can be calculated. This corresponds to the findings of Flessner et al. in which the steepest concentration gradient of EDTA in various parts of the peritoneal interstitium was found 400–600 μm from the serosa [32]. This is a factor 6 less than the 3 mm calculated on the basis of the unrestricted area over diffusion distance. This difference is likely to represent the restriction of the interstitial tissue to diffusion, compared with diffusion in water. The question arises whether this interstitial restriction is size-selective, i.e., the proportional restriction of solutes with various molecular weights is more pronounced than can be expected on the basis of free diffusion of these solutes only. The in vitro studies using an isolated mesentery suggested no size selectivity [22, 23], but the in vivo study on an isolated rat mesentery provided evidence that the apparent diffusion coefficients of various neutral dextran fractions were progressively lower than those in water [33]. No size selectivity was found for low molecular weight solutes.

The capillary wall is probably the most important restriction barrier. Solute transport occurs size selectively and is generally considered to take place through a system of pores [34, 35]. Although the vascular wall is likely to be

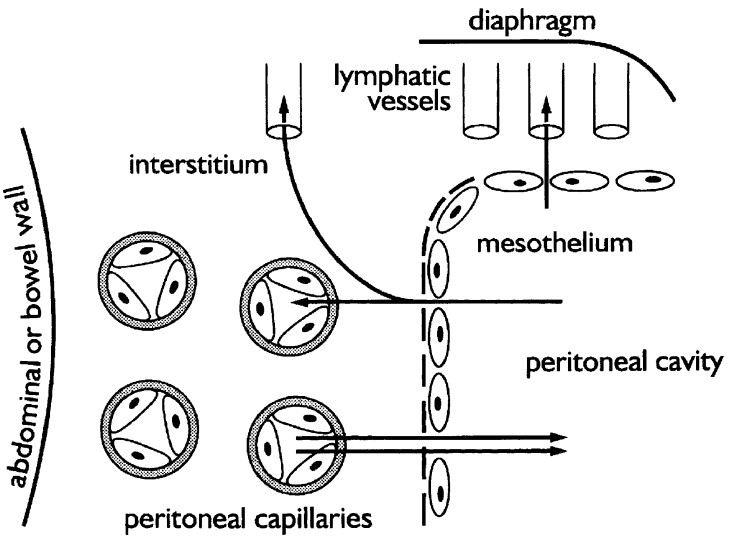

Fig. 6.1 A schematic representation of the peritoneal membrane. Diffusion and transcapillary ultrafiltration occur in two directions. Transcapillary ultrafiltration from the peritoneal capillaries to the peritoneal cavity occurs through small interendothelial pores and transcellularly through water channels. Lymphatic absorption from the peritoneal cavity is partly directly into the subdiaphragmatic lymphatics and partly into the lymphatics that drain the mesothelium

heteroporous, the capillary wall can be considered to function mainly as an isoporous membrane in combination with a small amount of very large pores, as has been described for the glomerulus [36]. This combination is known as the two-pore theory of capillary transport [37–39]. This theory assumes the presence of small pores with radii of 40–50 Å that are involved in the transport of low molecular weight solutes. Interendothelial clefts with radii of 40 Å have been considered the anatomical equivalents of the small pores [40, 41], but this is still an assumption. Transport through plasmalemmal vesicles, that would form channels, has also been suggested in electron microscopy studies [42]. It is not known to what extent the endothelial glycocalyx is involved in solute transport during peritoneal dialysis.

The two-pore model also consists of a small number of large pores with various radii, that are expressed as the average large-pore radius. The number of large pores is likely to be less than 0.1% of the total pore count and their average radius exceeds 150 Å. These pores are involved in the transport of macromolecules, such as serum proteins. The morphological equivalent of the large pores has not been established. Electron microscopic studies also suggested transport of macromolecules through plasmalemma vesicles [43]. Such a transport route would, however, require active metabolic processes and hence energy. Cooling experiments reduced the transcapillary passage of albumin only to the extent that cooling reduced passive transcapillary filtration, but not to the extent that would be expected due to decreased cell metabolism [44]. A light short-term fixation of vascular endothelial cells had no effect on their permeability to albumin [45]. Also the administration of transcytosis inhibitors did not reduce the peritoneal transport of albumin and LDL [46]. It follows from these experiments that the transcapillary transport of macromolecules is not an active process, but occurs by passive filtration and/or diffusion. Other possible morphological equivalents of the large-pore system are transcellular channels, vesicular-vacuolar organelles, or interendothelial gaps. It has been shown that the interendothelial vesicles that can be seen with electron microscopy are actual invaginations from either side of the cell membrane [47] with the possibility of a connection, thereby forming a channel. This theory has more recently been extended by the description of vesicular-vacuolar organelles (VVO) that would account for the increased vascular permeability of tumor vessels [48, 49]. VVO are grape-like clusters of vesicles and vacuoles present in the cytoplasm of endothelial cells lining venules and small veins. The individual vesicles and vacuoles are interconnected with each other and with the endothelial cell plasma membranes by means of fenestrae that may be open or closed by diaphragms. The function of these VVO is up-regulated by vascular endothelial growth factor [50].

Other candidates for the large pores are the postulated presence of very rare interendothelial clefts in which the adherence discontinuity is three to four times wider than in the ordinary clefts [38], or venular interendothelial gaps with radii of 500–5,000 Å, that can be provoked by the administration of histamine [51]. Such gaps could also be induced by other locally produced vasodilating substances. All this evidence indicates that the large-pore radius is not a constant value, but that it can be subject to variations. In other words, the capillary wall is a heteroporous membrane that can be described by the combination of a large set of small pores with uniform radii and an additional small set of large pores with different radii. The radius calculated for the large pores is therefore an average value.

The two-pore model with a predominance of small pores of uniform size does not explain the discrepancy between sieving coefficients and osmotic reflection coefficients that is found in peritoneal dialysis. The sieving coefficient (S) describes the magnitude of convective solute transport (solute transport coupled to the transport of water; solvent drag), while the reflection coefficient (σ) of a solute to a membrane determines its osmotic effectiveness. Both can range between 0 and 1 for a semipermeable membrane. For a homoporous membrane the relationship between the two is: $S = (1 - \sigma)$. Various studies on convective transport of low-molecular-weight solutes have reported sieving coefficients (calculated as solute clearance/net volume flow) of 0.6–0.7 [52–56]. However, estimates of the reflection coefficient of glucose yield values ranging between 0.02 and 0.05 [57–61]. This apparent discrepancy has been explained by assuming the presence of water-conductive ultrasmall pores in the plasma-lemma of endothelial cells with radii of 3–5 Å allowing the transport of water, but not of solutes (free water transport) [17, 62, 63]. This so-called three-pore model also explains why glucose is an effective osmotic agent during peritoneal dialysis despite its small size (radius 2–3 Å). According to this model about one-half of transcapillary ultrafiltration would occur through these ultrasmall pores, whereas the other half passes through the small interendothelial pores. Estimations in CAPD patients showed that transcellular water transport contributed about 40% to ultrafiltration, but with marked interindividual differences [64, 65].

At the time of the above computer simulations, a 28-kDa protein was discovered, present in the plasma membrane of red blood cells and *Xenopus* oocytes, that appeared to be involved in channel-mediated water transport [66]. This protein, originally named CHIP 28, and now aquaporin-1, was subsequently found to be the water channel in the proximal tubular cells of the kidney [67]; it is present both in the apical and basolateral membrane of these cells [68]. Water can be transported through it when an osmotic gradient is present. Aquaporin-1 is also present in various nonfenestrated epithelia [69]. It could be detected in endothelial cells of peritoneal capillaries and venules, both at mRNA and at protein levels [70, 71]. Peritoneal tissues also contain aquaporin-3 and -4, but their expression is much less pronounced [72]. Besides in endothelial cells, aquaporin-1 has also been shown in mesothelial cells of peritoneal biopsies [73]. Cultured mesothelial cells express aquaporin-1 and their expression is up-regulated by glucose [74].

A similar effect was found for aquaporin-3 [75]. Endothelial aquaporin-1 is likely to be the major water channel that constitutes the ultrasmall pore system. This is based on studies inhibiting aquaporin-1 function by the administration of mercury compounds [76]. Intraperitoneal administration of mercury chloride reduced free water transport, both in rats [77] and in rabbits [78]. Even more convincing are the results obtained in aquaporin-1 knock out mice. These animals showed a reduced peritoneal osmotic water permeability [79] and an absence of free water transport as judged from the sieving of sodium [80]. Heterozygotes had some reduction in sodium sieving.

Mechanisms of Solute Transport

Diffusion and convection are the mechanisms involved in the transport of solutes during peritoneal dialysis. Diffusion through a membrane takes place when a concentration gradient is present. According to Fick's first law of diffusion, the rate of transfer of a solute is determined by the diffusive permeability of the peritoneum to that solute (the ratio between the free diffusion coefficient of that solute and the diffusion distance), the surface area available for its transport, and the concentration gradient:

$$J_s = \frac{D_f}{\Delta x} \cdot A\Delta C \tag{6.1}$$

in which J_s is the rate of solute transfer, D_f is the free diffusion coefficient, Δx is the diffusion distance, A is the surface area, and ΔC is the concentration gradient. $D_f A/\Delta x$ is called the permeability surface area product or the mass transfer area coefficient (MTAC). During peritoneal dialysis, ΔC is the concentration difference between the plasma concentration of a solute (P) and its dialysate concentration (D):

$$J_S = \mathrm{MTAC}(P - D) \tag{6.2}$$

Convective transport or solute drag occurs in conjunction with the transport of water, and thus during ultrafiltration. It is determined by the water flux (J_v), the mean solute concentration ($\bar{C}$) in the membrane, and the solute reflection coefficient (σ):

$$J_s = J_v \bar{C}(1 - \sigma) \tag{6.3}$$

For reasons of simplicity $\bar{C}$ is often approached as:

$$\bar{C} = \frac{(P + D)}{2} \tag{6.4}$$

Staverman's reflection coefficient σ is the fraction of the maximal osmotic pressure a solute can exert across a semi-permeable membrane. It equals 1.0 for an ideal semi-permeable membrane and 0 when the membrane offers no resistance to the transport of a solute. With an isoporous membrane $\sigma = 1 - S$ in which S is the sieving coefficient. S is the ratio between the concentration of a solute in the filtrate divided by its concentration in plasma when no diffusion occurs. The explanation for the discrepancy between S and σ values has been discussed in the section on pathways and barriers.

Size-Selectivity

Diffusion of solutes across the peritoneal membrane is a size-selective process. It means that small molecules diffuse at a faster rate than large molecules due to differences in their free diffusion coefficients. The question whether the peritoneal membrane is a size-selective barrier in itself can be analyzed by relating transport by diffusion of various solutes to their molecular weights. When a particle is an ideal sphere the relationship between its radius (r) and molecular weight (MW) is given by:

$$\mathrm{MW} = \frac{4}{3}\pi r^3 \tag{6.5}$$

The relationship between the free diffusion coefficient (D_f) of a solute and its radius is given in the Einstein-Stokes equation:

$$D_f = \frac{RT}{6\pi\eta r N} \tag{6.6}$$

in which R is Bolzmann's gas constant, T is the absolute temperature, η is the viscosity of the solvent, and N is Avogadro's number. This implies that, in the case of an ideal sphere, the free diffusion coefficient of a solute is related to the cubic root of its molecular weight:

$$D_f = a\mathrm{MW}^{-0.33} \tag{6.7}$$

in which a is a constant.

It is evident from the above that relationships between solute transport and molecular weight should be expressed as power functions:

$$y = ax^b \tag{6.8}$$

or

$$\ln y = b \ln x + \ln a \tag{6.9}$$

This implies that the power (b) is the slope of the correlation line that is obtained when x and y are plotted on a double-logarithmic scale. Most solutes are not ideal spheres. When the free diffusion coefficients in water of urea, glucose, and inulin were plotted against their molecular weights on a double-logarithmic scale, the slope of the correlation line was −0.46 [81, 82]. This implies that values up to −0.46 are consistent with free diffusion across the peritoneal membrane. In that case only the surface area determines the maximal transport capacity. Values exceeding −0.46 imply size-selectively restricted diffusion. This means that the membrane itself (the pore size or the interstitium) offers an additional size-selective barrier to the transport of solutes. For the clearances of low-molecular-weight solutes up to β_2-microglobulin (MW 11.8 kDa), a value of −0.44 was found during intermittent peritoneal dialysis [83]. During CAPD we found a value of −0.50 (Fig. 6.2).

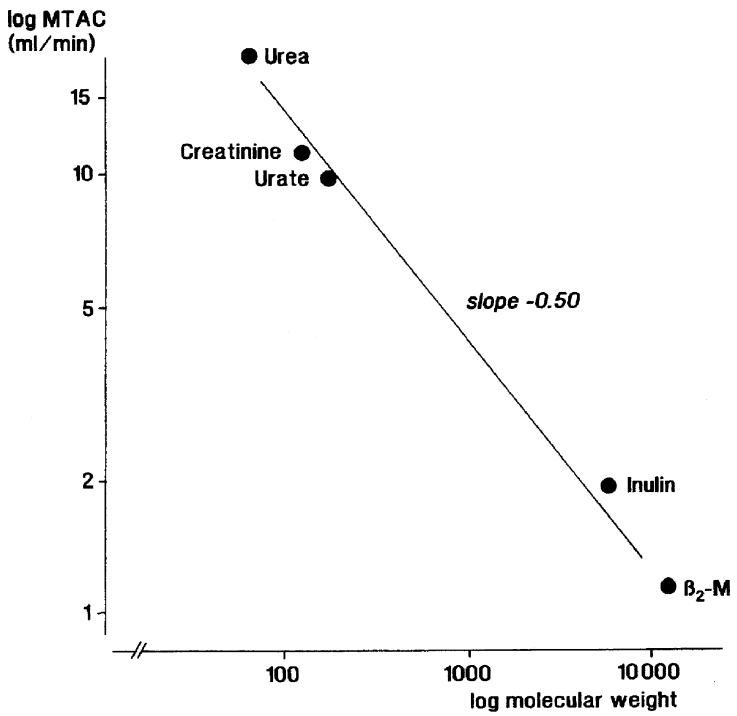

Fig. 6.2 The power relationships of MTAC of low- and middle-molecular-weight solutes with their molecular weights. Mean values are given. Based on data from [92, 98]. See text for explanation

These data give no indication for an important size-selective restriction barrier for low molecular weight solutes during peritoneal dialysis, but are more in favor of a transport process, similar to free diffusion in water, but in a colloid/water interstitial ground substance as vehicle for diffusion, instead of water. It follows from Eq. 6 that this will influence the magnitude of the diffusion rates, but the effects will be similar for all low-molecular-weight solutes. The functional or effective peritoneal surface area is mainly determined by the number of perfused peritoneal capillaries (the number of pores) in combination with interstitial resistances. No evidence is available that exogenous factors such as the hydration status of the interstitium would markedly influence MTAC of low-molecular-weight solutes. This contrasts with the observation that under basal circumstances only 25% of the peritoneal capillaries are perfused, and that this may be changed by exogenous stimuli (see section on regulation of peritoneal transport) [84]. In addition, it has been shown that splanchnic blood volume, not the flow rate, is an important determinant of peritoneal solute transport capacity [85]. It can therefore be concluded that the peritoneal vascular surface area is the main determinant of the MTAC of low-molecular-weight solutes. Consequently, the MTAC of such a solute, for example, creatinine, can be used as a functional measurement of the vascular peritoneal surface area. Changes in the MTAC of creatinine in individual patients are likely to reflect changes in their vascular peritoneal surface area.

Another approach to describe the size-selectivity of the peritoneal membrane is to relate MTAC of various solutes to their free diffusion coefficients in water, instead of to their molecular weights. This is based on the notion that the molecular weight of a solute is not the only determinant of its diffusion velocity. The density and the shape of a molecule can also have an effect. This is evident for nonprotein macromolecules, such as dextrans. Based on the equation: radius = 3.05 $MW^{-0.47}$ [86], as derived from the data of Granath and Kvist [87], it can be calculated that the dextran fraction with a diffusion radius identical to that of β_2-microglobulin (MW 820 kDa) has a molecular weight of only 4.6 kDa. For α_2-macroglobulin (MW 820 kDa) the molecular weight of the corresponding dextran fraction is 176 kDa [88]. Since diffusion is the most important mechanism for the transport of low-molecular-weight solutes, and restricted diffusion may be the most important mechanism for the transport of macromolecules, the establishment of power relationships between the MTAC of solutes and their free diffusion coefficients in water, is a more rational approach than the use of the molecular weights. A power relationship was found for peritoneal clearances (C) of proteins and their free diffusion coefficients in water (D_w) [89], according to the equation:

$$C = aD_w^{rc} \tag{6.10}$$

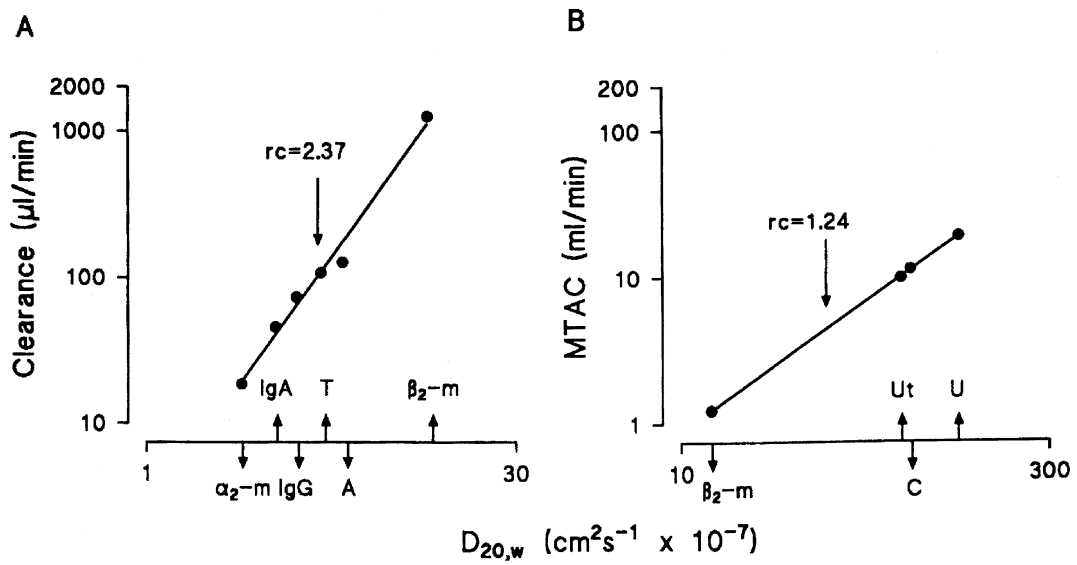

Fig. 6.3 The power relationship between MTAC of urea (U), creatinine (C), urate (Ut) and β_2-microglobulin (β_2-m) and their free diffusion coefficient in water ($D_{20,w}$) is given in panel (**a**) and the power relationship between the protein clearances of β_2-microglobulin, albumin (A), transferrin (T), IgG and α_2-macroglobulin (α_2-m) and their free diffusion coefficients in water is given in panel (**b**) All values are plotted on a double logarithmic scale. The slope of the regression line represents the restriction coefficient. A restriction coefficient of 1.0 means that a linear relationship is present between clearances of solutes and their free diffusion coefficients in water. For the low molecular weight solutes a slope of 1.24 ± 0.03 and for the proteins a slope of 2.37 ± 0.04 were found. Published with permission from [92] and from Blackwell Scientific Publications

Table 6.1 Relationship between parameters of solute transport and permeability characteristics of the peritoneal membrane

	Functional or vascular surface area	Size-selectivity or intrinsic permeability
MTAC or D/P ratio of low molecular weight solutes	+	–
Selectivity index or restriction coefficient to macromolecules	–	+

in which the slope (rc) was called the peritoneal restriction coefficient. The restriction coefficient represents the size-selective permeability of the peritoneal membrane: high values mean a low permeability. The application of the restriction coefficient in individual patients was validated both for proteins [90] and for dextran fractions [91].

A restriction coefficient that equals 1.0 means a linear relationship between MTAC and free diffusion coefficients, and no hindrance by the size-selective restriction barrier. In this situation differences in free diffusion coefficients of solutes are the only determinants of the differences in their clearances, and so the functional (vascular) peritoneal surface area is the only membrane characteristic that determines the differences in solute transport. In a study in 10 CAPD patients, a mean value for the restriction coefficient of 1.24 was found for low molecular weight solutes and of 2.37 for serum proteins (Fig. 6.3) [92]. These figures have been confirmed in a larger group of patients [93]. This is consistent with a mainly size-unrestricted diffusion process for low molecular weight solutes and a size-selectively restricted transport for macromolecules. In Table 6.1 a summary is given of the relationship between the parameters of solute transport and the permeability characteristics of the peritoneal membrane. The functional surface area can be characterized by the MTAC of creatinine. The size-selective permeability can be characterized by the calculation of the restriction coefficient. The functional surface area can be considered as a reflection of the number of pores, whereas the restriction coefficient mainly represents the size of the large pores and possible size-selective interstitial resistances.

Electric Charge

Glycosaminoglycans exhibit a negative electric charge. This is especially important in the glomerular basement membrane where the strongly negative charged glycosaminoglycan side-chains of heparan sulfate proteoglycan are involved in the charge-selective glomerular permeability [94]. Using ruthenium red staining, fixed negative charges have also been demonstrated in peritoneal tissue of rats not exposed to peritoneal dialysis [95], but with a much lower density than in the glomerular basement membrane. They were especially found on the basal lamina of the capillary endothelial cells and also along interstitial collagen fibers. It is, however, not established whether, and how, they influence solute transport during peritoneal dialysis. Intraperitoneal administration of protamine sulfate to rabbits led to increased concentrations of total protein in the effluent, that could be prevented by simultaneous administration of heparin [96]. This was interpreted as an effect of neutralization of anionic sites by protamine. Such an effect would particularly favor the transport of the negatively charged albumin molecules. A direct toxic effect on mesothelial cells leading to release of tissue proteins, however, could not be excluded [97]. No evidence for charge selectivity was found in a study comparing the transport of the negatively charged serum albumin with a dextran fraction of a similar diffusion radius in CAPD patients [98]. An opposite finding was reported in a study in rabbits that compared the transport of intravenously administered neutral and charged dextrans [99]. The positively charged dextrans were especially hindered in their transperitoneal transport. This could be explained by the assumption that the colloid-rich phase of the peritoneal interstitium behaves as a cation exchange column, facilitating the transport of negatively charged solutes through the tissue and retarding that of cationic macromolecules. Such effects are likely to disappear during steady-state conditions, as present for serum proteins during CAPD. In that situation the concentrations of serum proteins in the interstitium are probably in equilibrium with their plasma concentrations. Therefore, comparisons were made between the transport of proteins with (near)-identical sizes, but different charges. IgG subclasses range in isoelectric points between less than 6 and 8.7. Their clearances in CAPD patients were not different [100]. Comparisons between the peritoneal clearances of albumin and transferrin, β_2-microglobulin and lysozyme also gave no indication for a charge-selective barrier [101]. Only the clearances of lactate dehydrogenase (LDH) subclasses suggested charge selectivity. Observations during peritonitis showed that an alternative explanation is more likely. Fixed negative charges disappear during peritonitis [102], However, during peritonitis in CAPD patients signs of increased charge selectivity for LDH were found [101]. This could be explained by release of LDH by the cells present in the peritoneal effluent.

Taken together, most evidence points to an absence of charge selectivity of the peritoneum in the transport of macromolecules. This may be explained by the lower density of fixed negative charges in the peritoneum compared to the glomerular basement membrane. Another possibility might be the occurrence of loss of negative charges caused by the continuous exposure of peritoneal tissues to high glucose concentrations during peritoneal dialysis. Such loss has been shown to occur in the glomerular basement membrane in patients with diabetic nephropathy [103, 104]. Also a glucose-induced loss of endothelial glycocalyx might lead to loss of negative charge [105]. It is not known whether this phenomenon can also be observed in long-term peritoneal dialysis, or whether it has impact on peritoneal protein transport.

Peritoneal Blood Flow

The number of perfused peritoneal capillaries is dependent on peritoneal blood flow and blood volume [85]. Based on the anatomical situation, splanchnic blood flow is probably much more important than flow in the abdominal wall. Splanchnic blood flow averages 1,200 mL/min in normal adults [106]. Its distribution over the various splanchnic organs is markedly influenced by the instillation of dialysate. Experiments in rats, using microspheres, showed marked increases in the blood flow to the mesentery, omentum, intestinal serosa, and parietal peritoneum [15]. There was no effect on total splanchnic blood flow. Using the peritoneal clearance of hydrogen gas in rabbits [107], a value of 4.2 mL/min per kg body weight was found. Similar values could be calculated during peritoneal dialysis in rats with the microsphere technique [15]. Using the peritoneal clearance of carbon dioxide in rats an average value of 4.9 mL/min per kg was found after the instillation of an isotonic solution and of 8.1 mL/min per kg with a hypertonic dialysis fluid [108].

The relationship between peritoneal blood flow and solute transport in animals is only marginal. A reduction of blood flow in dogs by hemorrhagic hypotension caused only a 10–25% decrease in peritoneal urea clearance [109, 110]. More recent similar experiments in rats showed that a bleeding-induced reduction of peritoneal blood flow to 41% of the initial value decreased the MTAC of EDTA to 76% and that of glucose to 87% [111]. Instillation of sodium chromate in rabbits induces hepatic venous stasis leading to a decreased blood flow, but increased solute transport [85], indicating that peritoneal blood volume is more important than peritoneal blood flow. Intravenous isoproterenol in dogs increased peritoneal blood flow but had no effect on solute clearances [112]. Intraperitoneal isoproterenol resulted almost in a doubling of mesenteric blood flow, but this was accompanied by an increase in clearances of small solutes of only 20–30% [112]. More recent in vivo studies using a diffusion chamber in rats combined with laser Doppler flowmetry showed that a 70% reduction of blood flow did not alter the transfer rate of urea and mannitol across the abdominal wall [113] or hollow viscera [114]. Similar findings were done for osmotic water transport [115]. However, when blood flow was halted, the transport rates were reduced significantly. Only a reduction of the local blood flow to the liver induced significant decreases in solute transfer in this model [114], but the hepatic peritoneum makes up only a small portion of the effective exchange area. These studies imply that only a minimal blood flow is necessary for solute transport.

Estimation of peritoneal blood flow in peritoneal dialysis patients revealed lower values than in animals when expressed per kg body weight; it has been assumed to average 60–100 mL/min [116]. Studies in a limited number of intermittent peritoneal dialysis patients, using the peritoneal mass transfer area coefficient of carbon dioxide, yielded values ranging between 68 and 82 mL/min [117], or of about 150 mL/min [118]. Using the same technique in stable CAPD patients, values ranging from 20 to 151 mL/min were found in three studies using 1.36% glucose [119–121]. The median value averaged 66 mL/min. A much lower value of 25 mL/min has been estimated in one study [122, 123]. This was based on the relationship between the hydrostatic pressure and the plasma protein concentration obtained with a hollow-fiber hemofilter, and extrapolated to the situation in peritoneal dialysis. These authors also reported a linear relationship between blood flow and small solute clearances or ultrafiltration in an in vitro perfusion model of small vascular loops of isolated human peritoneal tissue [124, 125]. The "nearest capillary" hypothesis has been developed by the same group [126]. In this hypothesis it is assumed that the capillaries positioned closest to the mesothelium will be dilated and have low blood flow, while the most distal ones have the highest blood flow, but less effective diffusion due to interstitial resistances. The resulting "effective" peritoneal blood flow would be a limiting factor for solute clearances. It is difficult to predict to what extent the above models and hypotheses are important in clinical peritoneal dialysis.

In agreement with the data obtained in animals, the effects of peritoneal blood flow on solute transport in peritoneal dialysis patients are probably limited. This is supported by the following studies. (1) Effective peritoneal dialysis is possible in patients with intractable heart failure following an acute myocardial infarction [127], a condition in which decreased splanchnic blood flow can be expected. (2) CAPD with a 1.1% amino acid solution increased peritoneal

blood flow 55% compared to 1.36% glucose, but the increase in the MTAC of urea and creatinine averaged only 15% [119]. (3) Intraperitoneally administered nitroprusside had no effect on peritoneal blood flow [120, 128], but caused a marked increase in the MTAC of small solutes and macromolecules. These data make it likely that, similar to the situation in animals, peritoneal blood volume is more important than peritoneal blood flow in the transfer of solutes during peritoneal dialysis. Peritoneal blood volume can be increased by nitroprusside-induced vasodilation and by an increased venous pressure. This increased venous pressure is probably the explanation for the fact that effective peritoneal dialysis has been described in patients with severe congestive heart failure [129–133] and in patients with liver cirrhosis [134, 135].

Regulation of Surface Area and Permeability

In the previous section it has been shown that peritoneal blood flow is unlikely to be the main factor in the regulation of the peritoneal vascular surface area and permeability. Therefore endogenous substances with vasoactive properties may be involved. Plasma levels of catecholamines, vasopressin, aldosterone and plasma renin activity are elevated in CAPD patients [136–138]. This does not necessarily imply increased sympathetic activity, but could also be the result of a decreased clearance [137]. Dialysate levels of catecholamines have been measured in one study [136]. The dialysate/plasma ratio was 0.69 for epinephrine and 1.17 for norepinephrine, suggesting local production in the peritoneal cavity. A correlation was found between the dialysate levels of norepinephrine and the effective peritoneal surface area, represented by the mass transfer area coefficient of creatinine. Because this finding is the opposite of the effects of intraperitoneally administered norepinephrine, as will be discussed below, it may be that the large effective surface area causes the release of norepinephrine.

Prostaglandins and cytokines are likely to be produced locally in the peritoneal cavity during peritoneal dialysis. This has been shown for the prostaglandins 6-keto-PGF1α, prostaglandin E2 (PGE2), PGF2α, thromboxane B2 (TXB2), and 13,14-dihydro-15-keto-PGF2α [139–141]. The concentrations of the vasodilating prostaglandins exceeded that of the vasoconstricting ones. Drained peritoneal effluent also contains the cytokines tumor necrosis factor (TNF)α [142, 143], interleukin-1 (IL-1) [144, 145], IL-6 [146–148], and IL-8 [148]. The presence of TNFα in the dialysate of uninfected CAPD patients is probably caused by diffusion from the circulation [142, 143], while the other cytokines mentioned above are produced locally within the peritoneal cavity. A relationship has been reported between very high dialysate IL-6 levels in stable CAPD patients and a low peritoneal restriction coefficient, representing a high intrinsic permeability to macromolecules [147]. In that study, no relationship was found with the vascular peritoneal surface area. Marked elevations of prostaglandins and cytokines in dialysate are present during peritonitis [139–141, 146, 148, 149]. In addition, local production of TNFα also occurs during the acute phase of the inflammation [149]. It appeared that the increase in intrinsic permeability to macromolecules was especially correlated with dialysate PGE2 concentrations [149]. Intraperitoneal administration of indomethacin during peritonitis inhibited the increase of prostaglandins. This was accompanied by a reduction of the dialysate protein loss in one study [141], but this effect could not be confirmed in a longitudinal study during peritonitis [150]. Only a small effect on the peritoneal restriction coefficient for macromolecules was found [150]. Intraperitoneal indomethacin had no effect on peritoneal permeability characteristics in stable, uninfected peritoneal dialysis patients [151]. Relationships between cytokines in peritoneal effluent and permeability have been reviewed recently [152, 153].

Nitric oxide is the final common pathway for various vasodilating processes. Endothelial nitric oxide synthase (eNOS) is present in all types of peritoneal endothelia [71]. Nitric oxide is very rapidly converted into nitrite and nitrate. Dialysate concentrations of these metabolites have therefore been used to study possible involvement of nitric oxide in the regulation of peritoneal permeability. In contrast to nitrite in plasma, which is converted to nitrate, nitrite in fresh and spent peritoneal dialysis fluids is stable [121], but its concentration is much lower than that of nitrate. Comparing MTAC of nitrate with those of other solutes made it likely that dialysate nitrate concentrations in stable uninfected CAPD patients were dependent only on diffusion from nitrate from the circulation to the dialysate-filled peritoneal cavity [154]. Increased expression and activity of NOS, both endothelial and inducible, is present in a rat model of acute peritonitis [155]. Elevated dialysate nitrate concentrations have been found in some studies during the acute phase of peritonitis [154], but not in all [121]. Relationships between effluent nitrate levels and peritoneal permeability characteristics have not been established.

Possible effects of solutes, generally considered to be involved in the regulation of the permeability characteristics of the peritoneum, have been analyzed by studying transport kinetics during peritoneal dialysis after their intraperitoneal or intravenous administration. These include: 1) the dialysate itself; 2) hormones, such as catecholamines, gastrointestinal hormones and vasopressin; and 3) histamine and prostaglandins.

The administration of hypertonic and acid dialysate in the rat causes arteriolar vasodilation in the cremaster muscle preceded by an initial vasoconstriction [156–158], and also vasodilation of cecum arterioles [159]. This effect was more pronounced for acetate-buffered than for lactate-buffered dialysate, and also more pronounced for glucose 1.5% than for glucose 0.5%-containing dialysate. A more recent study using intravital microscopy confirmed that a conventional PD solution caused marked arteriolar vasodilation [160]. This effect was independent of the pH, but largely caused by the presence of glucose degradation products and to a lesser extent by the lactate buffer. The application of an iso-osmotic bicarbonate-buffered solution, which was not vasoactive in the rat cremaster muscle model, to patients treated with intermittent peritoneal dialysis, had no effect on the functional peritoneal surface area when compared with commercial dialysate [161]; however, it led to an increase in the total protein concentration of the dialysate. In further studies it appeared that this effect could not be explained solely by the osmolarity or pH of the dialysis fluid [162]. A more recent study using a single 4-h exchange with a hypo-osmotic bicarbonate-buffered solution confirmed the above findings for the clearances of individual plasma proteins [163]. However, clinical trials with bicarbonate-buffered glucose-containing solutions did not report alterations in the transport of low-molecular-weight solutes or dialysate protein loss [164–168].

Intravenously administered amino acids cause renal vasodilation [169, 170]. This effect is mediated by nitric oxide [171]. Therefore, effects on the permeability characteristics of the peritoneal membrane during CAPD could in theory be expected. However, the results of different studies on the use of amino acids are equivocal. In some studies, reviewed in [172], no effect was found on peritoneal transport [173–175], while others reported increased peritoneal protein loss [176–178]. This was accompanied by increased dialysate concentrations of PGE2. A study using a bicarbonate-buffered amino acid solution reported no effect on MTAC of low-molecular-weight solutes, increased peritoneal D/P ratios for serum proteins and increased dialysate concentrations of prostaglandins, IL-6, IL-8, and TNFα [167]. An effect on MTAC of low-molecular weight-solutes, reflecting the vascular surface area, was found in two studies [119, 179]. No increased protein clearances were present in these studies. Neither was an indication detectable for involvement of nitric oxide or prostaglandins likely [119]. It is possible that differences in the composition of the dialysis solutions can explain the divergent effects on peritoneal permeability characteristics.

Increasing the glucose concentration of the dialysis solution from 1.36 to 3.86% has no effects on the indices of the vascular peritoneal surface area or the intrinsic size-selective permeability [92]. Only the clearance of β_2-microglobulin is greater, with 3.86% glucose due to higher convective transport across the small pores [92]. The use of the glucose polymer icodextrin also increased β_2-microglobulin clearance [64, 180–182], but its administration has no effects on other peritoneal permeability characteristics [64, 180].

Intravenous administration of norepinephrine in rabbits leads to a decrease in vascular surface area as judged from the clearances of urea and creatinine [183]. In contrast, intravenous glucagon increases the clearances of urea and creatinine [184, 185]. As glucagon, a peptide with a molecular weight of 3484 Da, was not effective after intraperitoneal administration, these findings support a direct effect on the peritoneal microvasculature. The effects of glucagon have also been confirmed in dogs [112]. Vasopressin, administered either intraperitoneally [186] or intravenously [187], leads to a fall in solute kinetics consistent with a decreased effective peritoneal surface area. Topical application of histamine causes arteriolar vasodilation with leakage of proteins both in skeletal muscles and in the mesenterial vasculature [51, 188]. This would suggest an action both on the vascular peritoneal surface area and on the permeability to macromolecules. Intraperitoneal administration of histamine in rats caused a 10–20% increase in the clearance of urea [189]. This effect was not confirmed in rabbits in another study, but a marked increase was reported for the protein loss in the dialysate [190]. The histamine-induced protein loss could be blocked by a combination of H_1 and H_2 receptor antagonists. These antagonists were not effective when given alone or during desoxycholate-induced chemical peritonitis.

The possible role of prostaglandins on the functional peritoneal surface area has been studied by intravenous and intraperitoneal administration of vasodilating and vasoconstricting prostaglandins in rabbits [191–193]. In general, the effects were most pronounced after intraperitoneal administration. Arachidonic acid and the vasodilating prostaglandins led to an increase in the vascular peritoneal surface area, while the vasoconstricting PGF2α decreased the clearances of urea and creatinine. The oral administration of cyclo-oxygenase inhibitors had only a marginal effect. Combining these data with those obtained on effects of indomethacin in humans suggests that prostaglandins are not important in the regulation of peritoneal surface area and permeability during uninfected CAPD with glucose-based solutions.

Intraperitoneal administration of the direct nitric oxide donor nitroprusside in intermittent peritoneal dialysis patients causes an increase in clearances and MTAC of low-molecular-weight solutes and also in peritoneal protein loss [194, 195]. This effect markedly exceeded that of other vasodilators such as isoproterenol and diazoxide [194]. Nitroprusside, in combination with different buffer anions and varying pH, augmented peritoneal clearances in all solutions to a similar extent [196]. These effects of nitroprusside are also present during CAPD [120, 197]. In addition,

a decrease was found in the restriction coefficient to macromolecules [120]. Exposure of animal peritoneal tissues to nitroprusside caused opening of previously unperfused capillaries and increased the capillary pore area [195, 198]. These human and animal data all point to an effect of intraperitoneal nitroprusside on the peritoneal vascular surface area and the size-selective permeability to macromolecules. Involvement of nitric oxide in these processes was confirmed by an increase in the D/P ratio of the NO second messenger cGMP [120] and in the induction of an increased peritoneal albumin clearance after intraperitoneal administration of the nitric oxide substrate L-arginine in high dosages [198]. Administration of the NO inhibitor L-NMMA in this model had no effect on solute transport. These data suggest that nitric oxide is probably not involved in the regulation of peritoneal permeability during stable CAPD. The effects of nitroprusside should be regarded as a pharmacological phenomenon.

The peritoneal surface area and permeability are not only influenced by vasoactive substances, but physical phenomena might also affect them, such as position and intra-abdominal pressure. Most studies reported lower solute transport rates in the upright position than during recumbency [199–201], but another study did not report an effect of position [202]. Increasing the intraperitoneal pressure by the application of external pressure also decreased MTAC of low-molecular-weight solutes and clearances of serum proteins [203].

It can be concluded that many factors may be involved in the regulation of peritoneal surface area and permeability. Some of these factors have been identified but much uncertainty is present on the effects of many others.

Models and Parameters of Solute Transport

Because of the very complex structure of the various barriers to the peritoneal transport of solutes and fluid, the so-called distributed models are probably the most complete ones to describe peritoneal exchange [32, 204, 205]. They are, however, very complicated and based on a large number of assumptions. A much simpler approach is to consider the peritoneal tissues involved in the exchange of solutes and fluids as a single membrane that separates two well-mixed pools: the blood compartment and the peritoneal cavity compartment. In this membrane concept the peritoneal dialysis system is compared with an artificial membrane having cylindrical, fluid-filled pores, similar to the situation for transcapillary transport.

With these so-called "lumped" models the MTAC is determined. This parameter is the theoretical maximal clearance by diffusion at time zero, i.e., before solute transport has started. The MTAC can be calculated using very complicated models, but more simple equations can also be used. In general a distinction can be made between complicated numerical models and more simple analytical models (reviewed in [206]). The numerical models include those of Popovich and Pyle [207–209], Randerson and Farrell [210], Smeby et al. [211], and Waniewski et al. [212]. The analytical models generally start with the same mass balance equation, in which the accumulation of solutes in the peritoneal fluid in time is given by: $\mathrm{d}(VD)/\mathrm{d}t$, in which V is the dialysis volume and t is time. As this is the result of diffusion and convection, the mass balance equation using Eqs. 6.2–6.4 is:

$$\frac{\mathrm{d}}{\mathrm{d}t}(VD) = \mathrm{MTAC}(P - D) + 0.5J_{\mathrm{v}}(P + D)(1 - \sigma) \tag{6.11}$$

The most simple approach to solve this differential equation is to neglect the contribution of convective transport and to assume that the appearance rate of solutes in dialysate follows first-order kinetics. This is the basis of the Henderson and Nolph equation [213].

$$\mathrm{MTAC} = \frac{V_t}{t}\ln\left[\frac{P - D_0}{P - D_t}\right] \tag{6.12}$$

In this equation V_t is usually the drained dialysate volume. This method that can be considered a rough estimation has been used in a study on effects of various instilled volumes on the MTAC [214]. The Henderson and Nolph equation is especially useful during a period of isovolemia, as described by Lindholm et al. [215]. Correction for convective transport leads to the following equation:

$$\mathrm{MTAC} = \frac{V_t}{t}\ln\left[\frac{V_0^{1-f}(P - D_0)}{V_t^{1-f}(P - D_t)}\right] \tag{6.13}$$

in which f is a weighing factor between diffusion and convection, dependent on the transcapillary ultrafiltration, the sieving coefficient and the mass transfer area coefficient. When convection is relatively high compared to diffusion, f approaches zero. When diffusion is the principal transport mode, f rises to a limiting factor of 0.5. Garred et al. [216] developed a simple model based on multiple dialysate samplings, and assuming $f = 0$ and $S = 1$:

$$\text{MTAC} = \frac{V}{t} \ln \left[\frac{V_0(P - D_0)}{V_t(P - D_t)} \right] \tag{6.14}$$

This model could also be used taking samples only before instillation and after drainage, and taking the drained volume for V [217]. Waniewski et al. [218] pointed out that f values of 0.33 for a large degree of convective transport and of 0.5 for negligible convection are more justified. In addition, plasma concentrations of small solutes should be corrected for aqueous solute concentrations, either by a correction factor of 1.05 or using the total protein concentration in plasma [219]. However, in a comparison between the effect of 1.36% dialysate glucose and 3.86% glucose on the calculation of MTAC values for urea, creatinine, and urate, the difference was marginal between $f = 0$, 0.33, or 0.5 [92]. In all three models no significant difference was found for the MTAC of creatinine between the 1.36% glucose study (little convection) and the 3.86% glucose study (more convection). This indicates that all simplified models that correct for convective transport give MTAC values that represent diffusion, and that they are not influenced by convection to a clinically relevant degree. It should be appreciated that all simplified models use the intraperitoneal volume, instead of the volume that would have been present in the absence of lymphatic absorption, and also do not correct for solute loss due to uptake in the lymphatic system. However, the two factors are likely to compensate each other more or less.

The MTAC is usually calculated on solute concentrations obtained during 4–6 h exchanges. However, a number of studies have shown that MTACs are somewhat higher during the initial phase of a dwell, compared to the subsequent hours [16, 60, 92, 220, 221]. The explanation for this phenomenon is not clear, but it may be an aspecific reaction to the instillation of fresh dialysis fluids. It is one of the reasons that assessment of the MTAC by using solute clearances obtained during short dwell, as used in the mini peritoneal equilibration test, will overestimate MTACs [222]. Another problem with the use of short clearance periods is the relatively large contribution of time of inflow and drainage compared to the dialysis time, making it difficult to establish the precise dwell time. The contribution of convective transport will also be relatively large, leading to an inflated estimate of the MTAC.

Dialysate/plasma (D/P) ratios after a 4-h dwell and 24-h clearances are most often used in clinical practice. The time course of the D/P ratio of urea, creatinine and urate for a 1.36% glucose dialysis solution are shown in Fig. 6.4. It appears from this graph that D/P urea almost approaches 1.0. Consequently, the peritoneal clearance of this solute will mainly be determined by the drained dialysate volume. Therefore, the 24-h peritoneal clearance of low-molecular-weight solutes does not reflect their MTAC, but provides an overall estimation of the removal of urea (expressed as Kt/V_{urea}) and of creatinine. They can therefore be used as estimates of the adequacy of peritoneal dialysis with regard

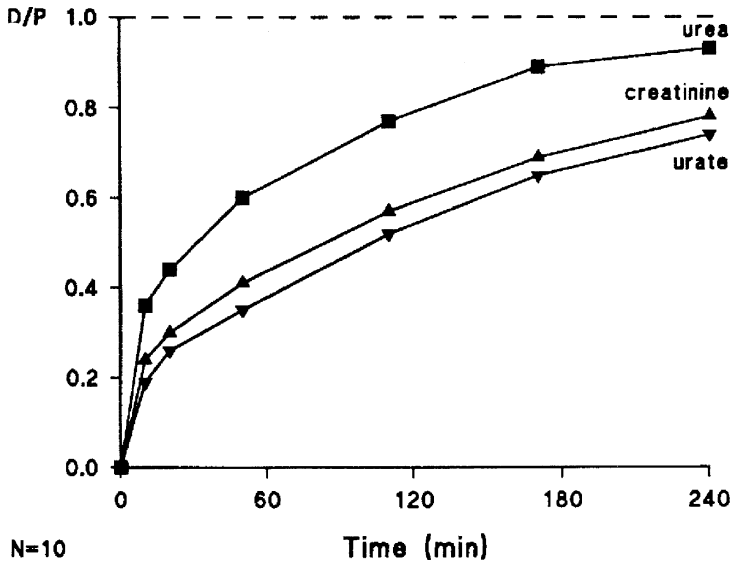

Fig. 6.4 The time-course of dialysate/plasma (D/P) ratios of urea (MW 60 Da), creatinine (MW113 Da), and urate (MW 168 Da). Mean values of 10 stable CAPD patients are given. Reprinted with permission from the Boerhaave Committee for postgraduate medical education of the faculty of medicine, Leiden University, The Netherlands

to solute removal. This is further discussed in Chapter 16. Good relationships are present between D/P ratios and MTAC [223, 224], but deviations from linearity are especially present in patients with very low and very high MTAC values [224]. D/P ratios overestimated the MTAC in the low ranges, whereas in the high ranges the MTAC values were underestimated. Both D/P ratios and MTAC have a high reproducibility in individual patients. This has been found for D/P ratios within a period of 3 months [225], but changes may occur in the long term [225, 226]. Using the simplified Garred model for the calculation of MTAC the intraindividual coefficient of variation averaged 7% [200].

Transport of Low-Molecular-Weight Solutes

Diffusion is quantitatively the most important transport mechanism for low-molecular-weight solutes, such as urea, creatinine, and uric acid. This is especially the case when the osmolality of the dialysate is low. Figure 6.5 shows the D/P ratios of urea and creatinine using 2.5% glucose-based dialysis solutions in the population of 86 patients studied by Twardowski et al. [227]. Normal values for the MTAC of urea, creatinine, and uric acid as obtained in a cross-sectional study using 1.36% glucose dialysate in 86 adult patients [224] are given in Table 6.2. Essentially similar values were found when a 3.86% glucose solution was used [228, 229]. Some relationship was present between MTAC creatinine and body surface area, but the variation is rather large. This suggests some relationship between peritoneal surface area and body surface area, but also underlines the fact that many other factors may influence peritoneal solute transport, such as the vascular peritoneal surface area. Nevertheless, MTAC are preferably expressed per 1.73 m^2 body surface area. A more detailed description of peritoneal function measurement is given in Chapter 15.

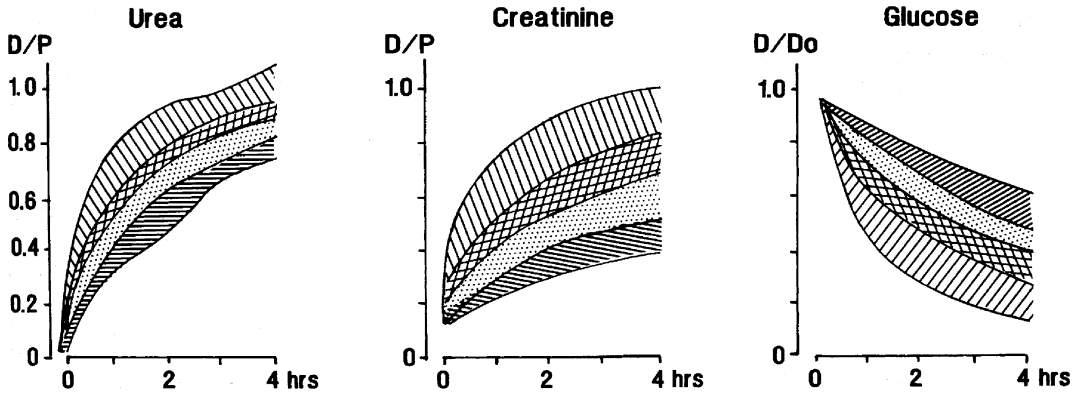

Fig. 6.5 The results of 103 peritoneal equilibration tests using glucose 2.5% dialysate. The upper zones of D/P ratios of urea and creatinine represent high transporters (> mean + SD), the adjacent zones high average transporters (between mean and mean + SD), the following zone (between mean and mean – SD) the low average transporters, and the lowest zone (< mean – SD) represents the low transporters. The same symbols, but in a mirror view, indicate the same transport categories for D/Do glucose. Redrawn from [228], with permission from the author and from Pergamon Press

Table 6.2 Normal values for the MTACs of low-molecular-weight solutes and clearances (Cl) of serum proteins (data from Ref. [226])

Parameter	Mean of normal distribution	95% Confidence interval
Simplified Garred model		
$MTAC_{urea}$ (mL/min per 1.73 m^2)	160	10.7–21.2
$MTAC_{creatinine}$ (mL/min per 1.73 m^2)	9.4	5.5–13.4
$MTAC_{urate}$ (mL/min per 1.73 m^2)	7.9	3.9–11.8
Waniewski model		
$MTAC_{urea}$ (mL/min per 1.73 m^2)	17.5	11.5–23.5
$MTAC_{creatinine}$ (mL/min per 1.73 m^2)	10.2	5.7–14.7
$MTAC_{urate}$ (mL/min per 1.73 m^2)	8.6	4.1–13.0
$Cl_{\beta 2m}$(μL/min/1.73 m^2)	853	400–1310
Cl_{alb} (μL/min/1.73 m^2)	89	34–144
Cl_{IgG} (μL/min/1.73 m^2)	45	15–76
$Cl_{\alpha 2m}$ (μL/min/1.73 m^2)	13	3–23

β_2m: beta-2-microglobulin; alb: albumin; α_2 m: alpha-2-macroglobulin

Transport of Electrolytes

The dialysate concentration of sodium decreases during the initial phase of a dialysis dwell using hypertonic solutions, followed by a gradual rise [55, 221, 230–233]. The minimum value is usually reached after 1 h. It is likely that this apparent sieving of sodium is caused by transcellular water transport through ultrasmall pores or, alternatively, temporal binding of Na^+ in the interstitial tissue. The time-course of the D/P ratio of Na^+ is shown in Fig. 6.6. Water transport rates are high during the initial phase of a hypertonic exchange; therefore, the decrease in dialysate Na^+ is a dilutional phenomenon [234]. This implies that during short dwells using hypertonic dialysate much more water than sodium is removed from the extracellular volume. This can lead to hypernatremia [235]. The gradual rise during the subsequent hours is probably caused by diffusion of sodium from the circulation. The effect of sodium diffusion on the D/P ratio of Na^+ is most marked in patients who also have high MTACs of other uncharged low molecular weight solutes [233].

The MTAC of sodium is difficult to calculate due to the small differences in dialysate and plasma concentrations. Using 3.86% dialysate glucose, an average value of 4 mL/min has been reported during a period of isovolemia [219, 231]. Using dialysate with a sodium concentration of 102–105 mmol/L, average values of 7–8 mL/min have been found [60, 236]. Corrections for Gibbs-Donnan equilibrium were applied in these calculations. The MTAC of chloride was 9 mL/min [60]. Both for Na^+ (MW 23 Da) and Cl^- (MW 35.5 Da), the MTAC values were considerably below those of urea (MW 60 Da), creatinine (MW 113 Da), and urate (MW 168 Da). As a consequence, these electrolytes are transported at a lower rate than expected on the basis of their molecular weight. The molecular radii of anhydrated sodium (0.98 Å) and chloride (1.81 Å) are also smaller than those estimated during peritoneal dialysis, based on computer simulations (2.3 Å for sodium and chloride) [17]. It is conceivable that interactions of these ions with H_2O molecules, leading to a water shell, may cause transport characteristics that suggest a higher molecular weight. In the study by Imholz et al., the calculated radius of sodium during peritoneal dialysis was 2.68 Å and that of chloride 2.42 Å [60]. The lower MTAC of sodium than that of chloride is in accordance with the lower permeability coefficient of sodium compared to that of chloride, present for transport across synthetic lipid bilayer membranes in vitro [231].

The Na^+ concentration that is most currently used in dialysis fluids is close to or slightly lower than the plasma Na^+ concentration, that is, Na^+ transport is accomplished almost in the so-called isocratic condition. Therefore, the diffusive transport component plays a minor role in peritoneal Na^+ transport, except in patients, where a high Na^+ gradient is present and that have a large vascular surface area. In general, however, convection, including ultrafiltration-induced Na^+ transport and transport by peritoneal absorption, dominates Na^+ transport [233]. Similar mechanisms apply for the transport of calcium [233, 237].

The finding that sodium diffuses as a larger molecule during peritoneal dialysis has focused attention on the potential use of ultra-low sodium dialysis solutions to improve net ultrafiltration, especially as Nakayama et al. reported favorable results of such a solution in overhydrated CAPD patients [238]. In two studies comparing dialysate with a normal sodium concentration with a dialysate containing an ultra low sodium concentration and that was made isosmotic by addition of more glucose, a slightly better net ultrafiltration was found with the low-sodium dialysate:

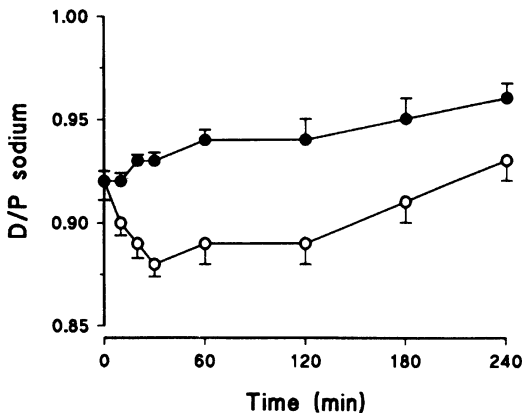

Fig. 6.6 The D/P sodium ratios in a group of 10 CAPD patients with normal net ultrafiltration (based on data from [92]). Mean and SEM values obtained with 1.36% glucose are presented as closed dots and those obtained with 3.86% glucose-based dialysate are presented as open dots. Published with permission of Multimed Inc

about 100 mL during a 6-h dwell [60, 239]. This difference could be explained by the calculated reflection coefficient of glucose (0.0326), that was slightly higher than the reflection coefficient of sodium (0.0297).

The clearance of potassium by diffusion during intermittent peritoneal dialysis averages about 17 mL/min [240]. Average MTAC values between 12 and 16 mL/min have been reported in CAPD patients [60, 219, 231], in between those of urea and creatinine. During the first hour of a dwell the value is 24 mL/min [60]. The most probable explanation for these high values is release of potassium from the cells that line the peritoneal cavity. This may be promoted by the initial low pH and/or by the hyperosmolality of the instilled dialysate. It is also supported by the finding of sieving coefficients of potassium exceeding 1.0 [180, 218]. It can be concluded that charged electrolytes are transported at lower rates than expected on the basis of their molecular weights, irrespective of the charge being positive or negative. For potassium release from intracellular sources during the initial phase of a dialysis dwell is likely to occur.

The standard peritoneal dialysis solutions contain 1.75 mmol/L Ca^{2+} and 0.75 mmol/L Mg^{2+}. The normal ionized concentrations of these electrolytes in plasma are 1.25 mmol/L for Ca^{2+} and 0.55 mmol/L for Mg^{2+}. Consequently, peritoneal dialysis will lead to mass transfer from the dialysate to the circulation by diffusion, especially when dialysis solutions inducing little convective transport are used. A positive mass transfer for Ca^{2+} of 0.96 mmol/4 h exchange and for Mg^{2+} of 0.21 mmol/4 h exchange has been found in stable CAPD patients using 1.36% glucose-based dialysate [241]. The balance will approach zero when 3.86% glucose is used because of convective transport from blood to dialysate, counterbalancing the diffusion [233, 241].

The MTAC of bicarbonate (MW 61 Da) has been reported to average 18 mL/min in intermittent peritoneal dialysis [242]. This may be an overestimation because of the short dwell time employed. From a more recent study using 24 h collections, an average value of 9.5 mL/min can be calculated [243]. The bicarbonate loss with the dialysate is slightly greater than the lactate gain using 35 mmol/L lactate [241], but a dialysis alkali yield of 31 mmol/day has been found in CAPD patients using 40 mmol/L lactate [243]. The total mass transfer of bicarbonate from the circulation to the dialysate is determined by the plasma bicarbonate concentration and the ultrafiltration rate [244, 245]. Bicarbonate loss is especially increased during high ultrafiltration rates due to additional convective transport.

Transport of Macromolecules

Macromolecules, such as serum proteins, are transported from the circulation to the peritoneal cavity at a much lower rate than low-molecular-weight solutes. Therefore, their dialysate concentrations are low and do not reach equilibrium with serum. Consequently, their clearances can be used as an approximation of MTAC. Normal values for the clearances of β_2-microglobulin (MW 11.8 kDa), albumin (MW 69 kDa), IgG (MW 150 kDa), and α_2-macroglobulin (MW 820 kDa) are given in Table 6.2. The transport of macromolecules is size-selective, both for proteins and uncharged dextran molecules [88, 246]. Similar to low-molecular-weight solutes, the relationship between clearances and molecular weights can be described as a power relationship [246, 247]. The slope of the regression line between molecular weights and clearances is however much steeper (−0.69) than that between molecular weights and free diffusion coefficients (−0.36) [246]. This indicates that the transperitoneal transport of macromolecules is hindered by a size-selective restriction barrier within the peritoneal membrane. Unlike the transport of low-molecular-weight solutes, that is mainly dependent on the functional surface area of the peritoneum, the transport of macromolecules is determined both by surface area and intrinsic size-selective permeability.

It is still controversial whether the main transport mechanism of macromolecules during peritoneal dialysis is by convection [248, 249] or by restricted diffusion [51, 98, 250, 251]. In vitro studies using endothelial monolayers on polycarbonate filters suggest that macromolecular transport in this system is caused by both diffusion and convection [252]. Restricted diffusion was especially present with highly confluent monolayers on filters with pores of about 400 Å, a situation probably similar to that in peritoneal dialysis. Convection requires fluid transport. This can occur by hydrostatic forces and by osmotic forces. An effect of osmotically induced convection has been demonstrated only for the low-molecular-weight protein β_2-microglobulin, but not for larger proteins such as albumin, transferrin, IgG, and α_2-macroglobulin, which are transported through the large pores [92]. A mathematical approach has been used in an attempt to demonstrate that proteins larger than 50 Å reach the peritoneal cavity exclusively by hydrostatic convection through the large pore system [62]. However, this can occur only when the pressure in the peritoneal blood vessels exceeds that in the interstitial tissue. The intraperitoneal pressure during CAPD averages 8 mmHg during recumbency [199]. This value is lower than that in the arterioles, but similar to that in the venules. This implies that the localization

of the large pores determines whether hydrostatic convection across them is likely to occur. Increasing the intraperitoneal pressure by 10 mmHg with the application of external compression decreased the clearances of proteins [203]. This effect was most pronounced for proteins with the highest molecular weights, suggesting an effect on the size of the pores. The measured data could be explained by convection through large pores with a radius of about 180 Å, but also by diffusion through large pores with an average radius of 1,000 Å. The large venular inter-endothelial gaps with radii from 500 to 5,000 Å, which can be found after the application of vasoactive substances, such as histamine [51], suggest that the latter value is not unrealistic.

It can be concluded that the peritoneal transport of albumin and larger proteins presumably occurs through the large pore system, and is size-selectively restricted. The mechanism involved may be restricted diffusion, or hydrostatic-induced convection, or a combination of the two, as has already been suggested by Renkin [37]. The localization and size of the large pore system determine which mechanism prevails.

Transport from the Peritoneal Cavity

Low-Molecular-Weight Solutes

The disappearance rate of intraperitoneally administered low molecular weight solutes from the dialysate is dependent on their molecular weights [82, 253]. This suggests a mainly diffusive process. As a consequence the absorption of lactate during a 4-h dialysis dwell was found to average 82% of the instilled quantity (data from [82]). For glucose a mean value of 66% has been reported, irrespective of the glucose concentration used in the dialysate [254]. This could range between 51 and 80% in individual patients. When the disappearance of glucose is expressed as the ratio between the dialysate concentration after a 4-h dwell and the initial dialysate concentration (D/D_0), as is usually done during PET tests, values ranging from 0.12 to 0.60 can be found [227]. Other low-molecular-weight solutes that can be used as osmotic agents during peritoneal dialysis, such as glycerol and amino acids, are also absorbed according to their molecular weights. The absorption of glycerol (MW 92 Da) averages 71% after a 4-h dwell [255] and 84% after a 6-h dwell [256], and that of amino acids (mean MW 145 Da) 73–90% [175, 257]. The absorption of these solutes by diffusion occurs mainly in the portal circulation [258].

Babb et al. were the first to study bidirectional solute transport [259]. This was done by comparing mass transfer area coefficients of radiolabeled sucrose and vitamin B_{12} in the same patients after intravenous and intraperitoneal administration. Higher MTAC values were found after intraperitoneal administration. Similar results have been reported for the clearances of the non-protein-bound antibiotics fosfomycin [260] and cefamandole [261], as well as for inulin [262, 263]. A difference between MTAC values after intravenous and intraperitoneal administration of the same order of magnitude is present when transport rates of endogenous creatinine and albumin are compared to those of intraperitoneally administered solutes with an almost identical molecular weight [253, 264]. These data are summarized in Table 6.3. When we assume that the peritoneal restriction barrier is symmetric in its hindrance to diffusion, i.e., there is bidirectional equivalency to diffusive mass transfer, then a molecular-weight-independent, convective transport out of the peritoneal cavity of 1–2 mL/min should be present for solutes that are administered intraperitoneally. Although such a bidirectional equivalency to diffusion has not been proven definitely, it is supported by the fact that the absolute difference between intravenous and intraperitoneal administration is always of the same order of magnitude, irrespective of the size of the solutes. However, the relative difference (compared to the MTAC after intravenous administration) ranges from 16% for low molecular weight solutes such as creatinine, to more than

Table 6.3 Comparison of bidirectional transport of solutes with similar molecular weights. Transport rates are expressed as mass transfer area coefficients (MTAC). Only paired data are used

Solute (IV/IP)	Molecular weight (dalton)	IV administration (mL/min)	IP administration (mL/min)	Absolute difference (mL/min)	Relative difference (%)
MTAC creatinine/ 5-flucytosine [257]	113/129	16.10	19.20	3.10	19
MTAC sucrose [263]	360	5.48	7.56	2.08	38
MTAC vitamin B_{12} [263]	1,355	3.30	4.85	1.55	47
MTAC inulin [266]	5,500	1.83	3.17	1.35	74
CI albumin/ hemoglobin [268]	69,000/68,000	0.12	1.53	1.43	1192

1,000% for albumin. When diffusion would not occur equally in both directions, but would always be systematically higher for intraperitoneally administrated solutes, a constant relative difference would have been expected. Furthermore, Leypoldt et al. compared the bidirectional transport of creatinine in rabbits using a kinetic model that included convective solute transport out of the peritoneal cavity, and found identical MTAC values [265]. This confirms the presence of a size-independent transport out of the peritoneal cavity from 1 to 2 mL/min.

The higher solute transport rates after intraperitoneal administration due to convection imply that MTAC calculations do not represent diffusion only, when they are calculated with simplified models that do not take into account convective transport out of the peritoneal cavity. This convective leak is probably caused by the lymphatic drainage from the peritoneal cavity, and by transmesothelial transport to the peritoneal interstitial tissue induced by abdominal pressure. The contribution of convection to diffusive transport is relatively small for low-molecular-weight solutes, but becomes increasingly more important the higher the molecular weight of a solute. The convection/diffusion ratio is about 0.1 for glucose, 1.0 for inulin [262], but 10 for intraperitoneally administered autologous hemoglobin [264], making the disappearance rate of macromolecules relatively independent of molecular size (see below).

It can be concluded that the absorption of intraperitoneally administered molecules is partly size-selective (diffusion) and partly non-size-selective (convection). The relative contribution of convection increases the higher the molecular weight of the solute. Size-selectivity is therefore most pronounced for solutes with a molecular weight of less than 500.

Effects of Bidirectional Anion Transport on Acid-Base Status

Lactate used in peritoneal dialysis fluids usually consists of a racemic mixture of L- and D-lactate. One study reported a greater absorption of L-lactate than of D-lactate in chronic peritoneal dialysis patients [266], similar to the stereospecificity of the blood-brain barrier [267]. However, in more recent studies similar peritoneal absorption rates were found for L- and D-lactate [268]. Absorbed L-lactate is converted by L-lactate dehydrogenase to pyruvate and then metabolized to bicarbonate. Lactate dehydrogenase is stereospecific and does not convert D-lactate. Accumulation of D-lactate could in theory cause metabolic acidosis. Such a D-lactate acidosis has been described in patients after extensive bowel surgery with bacterial overgrowth [269, 270]. In this situation the abnormal gut flora produced very large amounts of D-lactate. D-lactate can be metabolized in mammals, although slowly, probably by the enzyme D-2-hydroxy acid dehydrogenase [269]. Yet the capacity of the liver to metabolize D-lactate is probably sufficient for intravenous or intraperitoneally administered lactate solutions. Infusion of L- and D-lactate in the portal circulation of dogs showed hepatic extraction rates that were not different for both isomers [271]. Also, metabolic acidosis due to accumulation of D-lactate has not been found in peritoneal dialysis patients [242, 268, 271]. Impairment of lactate metabolism probably occurs only in patients with poor hepatic function [272].

Net base balance in patients treated with peritoneal dialysis is mainly dependent on the difference between the dialysate base gain (the difference between the mass transfer of bicarbonate and lactate) and the production of metabolic acids. As the latter is related to the breakdown of proteins, a relationship with the protein equivalent of nitrogen appearance (PNA) can be expected. Gotch et al. showed that the PNA multiplied by 0.77 corresponds well to the production of metabolic acids in stable patients [273]. Indeed, a negative relationship has been found between blood bicarbonate concentration and the estimated metabolic acid production [244]. The lactate mass transfer from the peritoneal cavity will be greatest during the beginning of a dwell, when the dialysate lactate concentration is highest. As a consequence, increasing the dialysis dose by performing more exchanges will increase the alkali gain. This explains the metabolic alkalosis that has been described in patients treated with high-dose CAPD [274]. The potential of bicarbonate-containing dialysis solutions in correcting acid-base disorders of CAPD patients is not essentially different from that of lactate-based fluids [245]. The net bicarbonate gain appeared to correlate with the ultrafiltration rate, the plasma bicarbonate level, and the dialysate bicarbonate concentration [275]. Similar to lactate-based solutions, the ultrafiltration rate was the predominant parameter. A dialysis solution with a combination of bicarbonate and lactate as buffer also showed good control of acid–base status [166, 168].

The use of acetate as a buffer has now been abandoned because of its association with the development of peritoneal sclerosis [276–278]. Comparison of acetate- with lactate-based dialysis solutions showed that the rise in pH after instillation was more rapid with lactate [279]. Using acetate, 18 min were required to reach a dialysate pH of 7, while this was only 7 min for lactate. The most probable explanation is the higher buffer capacity of acetate ($pK_A = 4.76$) compared to lactate ($pK_A = 3.86$) at pH = 5.6. This difference in pK_A is the reason for the much higher content of titrable acid in acetate than in lactate-buffered dialysis fluid [279].

Macromolecules

Particles, such as blood cells and bacteria, that are introduced into the peritoneal cavity, are absorbed in the diaphragmatic lymphatics (reviewed in [13]). It is therefore not surprising that a proportion of intraperitoneally administered macromolecules, during peritoneal dialysis, also disappears from the peritoneal cavity. Gjessing used dextran 70, 60 g/L as a dialysis solution in peritoneal dialysis patients treated with 30-min dwells. The recovery of dextran 70 in the dialysate averaged 92% after the dwell, while the plasma concentration increased to 1 g/L after 8 h dialysis and even to 4 g/L after 24 h [280]. Recoveries of intraperitoneally administered macromolecules of 70–90% after 4–7 h dwells in patients have been reported for radioiodine-tagged serum albumin [275, 281–285], for unlabeled human albumin [286], for dextran 70, 10 g/L [287] and 1 g/L [288], and for autologous hemoglobin [263, 284]. In only one study has a recovery of autologous hemoglobin in excess of 95% been reported [289]. A high recovery of one batch of unlabeled human albumin was found in another study [290]. This was shown to be caused by a high transport of endogenous albumin, because this particular batch contained a high concentration of prekallikrein activator that caused an inflammatory reaction.

The disappearance rate of intraperitoneally administered macromolecules is independent of molecular size, both in animals [25, 291, 292] and in CAPD patients [293]. Furthermore, it is linear in time [288–294]. In one study it was influenced by the osmolarity of the dialysis solution [284], but other studies could not confirm this [92, 294]. The disappearance rate is increased after the instillation of large dialysate volumes [82], and after the application of external pressure [202, 295]. It is likely that a proportion of the intraperitoneally administered macromolecules is taken up directly into the subdiaphragmatic lymphatic vessels, as has been shown in experiments using india ink [296]. Transmesothelial uptake, especially in the anterior abdominal wall, has been shown in rats using radiolabeled fibrinogen [297] and radiolabeled albumin [26]. Uptake of radiolabeled albumin in peritoneal tissues is also likely to be present in peritoneal dialysis patients [281]. The macromolecules transported to the interstitial tissue are probably taken up slowly in the lymphatic system, as continuous intraperitoneal administration of dextran 70 in CAPD patients had no effect on the magnitude of its disappearance rate from the peritoneal cavity [288].

In summary, the above data from the literature point to the presence of a non-size-selective mechanism for the disappearance of macromolecules from the peritoneal cavity. They are partly taken up directly by the subdiaphragmatic lymphatic vessels and partly in the peritoneal interstitium. Subsequent uptake into the lymphatics that drain the interstitial tissues is likely to occur.

Fluid Transport

Transcapillary Ultrafiltration

Fluid transport during peritoneal dialysis consists of water transport from the peritoneal capillaries into the peritoneal cavity by transcapillary ultrafiltration and by fluid loss out of the peritoneal cavity. The latter consists of transcapillary back-filtration and by fluid uptake into the lymphatic system. As a consequence, the changes in the in situ intraperitoneal volume are determined by the magnitude of the transcapillary ultrafiltration and lymphatic absorption. The water removal from the body at the end of a dwell period, defined as net ultrafiltration, is therefore the difference between the cumulative transcapillary ultrafiltration and fluid uptake into the lymphatic system.

The transport of water across the capillary wall occurs through the small pore system and through aquaporin-1, localized in endothelial cells of peritoneal capillaries and venules (see section on pathways and barriers). The small pores are mainly involved in transport by hydrostatic and colloid osmotic forces, transport through the ultrasmall pores is dependent on the osmotic gradient across the endothelial cells. Using the three-pore model it has been assumed that, during CAPD, 40% of the filtered fluid volume passes through transcellular water channels [62]. Using the relationship between the peritoneal removal of sodium and water during the first hour of a dialysis dwell with a 3.86%/4.25% glucose dialysis solution [222], a similar value for free water transport could be calculated in stable PD patients, but with a very large variation among the patients [65, 298].

According to Starling's law, the transcapillary ultrafiltration rate in peritoneal dialysis is determined by the ultrafiltration coefficient of the peritoneal membrane and the driving forces between the peritoneal capillaries and the abdominal cavity. These forces are exerted by hydrostatic, crystalloid osmotic, and colloid osmotic pressure gradients. The dependency of the transcapillary ultrafiltration rate (TCUFR) can be described by the following equation:

$$\text{TCUFR} = \text{UFC}(\Delta P - \Delta\Pi + \sigma\Delta O) \tag{6.15}$$

in which UFC is the peritoneal ultrafiltration coefficient, ΔP is the hydrostatic pressure gradient, $\Delta\Pi$ is the colloid osmotic pressure gradient, σ the reflection coefficient and ΔO the crystalloid osmolality gradient. The ultrafiltration coefficient of the peritoneum is the product of the hydraulic permeability and surface area. Little is known about determinants of the hydraulic permeability, which is most likely dependent on the combination of intracapillary pressure, and the number and size of the pores. The state of the interstitial tissue, possibly containing sites of fibrosis, may also be one of the determinants. In computer simulations of peritoneal transport, values of 0.04 and 0.08 mL/min per mmHg have been calculated for the ultrafiltration coefficient [63].

The hydrostatic pressure in the peritoneal capillaries is assumed to be 17 mmHg [299]. The intraperitoneal pressure during CAPD has been reported to average 2 mmHg [300] and 8 mmHg [200, 203] in the supine position, depending on the choice of reference point. It exceeds 20 mmHg while walking [300], and is dependent on the instilled dialysate volume [301]. This implies that the hydrostatic pressure gradient is determined mainly by the intraperitoneal pressure. The colloid osmotic pressure in the peritoneal capillaries probably averages 26 mmHg [299]. In CAPD patients who have a mean serum albumin concentration of 34 g/L [302], a value of 21 mmHg can be calculated [64]. The contribution of the dialysate to the colloid osmotic pressure gradient can be neglected because of its low protein content. The crystalloid pressure gradient is mainly determined by glucose. The effectiveness of this osmotic agent depends on the resistance the membrane exerts on its transport. This is expressed as the osmotic reflection coefficient (see section on pathways and barriers); it can range from 1 (no passage, ideal semipermeable membrane) to 0 (passage not hindered, no osmotic effect). In case of a reflection coefficient of 1, every mosmol exerts an osmotic pressure of 19.3 mmHg according to van't Hoff's law. The reflection coefficient for glucose during CAPD is very low, probably between 0.02 and 0.05 [57–61]. It must be appreciated, however, that these are mean values. The reflection coefficient for glucose across the ultrasmall pores will be 1.0, and will approach zero across the large pores. This might explain why glucose is an effective osmotic agent despite its small size.

The hyperosmolality of commercial dialysis fluid when compared to uremic plasma is about 45 mosmol/kg H_2O for the lowest glucose concentration (1.36%) and 180 mosmol/kg H_2O for the highest glucose concentration (3.86%). The osmotic pressure exerted by these solutions across the peritoneal membrane can therefore be estimated as 45×0.03 (reflection coefficient) $\times$ $19.3 = 23$ mmHg (lowest glucose concentration), and similarly 104 mmHg (highest glucose concentration). The various pressure gradients are summarized in Table 6.4. The values for the crystalloid osmotic pressure gradients are the maximum values, as present during the initial phase of a dialysis dwell. They will decrease in time due to absorption of glucose from the dialysate. This glucose absorption averages 61% of the instilled quantity during a 4-h dwell [224] and 75% after 6 h [231]. The absolute, but not the relative, absorption is influenced by the glucose concentration used [254]. As a consequence the transcapillary ultrafiltration rate has its maximum value at the start of dialysis and decreases during the dwell. The figures given in Table 6.4 imply that dialysate with a low glucose concentration will induce only a small amount of osmosis-induced transcapillary ultrafiltration. The maximal transcapillary ultrafiltration rate with 1.36% glucose during the initial phase of a dwell averages 2.7 [119] to 4.3 mL/min [63]. With 3.86% glucose-based dialysate, the initial transcapillary ultrafiltration during 4-h dwells averages 12–16 mL/min [63, 92, 232, 303]. Mean values for transcapillary ultrafiltration during 4-h dwells average 1.0–1.2 mL/min for 1.36% glucose [92, 119, 224] and 3.4 mL/min for 3.86% glucose [92]. The osmotic conductance to glucose determines its effectiveness as an osmotic agent. Mathematically, it can be expressed as the product of the ultrafiltration coefficient and the reflection coefficient. On average a value of 4.5 μL/min/mmHg can be calculated [304].

Dextrins are glucose polymers that can also be applied as osmotic agents during peritoneal dialysis. Icodextrin is a disperse mixture of dextrins with an average molecular weight of 16.8 kDa that is currently used in clinical practice

Table 6.4 Pressure gradients across the peritoneal membrane during the initial phase of a peritoneal dialysis exchange

	Pressure in peritoneal capillaries	Pressure in dialysate-filled peritoneal cavity	Pressure gradient
Hydrostatic pressure (mmHg)	17	8 recumbent	9
Colloid osmotic pressure (mmHg)	21	0.1	–21
Osmolality (mosmol/kg H_2O)	305	347 (glucose 1.36%)	
		486 (glucose 3.86%)	
Maximal crystalloid osmotic pressure gradient (mmHg)		(glucose 1.36%)	24
		(glucose 3.86%)	105

The reflection coefficient of low molecular weight solutes is set at 0.03

[305]. Due to its high molecular weight, icodextrin is likely to induce colloid osmosis [306]. This implies that macromolecules are able to induce transcapillary ultrafiltration even in an isotonic or hypotonic solution. The process of colloid osmosis is based upon the principle that fluid flow across a membrane that is permeable to small solutes, occurs in the direction of relative excess of impermeable large solutes, rather than along a concentration gradient. Consequently, dialysis solutions containing macromolecules to remove fluid from the body will induce water transport through the small pore system. When such a solution is not hypertonic, no water transport will be induced through the ultra-small water channels. The pressure gradients across the peritoneal membrane that can be expected using a 7.5% icodextrin-based dialysis solution are shown in Table 6.5. It follows from this table that the maximum pressure gradient across the peritoneal membrane is 42 mmHg, which is higher than the 12 mmHg exerted by 1.36%/1.5% glucose, but markedly less than the 93 mmHg exerted by 3.86%/4.25% glucose. However, because of its lower absorption than glucose, the gradient will remain present for a much longer time. It must, however, be realized that icodextrin is a polydisperse solution with a wide range of molecular weights, which might influence the overall values [307]. Using 7.5% icodextrin a UFC of 0.05 mL/min per mmHg can be calculated. This value can be employed to estimate the back-filtration of dialysis fluid into the capillaries by the colloid osmotic pressure gradient: back-filtration rate = 0.05 (9–21) = 0.6 mL/min. In a previous study using a dialysis solution without an osmotic agent, the overall back-filtration rate was 0.9 mL/min during a 4-h dwell [163]. It was highest during the start of the dwell (2.6 mL/min), because the solution was hypotonic to uremic plasma, and averaged 0.4 mL/min during the last 2 h. A value of about 1 mL/min can be calculated on data from a study using intraperitoneal 0.9% NaCl [281].

The absorption of icodextrin averaged 19% during an 8-h exchange [308]. Therefore, the transcapillary ultrafiltration rate induced by it is almost stable during an exchange [64, 309] and averages 1.4–2.3 mL/min [64, 309]. This could explain why icodextrin-based dialysis solutions are especially effective during dwells of 8–12 h [310].

Lymphatic Absorption

Direct measurement of the lymphatic flow from the peritoneal cavity is impossible in humans; therefore, indirect methods have been used. They include the disappearance rate (clearance) of intraperitoneally administered macromolecules from the peritoneal cavity, and their appearance rate in the circulation. Using the disappearance rate it is assumed that the administered macromolecule is removed from the peritoneal cavity by absorption into the lymphatic system. Human albumin [286], radioiodinated serum albumin (RISA) [221, 231, 285], autologous hemoglobin [232, 264, 284, 289], and dextran 70 [287] have all been used. This approach is justified because the disappearance rate of these solutes is constant in time [288, 294] and independent of molecular size [293] (see also the section on transport from the peritoneal cavity). Using these tracers average values of 1.0–1.5 mL/min have been found in CAPD patients [221, 224, 231, 264, 285–287,]. Local accumulation of intraperitoneal RISA has been found in the anterior abdominal wall of rats [26], most likely caused by transmesothelial transport. It is probable that macromolecules in the peritoneal interstitial tissue will eventually be taken up into the lymphatic system, as has been made plausible in mice [311]. This is supported by the observation that saturation of the peritoneal interstitium in CAPD patients by continuous administration of dextran 70 did not alter the appearance rate of this macromolecule [288]. Measurement of appearance rates requires the use of radiolabeled traces like RISA, because the plasma concentrations of the other markers, after a single intraperitoneal administration are too low. Comparing both methods using RISA, it appeared that the appearance rate in the circulation was only about 20% of the disappearance rate [281, 282]. Furthermore, the appearance rate shows remarkably little variability [312]. Half of the difference between the disappearance and appearance rates can be explained by the fact that only 40–50% of the total albumin mass is intravascular [313]. It can therefore be concluded

Table 6.5 Pressure gradients across the peritoneal membrane during the initial phase of a peritoneal dialysis exchange using 7.5% icodextrin

	Pressure in peritoneal capillaries	Pressure in dialysate-filled. Peritoneal cavity	Pressure gradient
Hydrostatic pressure (mmHg)	17	8 recumbent	9
Colloid osmotic pressure (mmHg)	21	66	45
Osmolality (mosmol/kg H_20)	305	285	
Maximal crystalloid osmotic pressure gradient (mmHg)			(285–305) × 0.03 × 19.3 = −12

It is assumed that the molecular weight of icodextrin is 16,800 and the reflection coefficient is 0.767. The reflection coefficient of low molecular weight solutes is set at 0.03

that the disappearance rate overestimates the true flow through the lymphatics, while the appearance rate underestimates it. The differences between the two methods has been assumed to represent transmesothelial clearance [312].

Direct measurement of lymphatic flow from the peritoneal cavity has been studied by the group of Johnston, both in anesthetized and conscious sheep [314–317]. In these animals the right lymphatic duct could not be cannulated. Anesthesia appeared to have a pronounced effect on the flow in the cannulated lymphatics, probably because of reduced movements of the diaphragm. The mean lymph flow in conscious sheep ranged from 1 to 1.5 mL/h per kg body weight, depending on estimations for flow in the right lymphatic duct. Comparisons of these measured flow rates with disappearance and appearance rates of RISA in sheep are difficult, because the disappearance rate of RISA was very high and the RISA appearance rate was 60% of the disappearance rate, i.e., a much smaller difference than in human CAPD patients. The amount of RISA administered intraperitoneally, recovered in the blood and in the drained lymphatic vessels, was always equal to the amount lost from the peritoneal cavity during a 6-h dwell. This is not supportive of marked accumulation of RISA in the anterior abdominal wall. The flow from the caudal mediastinal lymph node can be raised 200% in the awake sheep model by intraperitoneal administration of fluid [318]. In analogy, the disappearance rate of intraperitoneally administered autologous hemoglobin is higher in CAPD patients after the administration of a 3-L dialysate volume than with a volume of 2 L [82]. Increasing the intraperitoneal pressure in rats that underwent peritoneal dialysis also increased the RISA disappearance rate [295]. However, it had no effect on its appearance rate in the systemic circulation. Combining this observation with those in awake sheep and CAPD patients suggests that the disappearance rate of macromolecules can be used relatively easy in clinical practice for the analysis of fluid kinetics in CAPD patients.

It has been suggested that fluid transport associated with the disappearance of macromolecules should not be called lymphatic flow or lymphatic absorption, but simply fluid loss [319]. This is a simplification, because reabsorption of fluid into the capillaries by the colloid osmotic pressure gradient is not associated with the transport of macromolecules, as has been shown in studies using normal saline [281], or hypotonic dialysate without an osmotic agent [163]. The amount of saline absorbed during a 7-h dwell was 24% in the former study, but the amount of RISA that had disappeared was only 17%. In the latter study the dialysate concentration of intraperitoneally administered dextran 70 increased 10% during a 4-h dwell, most likely because of transcapillary back-filtration of water, caused by the colloid osmotic pressure gradient. This underlines that fluid loss from the peritoneal cavity is coupled mainly to the disappearance of macromolecules (lymphatic absorption), but is also partly uncoupled (back-filtration by colloid osmosis). Based on these data it can be concluded that the disappearance rate of intraperitoneally administered macromolecules cannot be used alone as a measurement of lymph flow through the subdiaphragmatic lymphatics, but also cannot be used as an overall indicator of fluid loss from the peritoneal cavity, irrespective of the mechanism involved. It is plausible that the disappearance rate can be used as a functional approach for the calculation of the effective lymphatic absorption from the peritoneal cavity during CAPD. Consequently, all pathways of lymphatic drainage from the peritoneal cavity, both subdiaphragmatic and interstitial, are included in the definition of the effective lymphatic absorption rate. The term *effective* is analogous to the effective renal plasma flow, where a clearance is used to estimate flow. The pros and cons of the concept of the effective lymphatic absorption rate have been subject of a recently published "controversy in peritoneal dialysis" [320, 321].

Intraperitoneal pressure is likely to be one of the determinants of the effective lymphatic absorption. Intraperitoneal administration of saline in rats causes an increase in the number of patent subdiaphragmatic stomata, not present when the intraperitoneal pressure was kept constant [322]. A relationship has also been found between intraperitoneal pressure in CAPD patients and the disappearance rate of intraperitoneally administered dextran 70 [323]. Increasing the intraperitoneal pressure 10 mmHg, by external compression, leads to a marked increase in the effective lymphatic absorption rate [203], and consequently a lower net ultrafiltration. Net ultrafiltration is also somewhat (16%) lower in the upright position compared to recumbency [200], caused by the combination of a small increase in the dextran disappearance rate and a slight decrease in the transcapillary ultrafiltration rate. The effects of higher intraperitoneal pressure in the upright position are probably counterbalanced by the effect of gravity leading to a decreased contact between the dialysate and the subdiaphragmatic lymphatics. The coefficients of intraindividual variation of the parameters of fluid transport average 17% [200]. The time course of transcapillary ultrafiltration, effective lymphatic absorption, and net ultrafiltration (the difference between the two) is shown in Fig. 6.7 for 1.36%/1.5% glucose, 3.86%/4.25% glucose, and 7.5% icodextrin. The transcapillary ultrafiltration rate on glucose-based solutions is negatively related to the MTAC creatinine (representing a large vascular surface area), but the relationship is positive when an icodextrin-based solution is used, as shown in Fig. 6.8. These relationships can be explained by the different properties of the two osmotic agents. The presence of a large vascular surface area allows high water transport rates, as many pores are available for transport. This explains the effects of icodextrin. For glucose-based solutions, however, the positive effects on water transport are counteracted by high glucose absorption rates, leading to a rapid disappearance of the osmotic gradient.

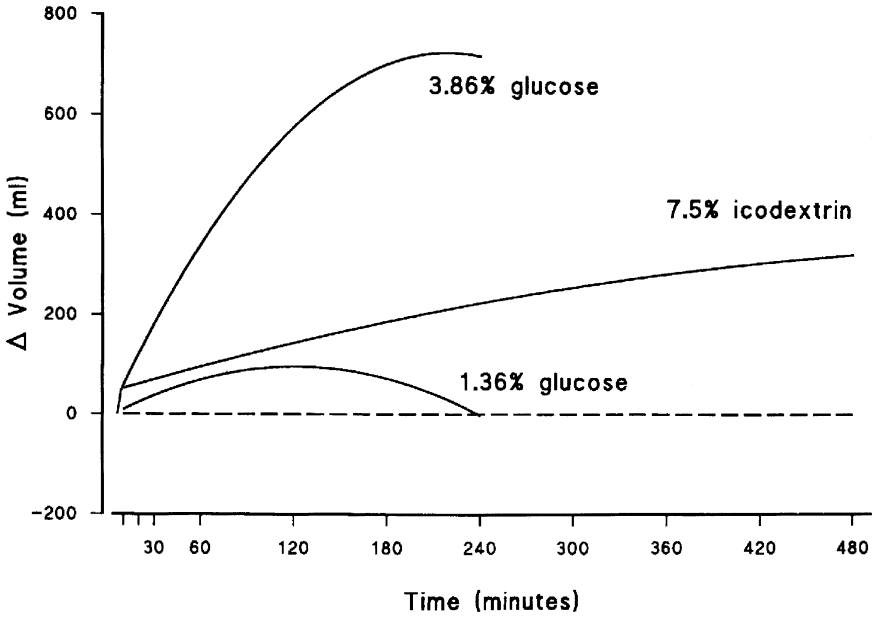

Fig. 6.7 The time-course of the intraperitoneal volume during a 4-h exchange with 1.36% glucose, a 4 h exchange with 3.86% glucose and an 8-h exchange with 7.5% icodextrin-based dialysis solution. Median values are given. Based on [64, 119, 314]

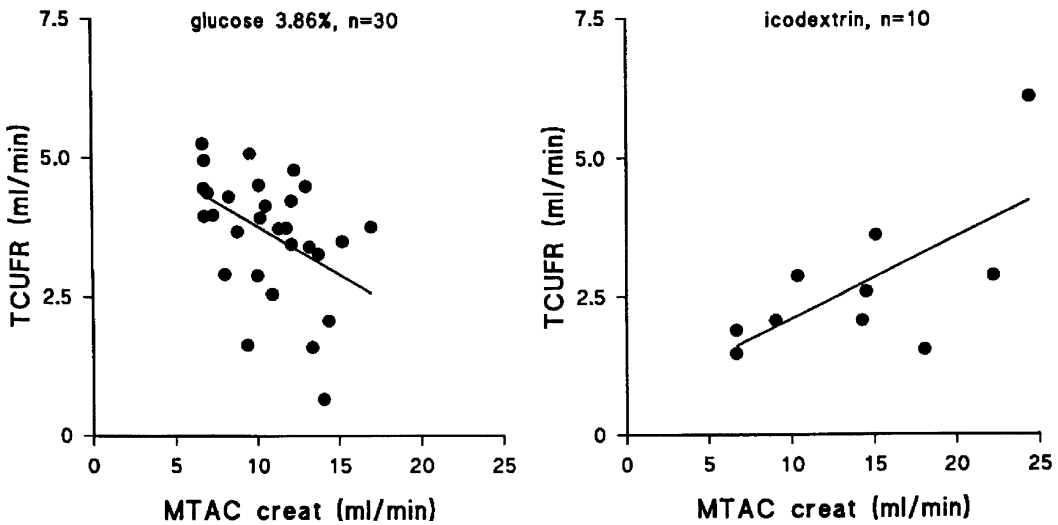

Fig. 6.8 The different relationships between the MTAC creatinine, representing the vascular peritoneal surface area and the transcapillary ultrafiltration rate obtained during 4-h exchanges with 3.86% glucose (left panel) and 7.5% icodextrin (right panel). The icodextrin data are from [64], the glucose data are from a randomly selected group of stable CAPD patients who underwent a standard peritoneal permeability analysis. Note that a high MTAC creatinine is associated with a low transcapillary ultrafiltration rate on glucose and with a high transcapillary ultrafiltration rate on icodextrin

Peritoneal Permeability in Systemic Diseases

Uremia

The uremic state is probably associated with more permeable serosal membranes than is the nonuremic situation. This is illustrated by the easy development of pleural and pericardial effusions. Increased capillary permeability has also been reported in the lungs during chronic uremia [324]. A similar increase has been found for the permeability characteristics of the peritoneal membrane during 3-h dialysis exchanges, when three patients with chronic renal failure were compared to four patients with normal renal function who were dialyzed because of psoriasis [325]. The uremic patients had higher transport rates for uric acid, phosphate, and protein than those with psoriasis, indicating a

larger effective peritoneal surface area in the uremic patients. The intrinsic permeability to macromolecules was not investigated in this study. On the other hand, decreased clearances of urea and creatinine have been reported during intermittent peritoneal dialysis in patients with severe hyperparathyroidism [326]. In acute renal failure due to rhabdomyolysis caused by heat stress and exercise, decreased peritoneal clearances have also been reported for creatinine and uric acid, but not for urea [327].

Diabetes Mellitus

Patients with diabetes mellitus have an abnormal microcirculation. Capillary basement membrane alterations with thickening and loose areas of the fibrillar meshwork are especially common [328]. Increased microvascular permeability to proteins is also present [328]. This may be due to loss of glycocalyx [105]. Peritoneal clearances of exogenously administered radiolabeled albumin in rats undergoing peritoneal dialysis have been found higher in animals with alloxan-induced diabetes mellitus than in those with gentamicin-induced renal failure [329]. This was especially the case in the rats with the most severe diabetes. A more recent study reported increased D/P ratios of low molecular weight solutes [330]. The findings in animal models cannot simply be applied for the situation in chronic peritoneal dialysis patients. The continuous exposure to extremely high dialysate glucose concentrations leads to diabetiform membrane alterations, such as reduplicated basement membranes [331], and neoangiogenesis [332] with deposition of collagen IV [333]. Vasculopathy, and especially venular subendothelial hyalinosis have also been described [334]. This may obscure differences between diabetic and nondiabetic patients that might have been present in the initial phase of peritoneal dialysis. Therefore, the various studies should be interpreted with caution.

Low peritoneal clearances of creatinine and urate have been reported in one patient with severe diabetes mellitus treated with intermittent peritoneal dialysis [335]. In contrast, the MTAC values of urea, creatinine, and glucose in a larger group of diabetic CAPD patients were similar to those of patients with renal failure due to a primary renal disease [336–338] (Table 6.6). In one study a dependency of D/P creatinine on peritonitis incidence has been described [339]: patients with a high incidence have higher D/P ratios than nondiabetic patients and patients with a low incidence had lower ratios. Reduced ultrafiltration was present during periods of hyperglycemia [339]. Patients studied during the initial period of CAPD had higher D/P ratios for creatinine than nondiabetic controls in one study [399], and lower transcapillary ultrafiltration rates in another one [340]. This could however not be confirmed in a more recent analysis [341]. Peritoneal protein losses in diabetic CAPD patients are not different from those of other patients [242, 342, 343]. As serum albumin concentrations are often low in some of them [313], this can mask increased permeability to macromolecules. In accordance with the findings in alloxan-induced diabetes in rats [329], clearances of albumin, transferrin, and IgG have been reported 30% higher in diabetic than in nondiabetic CAPD patients [246]. However, when larger numbers of patients were studied, the difference was no longer significant (Table 6.6). The explanation for this is probably the large variability in the effective peritoneal surface area and intrinsic permeability in the patients with a primary renal disease.

Systemic Lupus Erythematosus

Low clearances for urea, creatinine, and urate have been reported in one patient with fulminant systemic lupus erythematosus (SLE) and severe hypertension, treated with intermittent peritoneal dialysis [335]. More recent data

Table 6.6 Comparison of peritoneal permeability characteristics between 46 patients with a primary renal disease and 38 patients with systemic diseases. Permeability to low-molecular-weight solutes is expressed as mass transfer area coefficient (MTAC), that of proteins as clearance (Cl). Mean values ± SEM are given

	Primary renal disease ($n = 46$)	Systemic lupus erythematosus ($n = 7$)	Systemic sclerosis ($n = 2$)	Diabetes mellitus ($n = 23$)	Amyloidosis ($n = 6$)
MTAC creatinine (mL/min)	9 ± 0.4	10 ± 1	12 ± 1	10 ± 1	14 ± 2*
MTAC glucose (mL/min)	9 ± 0.4	11 ± 1	10 ± 1	11 ± 1	13 ± 2
Cl albumin (μL/min)	92 ± 6	92 ± 19	118 ± 11	97 ± 7	110 ± 21
Cl IgG (μL/min)	50 ± 3	47 ± 12	61 ± 2	53 ± 5	59 ± 13

*$p < 0.05$ versus primary renal disease

show that the prognosis of SLE patients on renal replacement therapy is similar to those with a primary renal disease [344]. In the literature, more detailed data on CAPD in SLE have only been reported in 16 patients [345–348]. Solute transport rates were published in four CAPD patients, indicating a normal vascular surface area and a decreased intrinsic permeability to macromolecules [337, 338]. This could not be confirmed when larger number of patients were studied (Table 6.6).

Systemic Sclerosis

Patients with systemic sclerosis can be treated with peritoneal dialysis, despite their low life expectancy [344]. Low peritoneal clearances of low-molecular-weight solutes have been reported in one patient on intermittent peritoneal dialysis [349], but essentially normal values were found in another one [350]. CAPD treatment has also been described to give good metabolic control [351] and acceptable clearances of low molecular weight solutes [352]. Data on solute transport in two patients are given in Table 6.6.

Amyloidosis and Paraproteinemia

Peritoneal dialysis as renal replacement therapy in patients with amyloidosis and/or paraproteinemia has given satisfactory clinical results [347, 350, 352]. Evidence for a large peritoneal surface area has been reported in four patients with amyloidosis [336, 348, 353]. This may be of importance because peritoneal dialysis can be used to remove immunoglobulins and light chains from the body, thereby preventing further amyloid formation, hyperviscosity syndromes, and, perhaps in some cases, reverse renal insufficiency in patients with nephrotoxic light chain–induced renal failure [354, 355]. Solute transport data in six patients with amyloidosis are given in Table 6.6.

It can be concluded that the presence of a systemic disease has no uniform effect on the permeability characteristics of the peritoneal membrane during CAPD, although some patients may present with abnormal high or low MTAC values. However, such abnormal values can also be found in patients with a primary renal disease. This implies that peritoneal dialysis should not be abandoned in patients with systemic diseases, because of the expectation of an abnormal peritoneal permeability.

Peritoneal Permeability During Infectious Peritonitis

Inflammation causes hyperemia, and therefore changes in the permeability characteristics of the peritoneal membrane are likely to occur. "Membrane failure," as judged from deteriorating biochemical control, has been reported in four of 35 intermittent peritoneal dialysis (IPD) patients with peritonitis [356]. In contrast, increased clearances of creatinine and urea during peritonitis have been found in four IPD patients who were studied both in the absence of, and in the presence of, peritonitis [357]. As the effluent volume was similar, increased permeability caused by inflammation was the most likely explanation.

The most striking clinical finding in CAPD patients with peritonitis is impaired net ultrafiltration, leading to weight gain and other signs of fluid overload [358]. This phenomenon is associated with increased transport of low-molecular-weight solutes and increased absorption of glucose [81, 121, 359–362]. These phenomena point to an increased vascular peritoneal surface area caused by hyperemia. This leads to rapid disappearance of the osmotic gradient, and thus to reduced net ultrafiltration. In this situation a high-molecular-weight osmotic agent should be able to induce more transcapillary ultrafiltration. This was confirmed by the use of icodextrin, which led to increased, instead of decreased, net ultrafiltration during peritonitis [363, 364]. The maximal intraperitoneal volume during peritonitis is reached at about 1 h after instillation of the dialysis fluid, compared to 2.5 h after recovery [81]. This may explain why a decrease in net ultrafiltration has not been observed during peritonitis in IPD patients. The steep rise in the intraperitoneal volume during the initial phase of a dwell is caused by high transcapillary ultrafiltration rates during this period, as shown with dextran 70 [121]. No evidence has been found for a decreased free water transport [365]. A contribution of an increased fluid absorption from the peritoneal cavity is equivocal. It was suggested in a study using autologous hemoglobin as a volume marker [81, 366] and also, but to a minor degree, in a study using kinetic modeling of fluid transport [18]. However, in a more recent study using dextran 70 no effect of the inflammatory reaction on peritoneal fluid absorption could be established [121]. The alterations in peritoneal transport during peritonitis return to normal values within 1–2 weeks after recovery from the infection [362, 367].

Protein loss in the dialysis effluent is also markedly increased during peritonitis [81, 246, 357, 360, 367, 368]. In contrast to CAPD, the losses in IPD can be as high as 48 g per dialysis and often remain elevated for several weeks [367]. These proteins could be produced locally, or originate from the circulation [369]. Serum proteins are quantitatively the most important in peritoneal effluent. The increment in their clearances of more than 100%, during peritonitis, favors increased transport [81, 249], due both to the increased effective surface area and increased peritoneal permeability to macromolecules [246]. In a longitudinal study in CAPD patients with peritonitis, Zemel et al. showed an increase in the vascular peritoneal surface area and a decrease in the restriction coefficient to macromolecules during the acute phase of the inflammation [149]. The decreased restriction coefficient, pointing to an increased permeability of the peritoneum, returns to normal values within 1–2 days [121, 149], but the vascular surface area remains increased for a longer time.

Possible causes for the changes in surface area and permeability include endotoxin and complement activation [368], as well as prostaglandins [121, 140, 141, 150], IL-6 [146, 149], TNFα [143, 149], and local production of nitric oxide [121, 153, 155]. Inhibition of the inflammatory reaction with indomethacin reduced dialysate prostaglandin concentration, and had some effect on the restriction coefficient to macromolecules [150]. The importance of the relative contributions of all these mediators in the functional alterations of the peritoneal membrane during infectious peritonitis is not known.

Peritoneal Solute Transport During Long-Duration Peritoneal Dialysis

Mass transfer area coefficients or D/P ratios are mainly determined by the vascular peritoneal surface area. This is not a static, but a dynamic parameter, because it can be altered by the number of perfused peritoneal capillaries, that is the effective surface area, or by the number of capillaries. An increase in the number of peritoneal vessels occurs in long-time PD [332, 333]. This leads to high volumes of MTAC and D/P ratios and, and also to a rapid absorption of glucose in the dialysate. The ensuing decrease in ultrafiltration is discussed in Chapter 17. Two prospective longitudinal studies on peritoneal solute transport with a follow-up exceeding 5 years have been published [370–372]. In the study of Selgas et al. [370], a slight increase of MTAC creatinine with time on dialysis during 5 years was found. The increase in D/P creatinine was more pronounced in the study of Davies et al. [371, 372]. Some other studies reported the presence of a U-shape: an initial decrease was followed by a subsequent increase of the MTAC creatinine [298, 373, 374]. In retrospect, such a U-shape can also be found in the study from Spain [370]. It suggests that patients may have relatively high MTACs in the first (few) years on peritoneal dialysis, possibly due to release of vasoactive mediators by mesothelial cells. The subsequent decrease may be caused by a decrease of mesothelial cell mass [334]. The neoangiogenesis that can develop during long-term peritoneal dialysis is the most likely explanation for the following increase.

No study has shown an increase or decrease in peritoneal total protein loss in relation with the duration of peritoneal dialysis [375–377]. When peritoneal clearances of individual serum proteins were examined, no effect of the time on peritoneal dialysis was found [373, 376, 377]. However, when the clearances of these proteins were used to calculate the peritoneal restriction coefficient for macromolecules (see section on size-selectivity), an increase of this parameter was found in long-term CAPD patients [93, 377]. The increase in the restriction coefficient to macromolecules was not present after 2 years of CAPD [373], but was evident after 4 years [93, 377]. It points to an increased size-selectivity of the peritoneal membrane. Whether this is caused by a reduction in the average radius of the large pore system, or by fibrotic interstitial changes, is unknown.

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Chapter 7
Physiology of High/Fast Transporters

R.T. Krediet

Patients on peritoneal dialysis have large interindividual differences in the velocity of solute equilibration between plasma and the dialysate [1]. In an attempt to standardize assessment of this variability, Twardowski et al. developed the peritoneal equilibration test (PET) [2]. In the PET solute transport after a standardized dwell of 4 h is expressed as the dialyse/plasma (D/P) concentration ratio of various solutes. D/P creatinine had a mean value of 0.65, but it ranged from 0.34 to 1.03 [3]. A similar range was reported in another study using the PET [4]. Based on D/P creatinine, patients have been divided into four transport categories: low, low average, high average, and high [3]. This categorization was based on the mean value and the standard deviation (SD). Low is less than 1 SD, low average is between the mean and –1 SD, low average is between the mean and +1 SD, and high is above 1 SD. The cut-off levels are: <0.50 for low, 0.50–0.65 for low average, 0.65–0.81 for high average, and >0.81 for high transporters. About 10% of prevalent PD patients can be classified as high transporters [5].

It should be appreciated that the net mass transfer of a solute is not only dependent on its D/P ratio, but also on the amount of drained dialysate: the peritoneal clearance is calculated as (D/P) × the drained volume. For solutes that are in (near) equilibrium, the D/P ratio approaches 1. In this situation the peritoneal clearance is almost exclusively determined by the drained volume. This is especially relevant for high transporters. These patients have a rapid disappearance of the glucose-induced osmotic gradient, caused by a high glucose absorption rate. It is not just a theoretical consideration: high transporters had a higher absorption of glucose after a dwell of 6 h, but a smaller intraperitoneal volume, while the removal of urea creatinine, sodium, and potassium was significantly lower than in the other transport categories [6]. A more detailed analysis of sodium kinetics showed that, irrespective of transport status, 69% of sodium transport is by convection, but that the high transporters had a significantly higher absorbed and lower removed sodium mass [7]. Therefore, the terms *high* and *low transport* are confusing. Patients who show a rapid equilibration could better be labeled fast transporters. Similarly the term *low* should be replaced by *slow*.

Fast Transport Status and Prognosis

The determination of peritoneal transport status was originally used to give recommendations on the dialysis prescription. For instance, the proposed treatment for fast transporters was either nightly intermittent peritoneal dialysis or daily ambulatory peritoneal dialysis [8]. In both modalities a long dwell is avoided to minimize absorption of the dialysis solution, and thereby trying to avoid the development of overhydration.

Wu et al. were the first to describe a higher drop-out rate in fast transporters when compared to other transport categories [9]. In 1998, two papers were published that reported a decreased survival for fast transporters [6, 10]. In a study from Sweden, prevalent continuous ambulatory peritoneal dialysis (CAPD) patients had a 2-year patient survival of 64%, which was significantly lower than the survival for the other transport categories. This effect was independent of age, gender, height and urine production. Diastolic blood pressure and bodyweight were higher in the fast transporters. All the deaths among the fast transporters were caused by cardiovascular diseases. These data suggest that overhydration may have been important. In the Canada-USA (CANUSA) study, performed in more than 600 incident CAPD patients, a PET was performed at enrollment [10]. No difference among the groups was found for patient survival, but fast transporters had a lower 2-year technique survival and a lower combined patient and technique survival. Fast transporters were older, more often male, and more often had diabetes mellitus and a lower serum albumin concentration. However, their nutritional status was not different from that of the other transport

R.T. Krediet (✉)
Academic Medical Center University of Amsterdam, Amsterdam, The Netherlands
e-mail: c.n.deboer@amc.uva.nl

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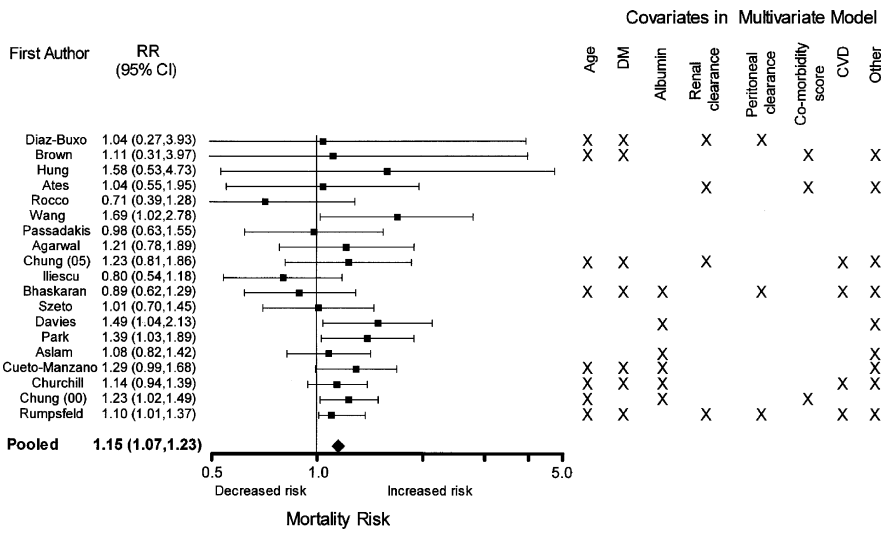

Fig. 7.1 Results of a meta-analysis on the mortality risk of patients with a fast peritoneal transport status. Taken from reference [28] (Brimble KS et al. Meta-analysis: peritoneal membrane transport mortality and technique failure in peritoneal dialysis. J Am Soc Nephrol 2006; 17: 2591–2598) with permission of the first author and of Lippincott, Williams and Wilkins

groups. Although residual renal function tended to be better in fast transporters, this was not significant. Fast transporters had a higher peritoneal creatinine clearance, a lower PET drain volume and a Kt/V_{urea} of 1.58/week compared to an average value of 1.68/week for the other transport categories. The cause of death was vascular in 73% of all patients. Taken together these data from the CANUSA study also suggest volume overload due to impaired peritoneal ultrafiltration as an important cause for the decreased patient and technique survival in fast transporters.

A large number of studies on mortality in fast transport patients has been published since then [11–27]. Among the 19 studies that assessed patient survival, five reported an increased mortality, while the other 14 showed no significant effect of peritoneal transport status. A recently published meta-analysis [28] done in 6,654 incident and prevalent PD patients showed a statistically significant overall increased relative risk of death in fast transporters of 1.15 (Fig. 7.1). A number of remarks can be made, however: 1) The majority of patients comes from one study [26]. 2) Four out of five studies showing a significant effect were done in CAPD patients [7, 12, 21, 25]. The fifth study, that is the large one from Australia/New Zealand, only found an effect in CAPD patients, not in those treated with APD [26]. In the two studies performed exclusively in APD patients, no effect of peritoneal transport status was present [14, 27]. 3) With the exception of the study by Brown et al. in APD patients [27], no study included patients in whom icodextrin was used for the long dwell. 4) A relative risk of 1.15, as reported in the meta-analysis, means that the chance of death is increased with 15%. Given a death rate in PD patients of about 15% per year, it means that the number of patients that die in 1,000 patient years will increase from 150 to 173. For comparison, the relative risk of death for start with hemodialysis compared to peritoneal dialysis is 1.59 in the United Kingdom [29], 1.16 in Denmark [30], and 2.33 in The Netherlands [31].

It can be concluded that the relationship between a fast peritoneal transport status and excess mortality has only been established in patients on CAPD treated with conventional PD solutions. The excess mortality is about 15%.

Physiology of Fast Transport Status

Diffusion through the so-called small pores is the most important transport mechanism for low molecular weight solutes that accumulate due to kidney failure. The rate of diffusion is determined by the product of the mass transfer area coefficient (MTAC, the maximum theoretical clearance by diffusion at time zero) and the concentration gradient between plasma and dialysate. Plotting MTACs of various low molecular weight solutes versus their free diffusion coefficient in water shows the presence of a power relationship between them [32]. It means that the relationship is linear when plotted on a double logarithmic scale. The slope of the regression line obtained when doing this for low molecular weight solutes was 1.24, which is close to 1.0. This is the expected value when the relationships between the magnitude of MTACs would only have been dependent of free diffusion. Consequently it is unlikely that the peritoneal membrane offers a size-selective hindrance to the transport of low molecular weight solutes. It implies that the MTACs or D/P ratios are mainly dependent on the number of perfused peritoneal microvessels, that is the vascular peritoneal surface area. This is discussed in more detail in Chapter 6.

The presence of a fast transport status reflects the presence of a large vascular peritoneal surface area. This area is not a statistical, but a dynamic property, because it is not only dependent on the number of microvessels but also on the number of perfused microvessels. The former is the anatomic surface area, the latter is often referred to as the effective peritoneal surface area. As discussed in Chapter 6, many vasoactive substances can influence the effective peritoneal surface area.

Types of Fast Transport Status

Inherent Fast Transporters

The prevalence of a fast transport status in new PD patients differs widely. Values of 7% [20] and of 29% [33] have been reported. In most studies an inherent fast transport status was present in 15–17% of the patients [10, 16, 34]. The last study comprised 523 incident PD patients with a fast transport status. Multivariate analysis revealed that this condition was associated with higher age, Maori/Pacific Islands racial origin, a BMI exceeding 25 kg/m^2, but not with co-morbidity. Male gender and the presence of diabetes mellitus were associated with a fast transport status in the CANUSA study [10]. A study from Korea confirmed that inherent fast transporters had a higher proportion of men, but – in contrast with the study from Australia/New Zealand – also a higher proportion of patients with co-morbid diseases and a lower initial serum albumin concentration [16].

Peritoneal transport status is a refection of the peritoneal vascular surface area, which can be influenced by vasoactive substances (see above). Besides urea and creatinine, the concentrations of which are determined by peritoneal transport, many substances can be detected in peritoneal effluent of PD patients that are locally produced or released. These include interleukin-6 (IL-6) [35, 36], vascular endothelial growth factor (VEGF) [37], and the mesothelial cell mass marker cancer antigen 125 (CA 125) [38]. Cross-sectional analyses in prevalent PD patients have shown significantly higher plasma and dialysate concentrations of IL-6 and VEGF in fast/fast average transporters than in slow/slow average ones [39]. Also, a strong correlation is present between the MTAC creatinine and effluent VEGF attributed to local production [37]. However, studies from Portugal in incident patients found no correlation between D/P creatinine and effluent or serum IL-6 [40]. Also, no differences were present between fast/fast average and slow/slow average transporters for serum VEGF, serum IL-6, and effluent IL-6. Only effluent VEGF was significantly higher in the fast/fast average transporters [41]. A similar finding was reported was reported in a study from The Netherlands [42]. These findings contrast those of a study from Sweden, in which a correlation was found between D/P creatinine at baseline and plasma dialysate IL-6 [43]. Population differences in inflammation may explain these differences. The average serum C-reactive protein (CRP) concentrations were 6 mg/L in the study from Portugal [41], 5 mg/L in the study from The Netherlands, in which patients with diabetes mellitus were excluded [42], and 15 mg/L in the study from Sweden [43].

Cultured mesothelial cells are able to produce various cytokines, chemokines, and prostaglandins, some of which are vasoactive [reviewed in ref. 44]. These include IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1), but not tumor necrosis factor (TNF)α, the concentration of which in peritoneal effluent of uninfected patients is dependent on diffusion from the circulation [45]. The in vitro production of the above substances is especially marked after stimulation, for instance with TNFα. In contrast, VEGF is spontaneously produced in large quantities by ex vivo cultured peritoneal mesothelial cells from PD patients [46]. Also, CA 125 is constitutively released by mesothelial cells. This release is not influenced by stimulation with cytokines [47].

Based on these data, it can be hypothesized that the magnitude of the mesothelial cell mass is indirectly involved in the regulation of the effective vascular surface area. Old data in cross-sectional studies on relationships between effluent CA 125 and peritoneal transport are equivocal. Some reported a positive correlation with D/P creatinine [48], while others were unable to establish this [49]. The discrepancy might be due to differences in the duration of peritoneal dialysis. As illustrated in Fig. 7.2, a correlation between effluent CA 125 and peritoneal solute transport is only present during the first two years on peritoneal dialysis (unpublished data). Especially in incident patients correlations are present between patients solute transport, effluent CA 125, and effluent VEGF [40–42]. By using a linear regression analysis to analyze the relationship between MTAC creatinine and effluent CA 125 in incident patients it was shown that this was not influenced by age, gender, and serum concentrations of acute phase proteins [42]. However, it was weakened when effluent VEGF was added to the model, but not when this was done for effluent IL-6 [42]. These data suggest that CA 125 in new PD patients is an independent determinant of the MTAC creatinine and that its effect is partly mediated by locally produced VEGF, presumably from mesothelial cells.

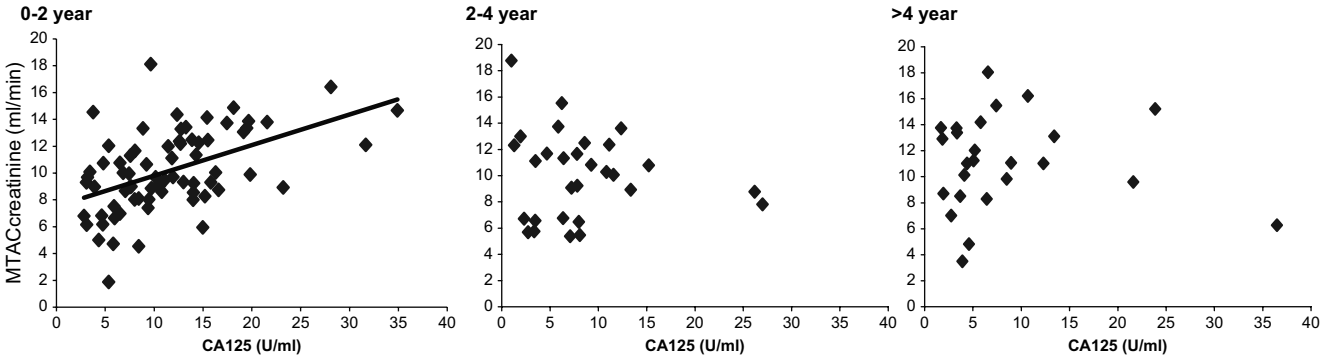

Fig. 7.2 Relationship between effluent CA 125 and the MTAC creatinine according to the duration of peritoneal dialysis. Only during the first 2 years a relationship is present

Table 7.1 Differences between the two types of an inherent fast transport status

Inherent fast transporters		
	Associated with co-morbidity	Associated with CA 125
Vascular surface area increase	Effective/anatomic	Effective
Cause	Inflammation	Vasoactive hormones produced by mesothelial cells
Time course	Poor prognosis	Spontaneous resolution

Taking all the data discussed above into account, the various results suggest that two types of inherent fast transporters can be distinguished: one related with co-morbidity and inflammation and another one related to mesothelial cell mass and/or function. The characteristics of these two types are shown in Table 7.1. The latter type is likely to disappear spontaneously with the duration of PD [32], because effluent CA 125 decreases during longitudinal follow-up [41, 50]. Although both types may cause ultrafiltration failure, the inherent fast transport status associated with CA 125 is unlikely to contribute to the excess mortality of fast transporters because most patients will have residual urine production. However, the type associated with co-morbidity and inflammation is likely to have a poor prognosis.

Acquired Fast Transporters

Here, two types can be distinguished. One occurs during peritonitis, the other one may develop during long-term PD. The characteristics are shown in Table 7.2.

Acute infectious peritonitis leads to an inflammation-induced peritoneal hyperemia. This causes some increase in peritoneal blood flow [51], but a much more marked increase of the transport of low molecular weight solutes [51, 52] and especially serum proteins [51–53]. It appeared that the changes in the parameters for the effective peritoneal vascular surface area were mediated by IL-6 and TNFα, while those for the intrinsic permeability of the peritoneum were associated with IL-6 and prostaglandin E2 [53]. The resulting decrease in ultrafiltration [51, 52] was purely due to a rapid decrease of the osmotic gradient, without signs of an impaired contribution of free water transport [54]. The vast majority of peritonitis episodes are cured by antibiotic treatment and peritoneal transport characteristics usually return to baseline in a few weeks [55].

Table 7.2 Differences between the two types of an acquired fast transport status

Acquired fast transporters		
	Associated with peritonitis	Associated with long-term PD
Vascular surface area increase	Effective	Anatomic
Cause	Infection	Glucose induced neoangiogenesis
Time course	Reversible after cure	Ultrafiltration failure

Patients on long-term peritoneal dialysis can develop ultrafiltration failure. This occurs in about one third of patients treated for 4–6 years [56, 57]. It is not only associated with a fast peritoneal transport status, but also with impaired free water transport [57–60]. Peritoneal neoangiogenesis induced by dialysis solutions is the main cause for this phenomenon [61–63]. It is also associated with low effluent CA 125 levels, suggesting extensive damage of the peritoneal dialysis membrane [57]. Most of the patients with this type of fast peritoneal transport status have no residual urine production. Therefore they are at great risk for the development of overhydration, which will lead to an increased mortality. Indeed, two studies performed in anuric patients have shown a relationship between peritoneal ultrafiltration and risk of death [64, 65].

Treatment of Patients with a Fast Transport Status

General principles of treatment include preservation of urine production and adjustments of the peritoneal dialysis prescription. Urine production can be preserved by avoidance of nephrotoxicity and the use of high-dose loop diuretics. The latter increase urine production, but have no effects on GFR [66] or its time course [67]. The use of an ACE inhibitor reduces the natural decline of residual GFR [68]. Modifications of the dialysis prescription consist of the use of icodextrin for the long dwell and/or the use of APD with short cycles. Two randomized studies showed that icodextrin treatment led to a significant reduction of total body and extracellular water and left ventricular mass [69, 70].

Specific treatment aimed at the cause of the fast peritoneal transport status is not always possible and also not always necessary. An inherent fast transport status associated with high effluent CA 125 levels requires no specific treatment. The condition is likely to disappear by itself. Treatment of the underlying condition of an inherent fast transport status associated with inflammation and/or co-morbidity should be attempted but is often impossible. This is especially the case for the malnutrition, inflammation, and arthrosclerosis syndrome, where an integrated approach should be investigated [71]. Prevention of the development of a fast transport status associated with long-term PD primarily consists of a reduction to the exposure to glucose and/or glucose degradation products [72]. The use of the so-called biocompatible PD solutions is promising in long-term animal models [73], but a sustained membrane protective effect in patients has not been established yet.

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Chapter 8
Animal Models for Peritoneal Dialysis Research

M.M. Zweers and P.J. Margetts

The concept of peritoneal dialysis as a therapeutic modality for end stage renal disease was first demonstrated by Putnam in 1923 in a canine animal model [1]. Over the past 30 years, as peritoneal dialysis has been increasingly used and modified as a therapy for renal failure, animal models have been used to understand the physiology of the peritoneum membrane, and to test new therapeutic interventions to improve the outcomes of patients treated with peritoneal dialysis.

The physiology of the peritoneal membrane has been studied in a variety of models using predominantly rats and rabbits [2], but other larger animals have also been studied. The usual technique employed is to instill peritoneal dialysis solution into the peritoneum of an animal and sample the fluid and blood over time to assess solute transport, reabsorption, and ultrafiltration.

Animal models are also used extensively to understand the immune response to infection and nonbiocompatible dialysis solutions in chronic and acute settings applying advanced techniques such as intravital microscopy [3]. With the publication of human peritoneal biopsy studies [4, 5] it has become clear that the peritoneal membrane changes over time on dialysis. These changes have been studied in animal models in order to understand the underlying mechanisms. Animal models have also been used extensively to study possible therapeutic interventions such as novel dialysis solutions and pharmacologic agents.

Experimentation to understand the basic molecular mechanisms of peritoneal membrane injury have traditionally been carried out in mesothelial cell culture systems. Recently, with the use of transgenic animals and gene transfer techniques, pathways leading to peritoneal membrane injury have been studied in vivo.

Acute Peritoneal Dialysis Models

The most straightforward animal model utilized is the introduction of a fluid into the peritoneal cavity and the study of the effects on transport parameters or inflammatory response. These models have recently utilized mouse, rat, rabbits, and sheep. These procedures have been carried out to better understand the anatomy and physiology of transport across the peritoneal membrane. Additionally, different dialysis solutions, or therapeutic agents, have been introduced in order to assess the potential clinical utility in peritoneal dialysis patients.

Model for Assessment of Peritoneal Transport Properties

A standard acute model of peritoneal dialysis exposure involves anesthesia of the animal and maintenance in homeostasis [6]. A temporary catheter is inserted in the peritoneal cavity and dialysis solution is infused. A volume marker such as radiolabeled albumin, is added. Over the course of the peritoneal solution dwell samples are taken. Intraperitoneal volume can be measured, along with transcapillary ultrafiltration and solute transport out of the peritoneal cavity. With measurement of small solutes, dialysate to plasma ratios or mass transfer area coefficients [7] can be calculated. This allows for an assessment of peritoneal membrane transfer properties or effective peritoneal surface area. The latter is, in essence, that part of the peritoneal membrane that is involved in solute transport. Intrinsic peritoneal permeability is characterized by the restriction coefficient of a solute, an expression of the peritoneal size selectivity. A restriction coefficient of 1.0 indicates free diffusion of the solute; a higher

M.M. Zweers (✉)
Academic Medical Center University of Amsterdam, Amsterdam, The Netherlands
e-mail: mmzweers@gmail.com

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restriction coefficient implies the presence of a size selective barrier. An example of size selectivity is the transport of macromolecules such as albumin and IgG [8].

Transport properties appear to be similar among different animal models and humans. However, there are notable differences. For example, rabbits demonstrate higher lymphatic absorption rates and clearances of macromolecules [7]; rats demonstrate greater glucose transport [9], and mice have lower macromolecular transport [10] compared with humans. In a study of peritoneal transport in response to an acute dwell, mouse transport data was similar to values found for rats [11]. Interestingly, Ni et al. also compared males and females and found female C57Bl/6 mice displayed less sodium sieving perhaps related to decreased aquaporin-1 expression. Volumetric measurement techniques have, in general, been validated with the caveat that only small volumes are removed for analysis [12]. An acute effect of PD fluid on the vasculature leading to vasodilation early in the dwell and increase in solute transport, has been identified [13]. The experimental procedure must be outlined in detail as small changes in technique such as the type of anesthesia used [14] and additives to PD fluids such as heparin [15] may have an effect on solute transport.

Solute transport across the peritoneal membrane depends on the characteristics of the membrane and the surface area involved. In an attempt to eliminate this second variable, Flessner et al. have developed an in vivo technique where the peritoneum of an anesthetized animal is exposed surgically, and a column is fixed to the surface [16, 17]. Standardized solutions and volume markers are added to the column, and solute transfer parameters are calculated. The area as a variable in solute transport is thus eliminated.

Anatomic/Physiologic Observations from Acute Models of Peritoneal Dialysis

The acute model of a single peritoneal fluid dwell has led to many important observations. From an anatomic perspective, the differences between the visceral, parietal, and diaphragmatic surfaces for lymphatic drainage and solute transport have been studied. The parietal peritoneum has been identified as the more important component of solute transport [18]. Lymphatic drainage across the diaphragm appears to be the most important route for macromolecular removal as seen both in rats [19] and sheep [20]. From these studies and others, it is clear that lymphatic drainage to the peripheral circulation is a minor route for macromolecular transport, and that local uptake by tissues is the major pathway [19].

The contact area between PD fluids and the peritoneal membrane has been studied in different ways. Using MRI in rats, Fischbach et al. demonstrated that only 30–40% of the peritoneal membrane was in contact with a standard dwell in the rat [21]. Using radiolabeled markers and autoradiography after an acute dwell in mice, Flessner et al. demonstrated about 40% of the peritoneal surface area in contact with a large inoculum of PD fluid (10 mL) [22]. They also demonstrated techniques to increase the contact area and therefore solute transport [22, 23]. The vascular surface area is an important determinant of solute transport, but the role of peritoneal blood flow has been somewhat more controversial. Rosengren et al. demonstrated a measurable decrease in solute transport in an acute dwell in rats where blood flow was limited by exsanguination of 25% of blood volume [24]. Contrary to this, using columns attached to peritoneal tissue, Flessner et al. identified no significant change in solute transport with up to 70% reduction in peritoneal blood flow, aside from some minor changes noted in the transport across the hepatic peritoneal surface [17]. Despite these somewhat discordant findings, it can be concluded that, overall, blood flow is a minor determinant of peritoneal solute clearance.

Over time on dialysis, the peritoneal membrane develops striking increases in interstitial matrix. The interstitium of the peritoneal membrane has therefore increasingly been studied using animal models. In a recent, novel technique, Rippe et al. directly measured interstitial colloid pressure in the peritoneum using implanted wicks in rats exposed to a single dwell of PD fluid [25]. The acute loss of colloid interstitial pressure may be related to a wash out of macromolecules such as hyaluronan from the peritoneal membrane [26]. The net effect is to significantly increase the hydraulic conductance of the interstitium after a single PD fluid dwell.

The basic mechanisms of solute and water transport have been studied using acute dwells of PD fluid, generally in rats [9, 19]. More recently, studies in transgenic mice have demonstrated the importance of aquaporin-1 in free water transport across the peritoneal membrane [27]. Peritoneal macromolecular transport was studied by Rosengren et al. in caveolin-1–deficient mice and showed that macromolecular transport was not dependent on vascular caveolae [28]. This same group used an acute dwell in rats cooled to 19°C to demonstrate that macromolecular transport is a passive rather than active process [29].

Important changes in attachment and morphology of mesothelial cells have been studied in rat [30] and rabbit [31] PD fluid studies. In an interesting adjunct study to the peritoneal biopsy registry [5], even minor mishandling of rat peritoneal tissue was shown to cause extensive artifactual changes, in the mesothelial cell layer [32].

More recently, the effects of acute exposure to PD fluid and high glucose concentration has been studied in rats with regard to outcomes such as anorexia [33], and changes in adipokine profiles [34].

In acute dialysis studies, therapeutic interventions have been carried out to alter or improve peritoneal solute transport and ultrafiltration. Different solutions such as low sodium [35] and biocompatible solutions have been studied [36, 37] and a broad array of pharmacologic interventions have been profiled [38]. One caveat to the use of the rat as an animal model for acute or chronic exposure to icodextrin is the observation that rats have increased intraperitoneal amylase that leads to rapid degradation of icodextrin and alteration in its properties as an osmotic agent [39].

Peritoneal Inflammation/Peritonitis

Models Utilized

Peritonitis is still the major complication of peritoneal dialysis. Animal models have been utilized to understand the impact of infection on the peritoneal membrane structure and function, and the complex peritoneal immune response. Several methods have been utilized to induce injury to the peritoneal tissues in order to mimic changes in peritoneal dialysis patients, to understand pathophysiology, and to evaluate therapies.

The standard animal model involves the introduction of bacteria or a proinflammatory bacterial product such as lipopolysaccharide (LPS) or *Staphylococcus epidermidis* supernatant [40] into the peritoneal cavity. The size of the inoculum needs to be optimized to allow measurable effects without significant mortality [41]. The bacterial species is also likely of significance but has not been studied in detail. Devuyst et al. have developed a unique model where normal skin flora is used as the infective agent in an attempt to more closely mimic human peritonitis [42]. LPS has been used as a single intraperitoneal injection in dosages between 50 and 200 μg [43], which induces a characteristic inflammatory response and leukocyte recruitment. Overexpression of inflammatory cytokines such as TNFα– or IL-1β by adenovirus mediated gene transfer to the peritoneum of rats has also been used to evaluate the effects of isolated inflammatory cytokines on structural peritoneal membrane changes [44].

The single dose of infective or inflammatory agent has been modified by various researchers to produce desired effects. In an attempt to create a more chronic model of peritoneal inflammation, multiple doses of LPS have been given alone or in association with chronic PD infusion [45]. Bacterial inoculum has also been incorporated into a model of chronic PD fluid infusion in order to assess the effect of PD fluid exposure on the inflammatory response [46]. Alternatively, *S. aureus* has been incubated with dextran microbeads and injected into the peritoneum to create a prolonged pro-inflammatory and fibrogenic response [47]. Inflammatory agents have also been combined with other peritoneal injuries, such as uremia, to identify the various complex interactions occurring in PD patients [48]. Transgenic animals have been used in order to clarify the details of the peritoneal immune system and effects on the peritoneal membrane. The role of IL-6 as a master switch between acute and chronic inflammation has been demonstrated using IL-6 transgenic mice [40]. The importance of nitric oxide as a mediator of peritoneal membrane functional alterations after an inflammatory stimulus has been assessed using animals lacking endothelial nitric oxide synthase (NOS) expression [49].

Measurements of Outcome

The complexity of the peritoneal immune response has been investigated using animal models of acute peritoneal inflammation. In the assessment of interventions meant to alter the effectiveness of the immune response, the simplest outcome measurement is clearance of bacterium as measured in the peritoneal effluent. For example, in one study, uremia did not alter the clearance of bacteria in a combined model of bacterial inoculation after chronic PD fluid exposure [46], whereas caspase inhibitors blocked neutrophil apoptosis and enhanced bacterial clearance [50].

Leukocyte vascular interactions have been studied in detail using intravital microscopy [3]. Intravital microscopy involves the analysis of blood vessels in the mesentery of the large bowel. The large bowel is exteriorized using carefully controlled techniques. The mesenteric segment is superfused with different dialysis solutions and numerous variables can be simultaneously analyzed. Aside from leukocyte endothelial interaction, these variables include blood flow rate, macromolecular permeability, and microvascular density [51].

Peritonitis leads to a well-documented increase in solute and protein transport with a subsequent loss of ultrafiltration capacity. These parameters are commonly assessed as outcomes after acute peritonitis in these studies [43, 52–55]. The elaboration of chemokines [46] and cytokines [48] important in the inflammatory response have been evaluated. Longer-term outcomes such as angiogenesis and fibrosis have also been assessed [44, 47].

Interventions

Various interventions have been studied in animal models of peritonitis in order to assess efficacy at improving antibacterial responses, or mitigating the effects of peritonitis on the structure and function of the peritoneal membrane. Extracellular matrix components such as n-acetylglucosamine [48], hyaluronan [53], and heparin [56] have all been studied in animal models of peritonitis for their anti-inflammatory properties. Prostaglandins have vasoactive properties and have been implicated in vascular and solute transport changes associated with peritonitis. Prostaglandin inhibitors, such as indomethacin, have therefore been studied in rabbit models of acute peritonitis and have shown benefits in improvement in solute transport [55] and protein leak [54]. Other interventions, such as NOS inhibition [57] and alternative dialysis solutions, have been studied in animal models [43].

Other Models of Peritoneal Injury

Over time, the peritoneal tissues of PD patients undergo fibrosis and angiogenesis. This process leads to altered transport properties and ultrafiltration dysfunction. In the extreme, some patients develop a fulminant fibrogenic process termed encapsulating peritoneal sclerosis (EPS). Researchers have tried to mimic these processes using animal models so that the pathophysiology can be clarified and therapeutic agents can be tested.

Chronic Peritoneal Exposure Models

A variety of chronic peritoneal infusion or exposure models have been developed, mainly in rats and predominantly designed to investigate effects of dialysis solutions on peritoneal membrane structure and function and to evaluate therapeutic interventions. Presumably, these in vivo models have the ability to provide valuable information on the major pathways involved in peritoneal transport pathophysiology, morphological alterations, and local defense mechanisms. These models should be applied to evaluate a clear hypothesis with adequate detailing of methodologies used to obtain the parameters of interest. The varied approaches, applications, and methodologies used in chronic peritoneal exposure models most recently have utilized rats.

Mortier and colleagues [58] elegantly reviewed a variety of animal models that are currently used in PD research. To briefly reiterate the rat models: the chronic exposure models comprise the direct intraperitoneal injection model (with or without anesthesia) and the so-called "open" and "closed" systems with indwelling catheters. The open systems comprise two approaches: 1) a sterile tube is inserted into a permanent peritoneal indwelling catheter for each exchange of dialysis solution [59], and 2) a permanent peritoneal catheter through which the dialysis solution is introduced [60, 61]. The so-called "closed" models all have a subcutaneous reservoir in the neck attached to a peritoneal catheter from silicon or polyurethane (Fig. 8.1). These models differ in actions to prevent, for example, peritoneal infection or fibrin formation–induced catheter obstruction, or no preventive measures at all [62–65]. The pros and cons of the chronic exposure models in rats are summarized in Table 8.1.

Chemical Irritants

Chlorhexidine

Chlorhexidine was used as a sterilizing agent peritoneal dialysis patients to prevent peritonitis until it was found to be associated with an increased risk of encapsulating peritoneal sclerosis. It has since been used in a rodent model of peritoneal injury. In general, a daily or every other day intraperitoneal injection of chlorhexidine gluconate and 15% ethanol dissolved in saline is administered in mice [66] or rats [67]. The response involves submesothelial thickening, fibrosis, and angiogenesis that persists and matures during the course of injections [66]. It is likely that these effects reverse to some extent after cessation in injections, but that has not been well documented. As opposed to observations from human peritoneal biopsy samples, there is a significant inflammatory response to chlorhexidine evidenced by infiltration of macrophages [68].

Numerous interventions have been used in this model, mainly targeting angiogenic responses [68–70], heat shock protein [71], or angiotensin converting enzyme [72].

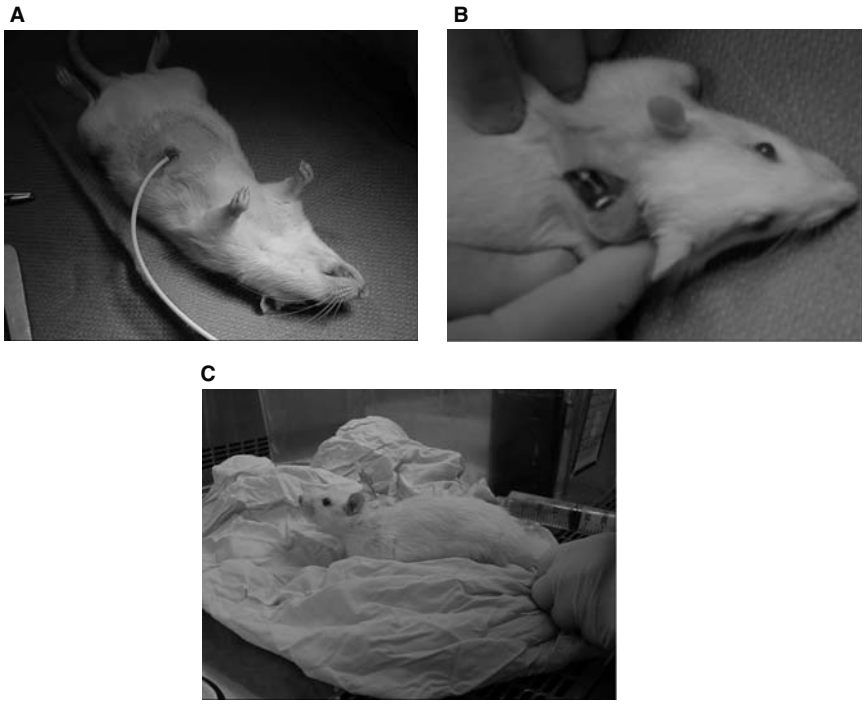

Fig. 8.1 Peritoneal catheter placement in a rat.(a)Introduction of the catheter tip into the peritoneal cavity. Thereafter the catheter is tunneled subcutaneously to the neck where the reservoir will be attached to the catheter. (b) The reservoir is attached to the catheter and placed subcutaneously in the neck. (c) Percutaneous infusion in the reservoir performed in an awake rat

Acidic Dialysis Solution

This model has been described by a few researchers [73, 74]. Daily injection of very low pH (pH 3.5) solution into the peritoneal cavity of rats over 40 days led to changes suggestive of encapsulating peritoneal sclerosis with fibrosis, cocooning of the bowels, inflammatory infiltrate, and adhesions. Angiotensin converting enzyme inhibition appeared to ameliorate this injury [73].

Other

Several other agents have been used in developing peritoneal injury models. A single injection of silica suspension in rats induced a significant fibrogenic response [75]. Fang at al. used this model to test the effects of pentoxifylline and showed significant benefit in the fibrogenic response. This model was carried out to 15 days after a single injection of silica, and it is not clear what the longer-term effects of this agent are.

In an interesting model of peritoneal injury, Gotloib et al. used a single injection of the oxidant agent deoxycholate to induce a severe oxidative injury to rats [76]. They demonstrated acute changes in solute transport and mesothelial cell morphology suggestive of acute inflammatory injury. Of note, they examined a group of animals 30 days after this single injury, and observed persisting solute transport abnormalities in the histological setting of peritoneal fibrosis.

Potassium cyanate injected into the peritoneum of rats induced a mild fibrotic response [77]. In a more dramatic model, sodium hypochlorite (bleach) was injected repeatedly to induce an obvious fibrogenic response [78]. In a second, related model, a single injection of bleach was followed 2 weeks later by an injection of blood. This combination led to fibrin formation and abdominal cocooning reminiscent of encapsulating peritoneal sclerosis [79].

Effects of Systemic Diseases on the Peritoneum

Uremia

Peritoneal biopsies taken from patients who have chronic kidney disease but before initiation of dialysis, demonstrated increased submesothelial thickening [5]. A partial nephrectomy of 70–85% in rats has been used in order to understand this phenomenon. The level of uremia and the duration of renal insufficiency, chronic or more acute, affect the applicability of the chronic exposure models and the development of peritoneal pathology. Five-sixths or 85% nephrectomy induces a 2–4 fold increase in plasma creatinine and urea [80]. Kakuta at al. [81], Zareie at al. [80], and

Table 8.1 Chronic peritoneal exposure models in rats

Model	Pro	Con
Injection model without anesthetic [107]	– Simple set up and cheap – No additional surgery	– No drainage – Risk of trauma to muscle, bladder, intestine, intraperitoneal bleeding – Repeated needle sticks – Introduction of infection
Injection model with anesthetic [108]	– Reduced risk of trauma – Reduced risk of infection – Possible up to 20 weeks	– Idem as injection without anesthetic – Anesthetic may affect peritoneal permeability [109] – Repeated anesthetics may influence metabolic status
Open system 1) using a sterile catheter in permanent tube to install and drain PDF [61]	– Easy instillation and drainage of PDF – Imitates PD more closely	– Extra step to introduce sterile tube – Risk of infection due to open connection and extra step – Substantial drop-out due to infection/obstruction
Open system 2) using the permanent tubing as catheter [60]	– Idem open system 1) – PD possible up to 24 weeks [110]	– Less steps to introduce PDF intraperitoneally – Reduced but still substantial risk of infection – Substantial drop-out due to catheter obstruction/infection
Closed system 1) subcutaneous reservoir in the neck attached to the peritoneal catheter (silicon/polyurethane), no preventive measures	– Less risk of infection than open systems	– No drainage – Reduced but still substantial drop-out due to catheter obstruction/infection – Expensive catheters
Closed system 2A) subcutaneous reservoir in the neck attached to the peritoneal catheter with heparinized PDF [16, 63, 65]	– Less drop-out due to catheter obstruction and adhesion formation	– No drainage – Modulates inflammatory cell activity, proliferation, and neoangiogenesis
Closed system 2B) subcutaneous reservoir in the neck attached to a heparin-coated peritoneal catheter [63]	– Less drop-out due to catheter obstruction and adhesion formation – Not the adverse of effects of heparin related adverse effects	– Very expensive catheters
Closed system 3) subcutaneous reservoir in the neck attached to the peritoneal catheter with prophylactic antibiotics [33, 62, 64]	– Prevents infection when administered during the whole experimental period – Antibiotics did not exert an adverse effect by itself on peritoneal function or structure	– Risk of introducing multiple resistant bacterial strains
Uremia: ~85% Nx up to 13 weeks [59, 80, 81]	– The more severe renal insufficiency may more rapidly induce uremia-related peritoneal alterations	– High morbidity/mortality in comparison with 70% Nx – Intraperitoneal infusion period only ~6 weeks, which may not be enough to induce significant peritoneal changes [80]
Uremia: ~70% Nx up to 16 weeks with nephroprotective diet [111]	– Infusion period up to 16 weeks: to induce more pronounced exposure related peritoneal alterations – Mimics chronic renal insufficiency better	– Less drop-out due to reduced renal insufficiency related morbidity/mortality – A longer infusion duration necessary to induce chronic pathology, therefore an increased risk of drop out exists.

others [2, 82] reported additive effects to the development of peritoneal alterations such as increased vessel density, when uremic and uremia with 6 weeks of peritoneal dialysis fluid exposed animals were analyzed.

An initial attempt to build a realistic, more clinically relevant model of uremia-induced peritoneal injury involved the complete removal of rat kidneys with subsequent maintenance on a catheter based peritoneal dialysis regimen [61]. The authors report the results after 4 days of dialysis.

The partial nephrectomy model has been used to confirm the effect of uremia on the structure and function of the peritoneal membrane [82]. More recently, the interaction between uremia and advanced glycation end products (AGE) has been studied in a uremic model [83]. Use of antibodies against the receptor of AGEs led to an improvement in the uremic-induced peritoneal membrane changes.

Diabetes

Microstructural alterations to the peritoneum resemble diabetic nephropathic changes including vasculopathy, extracellular matrix deposition, and basement membrane duplication. This likely represents the extensive exposure to a high glucose environment experienced by the peritoneum of PD patients. In light of this observation, researchers have used animal models of systemic diabetes to induce peritoneal damage. The original model was characterized by Stoenoiu et al. and involved the induction of diabetes using streptozotocin [84]. Four to 6 weeks after induction of diabetes, rats displayed increased solute transport, angiogenesis, increased NOS, and AGE expression. This model was subsequently used in conjunction with blocking antibody therapy to demonstrate the importance of VEGF [85] and receptor for AGE [86].

Genetic/Cellular Manipulation

Transgenic Mice

The present ability to alter the genetic environment in vivo has allowed peritoneal dialysis researchers the ability to begin to dissect the basic pathways involved in injury to the peritoneum. Mice with gene mutations or deletions are a powerful tool that has only recently been applied to peritoneal dialysis research.

To date, transgenic mice have been used mainly to study effects of single proteins on functional characteristics of the peritoneum after an acute dwell. For instance, the importance of aquaporin-1 in water transport and sodium sieving has been elucidated using aquaporin-1 knock out mice exposed to a single hyperosmolar dialysate dwell [27, 87, 88]. Caveolin-1–deficient mice lack vascular caveolae and have been studied in order to clarify the mechanism of macromolecular transport [28]. In a combination model, endothelial NOS-deficient mice were exposed to an infectious insult in order to understand the role of NOS in functional changes in peritonitis. The importance of IL-6 in the peritoneal inflammatory response has also been evaluated in transgenic animals [40].

Gene Transfer

The mesothelial covering of the peritoneum is epithelial-like and is thus theoretically suitable for a variety of gene therapy vectors. To date, adenovirus have been used most commonly. Two studies have identified the distribution and duration of expression of a marker protein after adenoviral transfer. When transferred in a small volume, gene expression is marked in peritoneal mesothelial cells [89], whereas in larger volumes, the vector is transferred to a wider cell population in the submesothelial tissue and beyond [90]. In a rabbit model, distribution of the adenovirus was enhanced when administered in icodextrin rather than phosphate buffered saline [91]. Overall, expression persists for 10 to 14 days, making this a very transient system. Adenovirus also induces a strong inflammatory response persisting for 72 h after delivery [92]. Adenovirus have been used to study fibrogenic events [89] (Fig. 8.2), inflammatory cytokines [44], epithelial mesenchymal transition of mesothelial cells [92], and as antiangiogenic therapy in a model of chronic PD fluid exposure [93].

Cell Transplantation/Depletion

The peritoneum offers a large surface area of fairly readily accessible cells that are easy to culture and manipulate. This has led researchers in the direction of cell-based therapies. The observation that the peritoneal mesothelial cells become

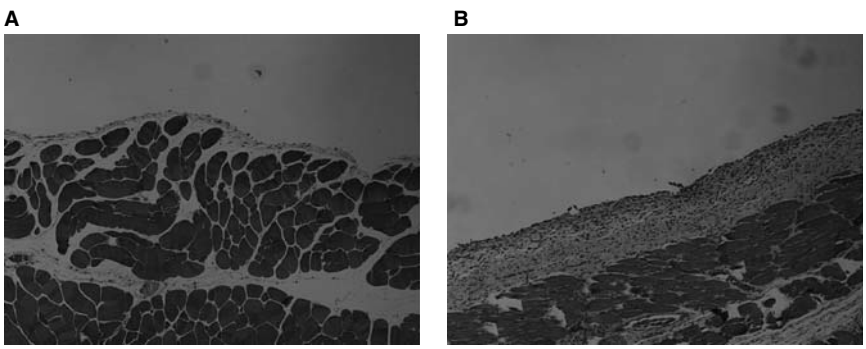

Fig. 8.2 (a) Mouse peritoneum 7 days after treatment with adenovirus expressing active TGFβ-1 demonstrates submesothelial expansion, fibroproliferation, and angiogenesis. (b) Mouse treated with control adenovirus demonstrates normal mouse peritoneal structure. Trichrome, 50× magnification

damaged and the peritoneum denuded over time on dialysis, or with acute peritonitis, has led to the fairly straight forward approach of autotransplant of mesothelial cells after damage. An initial positive study in rabbits led to this experimental approach being tried in a patient after peritonitis, with apparently successful implantation [94]. Hekking et al. have tackled this problem in a rat model of peritoneal injury, and have demonstrated successful implantation [95]. However, they also noticed that autologous mesothelial cell transport for some reason initiated an inflammatory reaction that had a negative impact on peritoneal structure [96].

Two studies have evaluated the possibility of using transplanted mesothelial cells as vectors for gene therapy [97]; in one case, an inducible promoter was used so that expression could be controlled exogenously [98]. Finally, an interesting model used to decipher the cellular basis of peritoneal injury allowed for the selective deletion of fibroblasts. A transgenic animal that expresses thymidine kinase under a fibroblast specific promoter was developed. Using chlorhexidine to induce peritoneal injury, the importance of fibroblasts in the propagation of peritoneal injury was described [99].

Measurements Tools in Animal Models for Peritoneal Dialysis Research

In order to elucidate the basic mechanisms of changes in the peritoneum in the models discussed above, tools have been developed at a molecular biology level and applied to peritoneal dialysis research.

Angiogenesis

Solute transport correlates with vascular surface area [100]. Because of this, many animal models are assessed for angiogenesis and angiogenic factors. Studies have used von Willebrand factor [92], CD31 [68], or α smooth muscle actin [65] immunostained sections of submesothelial or omental tissue to quantify vascularity. Simple counting or computerized image analysis has been used to assess stained sections. Vessels have been directly visualized using intravital microscopy of mesenteric windows and angiogenesis directly assessed along with vascular permeability to macromolecules [85]. Protein expression of angiogenic growth factors such as VEGF and NOS have been made by Western blot of omental tissue [82], in peritoneal dialysis effluent [89], or by quantitative immunohistochemistry [81]. Gene expression has also been assessed by extracting mRNA from peritoneal tissues and assaying by PCR [90] or quantitative real-time PCR extracted from peritoneal tissues [92]. Because each individual method has potential flaws and may be over interpreted, it is valuable to have concordant results from several different assays such as gene expression, protein expression, and immunohistochemistry.

Stem cells are increasingly recognized as having a potential role in peritoneal membrane injury, and these can be identified using a cell surface marker such as CD34 [69].

Fibrosis

Data from peritoneal biopsy studies have demonstrated that submesothelial thickening or fibrosis is the major finding in patients on peritoneal dialysis. It has been hypothesized that both angiogenesis and fibrosis are important in damaging the peritoneal membrane and leading to long-term functional changes such as ultrafiltration failure. Fibrosis is therefore an increasingly important outcome to be measured in animal studies.

The hallmark of fibrosis is the accumulation of extracellular matrix. Methods of evaluation include assays for hydroxyproline (a component of collagen), Western blot for collagen, or quantitative microscopy of sections stained for picrosirius red, or immunostained for collagen [71] or other extracellular matrix components. Picrosirius red staining and hydroxyproline assay has been compared favorably, especially in omental tissue [101]. Often, submesothelial thickness is taken as a surrogate marker of fibrosis, but correlation with other markers of fibrosis is lacking. A simple adhesion score has been developed [47].

Numerous fibrogenic related molecules have been assayed by immunohistochemistry, Western blot, or for gene expression by PCR. These markers include AGE, heat shock proteins, and TGFβ. Matrix metalloproteinases and their inhibitors are important in maintenance of fibrosis and have been assayed using gene expression analysis and zymography [102]. Finally, epithelial mesenchymal transition has recently been identified as an important initiating factor in peritoneal fibrosis and different techniques have been developed to assay for this process [83, 92].

Inflammation/Immune Response

Inflammation is an important component of peritoneal injury and response to peritonitis. This remains an important area of PD research and assays for inflammatory responses are used widely in animal models. Simple assays include bacterial clearance after acute peritonitis [103], along with simple counting of inflammatory cells [44]. Milky spots on the omental surface provide an estimate of leukocyte recruitment to the peritoneal cavity [104]. More sophisticated assays of peritoneal immune response include assays of the complement pathway [15, 58], or chemokine response [105].

Summary

The peritoneal membrane is a relatively simple structure, but the physiology and pathophysiology associated with peritoneal dialysis is complex. The interaction between the dialysis fluid, the structural components of the peritoneal membrane, the anatomic surface area, blood flow and vascular response is impossible to model in a cell culture system. Although useful mathematical models have been developed [106], understanding the peritoneal tissues as a dialysis membrane requires animal models. A variety of models have been developed to better understand peritoneal physiology, acute and chronic response to dialysate, and the molecular mechanisms of peritoneal injury and response. Insights derived from this work have led to advances in our understanding of the peritoneal membrane, new solutions for peritoneal dialysis, and new potential targets for therapeutic intervention. The goal of this work is to preserve the peritoneal membrane and improve outcomes for patients reliant on peritoneal dialysis. Through all this, researchers must maintain careful documentation of models utilized and a critical understanding of the potential and limitations of these models.

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Chapter 9
Pharmacological Alterations of Peritoneal Transport Rates and Pharmacokinetics in Peritoneal Dialysis

N. Lameire and W. Van Biesen

In the first part of this chapter, the effects of pharmacological manipulations on peritoneal transport will be discussed. Increased understanding of peritoneal transport mechanisms may lead to the development of clinically useful methods to augment peritoneal transport efficiency. In this chapter, only pharmacological tools for influencing peritoneal transport will be discussed. A detailed discussion of the physiology of peritoneal transport is provided in other chapters of this book. In the second part of this chapter, the pharmacokinetic concepts underlying transperitoneal drug transport and their implications for rational and safe use of drugs in patients treated with peritoneal dialysis (PD) will be discussed. Basic concepts of pharmacokinetics will be briefly reviewed as a starting point to elaborate further on general pharmacokinetic principles in patients with decreased renal function and in patients on PD. Tables with data and guidelines for prescription of specific drugs will be presented. An update on the most recent pharmacokinetic studies in PD will be provided.

Peritoneal Membrane Transport

(For details on peritoneal membrane transport, see Chapter 6.) Peritoneal transport comprises three processes that occur simultaneously: 1) diffusion, 2) ultrafiltration, and 3) fluid reabsorption. Transport of low-molecular-weight solutes during PD is primarily diffusive, whereas convective solute transport becomes more important with their increasing molecular weight. The absorption of intraperitoneally administered macromolecules is linear in time, irrespective of molecular size or concentration. Total removal of a solute is dependent not only on the peritoneal transport rate but also on the total drained dialysate volume. The latter is determined by the instilled volume and the net ultrafiltration. The effective peritoneal surface area used for transport of solutes is determined both by the number of perfused capillaries (and thus by splanchnic blood flow) and by the contact of the dialysate with the peritoneal surface.

It should be noted that diffusion in general does not depend on peritoneal blood flow, which at 50–100 mL/min, is already more than adequate relative to the mass transfer area coefficient (MTAC) values of even the smallest solutes. The ability of vasoactive substances to influence peritoneal transport is thus not related to their ability to increase peritoneal blood flow, but to the associated recruitment of larger numbers of perfused peritoneal capillaries that increase the effective peritoneal surface area. It should be realized that the proportion of peritoneal blood flow involved in peritoneal transport is unknown, and it is possible that in some areas of the peritoneum blood flow may limit diffusion.

Ultrafiltration occurs because of the osmotic gradient between the hypertonic dialysate and the isotonic capillary blood. Ultrafiltration is determined by a number of factors such as the hydraulic conductance of the peritoneal membrane, perhaps reflecting the density of small and ultrasmall pores in the capillaries as well as the distribution of the capillaries in the interstitium. A recent review on the mechanisms of peritoneal ultrafiltration has been published [1].

Recent experiments using knockout mice for aquaporin [2] provide direct evidence for the role of AQP1 during PD. The results validated essential predictions of the three-pore model: i) the ultrasmall pores account for the sodium sieving, and ii) they mediate 50% of ultrafiltration (UF) during a hypertonic dwell. Other factors are the reflection coefficient of the osmotic agent, the hydrostatic and osmotic pressure gradients, and the sieving process (for detailed review see other chapters in this book). Fluid absorption occurs via the peritoneal lymphatics at a relatively constant rate. This absorption occurs partly directly via the subdiaphragmatic lymphatics or, more importantly, through absorption into the tissues of the parietal wall where it is subsequently taken up by local lymphatics and perhaps by

N. Lameire (✉)
University Hospital Ghent, De Pintelaan 185, Ghent, Belgium
e-mail: Norbert.lameire@ugent.be

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peritoneal capillaries. The determinants of peritoneal absorption are the intraperitoneal (IP) hydrostatic pressure and the effectiveness of the lymphatic system.

Role of Electric Charges on the Transport Across the Peritoneal Membrane

Anionic sites predominantly composed of heparan sulfate and chondroitin sulfate are a constant feature of basement membranes of the microvasculature [3–5]. They are particularly abundant in fenestrated capillaries, some of which have been identified in human parietal and diaphragmatic peritoneum [6]. These anionic charges could, at least theoretically, restrict the diffusive and convective passage of charged solutes across the membrane. There is a paucity of data concerning the influence of the peritoneal membrane anionic sites on transport of charged macromolecules across the peritoneum. It is well established that an increased peritoneal permeability to albumin in diabetic animals is observed like in many other capillary beds. Shostak and Gotloib [7] could attribute this phenomenon to a reduced density of microvascular and submesothelial negative charges, equivalent to that induced by diabetes in other capillary beds. More recently, administration of aminoguanidine preserved both submesothelial and subendothelial electronegative charges in diabetic rats and restored the hyperpermeability for albumin [8].

Leypoldt and Henderson [5] demonstrated that peritoneal transport rates for cationic dextrans were less than for either neutral or anionic dextrans. These results differ from what one should expect. On the other hand, negatively charged amino acids such as glutamic acids show a slower transperitoneal mobility compared to neutral or positively charged amino acids [9]. In contrast, based on the determination of peritoneal clearances of ten different proteins and their isoforms, Buis et al. [10] concluded that the peritoneal membrane was not a charge-selective barrier for the transport of macromolecules between blood and dialysate. The effect of electrically charged drugs on peritoneal transport will be discussed later.

Part I. Pharmacological Alterations of Peritoneal Transport

Better knowledge of the pharmacological alterations of peritoneal transport that occur in PD patients may be useful for several reasons:

1. Co-morbidity is high in renal failure and these patients are exposed to a multitude of drugs that may affect the peritoneal transport of solutes and water. Knowledge of the effects of such agents on transport parameters can influence the appropriate selection of a drug.
2. There may be need for augmenting the peritoneal diffusive capacity. A redefinition of adequacy targets of PD has emerged over recent years. Many studies have focused attention on optimizing the quantity of solute clearance in an attempt to improve clinical outcome. Dialysis dose is currently quantified in terms of small solute clearances, fractional urea (Kt/V), and creatinine clearance rates. The target small solute clearances have been a source of some controversy and in many studies the amount of the residual renal function (RRF) has been a major confounding factor in the correct interpretation of the results. Where the magnitude of the RRF has a direct influence on outcome, it has been more difficult to demonstrate a similar effect for peritoneal clearance, at least within the range of dose prescriptions in typical clinical use. In particular the ADEMEX (ADEquacy of PD in MEXico) study showed no difference in technique or patient survival, or quality of life between a standard dose and a higher peritoneal clearance regimen [11, 12].
3. A major cause of cardiovascular morbidity and mortality, and also of technique failure, in PD, is the inadequate removal of fluid across the peritoneal membrane. A better knowledge of fluid transport (filtration and transcapillary and lymphatic absorption) may open possibilities for pharmacological manipulation of the peritoneal ultrafiltration capacity, or chemical modification of the dialysate, in order to prevent excessive fluid reabsorption from the peritoneal cavity.
4. Although to date the biocompatibility of the PD fluids has greatly improved, still adverse interactions of both the "classical" and the "new" solutions with the peritoneal membrane may provoke structural and functional alterations in the membrane which may end in peritoneal fibrosis [13–16]. Treatment with vasoactive and/or anti-inflammatory agents could be attempted in order to decrease these adverse effects.
5. When PD is used to remove exogenous toxins, it is usually mandatory that removal rates be maximal. Conversely, when protein loss is excessive it may be judicious to decrease the transport rates, at least of larger solutes.
6. Finally, pharmacological manipulation of peritoneal transport has increased our understanding of peritoneal physiology.

This part of the chapter will describe the several pharmacological manipulations on peritoneal transport, seeking enhanced understanding of transport mechanisms and clinically useful methods to either augment transport or to preserve the structural and functional integrity of the membrane.

Drugs Acting on the Peritoneal Blood Flow and Their Impact on Solute Transport

Greatly improved mass transport must depend on augmentation of blood flow or peritoneal permeability or area, just as hemodialyzer efficiency increases with larger surface area dialyzers, more permeable membranes, and higher blood flow rates. As stated above, the ability of vasoactive substances to influence peritoneal transport is not directly related to their ability to increase peritoneal blood flow, but rather to the associated recruitment of larger numbers of perfused peritoneal capillaries that increase the effective peritoneal surface area.

A detailed overview of the anatomy and physiology of the peritoneal circulation is discussed in Chapter 4 of this book.

Despite several lines of evidence suggesting that peritoneal blood flow should be high enough to avoid any limitation in solute clearances and ultrafiltration, the real impact of effective peritoneal blood flow on the efficiency of PD is still controversial [17]. Recent experimental work has suggested that, at least in some circumstances, peritoneal ultrafiltration and solute clearances may be blood-flow limited [18].Values of the peritoneal capillary blood flow vary between 50 and 100 mL/min, based on peritoneal gas clearances in animals [19]; others have found lower values [20]. In uremic humans, an indirect estimation of effective peritoneal capillary blood flow found values between 100 and 200 mL/min [21]. The impact of the application of the distributed model of peritoneal circulation and the hypothesis of the "nearest capillary" have recently been discussed and the reader of this chapter is referred to that paper [22]. In stable continuous ambulatory peritoneal dialysis (CAPD) patients, values ranging from 20 to 151 mL/min with a median value of 66 mL/min were found [23–25]. All these values assume that gas clearances represent the "effective" peritoneal blood flow. When mesenteric blood flow is doubled, the clearances of small solutes such as urea increase by 30–50% [26], consistent with a resting blood flow that exceeds the maximal rate at which the capillary diffusion capacity can completely clear the perfusing blood [27]. This is compatible with the results obtained by Douma et al. [24], finding an increase in MTAC of small molecules without a change in peritoneal "effective" blood flow as measured by the MTAC of CO_2.

The splanchnic vascular bed can sequester blood, excluding it from, or releasing it into, the circulation as systemic volume changes. Thus, hemodynamic effects of drugs can influence splanchnic blood volume and flow rate considerably. Because drugs usually affect the splanchnic blood flow and volume pari passu, changes in peritoneal transport that result from the altered volume can be misinterpreted as flow rate mediated. There is also evidence to suggest that splanchnic blood volume, rather than flow rate, determines the degree of peritoneal mass transfer [28]. For example, the volume contraction induced by the systemic administration of dihydroergotamine results in lower peritoneal clearances of potassium, urea, and phosphate [29], and this effect is due to a reduction in blood volume. On the other hand, both volume expansion by dextrose infusion [30] and sodium chromate-induced hepatic venous stasis increase these parameters. Current opinion prevails that, under physiological conditions, peritoneal blood flow does not limit the transfer of solutes. However, the effective blood flow available for transport will only be a fraction of the total blood flow through the tissues surrounding the peritoneal cavity, because most of the exchange capillaries are too far from the cavity to be active in the exchange process [31], or they are contained in tissues not in contact with the solution in the cavity [32]. In contrast, in the "nearest capillary" theory of Ronco [33], it is hypothesized that the capillaries positioned closest to the mesothelium are dilated and have a low blood flow, while the most distal capillaries have a higher blood flow, but with a less effective diffusion due to interstitial resistances. The resulting "effective" peritoneal blood flow in this hypothesis would be a limiting factor for solute clearance.

As outlined in Chapter 6, most data obtained in experimental animals, as well as in humans, suggest that the effects of small peritoneal blood flow changes on solute transport are probably limited.

The regulation of the mesenteric circulation is very complex (for further details, see Chapter 6). It is sufficient here to remind that both extrinsic and intrinsic autoregulatory control mechanisms exist. In the latter, the venous pressure and the ingestion of meals also have an effect. Food ingestion increases intestinal blood flow and this functional hyperemia is mediated by certain gastrointestinal hormones such as gastrin and cholecystokinin. Autoregulation of blood flow, i.e., the maintenance of a constant blood flow over a range of perfusion pressures, is not as well developed in the intestinal circulation as in other vascular beds, such as those in the brain and kidney. The principal mechanism responsible for mesenteric autoregulation is metabolic, i.e., any intervention that results in an oxygen supply that is inadequate for the requirements of the tissue prompts the formation of vasodilator metabolites. However, a myogenic

mechanism probably also participates. Adenosine is a potent vasodilator in the mesenteric vascular bed and may be the principal metabolic mediator of autoregulation.

Influence of Drugs Reducing Peritoneal Blood Flow

Drugs Decreasing Peritoneal Blood Flow

Catecholamines

To explore vasoactive effects on peritoneal transport, catecholamines have been studied in animals undergoing PD. Gutman et al. [34] noted lower increments in dialysate urea with large IP doses of dopamine in anephric dogs, but did not measure dialysate volume. Because blood pressure increased, the lower urea accumulation in the dialysate was attributed to splanchnic vasoconstriction. To offset vasoconstriction, Parker et al. [35] added an α-adrenergic blocker to the dialysis fluid. With IP phentolamine and IV dopamine, peritoneal clearances increased in dogs. In human patients, however, Chan et al. [36] observed no effect of low (4 mg/L) or high doses (20–160 mg/L) of IP dopamine on dialysate urea, creatinine, or phosphate.

In rabbits, IP dopamine caused dose-related (0.6–1.8 mg/kg) increases in peritoneal urea clearance [37]. The increments occurred with lower doses than those used by Gutman et al. [34] and drug concentrations (10–30 mg/L) within the range studied by Chan et al. [36].

IV 1-norepinephrine significantly decreased peritoneal clearances of urea and creatinine in unanesthetized rabbits [36, 37]. Dose-dependent decrements of the peritoneal clearances correlated with the pressor response [38]. Comparable pressor doses of IV dopamine increased clearances of urea and creatinine to 145% of control values, whereas low doses had minimal and inconsistent effects [38]. Osmotic water flux increased only slightly (from 0.18 to 0.24 mL/kg/min) but significantly. Because dopamine vasoconstricts venules relatively more than arterioles as compared to norepinephrine [39], augmented water flux could be mediated by increased hydrostatic pressure rather than a change in hydraulic permeability. The augmented transport is attributed to dopamine receptor-mediated mesenteric vasodilation and, in part, by general α-adrenergic vasoconstriction increasing blood pressure, while mesenteric blood flow is maintained. Although dopamine may not be suitable for augmenting efficiency of routine PD, these data strongly suggest that dopamine should be preferable to 1-norephinephrine when vasopressor therapy is required during PD.

Only minimal increments in fluid and solute flux occurred with ibopamine, an oral dopamine analogue, whether given by mouth, IV, or IP to normal rabbits [40]. Interestingly, the dialysate to plasma ratio for norepinephrine was 1.17 in CAPD patients, suggesting local production in the peritoneal cavity [41]. An unexpected correlation was found between the dialysate levels of norepinephrine and the effective peritoneal surface area, represented by the MTAC for creatinine.

Recent in vitro studies have investigated the effects of epinephrine on the electrical transmesothelial resistance (R(TM)) of the isolated parietal sheep peritoneum by means of Ussing-type chamber experiments [42]. A parietal peritoneal planar sheet was mounted in a Ussing-type chamber and epinephrine (10^{-7} Mol) was added to the apical and the basolateral side. The R(TM) was measured before and serially after the addition of epinephrine for 30 min. As active ion transport is temperature-dependent, all measurements were performed at 37°C. The addition of epinephrine to the basolateral side within 1 min induced a dramatic increase of R(TM) which decreased thereafter progressively to reach control values again after 15 min. A similar effect of epinephrine on the apical side was apparent with a rapid rise and a subsequent decrease of R(TM). A clear association between the R(TM) and active ion transport was established from previous studies. The results of this study indicate a rapid action of epinephrine on the parietal peritoneum permeability. Similar results were obtained with visceral peritoneum [43].

Vasopressin and Angiotensin

Vasopressin and angiotensin cause a generalized vasoconstriction with a disproportionate reduction in mesenteric blood flow [44]. Parenteral administration of vasopressin to anesthetized dogs decreased peritoneal clearances of small solutes, consistent with a hormonally mediated reduction in mesenteric blood flow [45, 46]. Since inulin clearance increased slightly under these circumstances, a concurrent increase in membrane permeability has been postulated [47], in accord with the accelerated transport that occurs in isolated membrane preparations [48].

Angiotensin II is probably mainly involved in the control of mesenteric blood flow during volume depletion. The effect of angiotensin II (AII) on peritoneal permeability and lymphatic absorption in the rat was studied by Go et al. [49]. AII was added to the dialysate and it decreased the transcapillary ultrafiltration rate from 15.7 ± 2.8 mL/4 h dwell

in control to 5.7 ± 1.5 mL/4 h dwell. Lymphatic absorption was increased in a dose-dependent fashion with no change in clearances of urea nitrogen or inorganic phosphate.

Drugs Increasing Peritoneal Blood Flow

Although the mechanisms of a decrease in solute transport by a reduction in peritoneal blood flow are important, much more attention has been paid to the study of the possibilities for augmenting peritoneal transport by systemic or IP administration of vasodilating drugs. Many studies suggest that peritoneal clearances will increase only if a vasodilator selectively affects the splanchnic vasculature or is applied locally, e.g., by IP instillation. When administered IV such drugs may cause widespread vasodilation, decreasing blood pressure, splanchnic perfusion, and splanchnic volume, thereby lowering peritoneal transport rates. To date, membrane-active agents have augmented transport only when applied locally, i.e., instilled intraperitoneally.

Increased splanchnic perfusion augments peritoneal clearances of larger solutes at least as much as the transport of smaller solutes. This suggests an increase in peritoneal surface area or permeability resulting from vasodilation, attributed to dilation of the functional peritoneal capillaries combined with perfusion of more capillaries. Spreading the same wall mass over a larger circumference decreases the wall thickness and stretches pores. Intercellular junctions widen, accelerating mass transport [50]. Raising blood flow by local application of vasodilators also opens previously closed capillaries, increasing the surface area available for transport [51, 52]. In the resting state, blood may circulate predominantly through metarterioles. Enhanced perfusion opens more capillaries, exposing blood to a more permeable surface. Furthermore, vasodilators with a predominant venular site of action may cause greater increases in diffusion rates, but arteriolar dilators may increase the ultrafiltration rate. By increasing blood flow, diffusion and ultrafiltration may occur throughout a greater length of the capillaries than occurs under resting conditions.

Depending on the nature of the vasodilating agent there may be an increase (arteriolar relaxation), decrease (lowered venular tone), or no change (balanced effects) in capillary hydrostatic pressure. This hydrostatic pressure may affect capillary diameter, volume, and permeability and is a major determinant of the filtration rate through the capillary. The solute transfer of small molecules, measured by their MTAC, is usually markedly increased during the first 15 min of PD dwells. Besides being caused by initial arteriolar vasodilation and. hence, recruitment of capillary surface area, other explanations for this rapid increase are possible. These include an initial discharge (or saturation) of solutes from (in) the interstitium or an increased mixing, i.e., "macrostirring" caused by the exchange procedure per se [53].

These possibilities have been investigated during acute PD in rats, by assessing the mass transfer coefficient for 51Cr-EDTA as a function of time [53]. The discharge effect was studied by saturating the peritoneal interstitium with 51Cr-EDTA by IV tracer infusion prior to each dwell. The potential effect of initial vasodilation was studied by adding isoproterenol to the dialysis fluid. Finally, the potential influence of an increased interstitial "macrostirring," induced by high glucose concentrations, was investigated by comparing 1.36% glucose with 3.86% glucose dialysate. The conclusion of these experiments was that vasodilation, but not interstitial discharge (or loading), may explain the sharp rise in mass transfer occurring during the initial part of PD dwells. In addition, "macrostirring," induced by the exchange procedure per se, may also be important.

Specific drugs may directly affect the permeability of the capillary or the mesothelium [54]. Drugs that influence membrane charge, cell volume, cell metabolism, or intercellular junction may directly influence peritoneal permeability without affecting flow rates.

Isoproterenol

Isoproterenol, a β-adrenergic agonist, relaxes the mesenteric vascular bed. In patients with reduced peritoneal clearance, Nolph et al. improved transport rates by adding isoproterenol (0.06 mg/L) to the dialysis solution [55, 56]. Mean clearances increased to the lower range of normal but only transiently, and improved significantly, though not in all patients [57]. No systemic effects of IP isoproterenol were detected even with cardiac monitoring. Such use of isoproterenol has been explored in greater detail in animals. In acute studies in anesthetized dogs, IP isoproterenol increased urea and creatinine clearance by 45 and 30%, respectively, but subpressor IV doses did not augment transport [34]. In unanesthetized rabbits, 0.04 mol/kg of IP isoproterenol raised urea and creatinine clearance by 50%, but osmotically induced water flux was unaffected [58]. No systemic effects were observed. Despite raising mesenteric blood flow to 188% of control by IV isoproterenol, Felt et al. [26] found no increase in clearances. With IP isoproterenol a comparable flow increase raised peritoneal inulin and creatinine clearances by 27 and 18%,

respectively. The disparity in blood flow and clearance changes suggests that capillary blood volume may be as important as blood flow in mediating changes in permeability.

Vasodilator Gastrointestinal Hormones

Secretin is a polypeptide gastrointestinal hormone that increases mesenteric blood flow by as much as 100% above baseline when given in pharmacological doses [59]. Secretin, like cholecystokinin, increases predominantly hepatic blood flow. Slight increments in urea and creatinine clearances occurred with IV secretin and cholecystokinin [60]. IV, but not IP secretin (10 U/kg) increased osmotic water flux in rabbits [60]. The endogenous release of cholecystokinin or secretin or their intra-arterial infusion relaxes precapillary sphincters and increases the capillary filtration coefficient [61]. Gastrin, structurally similar to cholecystokinin, also increases mesenteric blood flow [59]. The effects of secretin and cholecystokinin on mesenteric blood flow are additive and potentiated by theophylline [62]. This hormonal mesenteric vasodilation is attributed to direct relaxation of vascular tone, presumably mediated by cyclic AMP.

Glucagon is structurally similar to secretin, but has a more potent effect on the mesenteric circulation. When administered IV, immediately before dialysis, glucagon significantly increased peritoneal clearances of urea and creatinine in nonanesthetized rabbits [60, 63]. The same dose given IP did not affect clearances. Since this large molecule should traverse the peritoneum slowly, hormonal activity presumably occurs at the endothelial rather than at the mesothelial surface. In dogs, IV infusion of about 30 μg/kg/h glucagon increased mesenteric arterial blood flow and peritoneal inulin but not creatinine clearance, unlike IP [26]. Glucagon did not affect peritoneal water flux during dialysis in rabbits [60]. The separation of the effects of all these gastrointestinal hormones on diffusive and on convective transport, suggests the possible use of different pharmacological agents acting additively.

Prostaglandins

Arachidonic acid (AA) was recently, investigated for its vascular permeabilizing potential in the rat peritoneal cavity and for its mechanism of action [64]. The antagonistic potential of antioxidants (vitamin E, vitamin C, and troxerutin) was also evaluated. Vascular permeability was equated to the rate of extravasation of Evans blue dye from plasma into the peritoneal cavity. IV arachidonate induced an immediate, dose-related, and significant increase in permeability, which was comparable to the effect induced by similar doses of serotonin. Aspirin reduced the arachidonate-induced permeability by 75%, but, interestingly, neither the stable thromboxane A(2) receptor agonist U46619 (prostaglandin H(2) endoperoxide epoxymethane) nor prostacyclin were able to increase peritoneal vascular permeability. In contrast, the permeabilizing action of arachidonic acid was very sensitive to antioxidant agents. Thus, vitamin C and the flavonoid compound troxerutin fully abolished arachidonate-induced permeability, whereas vitamin E had only a partial effect. In conclusion, IV administration of AA strongly enhanced peritoneal vascular permeability in the rat, apparently via free radical generation.

There is evidence that the mesothelial cells, when exposed to cytokines, show a time-dependent increase in the levels of both COX-1 and COX-2 mRNA, with the greatest increase being seen for COX-2. These data demonstrate specific stimulation of eicosanoid metabolism in human peritoneal mesothelial cells (HPMC) by peritoneal macrophage-derived cytokines, indicating the possible importance of these mediators in the activation of IP prostaglandin synthesis [65].

Depending on the local concentration of the specific terminal enzymes, e.g., endoperoxide reductase leading to placental growth factor (PGF) 2α or endoperoxide isomerase leading to prostaglandin E2 (PGE2), a given product predominates in a given tissue. Regional blood flow is one determinant of enzyme activity. In the circulation, the prostaglandins are degraded during a single passage through the lung, thereby acting only locally with the exception of prostacyclin and thromboxanes, which have half-lives of a few minutes. Prostaglandins of the PGA, PGE, or PGI series are vasodilators, whereas PGF2α and thromboxanes are potent vasoconstrictors [66, 67]. These prostaglandins act locally in arterial walls to influence vascular tone and modulate the response of vascular smooth muscle to other vasoactive agents [68], for example, by modifying vasoconstrictor responses [66].

IP instillation of PGA1 or PGE1 moderately increased peritoneal clearances of urea and creatinine in nonanesthetized rabbits, whereas PGE2 significantly raised creatinine clearance to 132% and urea clearance to 180% of control values [69]. In contrast, IP administration of the vasoconstrictor PGF2α decreased peritoneal clearances to 80% (urea) and 82% (creatinine) of control [69]. These prostaglandins did not affect fluid flux and were ineffective when given IV. Neither IV nor IP administration of prostacyclin affected peritoneal solute or water transport significantly, nor did prostacyclin show pronounced effects on peritoneal transport under baseline conditions. Oral pretreatment with sulfinpyrazone, a potent stimulator of prostaglandin synthetase, did not alter peritoneal clearances significantly [70]. When mefenamic acid, a prostaglandin synthetase inhibitor, was administered either IV or IP to unanesthetized

rabbits in doses sufficient to inhibit platelet function, neither the peritoneal clearances of creatinine or urea nor water flux changed [70].

Oral pretreatment of rabbits with indomethacin blocked platelet aggregation but did not change clearance or ultrafiltration rates significantly [70]. IP indomethacin increases the size of pinocytotic vesicles and narrows intercellular spaces in the rabbit [71]. Alteration of prostaglandin synthetase affects both vasoconstrictor and vasodilator prostaglandins. Hence, regional blood flow may remain unchanged. Yet, when vasodilator prostaglandin activity predominates to compensate for increased renin-angiotensin activity or ischemic vascular disease, aspirin and indomethacin decrease regional blood flow. However, the reduction of clearances induced by IV 1-norepinephrine, which should be accompanied by vasodilator prostaglandin stimulation, is exaggerated by pretreatment with indomethacin in only half of the animals so studied. These results suggest that endogenous prostaglandins do not play a major role in regulating peritoneal blood flow under ordinary circumstances. However, in patients who depend on vasodilator prostaglandins to maintain organ perfusion, blockade of prostaglandin synthetase could impair transport, and a history of exposure to such drugs should be sought if clearances are low. Intraperitoneally, the prostaglandin precursor AA (1.5–5.6 mg/kg) increased creatinine clearance and urea clearance, suggesting an effect of endogenous prostaglandins, but systemic use of indomethacin did not block this increase [70, 72].

In patients with peritonitis, the increased solute transport rates are accompanied by augmented prostaglandin release, abnormalities that can be blocked by indomethacin [73]. However, this effect was not confirmed in a longitudinal study in peritonitis [74].

The effects of nitroprusside on the peritoneal circulation and transport have been detailed in Chapter 4.

Other Vasodilators

No consistent change in peritoneal clearance of urea or creatinine was observed in patients given IP hydralazine, which decreased blood pressure slightly [57]. Theophylline acts as a nonselective antagonist of two types of adenosine receptors that mediate opposite effects on vascular tone [75]. In rabbits, changes in solute and water fluxes were inconsistent after IP or IV aminophylline in doses exceeding the therapeutic range [76]. Presumably widespread vasodilation blunted any potential gain in peritoneal blood flow.

Diazoxide caused a modest increase in peritoneal clearances of urea and creatinine and a significant decrement in blood pressure when IP administered to patients [57]. An increase in ultrafiltration rate approaching 50% of control values was found inconsistently. The IP administration of 5 mg of phentolamine to patients did not influence peritoneal solute transport rates, nor did it affect osmotic water flux [57].

In anesthetized rats, histamine raised only modestly the clearances of urea and inulin, whereas bradykinin augmented these clearances more substantially [77]. Histamine causes overt capillary dilation and increases permeability with protein exudation, which can be blocked in rabbits by both H1 and H2 receptor antagonists [78]. Minimal effects of histamine on small solute transport may reflect decreased plasma volume due to protein loss. In isolated rat mesentery, viewed by television microscopy after fluorescein labeling, protein exudation is also demonstrable with histamine [50]. Dilation is most prominent in the venous end of the capillary and similar changes are noted with nitroprusside.

The effects of calcium channel blockers on peritoneal mass transport have been studied by several investigators. In the anesthetized rat model, verapamil and diltiazem, given locally, modestly but significantly increased peritoneal clearances of urea without enhancing protein losses [79]. Kumano et al. [80] explored the effects of the IP administration of nicardipine, diltiazem, and verapamil in rats. All three vasodilators caused a decrease in blood pressure, which was associated with a decrease in net ultrafiltration rate. The drugs increased peritoneal net fluid absorption rate in a dose-dependent way. Nicardipine and verapamil increased the permeability to urea and glucose but not to protein. Diltiazem caused no change in permeability. Significant augmentation of small solute clearances and ultrafiltration associated with diminished glucose reabsorption were reported with IP verapamil and nifedipine in CAPD patients [81, 82]. In hypertensive CAPD patients, oral nifedipine administered in blood pressure-controlling doses significantly increased peritoneal clearances of creatinine and β2-microglobulin, associated with higher glucose reabsorption, while the rate of ultrafiltration remained unaffected [83]. These studies suggest that calcium channel blockers act on the arteriolar end of peritoneal capillaries without a consistent effect on venular permeability.

A recent clinical study evaluated the effects of oral losartan, prazosin, and verapamil on peritoneal membrane transport during a peritoneal equilibration test (PET), as well as the effects on creatinine clearance (CrCl), Kt/V urea, 24-h protein in drained dialysate, and drained volume [84]. None of the studied drugs significantly modified the peritoneal transport of creatinine, glucose, urea, sodium, potassium, or total protein as evaluated by PET. Verapamil significantly increased peritoneal CrCl, weekly Kt/V urea, and drained dialysate volume. It was concluded that oral administration of losartan, prazosin, and verapamil did not modify the peritoneal transport of solutes during a 4-h

PET, but oral small solute clearances and 24-h drained dialysate volume. Verapamil could thus be considered as an alternative in patients requiring increased dialysis dose and/or ultrafiltration.

In rats, modest increases in urea clearance and glucose absorption and a marked exaggeration of protein loss was seen following IP instillation of very large doses of captopril, an angiotensin-converting enzyme inhibitor [85]. These increments, despite drug-induced systemic hypotension, may reflect increased blood flow, surface area, or permeability. In the above-mentioned study by Kumano et al. [80], captopril was also investigated after IP administration. Captopril increased membrane permeability to small and large molecular solutes, with a consequent decrease in ultrafiltration rate. In a clinical study [86], six hypertensive CAPD patients received IP enalaprilat and five of them also received oral enalapril. After IP enalaprilat, blood pressure declined significantly, and plasma angiotensin-converting enzyme (ACE) activity was suppressed below detectable limits. There were no changes in peritoneal transport characteristics. In contrast, in another study in CAPD patients, glucose, creatinine, and β2-microglobulin transport rates were increased after oral administration of hypotensive doses of enalapril [83]. Smaller doses of oral captopril significantly reduced peritoneal protein loss in diabetic CAPD patients, with only a small decrease in their mean blood pressure [87].

Coronel et al. [88] evaluated the action of irbesartan, an angiotensin receptor blocker (ARB) with a long half life, on proteinuria, peritoneal protein losses, and peritoneal transport. After 30 days of treatment with irbesartan (145 ± 72 mg/day), and no changes in blood pressure level as compared with baseline, a reduction in proteinuria, decreased peritoneal protein losses at 4 h and 24 h dwell time, decreased peritoneal Kt/V urea, and increased peritoneal creatinine clearance were observed. Levels of serum albumin, prealbumin, and transferrin increased after treatment with irbesartan. Treatment with irbesartan in PD patients apparently modifies peritoneal transport and reduces peritoneal and urinary protein loss. This effect probably has a positive impact on nutritional parameters.

Using a sophisticated intra-abdominal camera, Ishida et al. [89] tested several antihypertensive drugs on the peritoneal capillaries in renovascular hypertensive dogs with mild renal insufficiency. The diameters of the small arteries of the peritoneum were measured after 3 days' oral administration of placebo, a selective ARB, or benazepril, an ACE inhibitor, or amlodipine, a calcium antagonist. A similar decrease in blood pressure was observed with all drugs. The diameter of the small vessels increased by 28% in dogs receiving the ARB and by 24% in dogs receiving benazepril, as compared with only 3% in dogs receiving the calcium antagonist.

Besides the hemodynamic effects that blockers of the angiotensin pathway may exert on the peritoneal structure and function, angiotensin is also thought to contribute to peritoneal fibrosis when the membrane is exposed to high glucose concentrations in PD [90], and ARBs may have a key role in preventing fibrosis as they may inhibit the TGF-beta1-Smad pathway [91]. However, another recent study found no differences in the protective effect on the membrane of either an ACE inhibitor or an ARB [92], but the expression of AQP-1 and AQP-4 in the mesothelium was significantly suppressed, accompanied by loss of peritoneal ultrafiltration in ACEI- and ARB-treated compared with control rats [93]. These results suggest that the renin-angiotensin system plays an important role in the regulation of water transport in the peritoneum and that administration of ACEI or ARB in patients CAPD should be carried out with caution.

The influences of a variety of other agents on peritoneal mass transport have been explored.

Statins have anti-inflammatory properties that may be of value in modulating responses to injury. The capacity of atorvastatin to modify peritoneal alterations secondary to hypertonic glucose were recently explored [94]. Administration of atorvastatin resulted in preserved ultrafiltration, protein loss, and peritoneal thickness.

Atrial natriuretic peptide (ANP) is a hormone with well-known diuretic and vasodilating properties. It has recently been reported that ANP could increase peritoneal fluid formation and increase peritoneal solute clearance. Recent studies in rats [95] suggest that ANP may decrease peritoneal fluid absorption by 51%, partially because of decreasing the direct lymphatic absorption, resulting in a significant increase in peritoneal fluid removal and small solute clearances. While the basic diffusive permeability of the peritoneal membrane was not changed, the peritoneal glucose absorption was retarded by adding ANP to peritoneal dialysate, perhaps through interaction of ANP with glucose metabolism.

The peritoneal transport rates of potassium and iodide-131 increased when streptokinase or serotonin was administered systemically to anesthetized dogs [45]. Whether these agents affect peritoneal permeability directly, or augment blood flow, remains to be determined.

In sedated rabbits dialyzed with a hypertonic dialysis solution, 0.25% procaine hydrochloride increased peritoneal urea and inulin clearances by more than 60% [96]. The effect persisted for at least 1 h after procaine was discontinued. Procaine may augment transport by vasodilation. However, the addition of procaine to either side of the isolated mesothelium increased transport, after a transient decrease. This effect may be due to disruption of the microfilaments of tight junctions between cells.

Using direct videomicroscopy of the peritoneal vasculature in rats, Mortier et al. [97] found that local application of acetylcholine, nitroglycerin, verapamil, and papaverine caused significant vasodilation of mesenteric arteries in the absence of any effects on systemic BP. Nitroglycerin 10^{-4} Mol induced a maximal and rapidly reversible vasodilation and acts independently of the endothelium.

The nitric oxide system and the peritoneal circulation and transport (see also Chapter 4).

Nitric oxide (NO) is the final common pathway for many of the vasodilating processes, including nitroprusside. Besides the expression of aquaporins (see below), Devuyst et al. [98] investigated the expression of endothelial nitric oxide synthase (eNOS) in 19 peritoneal samples from normal subjects, from uremic patients treated by hemodialysis (HD) or PD, and from nonuremic patients using Western blotting and immunostaining. eNOS was located in all types of endothelium and was up-regulated in the three patients with ascites and/or peritonitis. An adaptation of the L-citrulline assay to measure specific NOS activities within the peritoneum was more recently described; it appeared that the peritoneum lysate assayed for NOS activity can also be used for characterizing NOS isoform expression by immunoblot analysis [99].

Nitric oxide (NO) generation within the peritoneum could potentially affect peritoneal transport by increasing capillary vasodilatation, and increase peritoneal permeability during episodes of bacterial peritonitis. As peritoneal mesothelial cells have a common embryological derivation with endothelial cells, then mesothelial cells could potentially be a major source of locally produced NO. Davenport et al. [100] measured NO in fresh and spent dialysate effluent (SPDE) from uninfected CAPD patients, and from those during episodes of bacterial peritonitis. The results suggest that HPMC may be an important source of locally generated NO within the peritoneal cavity under basal conditions, but as they do not contain iNOS, the increased NO produced during episodes of acute bacterial peritonitis is more likely due to a combination of increased NO production by peritoneal endothelial cells and transmigrating macrophages. NO is very rapidly converted into nitrite and nitrate and the dialysate concentrations of both products have been used to estimate peritoneal NO production. In contrast to nitrite in plasma, which is rapidly converted to nitrate, nitrite in fresh and spent dialysis fluid is stable [101]. However, interpretation of such results should be made with caution. It is likely that the L-arginine–NO pathway is not the only route for generating nitrate, and that nitrate and nitrite are not acceptable measures of biologically active NO [102].

It is well known that different isoforms of NO synthase exist; the two most relevant ones in PD being eNOS and iNOS. The latter is induced whenever immunological stimulation is present. Peritoneal macrophages are an important source of iNOS [103–105]. Combet et al. [106] were able to demonstrate a strong increase in total NOS activity in an experimental model of peritonitis in the rat. This increase was inversely correlated with peritoneal free-water permeability. It is thus conceivable that the elevated levels of nitrate in peritonitis are derived from iNOS activity and not from the "hemodynamically active" pool of eNOS.

With these reservations in mind, nitrate in plasma and dialysate was measured [107] in stable CAPD patients and in patients with 11 peritonitis episodes in the acute phase and after recovery. The correlation between the MTAC of nitrate and the MTAC of creatinine indicated diffusion from the circulation and not local production of NO in the stable patients. From these studies it was suggested that D/P ratios of nitrate exceeding 1.0 during the acute phase of peritonitis are probably the result of local NO production, which may contribute to the marked vasodilation during peritonitis.

An important animal study showed that chronic uremia induces permeability and structural changes in the peritoneum, in parallel with AGE deposits and up-regulation of specific NOS isoforms and growth factors. These data suggest an independent contribution of uremia in the peritoneal changes during PD and offer a paradigm to better understand the modifications of serosal membranes in uremia [108]. Another study of the same research group demonstrated that long-term exposure of the human peritoneal membrane to dialysis solutions led to a significant increase in vascular density and endothelial area in the peritoneum in association with an up-regulation of NOS, vascular endothelial growth factor (VEGF), which co-localized with the advanced glycation end product pentosidine deposits. These data provide a morphologic (angiogenesis and increased endothelial area) and molecular (enhanced NOS activity and endothelial NOS upregulation) basis for explaining the permeability changes observed in long-term PD [109].

More recent studies have also suggested a major role for nitric oxide (NO) in the permeability changes and loss of ultrafiltration induced by acute peritonitis. Both in eNOS wild-type and knockout mice [110, 111] or with NOS blockade in wild-type mice the potential role of NO in peritonitis was explored. The results revealed that the permeability modifications and structural changes induced by acute peritonitis were significantly reversed in eNOS knockout mice, resulting in a net increase in ultrafiltration [110]. These results confirm that increased NO mediates permeability modifications during acute peritonitis. Breborowicz et al. [112] studied peritoneal transport of small and large solutes, and net ultrafiltration in rats during PD with glucose 3.86% solution, where L-NAME was used as an additive to dialysis fluid. In addition, the effect of IP L-NAME during acute peritonitis induced by lipopolysaccharides

was evaluated. L-NAME increased the peritoneal selectivity and net ultrafiltration. Lipopolysaccharides alone induced a significant decline in net ultrafiltration while, together with L-NAME, no changes in transperitoneal transport of small and large molecules was observed, nor a significant decline in net ultrafiltration. L-NAME given intraperitoneally reduced both local and systemic production of NO, which might explain its effects on peritoneal transport.

The effects of conventional and more biocompatible solutions on the peritoneal circulation will be discussed in Chapter 12.

Dipyridamole

Dipyridamole rapidly but transiently vasodilates [113] and has a sustained antiplatelet effect, which may explain the restoration of clearances towards normal in patients with intravascular platelet aggregations [114]. Peritoneal transport of urea and creatinine increased by 43 and 70%, respectively, in patients with normal vasculature given oral 300 mg/day of dipyridamole [115]. In rabbits, IV or IP dipyridamole increased urea and creatinine clearances by 39 and 16%, respectively [114]. The limited effectiveness and the transient vasodilator response of dipyridamole are reflected by two randomized control studies that did not demonstrate significant increases in peritoneal transport [47, 116]. Reduced peritoneal transport rates complicating some vascular diseases (vasculitis, diabetes mellitus, lupus, etc.) are improved by dipyridamole [117]. The augmentation of peritoneal transport rates persists after dipyridamole vasodilation abates, and is attributed to its antiplatelet effect. Peritoneal clearances of patients with normal vasculature improve only minimally and transiently with oral or IP dipyridamole [114]. Nevertheless, dipyridamole may be useful for selected patients when systemic disease with platelet thrombi affects mesenteric vessels, and an oral agent is preferred.

Alterations of the Electric Charges

Charged macromolecules may interact with peritoneal anionic sites, altering membrane ultrastructure and permeability. In rats, local administration of protamine, a polycation, markedly increases peritoneal permeability to inulin and, to a lesser extent, urea, associated with a partial disruption of the mesothelial junctions [118]. In rabbits, protamine-induced rise in peritoneal permeability to proteins can be reversed by heparin, which provides additional evidence for the physiological importance of negative electric charges on the membrane [119]. Also cationic poly-L-lysine augments peritoneal permeability for urea, inulin and albumin, while with the anionic poly-L-glutamic acid there was an opposite trend in rats [120]. These results were confirmed in a rabbit model by Pietrzak et al. [121]. Agents such as poly-L-lysine, polybrene, and procaine hydrochloride block the negative charges on the capillary walls and higher mass transports ensue, especially for charged solutes [122]. A poly-L-lysine -induced modest increase in the transfer rate of large uncharged molecules such as dextrans may be attributed to an effect on pore dimensions.

These findings contrast with those of Breborowicz et al. [123], who found decreased hydraulic permeability of the mesothelium in vitro when exposed to cationic ferritin or Alcian blue. In vitro studies of isolated mesothelium, however, may not relate closely to in vivo conditions, in which the capillary wall and interstitium are the more important transfer barriers. Further evaluation of polycations as transport accelerators, particularly for patients with impaired peritoneal transfer capacity, is undoubtedly warranted.

Influence of Pharmacological Substances on Peritoneal Convective Transport

As outlined in the chapter of peritoneal physiology, according to the three-pore model [124], the existence of a third, ultrasmall pore or aquaporin could explain the dissociation between water and sodium transport observed during PD, mainly when using hypertonic dialysis solutions. Aquaporin-1 has recently been recognized as the molecular correlate to such channels and positive staining for aquaporin-1 has recently been reported in the endothelial cells of the peritoneum of normal and uremic subjects [98, 125]. Aquaporins can be inhibited by mercurials, and in a study by Carlsson et al. [126], $HgCl_2$ was applied locally to the peritoneal cavity in rats, dialyzed with a hypertonic 3.86% glucose solution. $HgCl_2$ treatment reduced water flow and inhibited the sieving of $Na+$ without causing any untoward changes in microvascular permeability, compared with that of control rats. At least eight isoforms of aquaporins are now described, and besides aquaporin 1, aquaporins 3 and 4 are also present in the peritoneum [127].

Imai et al. [128] used a rat model of peritoneal sclerosis and could demonstrate that, in this model, the expression of AQP-1 and AQP-4 were significantly suppressed, and ultrafiltration volume was lost. The use of prednisolone in this

model completely restored the expression of AQP-1 and AQP-4, and peritoneal function improved. These findings were later confirmed by Stoenoiu et al. [129], who demonstrated that corticosteroids were able to induce an upregulation of aquaporin 1 in the peritoneal membrane with an associated increase in transcellular water transport across the peritoneal membrane.

Some drugs can also specifically affect the capillary filtration coefficient, i.e., the volume filtered per unit of pressure per unit of time (mL/mm Hg/min). The rate of ultrafiltration is largely determined, however, by the osmotic gradient across the peritoneum induced by dextrose. The gross ultrafiltration rate and solute mass transfer are offset by dialysate absorption; hence, lowering lymphatic flow rates raises net ultrafiltration and peritoneal clearance of solutes.

Diuretics

The addition of 1 mg/kg of furosemide to hypertonic PD solution augmented sodium movement, accompanying osmotically induced water flux in rabbits [130]. Normally, electrolytes do not accompany water in the same concentration as exists in plasma water, suggesting that membrane charge impedes transport, a phenomenon that is interrupted by furosemide. IP furosemide also caused an increase in peritoneal urea clearance, but no demonstrable changes in transport rates occur in patients undergoing intermittent PD when treated systemically with this diuretic. Moreover, oral administration of furosemide did not affect sodium, potassium, or water transport in patients undergoing CAPD [131]. Furosemide, however, does increase the peritoneal transport of uric acid and of barbiturates [132]. Intraperitoneally, 1.25 mg/kg of ethacrynic acid did not affect sodium flux accompanying the bulk flow of water across the peritoneum, but augmented urea clearance to about 165% of baseline [130]. Patients treated by CAPD may experience a restoration of lost ultrafiltration capacity after treatment by furosemide or by hemofiltration [133]. A specific effect of furosemide has been postulated, but correction of an overexpanded splanchnic volume by decreasing glucose absorption was able to restore the ultrafiltration capacity.

Amphotericin B (AmB)

AmB increases the rate of ultrafiltration per osmotic gradient, i.e., the ultrafiltration coefficient [134]. Above 0.5 mg/kg there is no dose effect, and it is effective only from the serosal side [134, 135]. AmB creates channels in biological membranes for solute and water penetration. Increments in peritoneal solute clearances are only modest and can be accounted for by enhanced convection [134]. Peritoneal mass transport of sodium also increases. Because osmotic ultrafiltrate during PD is hyponatric, the sodium gradient so established is an impediment to water transport that is cancelled by AmB [135]. IP use of use of AmB has been reported to increase ultrafiltration during short peritoneal dwell in rabbits. However, IP AmB did not increase peritoneal fluid removal after 4 h of dwell in a rat model [136]. Although the basic membrane permeability may not be altered by this drug, the D/D0 ratio for glucose and dialysis-over-plasma concentration ratio (D/P) values for urea, sodium, and total protein, as well as the diffusive mass transport coefficient values for these solutes did not differ among the different experimental groups (with and without AmB). However, the D/P values as well as the diffusive mass transfer values for potassium were significantly higher in the drug-treated animals as compared to the control group, resulting in significantly higher potassium clearances in the AmB-treated animals as compared to the control group. These higher clearances for potassium in the AmB groups may suggest a local release of potassium due to the cytotoxic effect of AmB. The contribution of water release from local cells to the increase in IP volume in animals treated with a high dose of AmB cannot be ruled out. Based on these results, it was concluded that AmB is not useful for improvement of PD efficiency [136]. Another experimental study with IP administration of AmB in rabbits [137] found also that the drug acutely enhanced a change in IP volume during a 1-h dwell after 3-day IP treatment with a low dose but did not affect peritoneal solute permeability. This was likely mediated by transcellular water channels, but not by aquaporin-1. No beneficial effects on the ultrafiltration were found with prolonged treatment or with the higher dose. Also these investigators found that AmB has no major clinical relevance in treatment of ultrafiltration failure in PD patients.

Beta-Blockers (β-Blockers)

Use of β-blockers has been associated with peritoneal ultrafiltration failure [138]. Of 13 patients with ultrafiltration failure, 12 had used β-blockers, compared to 18 patients without these problems, where only two patients used these drugs. Possible mechanisms explaining this observation have been reviewed [139]. From a theoretical point of view, either a decrease in portal venous pressure or an increase in lymphatic absorption is a possible mechanism.

Increasing Ultrafiltration Rates by Miscellaneous Drugs

Secretin increases the hydraulic permeability of the peritoneal membrane [140]. This selective action on the splanchnic bed occurs from the vascular side only. The aminonucleoside puromycin also induces this effect on peritoneal capillaries [141]. Chlorpromazine (2 mg/L) IP increases the ultrafiltration rate and solute clearance, largely by increased convection and presumably by its surfactant effect [142]. This drug decreased surface tension of the dialysate.

Neostigmine decreases the rate of lymphatic flow and thereby increases net ultrafiltration in rats [143]. Anticholinesterase agents have complex hemodynamic effects that could influence peritoneal transport and increase gastrointestinal motility, which would enhance dialysate mixing.

Higher ultrafiltration rates due to diminished glucose reabsorption were reported with IP calcium channel blockers in CAPD patients [81, 82]. Ronco et al. [17] suggested that maximal rates of ultrafiltration are inhibited by the steep curvilinear rise in plasma protein oncotic pressure in the peritoneal capillaries, reflecting the limited blood flow rate. Maher et al. [144] demonstrated that the ultrafiltration coefficient decreases in rabbits as IP dwell is prolonged, suggesting some concentration polarization, which could be corrected by increasing turbulence at the membrane interfaces. Increased absorption of dextrose will accompany most manipulations that enhance solute permeability and hence dissipate the glucose osmotic gradient faster, reducing ultrafiltration. Insulin is required to maintain low plasma glucose levels and achieve the maximal gradient. Exogenous insulin added intraperitoneally does not increase the glucose mass transfer coefficient [145].

Lymphatic Absorption

Lymphatics are the primary route for absorption from the peritoneum of isotonic dialysate including macromolecules, particles, and formed blood elements [146]. Most absorption occurs via the subdiaphragmatic lymphatics, with lesser amounts via the mesenteric lymphatic vessels [147]. Yet before reaching lymphatic channels macromolecules are probably distributed in the large peritoneal tissue compartment [148] (see Chapters 5 and 6 in this book).

The rate of lymphatic flow from the peritoneum correlates positively with ventilation (diaphragmatic movement) and negatively with end-expiratory pressure; it decreases with erect posture and with dehydration [149].

In the rat PD model, neostigmine increased net ultrafiltration and solute transport by reducing the cumulative lymphatic absorption, without an increase in total transcapillary ultrafiltration [143]. Lower doses of IP failed to influence lymphatic absorption in CAPD patients [150], but the animal data were confirmed by a report of a CAPD patient suffering from myasthenia gravis who required high oral dosage of this drug [151]. In another animal study, phosphatidylcholine augmented net ultrafiltration and solute clearances without increasing flux of water and solutes into the peritoneal cavity, thus acting by reducing lymphatic reabsorption [152]. Similar results were reported in a clinical study [153]. It has been suggested that phosphatidylcholine affects peritoneal fluid kinetics through its cholinergic action [154]. These studies indicate that limiting lymphatic absorption is a potential mechanism for augmenting peritoneal clearances that should be explored further.

The Study of Different Additives to the Dialysate

Hyaluronan

Using the rat model it has been found that peritoneal absorption was significantly reduced and peritoneal small solute clearance substantially increased by adding to the peritoneal dialysate 0.01% hyaluronan, a long polysaccharide chain that consists of repeating disaccharide units of N-acetylglucosamine and glucuronic acid [155, 156]. It is speculated that the effect of hyaluronan is due to the accumulation of a restrictive filter "cake" of hyaluronan chains at the tissue–cavity interface [156].

Hyaluronan plays an important role in tissue hydraulic conductivity and has been shown to exhibit a high resistance against water flow. It can thus act in tissue as a barrier against rapid changes in tissue water content [157], impeding the efflux from the peritoneal cavity. This effect of hyaluronan is both size- and concentration-dependent [156].

It is also possible that exogenous high-molecular-weight hyaluronan stabilizes the endogenous hyaluronan, which forms a stagnant layer at the mesothelial cell surface [158]. Effluent dialysate from CAPD patients stimulates production of hyaluronic acid by human mesothelial cells and acts synergistically with cytokines, such as interleukin (IL)-1 [159]. It has been shown that normal human mesothelial cells in vitro surround themselves with a particular matrix, "coat," containing mainly hyaluronan [160]. In a prospective, randomized crossover study [161], PD patients

were submitted to three dialysis treatments using the following PD solutions: 1) a commercially available PD solution (Dianeal PD-4, 1.36% glucose), 2) Dianeal PD-4 containing 0.1 g/L hyaluronan (HA), and 3) Dianeal PD-4 containing 0.5 g/L HA. There were no significant differences in net UF or peritoneal volume profiles among the three treatments. Mean net UF calculated using residual volumes, estimated by RISA dilution, tended to be slightly higher during treatment with solution containing 0.1 and 0.5 g/L HA. These data support the acute safety of HA when administered IP to PD patients. Although not statistically significant, there was a trend toward decreased fluid reabsorption during treatment with HA.

N-acetylglucosamine

Related to the effects of hyaluronan, N-acetylglucosamine (NAG) has been used either as osmotic agent for PD [162, 163] or as an additive to classical dialysate. Chronic PD with dialysis solution supplemented with NAG (50 mmol/L) causes accumulation of glycosaminoglycans in the peritoneal interstitium, which results in a change of peritoneal permeability [164]. Supplementation of the dialysate with NAG could enhance the synthesis of hyaluronan by the mesothelial cells, since hyaluronan contains both glucuronic acid and NAG. In rats, equivalent concentrations of NAG and glucose were associated not only with a greater ultrafiltration with NAG [163], but also with a greater in vitro synthesis of hyaluronan [162].

Chronic PD in rats with a solution supplemented with NAG showed an accumulation of polyanionic glucosaminoglycans in the submesothelial interstitium that must be associated with a decreased hydraulic permeability of that tissue [165].

Glycosaminoglycans (GAGs)

Enhanced IP synthesis of GAGs increases the permselectivity of the peritoneum and preserves its function during chronic PD [166–168]. To verify whether the favorable effects of GAGs are purely functional or involve a morphological amelioration of the peritoneal membrane structure, a study was carried out in an animal model of plasticizer-induced peritoneal fibrosis [169]. Subtotally nephrectomized rats received either placebo, plasticizers (IP), or GAGs (SC), or plasticizers (IP) and GAGs (SC). In plasticizer-treated animals, peritoneal function tests and morphology were dramatically deranged. On the contrary, the SC administration of GAGs in plasticizer-treated rats maintained the peritoneal physiology and normal structure. The SC administration of GAGs apparently protects peritoneal functions by affecting the remodeling of the peritoneum, rather than by a purely functional or simple mechanical effect.

Heparin

In an animal model of chronic PD with repeated dwell studies it was shown that heparin may improve peritoneal fluid transport, possibly due to better healing and reduced peritoneal inflammation [170]. In a clinical study, Sjoland et al. [171] showed that IP tinzaparin reduces peritoneal permeability to small solutes and increases ultrafiltration in PD patients. In a recent experimental study [172], exposure to PD fluid induced activation of IP complement formation of C3a(desArg) and increase of C5a-dependent chemotactic activity, and coagulation (formation of thrombin–antithrombin complex) and recruitment of neutrophils. In the case of IP injection, neutrophil recruitment and complement activation were inhibited by low-molecular-weight heparin (LMWH). LMWH inhibited thrombin formation, reduced complement-dependent chemotactic activity, and increased the IP fluid volume, indicating an improved ultrafiltration.

Chondroitin Sulfate (CS)

CS, another naturally occurring polyanionic polymer GAG has been tested as an alternative osmotic agent or has been added to saline [173] or conventional dialysis solution to enhance peritoneal ultrafiltration [167]. In the presence of CS, net peritoneal ultrafiltration increased, while absorption of glucose and horseradish peroxidase from the peritoneal cavity decreased [173, 174]. It is postulated that the polyanionic CS molecules are trapped in the peritoneal interstitium, thus decreasing its hydraulic conductivity and permeability, which in turn increases net fluid removal during PD because of its slower absorption from the peritoneal cavity.

Phosphatidylcholine

In 1985, Grahame et al. detected the presence of surface-active material (phospholipids) in the peritoneal effluent of CAPD patients [175].The surface-active material, lining the peritoneal membrane, is mostly composed of phosphatidylcholine (lecithin). Peritoneal efficiency may be altered by the constant removal of phosphatidylcholine and other phospholipids in the dialysate effluent [175]. A decrease in dialysate phospholipids was reported in patients with a low ultrafiltration capacity and in those with peritonitis [176]. IP phosphatidylcholine promptly raised the ultrafiltration rate, while after oral administration about 30 days were required to achieve this effect. It was suggested that lecithin administration restored the normal peritoneal surfactant lining [176]. To explain augmentation of ultrafiltration after phosphatidylcholine, another group proposed that these phospholipid molecules bind to the anionic sites on the luminal side of the mesothelium, creating a water-repellent surface that diminishes the thickness of the unstirred dialysate. This would augment diffusion of solutes from blood to the peritoneum while the hydrophobic lecithin molecules would impede water absorption, favoring ultrafiltration [177].

In rabbits, phosphatidylcholine increases net ultrafiltrate volume [177], an effect that becomes significant only after hours of PD, and does not show up during hourly exchanges.

Clinical studies have shown that a phosphatidylcholine premixed dialysis solution significantly enhances ultrafiltration also in patients without ultrafiltration loss [153], but other results were controversial [178, 179]. Besides its surfactant effect, phosphatidylcholine may impede lymphatic absorption [152]. In rat experiments, administration of 50 mg/L phosphatidylcholine to a dialysate of 4.25% glucose leads to a reduction in lymphatic absorption without increased transperitoneal transport of water. However, in in vitro experiments, phosphatidylcholine was cytotoxic to human mesothelial cells, as indicated by the release of lactate dehydrogenase from their cytosol. These results suggest that the positive short-term effect of the addition of phosphatidylcholine to the dialysis solution (i.e., an increase in ultrafiltration) may be masked by its deleterious action on human mesothelial cell membrane [180].

Dioctyl Sodium Sulfosuccinate (DSS)

Dioctyl sodium sulfosuccinate (DSS) is a surfactant and has been shown to increase peritoneal small solute clearance. Penzotti and Mattocks [181, 182] accelerated peritoneal transport of labeled urea and creatinine in sedated rabbits by adding a variety of surface-acting agents including DSS and setyl trimethyl ammonium chloride. Dunham et al. [183] found a dose-dependent rise in creatinine and urea clearances when docusate sodium was given intraperitoneally to tranquilized rabbits. The effect persisted for 5 h. DSS was found to increase peritoneal fluid and small solute removal whereas the peritoneal solute transport rate did not change [184].

Cytochalasins

These molecules disrupt microfilaments of cellular junctions. IP cytochalasin D raises the clearances of creatinine and urea in the rabbit, consistent with augmented diffusion through intercellular gaps [185]. Similarly, cytochalasin B, D, and E increase permeability of the peritoneum to urea, inulin, and albumin in rats [186]. Only cytochalasin B effects were clearly reversible, which may relate to its unique ability to affect carrier proteins of the cell membrane.

Antioxidants and Free Radical Scavengers

Breborowicz et al. [187] tested the effect of L-2-oxothiazolidine-4-carboxylate (procysteine), a precursor of intracellular cysteine, on the function of human mesothelial cells in culture. Procysteine stimulated the proliferation of these cells and decreased their spontaneous death rate. The cells, when pretreated with procysteine, were resistant to injury by free radicals. Procysteine also reversed the cytotoxic effects of a mixture of essential and nonessential amino acids on the cells. The same drug was also studied in an in vivo model of lipopolysaccharide (LPS)-induced peritonitis in rats [188]. The addition of LPS to dialysis fluid increased the white blood cell count and the nitrite level (index of NO synthesis) in the dialysate. Simultaneous addition of procysteine to the dialysis fluid prevented an increase of while blood cells, but not of nitrites in the dialysate. The IP inflammation was accompanied by a decrease in net transperitoneal ultrafiltration, an increase in the absorption of glucose, and a loss of protein into the dialysate. Procysteine partially reversed the effect of peritonitis on net ultrafiltration.

Peritoneal leukocytes from rats exposed to LPS showed a reduced concentration of glutathione, an effect that was reversed in the presence of the drug. These results show that the addition of procysteine to dialysis fluid modified the peritoneal reaction to acute inflammation. The same group [189] showed that supplementation of IP infusion of saline with vitamin E decreased the peroxidation of peritoneum estimated as the malondialdehyde (MDA) level in rats'

omentum. However, the permeability of the peritoneum to glucose and protein in vitamin E-treated rats was increased. Vitamin E appeared to be cytotoxic to human mesothelial cells, as measured by inhibition of their proliferation, and this effect was irreversible.

Influence of Drugs on Peritoneal Mesothelial Cells

The short-term effects of antineoplastic agents such as methotrexate, doxorubicin, and mitoxantrone on the integrity of human peritoneal mesothelial cells (HPMC) membrane and mechanisms of intracellular potassium transport were assessed [190]. There was no evidence of significant cytotoxicity to either methotrexate, doxorubicin, or mitoxantrone. However, methotrexate diminished Na,K,ATPase activity and simultaneously enhanced 86Rb transport via a furosemide-sensitive pathway. Mitoxantrone reduced the furosemide-sensitive 86Rb influx in a dose-dependent manner. These data demonstrate that antineoplastic agents interfere with HPMC function, which might contribute to the oncostatic-induced peritoneal toxicity. The same group investigated the effects of insulin on the Na + /K(+)-ATPase expression and activity in human peritoneal mesothelial cells [191]. A time- and dose-dependent increase in the Na + /K(+)-ATPase activity was found. This effect appears to be mediated by an increase in [Na +]i and is not related to alterations in Na + /K(+)-ATPase subunit mRNA expression.

Transport Acceleration of Specific Solutes

Removal of barbiturates may be accelerated by increasing dialysate pH with Tris buffer, thereby influencing the rate of nonionic diffusion [192]. Alkalinization of peritoneal dialysate by THAM also raised uric acid transport [193]. Drugs that counteract the membrane anionic charge should enhance removal of charged solutes. Adding albumin to a PD solution enhances removal of barbiturates [194], ethchlorvynol [195], and salicylate [196], and is expected to augment the clearance of numerous other drugs that circulate bound to plasma proteins, such as quinine and phenytoin. For lipophilic drugs such as glutethimide and short-acting barbiturates, transport can be enhanced by adding lipid to the dialysate [197]. In general, for treating severe overdosage, the removal of drugs by PD is too slow. Specific effects such as chelation, however, may influence concentrations of drugs and certain uremic metabolites.

Peritoneal Protein Loss Attenuation

In a preliminary study, captopril significantly reduced protein loss into the peritoneum in diabetic CAPD patients, presumably by modulating vasoconstrictive responses of peritoneal capillaries [87]. In rabbits a marked increase in protein elimination into the peritoneum occurred after addition of histamine, an effect blocked by its antagonist [78]. Because histamine may be involved in the pathogenesis of hypersensitivity reactions to drugs, leachables or contaminants of the dialysis solution, antihistamine agents could be of value in such circumstances.

Several lines of evidence support the role of intact anionic sites on the peritoneal transport barrier in the restriction of the passage of charged macromolecules to the peritoneal cavity. Partial neutralization of anionic sites may account for the findings from an animal study in which dialysate pH adjustment from 5.6 up to 7.4 significantly increased peritoneal protein loss in the presence of nitroprusside [51]. Another group demonstrated that, in rabbits, transperitoneal protein loss was substantially enhanced by protamine. Neutralization of protamine with heparin prevented this effect [119]. In an animal study [5], blood to peritoneum transport rates of cationic DEAE dextran were less that those of both neutral dextran and dextran sulfate. The effects of chondroitin sulfate have been described above.

Conclusions of Part I

It is easy for clinicians as well as basic scientists to forget that the peritoneum, unlike synthetic hemodialysis membranes, is alive. The mesenteric circulation is remarkable for its size and complexity, and until recently not much was known about its physiology. The numerous drugs and hormones that affect mesenteric blood flow and membrane physiology have predictable effects on peritoneal transport parameters [198, 199]. Patients undergoing chronic dialysis often take several drugs, many of which have hemodynamic and membrane transport effects. The influences of these agents on the peritoneum must be ascertained. Patients treated for acute problems, for example, in

an intensive care unit, are exposed to an even greater abundance of drugs potentially altering transport. Rational use of drugs and other physiological manipulations in patients maintained by PD requires an understanding of their effects on peritoneal blood flow and permeability. It is naive to consider the peritoneum as an inert membrane with constant blood flow and transport characteristics. Further investigation of the interactions of drugs and the peritoneum may identify optimal methods for augmenting transport efficiency safely.

Part II: Pharmacokinetic Aspects of Peritoneal Transport of Drugs

This part of the chapter has been divided in two major sections: the first section covers some basic pharmacokinetic concepts in the presence of normal and abnormal renal function. More detailed information on this subject is available in standard textbooks and reviews on pharmacokinetics [200–202] and in chapters of textbooks in nephrology [203, 204]. Also in this first section a general discussion on the major factors determining the transperitoneal transport of drugs after systemic and IP administration will be provided.

In the second section the pharmacokinetic data obtained with drugs, commonly used in continuous ambulatory or automated PD (CAPD or APD) patients, have been listed in tables. Following each table, recommendations for possible dose adaptations in PD patients are provided.

Basic Pharmacokinetics

Drugs produce their therapeutic or toxic effects in biological systems by reacting with receptor sites or other sites of action located in target tissues. The intensity of these effects is, in most cases, determined by the concentration of the drug in the direct environment of the site of action (the "biophase"). It is not possible to determine drug concentrations in the biophase. However, all tissues are supplied by blood (or plasma). Although often a complex relationship exists between the drug concentration in the biophase and that in plasma water, the latter is an alternative and more accessible site to measure the drug concentration. Responses to a particular drug are therefore commonly related to the concentration of the drug (or in some cases of its metabolites), in plasma water. After administration of a drug, absorption from the site of administration to the plasma (in case of extravascular administration), distribution from the plasma to organs and tissues, and elimination by biotransformation (predominantly in the liver) or by excretion of the chemically unaltered parent drug (predominantly via the kidneys) take place. However, after biotransformation, the metabolites are often excreted by the kidneys, even when the parent drug is not. In the situation in which the metabolite(s) is pharmacologically active, dose adaptation in renal failure of drugs that are not primarily eliminated by the kidney may be necessary. As a consequence of these events, drug concentrations in plasma water, and in the biophase, change with time, as does the pharmacological effect.

In addition, drugs can be bound to proteins, and their effect may depend on the free/protein-bound ratio. With the usual methods, however, total plasma drug concentrations are measured, i.e., free drug and drug bound to plasma proteins together. If the protein binding of the drug is constant, total drug concentration in plasma water can be used as an index of free drug concentration. If, however, the protein binding of the drug has changed, e.g., because of renal failure or by interaction with other drugs, this relationship will change and the intensity of effect will be smaller or larger than expected for a particular total plasma drug concentration.

Compartmental Models

Pharmacokinetics involve the mathematical description of the time-course of the concentration of the drug (and, in some cases, its metabolites) in biological fluids after its administration. In most models, compartments are used; it is important to realize that a pharmacokinetic compartment does not necessarily correspond to a given anatomical body fluid compartment. The time-course of the plasma drug concentrations can usually be adequately described by a one-compartment model, in which the body is viewed as one space, in which the drug is distributed rapidly and homogeneously. Although this is an oversimplification, such a one-compartment model is often satisfactory for the study of the pharmacokinetics of a drug, e.g., in order to determine its optimal dosage.

A two-compartment model (Fig. 9.1) consists of a central and a peripheral compartment. The central compartment includes the plasma, but also the extracellular fluid of highly perfused organs such as heart, lung, liver, and kidney. The peripheral compartment involves the compartment in which the drug is distributed at a slower rate. Transfer between

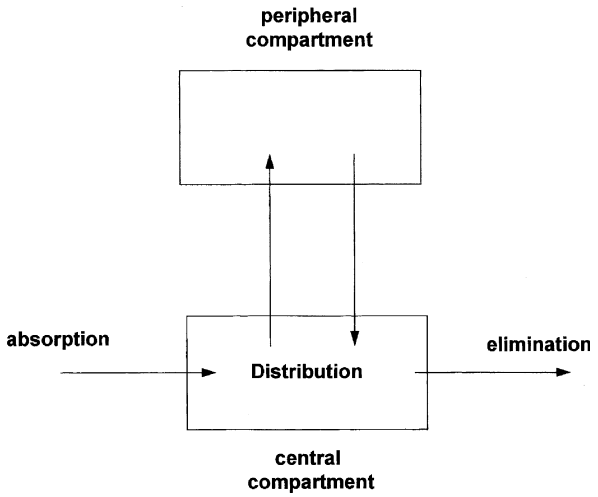

Fig. 9.1 Schematic representation of a two-compartment model

the two compartments is slow, and changes in concentration in one compartment will only be accompanied by changes in the other compartment with a certain delay. What parts of the organism belong to the central or to the peripheral compartment will depend upon the physicochemical characteristics of the drug, and of the general condition of the tissues involved. In a patient with sepsis, for example, the separation between central ("vascular") and peripheral ("interstitial tissue") compartments has greatly disappeared by the generalized hyperpermeability of the capillaries. Although three- and even more-compartmental models describe the situation more correctly, they are difficult to handle and their use is usually not needed.

Plasma Concentration–Time-Course

In Fig. 9.2 the time-course of the plasma concentrations of a drug after IV injection of a single dose is shown for both a one-compartmental and a two-compartmental model. Factors such as absorption, distribution, elimination, and excretion usually follow first-order kinetics. When first-order kinetics apply, the changes in concentration occurring are proportional to the drug concentration at that particular moment. After absorption and distribution are completed, the fall of the plasma concentration is only determined by elimination. As illustrated in Fig. 9.2, if elimination follows first-order kinetics, the log concentration versus time curve in a two-compartment model is a straight line. From the plasma concentration–time curve a number of pharmacokinetic parameters can be calculated. These are useful in the procedures for dose adaptation in different situations.

The elimination serum half-life of the drug ($t_{1/2}$), is the time taken for the plasma concentration as well as the amount of drug in the body to decrease by 50%. A closely related parameter is the elimination constant (K_e), where:

$$K_e = 0.693/t_{1/2} \tag{9.1}$$

The apparent volume of distribution (V_d) of a drug relates the total amount of drug in the body to the concentration of drug in plasma at the same moment.

The V_d can be calculated from:

$$V_d = D/C_0 \tag{9.2}$$

where D equals the dose given and C_0 equals the plasma concentration at the time 0, the time of administration. The V_d can be calculated only when the dose of the drug entering the body is known; that means when the drug is either given IV or if the exact amount absorbed is known.

The V_d provides an estimate of the extent of distribution of the drug throughout the body. If there is important uptake of the drug by the tissues, a V_d several times larger than the total body fluid volume (approximately 42 L for a body weight of 70 kg) can be found.

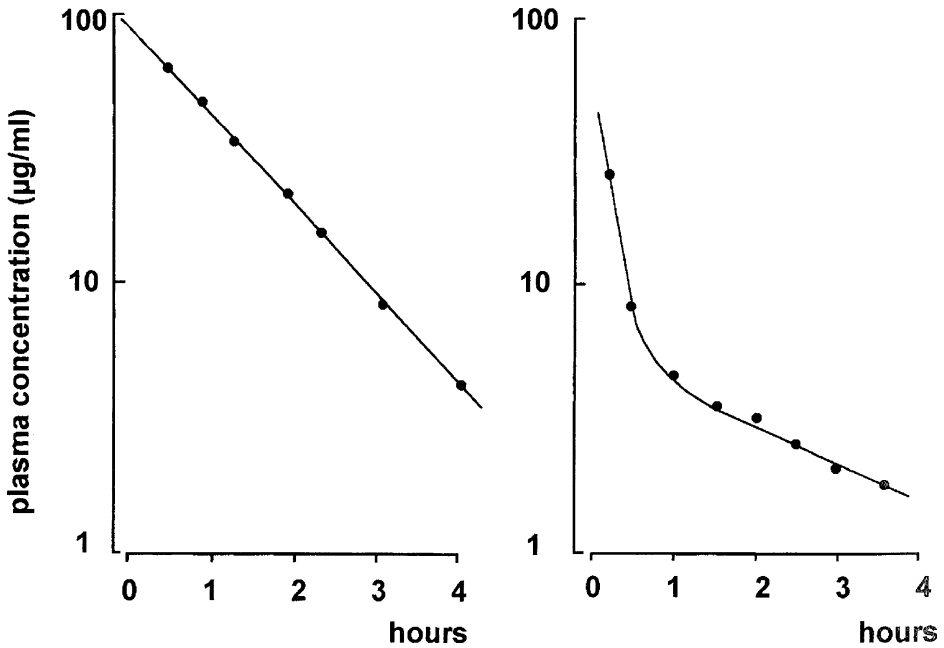

Fig. 9.2 Plasma concentrations as a function of time; in the left panel the logarithm of the plasma concentration is plotted for a drug for which a one-compartmental analysis is appropriate. In the right panel, log plasma concentrations are shown for a two-compartmental analysis. After the distribution phase there is a linear decay of the concentration, corresponding to the elimination phase

One of the important factors determining the size of the apparent V_d is the degree of plasma protein binding. The relationship between the apparent V_d of a drug and its protein binding is as follows:

$$V_d = V_B + V_T(F_B/F_T) \tag{9.3}$$

V_B and V_T are the volumes of water in blood and in tissues, respectively, and F_B and F_T are the fractions of free drug in blood and tissues, respectively. An increase in F_B without a proportional increase in F_T would produce an increase in the apparent V_d.

The apparent V_d can also be calculated from the area under the plasma concentration versus time-curve (AUC), and K_e:

$$V_d = D/AUC \times K_e \tag{9.4}$$

or

$$V_d = (D \times t_{1/2})(AUC \times 0.693)$$

Total body clearance or total plasma clearance is the volume of plasma that is cleared completely of the drug per unit time: it gives an estimate of the efficiency of the elimination of the drug by organs such as liver or kidney. Total body or plasma clearance is the sum of the clearances by the individual elimination routes, mainly biotransformation in the liver and excretion by the kidneys. For some substances elimination takes place only via the kidney, and then total body clearance equals renal clearance.

Total body clearance (Cl_{tot}) can be calculated by means of the equations:

$$Cl_{tot} = 0.693\ V_d/t_{1/2} \tag{9.5}$$

$$Cl_{tot} = D/AUC \tag{9.6}$$

Although clearance can be calculated from V_d and $t_{1/2}$, it does not depend on these parameters. On the other hand, $T_{1/2}$ of elimination is dependent not only upon the clearance, but also upon the V_d. Although gentamicin and digoxin are both cleared by the kidneys to approximately the same extent as creatinine (this means at a rate of approximately

120 mL/min in a normal situation), the elimination $T_{1/2}$ of digoxin is 36 h, while that of gentamicin is only 2 h. This is due to the fact that the V_d of digoxin is more than 500 L, while that of gentamicin is only about 15 L. When elimination in different situations is compared (for example, in patients with renal failure compared to healthy individuals, or in predialysis patients compared to those on dialysis), clearances and not only half-lives should be calculated whenever possible. Elimination $T_{1/2}$ should not be confused with duration of action. The latter is determined by the time during which drug concentrations are above a minimal effective concentration (MEC). For antibiotics, usually the minimal inhibitory concentration (MIC) of the susceptible antibiotic is considered.

The duration of drug action is dependent not only on the elimination $T_{1/2}$ of the drug but also on the dose given, bioavailability and of the drug distribution.

Total body clearance can be measured exactly only after IV drug administration or when the bioavailability, F, is known. Drugs are, however, often administered orally without knowing their exact bioavailability.

While the pharmacokinetic behavior of a drug is usually studied after single-dose administration, it is of utmost importance to know what happens after chronic administration of a drug. For some drugs at the moment of the second administration the amount still present in the body is negligible, so that after the second administration concentrations in the plasma will be similar to those after the first administration. This is, for example, the case when, in patients with normal renal function, gentamicin (with an elimination $T_{1/2}$ of 2 h) is administered three times a day. When, however, drugs are administered at dosing intervals shorter than four half-lives, an important fraction of what was introduced with the last administration is still present at the time of the second dosage. Consequently, the concentration after the second dose will be higher than that after the first dose, i.e., accumulation of the drug occurs. In that case, steady-state concentrations are obtained only after a number of administrations. The time to reach steady-state plasma concentrations depends only on the $T_{1/2}$, and is approximately four to five times the $T_{1/2}$ of the drug. For example, for digoxin, with its $T_{1/2}$ of 1.5 days, this works out at approximately 1 week. If the steady-state levels are to be achieved earlier, a loading dose of the drug must be given. The extent of accumulation (i.e., how much higher the steady-state levels will be than those after the first administration) depends on the $T_{1/2}$ and the dosing interval.

Pharmacokinetic Alterations in Patients with Decreased Renal Function

In patients with renal failure the fate of a drug can be altered profoundly. Gastrointestinal absorption after oral administration of a drug may be impaired in uremic patients because gastrointestinal pH or motility are altered. Biotransformation of drugs can be decreased or increased in uremic patients. There is also much interest in alterations in plasma protein binding of drugs in these patients. For a number of acidic drugs, which are mainly bound to plasma albumin, binding is often markedly decreased, due either to a decrease in albumin concentration in the plasma or to a decrease in the affinity at the binding sites; the decrease in affinity can be due to structural changes of the albumin molecules or to the presence of endogenous inhibitors. Some basic drugs bind mainly to α1-acid glycoprotein (α1-AGP). In renal failure the binding of these drugs may be increased due to the elevated α1-AGP concentrations in the plasma. These changes in protein binding can markedly affect the calculated pharmacokinetic parameters, and they can in some circumstances lead to changes in free drug concentration in plasma, to changes in efficacy and to side-effects.

Most important, of course, is the decrease in renal excretion of the drug. The renal clearance of a drug is usually decreased proportionally to the decrease in glomerular filtration rate. If renal excretion is the only elimination route of the drug, total body or plasma clearance will be reduced to the same extent. For substances that are only partly eliminated by the kidneys, the alteration in total body clearance will depend upon the relative importance of the renal versus the nonrenal elimination. It should, however, be re-emphasized that it is not because a drug is not eliminated via the kidney, that total body clearance is not altered in patients with renal failure. For example, hepatic clearance can also be affected by a change in protein binding or because of accumulation of other molecules. However, the V_d of drugs in these patients is often also different due to the changes in binding in plasma or in tissues. The plasma $T_{1/2}$, which depends on both V_d and Cl, is therefore not always a good parameter of the drug clearance in these patients. For example, digoxin is not bound to a significant extent to plasma proteins, but it is bound extensively to tissues of the kidneys, liver, and myocardium. This binding is decreased in patients with renal failure. As apparent from Eq. 9.3, a decrease in drug tissue binding without a corresponding decrease in drug plasma binding results in a decrease in the apparent V_d. In several studies it has been observed that the V_d of digoxin is significantly smaller in patients with chronic renal failure (230–280 L versus 500 L in normals).

The pharmacokinetic changes in chronic renal failure can, mainly after chronic administration of a drug, lead to important changes in total and free plasma concentrations, if the dose is not adjusted. Drug concentrations in the body can be much higher and the time to reach steady state (at a higher level) can be increased if the $T_{1/2}$ is prolonged. This

explains why, in patients with renal failure, a loading dose is often needed. Thus, for many drugs, dose adjustments will be necessary in chronic renal failure. The mean steady-state levels (Css) that will be achieved in a given situation can be calculated with the following equation:

$$\text{Css} = (F \times D)/(Cl_{\text{tot}} \times T) \tag{9.7}$$

where F = fraction absorbed, T = the dosing interval, and D the maintenance dose. This can also be expressed as:

$$\text{Css} = (F \times D)/Cl_{\text{tot}} \times T) \tag{9.8}$$

From these equations the maintenance dose needed for a given Css can be calculated. The many nomograms available for calculation of maintenance doses are based on these principles.

The loading dose (D*), i.e., the dose needed to obtain a given Css at once, can be calculated by the equation

$$D* = V_{\text{d}} \times \text{Css} \tag{9.9}$$

Pharmacokinetic Alterations in Patients on PD

PD can alter the pharmacokinetics of a drug, depending upon the route of administration of the drug and rate of removal via the dialysate. This can necessitate dose adaptations.

Pharmacokinetics of Drugs After Systemic Administration: Assessment

Plasma and dialysate concentrations can be measured as a function of time. To evaluate whether systemic kinetics are affected by dialysis, serum $T_{1/2}$, V_{d} and total body clearance (and in some cases residual renal clearance) can be calculated and compared to the values obtained in terminal chronic renal failure patients without dialysis. The amount recovered from the peritoneal dialysate over the period of time (Aper), can be used to assess the need for dose adaptation. This amount should be viewed in relation to that lost in the body over the same period of time by other routes, such as hepatic biotransformation or residual renal excretion.

The PD clearance (Clper) can be calculated from the equation:

$$\text{Clper} = (\text{Apert1} - \text{t2})/\text{AUC t1} - \text{t2} \tag{9.10}$$

where Aper t1 – t2 is the amount recovered in the dialysate over a given time period and AUC t1 – t2 is the area under the plasma concentration curve over the same time period. The peritoneal clearance should be compared to the total body clearance (Cl_{tot}). Indeed, the increased plasma clearance that can be found with dialysis is dependent of the peritoneal clearance of the drug, the residual renal clearance and the nonrenal clearance.

Factors Influencing Peritoneal Drug Clearance After Systemic Administration

The dialysis clearance of a systemically administered drug in the PD setting will depend upon factors that are summarized in Table 9.1. The peritoneal membrane characteristics have been described in the first part of this chapter. Only some of the other factors will be discussed below.

Dialysate Flow Rate

The most important factor in determining the magnitude of the peritoneal clearance of a drug is the dialysate flow rate, which is around 6–7 mL/min in CAPD. Small solute peritoneal clearances are largely dialysate flow-dependent. During the long dwells of CAPD, the transport rate of small solutes per unit of time is high at the beginning of the dwell and decreases with time because diffusion equilibrium is either obtained or approached. With increasing molecular weight of the solute the transport rate during the dwell becomes more homogeneous.

Table 9.1 Factors affecting peritoneal drug clearance after systemic administration

Dialysate properties
Flow rate
Temperature
pH
Osmotic content
Drug properties
Molecular weight
Ionic charge
Distribution volume (Vd)
Protein binding
Extrarenal clearance
Lipid or water solubility
Characteristics of the peritoneal membrane
Surface and charge
Permeability
Peritonitis
Sclerosis
Peritoneal blood flow
Stagnant layers
Ultrafiltration

The dialysate flow rate is greater during the rapid exchanges in some automated PD (APD) regimens. This explains why, during the rapid exchanges in APD programs, clearances of solutes with low molecular weight are increased. During the rapid exchanges of continuous cyclic PD (CCPD) (for example, four exchanges of 2.5 L over 8 h overnight, followed by a long diurnal dwell time of 10–12 h), the dialysate flow rate can be around 15–20 mL/min, values much greater than those for CAPD. Dialysis clearances during the short dwell times could be higher, because sink conditions tend to be maintained. It could be that during the rapid exchanges a significant fraction of a systemically given drug is removed through the peritoneum.

The first comprehensive reviews on the pharmacokinetic principles in the antibiotic treatment of peritonitis in APD have been published by Diaz-Buxo et al. [205] and Manley and Bailie [206]. Results from various APD and comparative CAPD pharmacokinetic studies were reviewed. In APD patients, antibiotic half-lives were shorter during the cycler exchanges. Antibiotic peritoneal clearance was greater in patients treated with APD than those treated with CAPD regimens. Antibiotic clearance depends upon RRF and dialysate flow rate.

Table 9.2 is taken from [206] and shows that the peritoneal clearances of different antibiotics are systematically higher in APD than in CAPD. To ensure that maximal antibiotic bioavailability occurs with intermittent IP dosing, it is recommended that the antibiotic-containing dialysate must dwell at least 4 h to ensure an adequate antibiotic depot in the body.

To determine the impact of dialysate flow rate (DFR) on cefazolin pharmacokinetics in PD patients, Manley et al. [207] performed a meta-analysis of published reports, and the data were analyzed based upon low DFR ($\leq$ 5.50 mL/min) or high DFR ($>$ 5.50 mL/min). Published literature provided data on 55 PD patients (12 high DFR, 43 low DFR). Regardless of data origin a prominent coefficient of determination ($p < 0.0001$) existed between DFR and all cefazolin pharmacokinetic data except peritoneal clearance. These findings demonstrate that an increased DFR leads to an increased rate of cefazolin clearance in APD patients. Clinicians dosing cefazolin in PD patients using a higher DFR than that used to determine cefazolin pharmacokinetics should use increased doses or prescribe lower/comparable DFRs. Data are not yet available for patients prescribed very high DFRs (e.g., continuous flow PD).

Table 9.2 Comparison of various antibiotic clearances in CAPD and APD patients (from [206])

	Dialysate flow (mL/h)		Peritoneal clearances (mL/min/1.73m^2)	
Antibiotic	APD	CAPD	APD	CAPD
Cefazolin	416.7	333.3	2.2 ± 0.7	1.0 ± 0.3
Tobramycin	416.7	333.3	4.2 ± 0.9	1.1 ± 0.8
Vancomycin	416.7	333.3	2.1 ± 0.7	1.2 ± 0.5
Piperacillin	416.7	333.3	5.3 ± 1.1	3.6
Fluconazole	500–687.5		11 ± 2.7	4.3–5.5

However, the concentration of most systemically administered drugs achieved in the drained dialysate after 2 h will be much lower than after long dwells so that the total amount of drug removed over 24 h in APD will be not much different from CAPD. We therefore suspect that the daily peritoneal removal of most drugs after systemic administration is also in the APD setting, as a rule, clinically unimportant.

The Molecular Weight of the Drug

The molecular weights of most drugs range between 100 and 700 Da, with some notable exceptions such as vancomycin (MW 1,450), insulin (MW 6,000), and Epo (MW 30,400). The diffusion of a solute from blood to dialysate is inversely proportional to the square root of the solute mass, both in HD and PD [208, 209].

Drug Protein Binding

Since only unbound, free drug is available for diffusion, a drug with a high plasma protein binding usually shows a low peritoneal clearance. The effect of plasma protein binding on the peritoneal transport of IV administered β-lactam antibiotics has been investigated in rats [210]. The antibiotic concentration–time profiles obtained in the dialysate were compatible with the concept that only unbound antibiotic is available for peritoneal transport. Although Flessner et al. [211] reported that bovine serum albumin is transferred through the peritoneal tissues from plasma to the peritoneal cavity in rats, the capillary membrane permeability of cephalosporins was 5–17-fold higher than that of albumin. Therefore, even if molecules bound to albumin can be transported through the peritoneal membrane, the contribution of this fraction is probably minor. For practical purposes this implies that the peritoneal membrane plays no important role in the transport of endogenous substances highly bound to proteins [212]. Dialysate concentrations of proteins are lower than serum concentrations and the protein binding of drug molecules in the peritoneal compartment is believed to be of minor clinical significance [213]. Based upon these considerations, a reasonably accurate formula for the prediction of the peritoneal clearance in CAPD after systemic administration of drugs has been proposed [214], where:

$$\text{Clper(mL/min)} = 75\sqrt{(\text{fU})}/\sqrt{(\text{MW})} \tag{9.11}$$

In this formula, fU represents the free fraction in the serum and MW the molecular weight of the drug. This formula is valid for a 2 L dialysate and a 6 h dwell, in the absence of peritonitis. Erythromycin, for example, has a molecular weight of 730 and a free fraction of 0.30; therefore, the peritoneal clearance is estimated to be 1.52 mL/min. The validity of the formula was tested by comparing the predicted values with the observed clearances in 19 clinical studies. A linear regression analysis yielded a correlation coefficient of 0.958.

A drug with a low molecular weight (<500 kDa) and with a low plasma protein binding can have a clinically relevant PD clearance.

Need for Dose Adaptation After Systemic Drug Administration in PD

The dialyzability of a drug in any dialysis strategy is clinically relevant only when at least two conditions are fulfilled. First, the dialysis clearance should be at least 30% higher than the endogenous total plasma clearance; otherwise the additive effect of dialysis clearance on overall drug elimination is negligible [215]. Second, the V_d of the drug should be less than 1 L/kg body weight. If V_d is larger, only a small fraction of the drug is available in the plasma for elimination via dialysis, and the amount of drug removed is small, even for a high clearance. Since in terminal chronic renal failure for most drugs, the total endogenous drug plasma clearance is higher than 20–30 mL/min, and the V_d is more than 1 L/kg body weight, the peritoneal drug clearance rarely contributes significantly to drug removal in the CAPD setting. Therefore, additional dose adaptations for CAPD beyond the recommendations for terminal chronic renal failure are very rarely necessary. Notable exceptions are drugs with a small V_d, low protein binding and a small total plasma clearance in uremia.

The presence of peritonitis does not significantly influence the magnitude or rapidity of drug transport into the peritoneal cavity after systemic administration. For example, the peritoneal clearances of netilmicin and of ciprofloxacin in patients with or without peritonitis were not different [216, 217].

Studies after systemic administration of a drug are of interest not only to evaluate the need for dose adaptations to maintain adequate systemic concentrations, but also for knowing the dialysate drug concentrations. The low peritoneal drug clearance does not exclude that, for example, for an antibiotic, therapeutically effective concentrations

can be achieved in the dialysate after systemic administration, due to the low volume (2–3 L) in which the drug diffuses. The rapidity with which therapeutic concentrations are achieved in the dialysate may be influenced by the presence of peritonitis. For example, after IV administration, therapeutic vancomycin concentrations in the dialysate are reached after 30 min of dwell in peritonitis patients, vs. 2–4 h in a noninflamed peritoneum [218].

The concentrations of antibiotic drugs that are achieved in the dialysate after systemic as well as after IP administration must be viewed against their activities against the strains that are isolated from patients with peritonitis. As pointed out by several workers, used PD fluid is a better medium to test these activities than the classically used broth [219–221]. Furthermore, recent work has shown that culturing conditions, dialysate manipulations, and adherence capacity of germs are critical factors affecting antibiotic activity [222]. For drugs that are metabolized by equilibrium-rated reactions to metabolites that are removed by PD, a higher total clearance of the parent drug may also be present during PD, even if the drug itself is not found in the dialysate. Thus, the absence of the drug in drained dialysate does not mean that total clearance of that drug is not altered by CAPD. An example of this phenomenon has been described for mycophenolate acid and its metabolite mycophenolate glucuronide, where a significant amount of mycophenolate acid was removed in the dialysate, almost completely in its glucuronidated form [223].

Pharmacokinetics of Drugs After IP Administration

Peritoneal transport is also of interest with regard to IP administration of drugs. For example, the IP doses of insulin or Epo required to achieve adequate systemic concentrations, or of antibiotics for local treatment of peritonitis, need to be carefully calculated. There are two sources of blood supply to the organs of the peritoneal cavity, one to the parietal and the other to the visceral peritoneum; both layers are rich in lymphatic circulation. The venous blood of visceral peritoneum returns to the portal circulation, while the venous return from the parietal peritoneum drains into the systemic rather than into the portal circulation. Earlier pharmacokinetic studies have indicated that, after IP injection, drugs such as atropine, caffeine, glucose, glycine, and progesterone are absorbed predominantly via the visceral peritoneum [224]. Therefore, these drugs, when introduced IP, are subject to immediate handling by the liver and some of them might undergo a first-pass metabolism. After IP administration, drug concentrations can be measured as a function of time in both dialysate and plasma. In view of the low peritoneal clearance of drugs after systemic administration, the rapid drug disappearance out of the peritoneum when the drug is given via the IP route is at first sight surprising. It is, however, merely the consequence of pharmacokinetic factors, i.e., V_d and protein binding. The contrast between the small dialysate volume and the very large V_d of the drug in the body, leads to a high concentration gradient. This is illustrated for vancomycin in Fig. 9.3 (adapted from [225]).

Studies after IP administration of glycopeptides show that bioavailability increases with dwell time. The data in Fig. 9.4 (from [226]) show that bioavailability is highly variable at early dwell times so that, to ensure consistent absorption of an intraperitoneally administered drug, short dwell times are not recommended. This may be relevant for APD patients who receive antibiotics intraperitoneally during the rapid exchanges. It is likely that these patients may not be receiving their full dosages due to decreased dwell time in the peritoneal cavity. The bidirectional passage of a drug molecule across the peritoneum is influenced by the same factors that regulate the passage of creatinine, urea, and glucose, the molecules commonly used as markers of membrane transport status. Therefore, it is hypothesized that correlations exist between the pharmacokinetic variables used to describe and predict drug disposition in the PD patient and the transport parameters readily available for that patient. If so, these measures (peritoneal equilibration test (PET)), Kt/Vurea, and creatinine clearance (CCr)) could be used to individualize the PD patient's antibiotic regimen, drugs could be more accurately dosed, and better outcomes possibly achieved. Elwell et al. attempted to determine the correlations between pharmacokinetic variables and patient membrane transport characteristics [227]. This retrospective study re-evaluated data collected during previous pharmacokinetic studies for IP administered cefazolin, ceftazidime, and gentamicin in CAPD patients, and IV cefazolin and tobramycin in APD patients. Prominent correlations were found between renal CCr and renal Kt/V, with renal clearances of for CAPD cefazolin and ceftazidime, and for APD tobramycin and cefazolin. Correlations of total and renal CCr with drug CLtotal were found in the pooled cefazolin group. Total CCr also correlated well with cefazolin total clearance in the APD group, although the correlations between the PET classification and drug clearance were difficult to interpret due to few data in the APD cefazolin group. However, there was a trend observed between cefazolin CLp and the 4-h PET values for D/P creatinine. Future studies will be needed to establish a firm relationship between peritoneal membrane characteristics and peritoneal drug clearances. The high protein binding of some drugs in the plasma, versus a negligible protein binding in the dialysate, further promotes this apparent one-way diffusion from dialysate to blood.

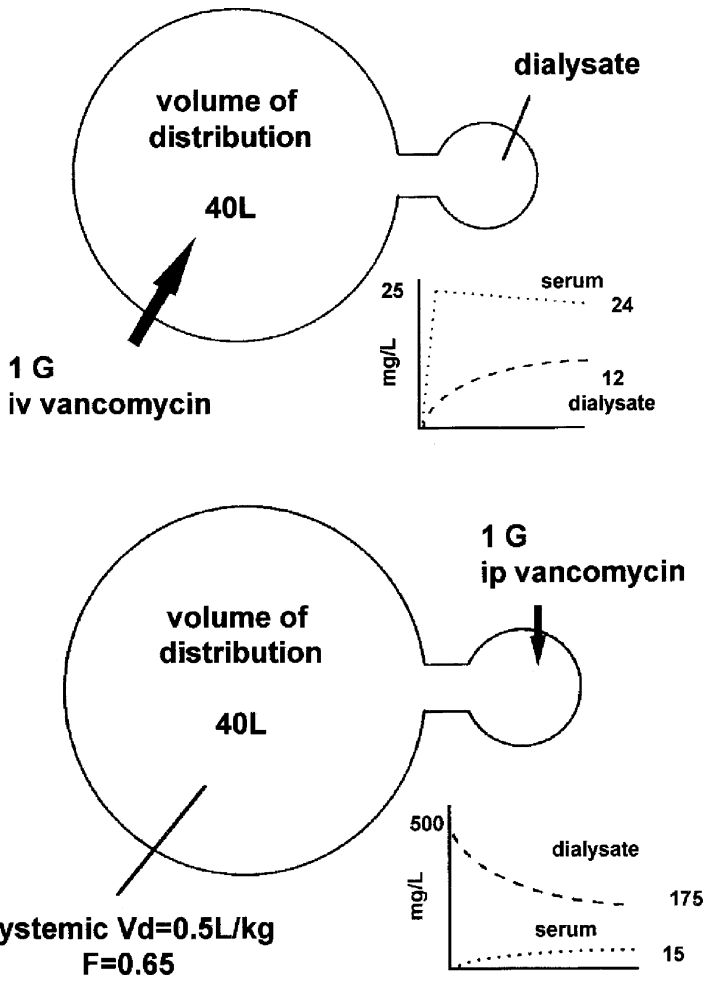

Fig. 9.3 Upper part: Model of pharmacokinetics in PD after IV administration of 1 g of vancomycin into a theoretical VD of 40 L (0.5 L/kg in an 80 kg patient). The inset shows the relationship of serum and dialysate concentrations over the duration of the 4-h dwell, which started at the same time as the IV administration. Lower part: Model of pharmacokinetics of vancomycin in PD after IP administration of 1 g of vancomycin into a 2 L exchange in a patient with a theoretical volume of 40 L. The inset shows the relationship of serum and dialysate concentrations over the 4-h duration of the vancomycin-containing exchange

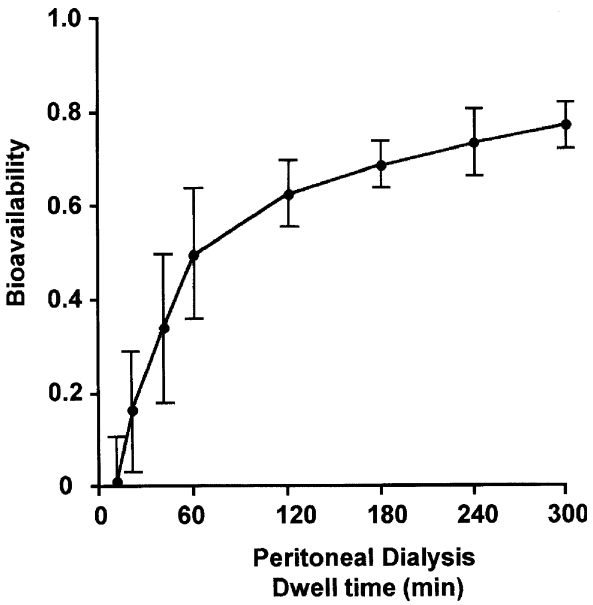

Fig. 9.4 Relationship between systemic bioavailability and dwell time when teicoplanin is administered intraperitoneally. Bioavailability was calculated by comparison of AUC values following single IP and IV doses, as well as from the amount of drug remaining within the peritoneal cavity with time. From Brouard et al. [226], with permission

Factors Affecting Transperitoneal Drug Absorption After IP Administration

These factors are summarized in Table 9.3; only a few of them will be discussed here; some of them have been described in the first part of this chapter. An important factor influencing drug transport after IP administration is the electric charge of a drug. As outlined in the first part of this chapter, there exist anionic charges on the peritoneal basement membrane and capillaries subjacent to it [6, 228]. The presence or absence of these peritoneal anionic charges can influence transperitoneal absorption of cationic drug molecules such as aminoglycosides. We and others have, however, shown a much-enhanced transperitoneal absorption of gentamicin, netilmicin, and tobramycin during peritonitis [217, 229, 230] (see below). These observations are difficult to explain if electric charges are important in their transport. Similarly, conflicting effects on the transport of gentamicin with IP heparin, a negatively charged drug, have been reported. One earlier study reported lower blood gentamicin concentrations with IP heparin [231], while another study revealed that heparin caused an increase in transport of uncharged molecules such as urea and creatinine and of the positively charged gentamicin [232].

It is possible that incorporation of proteoglycans such as heparin, hyaluronic acid, or chondroitin sulfate in the peritoneal membrane alters peritoneal transport by mechanisms other than by electrical charge, as was shown by Hadler [233]. The effects of these molecules on peritoneal transport have been discussed separately in the first section of this chapter.

As the electrical charge of a molecule in solution depends upon the pH of the fluid, theoretically at least, drug transport characteristics could change when bicarbonate-containing dialysate solutions are used. It is, however, accepted that the conventional (acidic) glucose-containing dialysate solutions rapidly correct their pH to physiological values after instillation. Studies in rats have shown that a significant proportion of the transport of macromolecules from the peritoneal cavity to the plasma is via convective transport via peritoneal lymphatic absorption [234, 235].

As reviewed by a number of authors [212, 236–238], the systemic absorption of IP antibiotics varies from 50 to 80% within a dwell period of 6 h in CAPD. The amount absorbed can easily be measured by subtracting, from the amount of drug initially instilled, the amount of drug that is present in the first peritoneal outflow. This, however, assumes that there is no degradation of the drug over the time interval in the dialysate. Most commonly used antibiotics are stable in peritoneal dialysate, either alone or in combination, or in the presence of additives such as insulin or heparin [239–243]. However, for some cephalosporins a degradation of 12–6%, and for rifampicin a degradation of 6%, was found in CAPD solutions or in effluent over 6 h [239]. This may lead to an overestimation of the amount of drug absorbed after IP administration. Vancomycin is not stable at basic pH, and complex formation may occur after addition to bicarbonate-containing dialysate.

More recent studies have further explored the stability of antimicrobial chemical and bioactivity of antibiotics. Dooley et al. [244] evaluated the stability of gentamicin, vancomycin, and gentamicin and vancomycin in combination, and the stability of the bioactivity of ceftazidime, admixed in standard PD solutions and then maintained over a 14-day

Table 9.3 Factors affecting transperitoneal drug absorption after IP administration

Dialysate properties
Flow rate
Temperature
Volume
Chemical composition
pH
Drug properties
Molecular weight
Ionic charge
Distribution volume (Vd)
Binding to membrane
Lipid or water solubility
Characteristics of the peritoneal membrane
Surface and charge
Permeability
Peritonitis
Sclerosis
Peritoneal blood flow
Lymphatic absorbtion
Stagnant layers

period at room temperature or under refrigeration. Antibiotic concentration by immunoassay did not significantly deteriorate over 14 days for vancomycin or gentamicin when either room temperature or refrigerated samples were studied. By bioassay, gentamicin and ceftazidime, but not vancomycin, lost moderate but significant activity over 14 days when refrigerated bags were assayed (except for an insignificant decrement in gentamicin in the combined vancomycin and gentamicin bags). Bags stored at room temperature, in general, lost significant bioactivity over 14 days, but to levels where clinical efficacy would still be expected. The vancomycin bioassay performed on the combination bags demonstrated a remarkably enhanced bioactivity, presumably reflecting synergy with gentamicin. These data indicate thus that these antibiotics admixed with PD fluids retain a stable chemical activity, whether refrigerated or kept at room temperature, for at least 14 days.

Voges et al. [245] evaluated the stability of gentamicin, tobramycin, netilmicin, vancomycin, cefazolin, unfractionated heparin, and low-molecular-weight heparin when added to four different PD solutions (Extraneal® (Baxter Healthcare, Castlebar, Ireland); Physioneal®, Nutrinea®, and Dianeal® (Baxter Healthcare, Grosotto, Italy)) in new, non-PVC Clear-Flex containers. Netilmicin, vancomycin, cefazolin, and heparin in Physioneal®, Nutrineal®, Extraneal®, and Dianeal® were stable for at least 24 h at 25°C and for an additional 4 h at 37°C. Gentamicin in Nutrineal®, Extraneal®, and Dianeal® was stable for at least 24 h at 25°C and for an additional 4 h at 37°C; gentamicin in Physioneal® was stable for less than 24 h at 25°C. Tobramycin® in Nutrineal® and Extraneal was stable for at least 24 h at 25 °C and for an additional 4 h at 37°C; tobramycin in Physioneal® and Dianeal® was stable for less than 24 h at 25°C

Vancomycin stability in icodextrin has also been tested [246]. Premixed vancomycin-icodextrin PD solutions, whether stored refrigerated or at room temperature, were recently found to be stable for up to 7 days. However, it is recommended that these solutions be kept refrigerated whenever possible. Solutions stored at body temperature were stable for up to 24 h, permitting the practice of prewarming solutions prior to administration.

A faster and more important absorption of antibiotics such as aminoglycosides, vancomycin, piperacillin, and various β-lactam antibiotics in peritonitis patients has been frequently demonstrated[217, 229, 230, 247–249]. Figure 9.5, taken from the paper by De Paepe et al. [229], illustrates the difference between peritonitis and nonperitonitis. It is also apparent, that after IP administration of gentamicin, the decrease in dialysate concentration is much more pronounced than the increase in plasma concentrations. This is not surprising as the V_d of the body is much larger than the volume of the PD fluid. Equal concentrations of gentamicin in serum and dialysate were achieved at approximately 24 h. The clinical relevance of the higher systemic availability during peritonitis is questionable for drugs with a wide therapeutic toxic margin. However, if a drug with a narrow therapeutic index is only negligibly cleared after transport to the systemic circulation, systemic accumulation after repetitive IP administration of the drug could occur. After chronic administration of gentamicin into the PD fluid for 2–3 weeks, plasma concentrations approach the end of dwell-time dialysate concentrations [229]. This can lead to potentially toxic concentrations and necessitates dose reduction. After IP

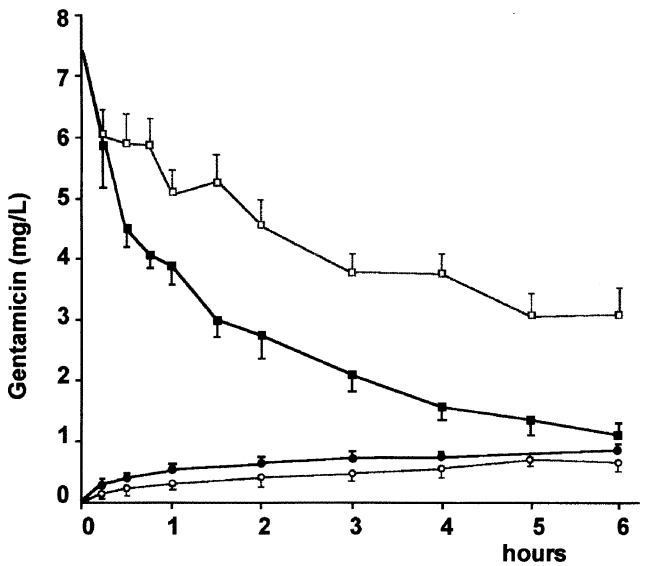

Fig. 9.5 Concentrations (mean ± SEM) of gentamicin in serum (○) and dialysate (□) in five patients without peritonitis and in serum (●) and dialysate (■) in five patients with peritonitis. Gentamicin was added in a concentration of 7.5 mg/L to the dialysate at time 0

administration of a single dose of 0.6 mg/kg of gentamicin, both total body clearance and the mean serum concentrations at 24 h were significantly lower in patients with, compared to patients without RRF [250].

Adverse Effects

Rapid transperitoneal drug absorption may cause adverse systemic effects. The "red man syndrome" has been described after rapid IP administration of 1 g of vancomycin diluted in 2 L of dialysate [251]. Drugs, when given intraperitoneally in therapeutic doses, may also cause peritoneal irritation. This has been described with a fixed combination of cilastatin/imipenem [212], AmB [252–255], certain brands of vancomycin [256], methylene blue [257], and angiotensin I [258].

Effect of PD on Drug Plasma Protein Binding

There are only a few studies in which the influence of PD, notably CAPD, on drug binding has been assessed. Drug protein binding of acid drugs in PD patients is expected to be lower than in undialyzed or HD patients. This may be secondary to the often poor nutritional status of these patients, as reflected by serum albumin concentrations in the lower normal range, the continuous peritoneal losses of proteins during the dialysis process, and accumulating endogenous compounds competing for occupation of binding sites. Changes in protein binding and total and free concentrations of digitoxin have been reported for CAPD and hemodialysis patients. The binding of digitoxin was $94.7 \pm 1.5\%$ in CAPD, significantly less than that observed in HD patients ($96.2 \pm 1.3\%$). Following a 0.1 mg oral dose of digitoxin, the mean free serum concentrations in CAPD and HD were 0.8 and 0.9 ng/mL, respectively, which is not significantly different [259]. One can also expect that in some malnourished PD patients the binding to serum albumin of several acid drugs may be lowered, possibly leading to elevated free drug concentrations. Protein binding of the antifungal drug ketoconazole was also lower in CAPD patients (98.5%) than in control subjects (99%) [260].

The influence of CAPD on the concentrations of α1-AGP in serum and dialysate and on the serum binding of two basic drugs (oxprenolol and propranolol) and of one acidic drug (phenytoin) has been reported [261]. Before starting CAPD treatment, the protein binding of oxprenolol and propranolol was higher, related to the elevated serum levels of α1-AGP concentrations in uremia [262], while the binding of phenytoin was lower than in healthy volunteers. During the first week after starting CAPD, the serum α1-AGP concentrations rose with a concomitant increase in the binding of oxprenolol and propranolol. Subsequently, however, the α1-AGP levels and the binding of oxprenolol and propranolol decreased to the values found before starting CAPD. The binding of phenytoin, which was lower than in normal healthy volunteers, did not show any change during CAPD. It must, however, be emphasized that, in general, changes in plasma protein binding of a drug only exceptionally lead to relevant changes in plasma drug concentrations. Changes in free drug concentration are immediately associated with changes in the V_d of the drug which "buffer" against major fluctuations in free drug plasma concentrations.

Peritoneal Pharmacokinetics of Common Drugs and Dose Recommendations

Description of the Tables

Since the tables in the previous edition of this book described the pharmacokinetics per class of drug studied during CAPD or CCPD, and most of the drug information on protein binding, elimination $T_{1/2}$, V_d and total plasma clearance in the presence of normal renal function, and on elimination $T_{1/2}$ and total plasma clearance in end-stage chronic renal disease (ESRD) have not changed, the tables of the previous edition have been reproduced in this chapter. However, the studies on pharmacokinetics of new drugs, not covered in the previous edition, or more recent pharmacokinetic data in PD of older drugs will be discussed under the respective drug classes. For a more general pharmacokinetic information on individual and more recent drugs outside the field of PD, the reader is referred to recent standard textbooks [263–265].

The pharmacokinetic data have been updated from reports published up to the beginning of 2007. Many papers contain results obtained in crossover studies after either IV, oral, or IP administration. Therefore, the data published per individual paper have been included in the tables. The dose/route column indicates the dose and the route of drug administration in each respective study. When available, the loading dose or maintenance dose is given. Data on serum $T_{1/2}$, maximal – or, occasionally, steady state (SS) – serum concentrations achieved, total plasma clearance and

peritoneal clearance are given. A comparison of these values with data obtained in normal renal function and in terminal renal failure shows the effect of PD on these parameters. Finally, the percentage of dose either removed from the body by PD (in case of systemic administration) or absorbed across the peritoneal membrane (after IP administration) is provided, whenever it has been calculated. Each table is accompanied by a brief discussion of the need for dose adjustment in PD, for drugs that are frequently used in these patients.

Pharmacokinetic Data in CAPD

Tables 9.4–9.14 summarize the pharmacokinetic data on systemic and IP drug administration in CAPD.

Cardiovascular Drugs (Table 9.4*)*

Based on the pharmacokinetic data, dose adaptation for digoxin is not necessary in CAPD patients beyond that for ESRD.

Data on pharmacokinetics of ACE inhibitors are scarce. In a study of five patients on CAPD, captopril was detectable in the dialysate after a single dose of 50 mg. However, the impact on total elimination varied widely between individuals [266]. After 24 h, only 0.5% of a dose of 2.5 mg quinaprilat was removed by PD. The elimination $T_{1/2}$ of quinaprilat is prolonged in patients with renal failure, and an inhibition of >90% of ACE was observed after administration of 2.5 mg of quinaprilat in CAPD patients. This dose can thus be recommended as starting dose in CAPD patients. Fosinoprilat was found to be cleared only to a limited extent by PD. Fosinoprilat, however, is also cleared by biliary secretion, that might compensate for the reduced renal clearance. In six CAPD patients, serum ACE activity remained significantly suppressed at 24 and 48 h after administration of 10 mg fosinoprilat [267]. The moderate pharmacokinetic alterations observed in these patients compared to those with normal renal function suggest that in most CAPD patients initial dose modifications are not necessary.

The pharmacokinetics and pharmacodynamics of ACE inhibitors and ARBs in ESRD have been extensively reviewed by Sica and Gehr in 2002 [268]. Table 9.5 is taken from this review, summarizing the protein binding, the hemodialysance, and the mode of systemic clearance of most of the currently used ARBs. The pharmacokinetics and pharmacodynamics of losartan and its active metabolite, E-3174, were studied in hypertensive CAPD patients [269]. Following a 1-week washout period, subjects received 100 mg of losartan orally for 7 days. On days 1 and 7, hemodynamic and hormonal responses were determined, as were pharmacokinetic parameters on day 7. The values of AUC0-24 and $T_{1/2}$ for losartan and E-3174 were 95 ± 49.9 μg/min/mL and 176 ± 82.1 μg/min/mL and 172.5 ± 86.7 min and 628 ± 575 min, respectively, and are similar to those of normal subjects and subjects on HD. Peritoneal clearance of losartan and E-3174 was negligible. In conclusion, the dose of losartan in CAPD patients should not be reduced compared with patients with normal renal function and the peritoneal elimination of the drug is negligible. Table 9.6, adapted from a review by Barbour and McKindley [270], provides some maintenance dose recommendations for various cardiovascular drugs in renal failure and during HD and PD treatment.

Table 9.7 summarizes the studies with β-lactam antibiotics and glycopeptides. In general, the amount of penicillin lost in the peritoneal cavity after systemic administration is negligible; on the other hand, the transperitoneal absorption can be as high as 90% in the presence of peritonitis. First-, second-, and third-generation cephalosporins have been extensively studied. Based on the adequate dialysate levels that are achieved after oral administration (cephadrine or cephalexin), some authors have used this group of antibiotics as first choice for initial treatment of peritonitis either as single drug or in combination with other drugs [271–275].

Cefazolin

CAPD patients without active peritonitis received a single IP dose of 1 g of cefazolin sodium for a 6-h dwell [276]. The bioavailability was found to be 77.9 ± 3.1%, V_d 0.20 ± 0.05 L/kg, and plasma $T_{1/2}$ 39.9 ± 25.4 h. Mean total, renal, and peritoneal clearances were 4.5 ± 2.3, 1. 4 ± 1.1, and 3.5 ± 1.8 mL/min, respectively. Mean plasma and dialysate concentrations at 24 h were 42.8 ± 14.3 and 31.8 ± 11. 7 μg/mL, respectively, well above the MIC of susceptible organisms. A once daily IP cefazolin dose of 500 mg/L gave desirable pharmacokinetic attributes for use as a suitable alternative to vancomycin for empiric treatment of CAPD-associated peritonitis.

In more recent years, cefazolin has been studied, either in combination with aminoglycosides and more in particular in APD. A study in Thailand [277], following the International Society for Peritoneal Dialysis (ISPD) 1996 recommendations for empiric treatment of peritonitis, studied the pharmacokinetics of a continuous IP cefazolin and

Table 9.4 Pharmacokinetic studies with cardiovascular drugs in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Digoxin	20–30	36	7.1 ESRD 4.2!	160	100	35	O 0.125 mg daily 5 days SS ($n = 1$)	97.9 at 2 h	3.2 ng/mL	12.6	2.0	<4/24 h	[437]
							O 0.50 mg	–	3.8 ± 2.3 ng/mL at 0.56 h	–	3.0 ± 1	1/24 h	[438]
							O 0.1 mg/day SS	–	–	–	3.9 ± 1.3	<2/24 h	[439]
							O 0.125 mg every 2–3 days	54–141	–	11–52	2.3–3.1	<10/4 days	[440]
							O 0.125 mg per day	–	–	–	3.6 ± 0.4	7.6 ± 0.9/24 h	[441]
Digitoxin	90 86–89 ESRD	145	0.5	3	200	2	0.1 mg/day SS	7.5 days	–	3.5	0.7 ± 0.3	<2/24 h	[439]
Quinidine	80–85	6	2	270	6	270	O 350 mg 4 × /day	5.4	–	154.2	0.79	0.6/24 h	[442]
Denopamine							O 10 mg SD	4.6 ± 2.5	0.0123 ± 0.0067	–	0.10 ± 0.05	<0.1/6 h	[443]
Labetalol	50	7	5.6	1,700	13	1,198	IV 0.7–1 mg/kg	13.05 ± 6.32	–	1,397.2 ± 272.3	1.94 ± 0.65	0.14/72 h	[444]
Propranolol	93	3.5	3	695	3.5	695	O 320 mg/day	–	–	–	–	3.3/24 h	[445]
							O 20 mg/day	–	–	–	–	5.2/24 h	
Atenolol	<5	5.5	0.7	176	73	13	IV 20 mg	27.6 ± 2.18	–	21 ± 1.4	2.53 ± 0.3	6/24 h	[446]
Esmolol	–	0.2	3.2	19,950	–	–	IV 150 mg/kg/min for 4 h	0.1 ± 0.06	0.8 (0.5) Css (80 kg)	20,504 ± 11,448	0	0	[447]
Betaxolol	55	14–22	6	327	30	200	–	27			–		[448]
Nifedipine	90–95	2	1.4	1,100	2.6	1,100	O 2 × 20 mg/day					<1/24 h	[449]
Isosorbide-5–nitrate	16–28	0.2–0.5	1.8	–	0.2–0.5	–	0.3 × 20 mg/day	4.2 ± 1.1	448 ± 118	–	4.3 ± 2.7	1–6/24 h	[450]
Diltiazem	80–85	4.0	5.3	1,400	3.4	1,400	O 60 mg	3.09 ± 1.15	95.8 ± 63.8 (3 h)	2,653 1,316 (70 kg)	1.5 ± 1.0	<0.1/24 h	[451]
Captopril	25–30	1.9	3	1,277	35	69	O 50 mg SD						
Free captopril								1 ± 0.3	0.387 ± 0.0075 2.77 ± 0.43			<1%/6 h	[452]

Table 9.4 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Total quinapril*	–	1*	–	–	0.9*	–	O 20 mg SD	1.0 ± 0.3	0.107 ± 0.067	2,207 ± 1,621	–	0	[199]
Quinaprilat	97*	–			12.5*			20.1 ± 0.124	0.689 ± 0.124	19 ± 8.3		2.6 ± 1.2/24 h	
Quinaprilat	90						O 2.5 mg	34.1	64.3	11.9	–	–	[453]
Iate	95	15	0.15	–	19–28	–	O 10 mg	19.5 ± 7.5	0.202 ± 0.071	70.6 ± 38.5	0.09 ± 0.07	2 ± 1.4/48 h	[267]
Guanfacine	30	17	4	–	14	–	–	–	–	–	1.5	–	[454]
Tocainide	10–15	11–14	3.2	182	17–43	100	O 400 mg SD	15 ± 5	3.2 ± 1	83 ± 36	<5 mL/min	2.2 ± 2/24 h	[455]
Flecainide	40	14–26	8.7	567	19–26	357	O 100 mg/day	40	–	30	2.2	1/24 h	[456]
Procainamide	14	3			14			34.1	64.3	11.9	–	–	[457]
	15	2	2	810	8	200	O 625 mg SD	26	1.9–4.8	143	0.28–5.55	<5/days	[458]
N-acetylprocainamide	10	6	1.5	200	4.2	29		42.8	–	29.8	1.74–7.20	<5	
Furosemide	95	0.5	0.12	162	1.4	105	O 500 mg						
							SD – perit	10.5 ± 1.2	12.8 ± 2.1	–	0.5 ± 0.1	0.9 ± 0.2/24 h	[459]
							+ perit	11.6 ± 3.3 O 500 mg	6.6 ± 0.4	–	0.5 ± 0.1	0.6 ± 0.1/24 h	
							SD – perit	12.5 ± 3.4	7.7 ± 0.6	–	0.4 ± 0.1	0.6 ± 0.1/24 h	[460]
							O 80 mg SD – perit	3.87 ± 1.26	3.2 ± 1.4	–	–	–	[461]
							IV 80 mg SD – perit	2.7 ± 0.83	–	60 ± 18	–	<1/24 h	
Theophylline	60	8.7	0.45	46	7.3	67		4.7	–	–	1.5	–	[462]
Mexiletine	64	5–9	5–6	846	22	200	IV 250 mg	10.5	–	25.6/kg	9.22/kg	<1%	[463]

*Data from [464].

Table 9.5 Important pharmacokinetic data for angiotensin receptor blockers (ARBs)

Compound	Protein binding (%)	Hemodialysance (mL/min)	Renal clearance	Hepatic clearance
Losartan	98.7	0	10	90
E-3174	99.8	0	50	50
Irbesartan	90	0	1	99
Valsartan	95	Not available	30	70
Eprosartan	98	11	30	70
Candesartan	99	0	60	40
Olmesartan	99	Not available	35–50	50–65
Telmisartan	99.5	0	1	99

Source: Adapted from Sica and Gehr [268].

Table 9.6 Maintenance dosage adjustment recommendations for various cardiovascular drugs in renal insufficieny and during hemo- and peritoneal dialysis

		Dosage adjustment based on Cr Cl (% of normal daily dose)		Significant dosage adjustment required	
	Drug	10–50 mL/min(%)	<10 mL/min(%)	HD	PD
Ace inhibitors	Benazepril	100	50	No	No
	Captopril	25–50	<25	Yes	No
	Enalapril	75–100	50	Yes	No
	Lisinopril	50–75	25–50	Yes	No
	Quinapril	50	25	No	No
	Ramipril	50–75	25–50	Yes	No
Antiarrhythmics	Bretylium	25–50	25	No	No
	Digoxin	25–50	<25	No	No
	Disopyramide	(based on TDM)	(based on TDM)	?	No
	Flecainide	25–50	25	No	No
	Procainamide	100	50–75	Yes	No
	Quinidine	Based on TDM	Based on TDM	Yes	No
	Tocainide	Based on TDM	Based on TDM	Yes	No
		100	50		
Beta-blockers	Atenolol	25–50	<25	Yes	No
	Metoprolol	100	100	Yes	No
	Nadolol	50	25	Yes	No
	Propranolol	100	75–100	No	No
	Sotalol	30	15–30	Yes	ND
Miscellaneous	Methyldopa	75–100	25–75	Yes	No
	Milrinone	100	50–75	ND	ND

Source: Adapted from Barbour and McKinley [270].

once-daily IP aminoglycoside administration. Cefazolin was administered as loading and continuous maintenance doses of 500 and 125 mg/L dialysate, respectively. Gentamicin, 0.6 mg/kg body weight, was given IP once daily. Duration of treatment was 120 h, serum cefazolin reached levels higher than the recommended levels (8 μg/mL) at 3.3 min after drug administration, and persisted through the 5-day duration of the study. Dialysate cefazolin levels during the studied period also were persistently higher than the recommended values. The peak serum gentamicin levels were lower than the suggested values of 4 μg/mL, whereas the trough serum gentamicin levels were higher than the minimal toxic concentrations (2 μg/mL). Dialysate gentamicin levels were higher than therapeutic concentrations for only 4.75 h in each day. It was difficult, using pharmacokinetic studies, to adjust the dosage regimen of gentamicin to achieve appropriately therapeutic levels in both serum and dialysate. It was concluded that the ISPD 1996 recommended dosage of continuous IP cefazolin was appropriate for the treatment of CAPD-related peritonitis, but once-daily IP gentamicin administration, had less therapeutic benefit.

The combination of cefazolin and tobramycin was also studied in APD patients [278] after a single IV dose of cefazolin (15 mg/kg) and tobramycin (0.6 mg/kg). Cefazolin and tobramycin half-lives were markedly shorter on cycler than off cycler. Mean serum and dialysate concentrations were above MIC of susceptible organisms throughout the

Table 9.7 Pharmacokinetic studies with β-lactams and glycopeptide antibiotics in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
I. Beta-lactams													
Ampicillin	16–20	1.2	0.48	325	14	30	IV 2 g	9.5 ± 2.2	170.3 ± 56.6	25 ± 7.7	2.7 ± 0.5	11.3 ± 2.2/48 h	[465]
							IP 1 g/L	9.6 ± 2.6	48 ± 7.6	25 ± 7.7	-	60 ± 13/48 h	
Sulbactam	–	0.25	0.2	250	21	–	IV 1 g	9.7 ± 2.2	87.5 ± 29.9/5–6 h	22.6 ± 3.2	3.4 ± 0.4	152 ± 1.9/48 h	
							IV 1 g	9.4 ± 3.2	27.8 ± 4.1/5–6 h	22.6 ± 3.2	–	68 ± 13/48 h	
Imipenem	13–21	1	–	205	1	205	IV 500 mg SD	3.28 ± 0.59	29.3 ± 10.5	66.8 ± 18.1	–	3.2 ± 0.5	[466]
							IP 500 mg/L	–	–	–	–	79 ± 8	
Cilastatin	13–21	1	0.31	238	3.7–4.8	54	IV 500 mg SD	8.84 ± 3.8	34.8 ± 6.5	24 ± 14.9	–	5.2 ± 0.5	
Imipenem							IV 500 mg SD	6.2 ± 1.4	29.5 ± 12.2	76.3 ± 23.5	4.8 ± 0.6	–	[467]
							IV 1,000 mg SD	6.9 ± 1.1	69.5 ± 9.5	50.6 ± 15.6	5.4 ± 0	–	
							IV 500 mg	22.6 ± 6.4	51.9 ± 13.4	8.1 ± 1.8	5.4 ± 0.4		
							IV 1,000 mg	15.4 ± 5.0	110.8 ± 20.3	10.7 ± 1.4	5.4 ± 1.2		
Piperacillin	21	1	0.21	188	3.3	57	IV 2 g SD	2.43 ± 0.84	104.4 ± 26.1	104 ± 37.7	3.17 ± 0.67	2.5 ± 0.7/6 h	[249]
							IP 500 mg/L						
							–petit	–	6.8 ± 2.9/2.6 h	–	–	67.8 ± 8.5/6 h	
							+perit	–	8.9 ± 2	–	–	83.4 ± 4.6/6 h	
							IV 1 g SD	2.41 ± 0.49	–	100.2 ± 13.8	2.7 ± 0.8	–	
							IP 1 g/L + perit	–	–	–	–	96.3/6 h	
							IV 3 g SD	2.12 ± 26.3	270 ± 31	65 ± 12.9	3.6	5.5/28 h	[288]
Tazobactam	–	0.89 ± 4.5	15.91 ± 1.9	219 ± 25	3.58 ± 46.5	49.5 ± 8	IV 0.375 g	6.36 ± 876.1	28.6 ± 5.7	36.9 ± 11.8	3.8	10.7/28 h	[288]
Temocillin	63–88	5–6	0.29	44	16–28	9	IV 15 mg/kg SD	13.4 ± 3.9	–	9.3 ± 1.8	–	8 ± 2.6/24 h	[468]
Cefamandole	67–80	0.7	0.16	109	15	9	IP 500 mg/L SD	10.4 ± 7.3	31.3 ± 4.7/6 h	20 ± 6.2	3.2 ± 1.6	71.7 ± 12.8/6 h	[469]
							IV 1 g SD	9.02 ± 1.0/1 h	65 ± 10	24.4 ± 6.4	1.48 ± 0.41	5 ± 2/24 h	[470]
							IP 500 mg	8.1 ± 1.2	33 ± 3/6 h	25.4 ± 6.6	2.5 ± 0.7	71 ± 10/6 h	
							IV 1 g	6.1 ± 1.7	–	21.9 ± 9.7	0.92 ± 0.25	5 ± 2.4/54 h	[471]
Cefazolin	70–85	1.8	0.14	60	27	5	IV 10 mg/kg	33.1 ± 1.0	–	5.7 ± 0.6	1.0 ± 0.4	–	[472]
							IP 10 mg/kg	–	30	5.85 ± 0.7	0.81 ± 0.14	73.7/4 h	
							IP 500 mg/L LD	–	54.8 ± 6.7	7.8	–	88/6 h	[473]
							250 mg/L MD perit +	–	110.9 ± 6.7	–	–	65/24 h	
							125 mg/L perit +	29.2 ± 16.2	141.3 ± 51.9	2.8 ± 1.5	–	–	[474]
Cefepime							IV 1 g SD	17.6 ± 2.9	62.9 ± 15.8	15.4 ± 4.9	3.86 ± 0.59	25/72 h	[285]
							IV 2 g SD	18.8 ± 1.6	124 ± 14	14 ± 1.3	4.35 ± 0.69	–	
Cefepime		1.3–2.3	20.5 ± 4.8	89–178	13.5 ± 2.6	18.7 ± 5.18	IV 1 g	17.6 ± 2.9	62.9 ± 15.8	15.4 ± 4.9	–		[284]
Cefodizime	88						IV 1 g SD	4.1–6.8	–	1.6–31.7	0.3–0.9	1.2–6.4/24 h	[475]
							IP 500 mg/L SD	4–9.8	–	19.7–39.2	–	41–100/24 h	
Cefoperazone	65–90	1.8	0.22	100	2.9	78	IV 1 g	–	104.2 ± 29.1	80 ± 20	–	–	[476]
							IP 1 g/L		33.2 ± 5.3/6 h	–	–	95 ± 12/10 h	

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IV 1 g day 1–3	2.65 ± 0.39	–	70.1 ± 19.2	6.9 ± 1.0	–	[477]
							IP 2 × 1 g/2 L 2 days	–	–	–	–	63.8 ± 4.8	
Cefoperazone Sulbactam							IV 2 g ± 0.82	2.08 ± 21.2	280.9 ± 33.4	71.9	0.55 ± 0.08	1.0/48 h	[478]
Cefoperazone							IV 1 g/L	2.33 ± 0.96	38.9 ± 12.42/2–4 h	71.9 ± 33.4	–	64 ± 14/6 h	
Sulbactam							IV 1 g	6.86 ± 1.67	82.2 ± 16.2	33.4 ± 5.3	3.6 ± 0.2	11.1 ± 1.4/48 h	
							IP 0.5 g/L	6.26 ± 1.45	82.2 ± 2.0	33.4 ± 5.3	–	70 ± 10/6 h	
Cefoperazone							IP 62.5 mg/L for 10 days + perit	–	10 at 24 h	–	–	–	[479]
Cefotaxime	36	1	0.28	322	2.5	135	IV 30 mg/kg	–	–	–	3.2	–	[480]
							IV 2 g	1.8 ± 1.2		65 ± 25	2.4 ± 0.8	–	[481]
							IP 1 g/L	2.6 ± 0.3	–	88 ± 39			
Cefotaxime (CFT)							1 g	3.1 ± 1.3		87.2 ± 34.3	1.93 ± 1.0	2.18/6 h	[482]
							IP 0.5 g/L	–	10–12/2–3 h	–	–	90/9 h	
						CFT	IV 1 g	2.31 ± 0.20	–	118.7 ± 12.3	6.7 ± 1.3	4.9 ± 0.7/24 h	[483]
						DAC*		11.4 ± 1.9	–	–	3.6 ± 0.9	2.6 ± 0.6/24 h	
						CFT	IP 0.5 g/L	2.3 ± 0.3	15 ± 1.5/2 h	–	–	58.7 ± 6.4/4 h	
						DAC		13.2 ± 4.3	9.7 ± 1.4/6 h	–	–	–	
						CFT	IV 2 g	2.24 ± 1.04	322.9 ± 105.2	81 ± 31	1.82 ± 0.43	–	[484]
						DAC		18.9 ± 21.7	37.8 ± 19.4	–	2.84 ± 0.7	–	
						CFT	IP 1 g/L	2.57 ± 1.03	29.7 ± 9.2/4–8 h	71.2 ± 29.3	11.5 ± 6.9	74.6 ± 21.3/6 h	
						DAC		25.3 ± 33.8	19.5 ± 12.6/7.1 h	–	3.46 ± 1.03		
						CFT	IV 1 g	1.59 ± 0.47	156/5 min	–	–	3.5/6 h	[485]
						DAC		–	17.4/2 h	–	–		
						CFT	IP 0.5 g/L	–	9.1/2 h	–	–	65/6 h	
						CFT	IP 250 mg/L						[486]
							+ perit	–	–	250.8 ± 59.5	–	90/24 h	
							– perit	–	–	94.8 ± 23.4		67/24 h	
						CFT	IV 1 g	2.3 ± 8.2		11–103	–	1.4–4.2/6 h	[487]
						DAC		–	10–60	–	–		
*Desacetyl Cefotaxime													
Cefotaxime						CFT	IP 500 mg/L (2 children)	1.83–2.49	11.9–13.1/4.08 and 2.22 h	79–62	1.14–2.81	56.6 and 64.8/5 h	[488]
						DAC		11–8.1	5.16–9.29/5.73–5.33		1.88–4.15		
						CFT	IP 500 mg/L + perit (children)	–	26.9 ± 7.8	–	–	–	[489]
Cefotetan	78–91	3.7	0.15	39	35	4	IV 1 g	15.5 ± 1.9	–	6.5–20	1.1–3.2	5–9/24 h	[490]
Cefotiam							IV 1 g	8.1 ± 2.4	–	20.9 ± 3.8	3.3 ± 0.2	6 ± 1.4/5 h	[491]
							IV 1 g	5.1	103	–	–	–	[248]
Cefoxitin	50–60	0.9	0.3	290	22	12	IV 2 g	7.8 ± 1.1	197	20.4 ± 1.45	1.44 ± 0.25	–	[492]

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IP4 × 50 mg/L 4 × 100 mg/L/24 h	20.2 ± 3.7	15 7	13 ± 3.3	4.1 ± 2.3	71.2/24 h	[493]
Cefpirome							IV 1 g	15.4 ± 1.9	–	15.4 ± 2.4	1.62 ± 1.5	12.4–96 h	[494]
Cefsulodin							IV 1 g SD	11.6 ± 4.7	–	14.7 ± 5.4	4.3 ± 1.7	8.7 ± 13/5 h	[491]
							IP 1 g						
							– perit	11.2 ± 1.9	–	26.5 ± 9	–	81 ± 3.6/5 h	
							+ perit	9.4 ± 1.3	–	23.9 ± 11.1	–	84 ± 6/5 h	
Ceftazidime	10–17	2	0.24	130	25	7	IP 4 × 125 mg/L						
							– perit	–	9.27–22.24 (6–24 h)	–	1.47–4.13		[495]
							+ perit	–	13.1–25.3 (6–24 h)	–	2.43–3.89	65–75/24 h	
							IV 1 g	–	–	–	3–4	4.3–7/4–6 h	[496]
							IV 1 g	1.9		8.7	–	–	[280]
Ceftazidime							IP 15 mg/kg single dwell	22 ± 5		14.1 ± 4.25	5.74 ± 1.6		[279]
Ceftazidime	10–17	2	0.24	130	25	7	IV 1 g	1.9		8.7	–	–	[280]
Ceftazidime							IP 15 mg/kg single dwell	22 ± 5		14.1 ± 4.25	5.74 ± 1.6		[279]
Ceftizoxime	31	1.4	0.4	190	35	6	IV 500 mg	10.2 ± 5.8	–	27.7	2.9	4.8 ± 2.1/6 h	[497]
							IV 1 g	12 ± 4.8	–	22.8	3.4	4.4/6 h	
							IP 250 mg/L	–	12.5/5 h	–	–	78 ± 4	
							IV 3 g	9.7 ± 5.1	411 ± 137/0.25 h	17.1 ± 7.4	2.8 ± 0.7	–	[498]
Ceftriaxone	85–95	6–9	0.09	15	12–57	8	IV 1 g	12.3 ± 4.4	412 ± 354	14 ± 5.6	0.6 ± 0.4	4.5 ± 2.9/72 h	[483]
							IP 1 g	13.7 ± 10.1/ 42 h	38.8 ± 11.6	–	–	44 ± 13/4 h	
Cefdinir							O 100 mg	10.8–21.9	1.64–4.43				[499]
Quinupristin–Dalfopristin	23–32	0.93 ± 0.15	1.07 ± 0.27	780 ± 120	–	–	IV 7.5 mg/kg	0.83 ± 0.13	2.89 ± 0.85	710 ± 200	–		[500]
Dalfopristin	50–56	0.71 ± 0.18	0.77 ± 0.34	770 ± 180	–	–		0.76 ± 0.29	8.52 ± 3.25	670 ± 360			
Ceftriaxone							IV 2 × 2 g at 24 h interval						
							– perit	9.8 ± 1.9	285 ± 69	13.3 ± 5	0.67 ± 0.5	–	[501]
							+ perit	14.8 ± 12.7	272 ± 54	15 ± 10	2.05 ± 1		
							IP 500 mg/L	10.5 ± 2.3	58.9	14.8	–	70.6 ± 7.9/4–6 h	[502]
							IP 1 g/L	–	71.1	–	–	–	
							IP 1 g/L	12.7 ± 2.9	–	10.1 ± 3.0 mL/ kg/h	0.69 ± 0.2 mL/ kg/h	71.4/5 h	[503]
							IV 1 g	12.2	–	7.4 (4–12.9)	–	–	[504]
Cefuroxime	33	1.3	0.2	140	20	15	IV 15 mg/kg	14.7 ± 1.1	–	–	3.59 ± 0.8	–	[505]
							IV 500 mg – perit	15.1 ± 1.9	24.2 ± 6.4	21.5 ± 1.2	4.2–2.9 ± 1.2–1.3	–	[506]
							IP 250 mg/L – perit						
							– perit	14.4 ± 2.1	12.1 ± 2.2	20.3 ± 1.4	2.3–6.5	70	

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IP 1 × 250 mg/L LD + 125 mg/L MD		43.2 ± 7.5 SS	–	9.9–12.4		
Cephalexin	18.537	0.8	0.26	263	20	10	O 500 mg SD	8.6 ± 0.9	–	18.4 ± 2.71	2.29 ± 0.63	–	[507]
							O 1–2 g/days for 3 days	–	97.8 ± 24.2/4 h	–	55 ± 19.4 in dialy sate day 1	16.5/day 1–25.5/day 2	[507]
Cephalothin	60–65	0.6	0.26	350	10	21	IP 100 mg/L 4 exch/24 h	–	5.6 ± 2.2/24 h	–	–	–	[508]
							IV 1 g + IP 250 mg/L	17.1 ± 6.0 ± 6.0	100.3 ± 39.2	11.1 ± 12.7	–	–	[474]
							IV 1 g	3.0	111.0	–	–	–	[248]
							IP 0.5 g/L	–	18.4/2 h	–	–	–	
Cephradine	7.519	1.0	0.31	323	12	20	O 500 mg SD	–	–	–	2.8–3.5	6.9/48 h	[509]
Moxalactam	50	2.5	0.3	97	20	12	IV 1 g	16.7 ± 2.9	123 ± 9	10.6 ± 2.0	2.7 ± 0.5	17.4 ± 3.1/24 h ± 60/4 h	[510]
							IP 0.5 g/L IV 1–2 g SD	13.2 ± 2.9	38.6 ± 12.7/4 h	11.5 ± 2.4	2.3 ± 0.5		[511]
							R MOX	17.3 ± 3.4	–	12.9 ± 6.9 (mL/h/kg)	1.1 ± 0.6		[287]
							S MOX	18 ± 3.3	–	13 ± 5.5 (mL/h/kg)	1.27 ± 0.62		
Moxalactam							IP 0.5–1 g/L SD						
							R MOX	–	–	–	–	71 ± 18	[483]
							S MOX	–	–	–	–	79 ± 18	
							IV 1 g SD	17.9 ± 4.2	171 ± 62/0.08 h	12.8 ± 7.7	2.1 ± 0.5	20.2 ± 8.3/48 h	
II. Glycopeptides Vancomycin							IP 0.5 g/L SD	15.4 ± 4.1	34.1 ± 8.5/4.3 h	–	–	57 ± 16/4 h	[52]
	10	7	0.47	55	240	2	IP 500 mg/L	–	23.7 ± 6.5	–	2.4 ± 0.08	53/6 h	[512]
							IP 10 mg/kg	81		9.4 ± 1.9	1.48 ± 3.6	–	
							IP 10 mg/kg 2 L	65.8 ± 10.7	6.3	15.1 ± 2.0	2.50 ± 0.33	65/4 h	
							IV 10 mg/kg	90.2 ± 24.2		6.45 ± 1.1	1.35 ± 0.35		[513]
							IP 500 mg/L LD	–	9.1/5 h	–	–	71.3/6 h	[514]
							IP 500 mg/L + perit	62.3	35.3 ± 19.1/6 h	–	–	–	[515]
							300 mg/kg per 2 L IP – perit	–	–	–	–	50.8/6 h	[247]
							300 mg/kg per 2 L IP – perit	–	–	–	–	73.9/6 h	
							IV 25 mg/kg + perit	115 ± 6	56.8 ± 4.7	7.2 ± 0.3	1.4 ± 1.05	–	[516]
							IV 15 mg/kg	111 ± 22	S57.1 ± 9.3	5.0 ± 1.4	1.2 ± 0.5		
							IP 30 mg/kg	91.7 ± 28	S30.4 ± 7.2	5.0 ± 1.3	1.7 ± 0.9	46/6 h	
							IP 1 g/2 L LD		15.5 ± 12.3/4 h	8.52	–	–	[517]
							IP 15 mg/kg LD		16.2 ± 1.75	–	–	–	
							IP 37.5 mg/L	–	13.3 ± 4.5	–	–	70 ± 15/3 h	[518]

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							CAPD + perit						
Vancomycin							IP 37.5 mg/L	–	8.8 ± 2.5	–	–	39 ± 13/3 h	
							CAPD – perit						
							IP 15 mg/kg/2 L LD + MD 25 mg/L		17.8 ± 2.2/1–6 h			63 ± 10.1/4 h 71.9 ± 17.5/4 h	[225]
							IP 25 mg/L no LD		0.27 ± 0.42/6 h				
							IV 1 g perit +	103.9 ± 57.2	–	4.09 ± 0.45	3.84* ± 0.75 *max perit	–	[218]
Teicoplanin	95	41–62	0.84–1.13	36.438	124	<2	IV 3 mg/kg	162 ± 52	–	5.15 ± 1.34 mL/h/kg	0.34 ± 0.02 mL/h/kg	6.8 ± 1.2/6 days	[519]
							IV 6 mg/kg	242 (202–273)	–	5.7 ± 2.00.2	–0.4	–	[520]
							IV 3 mg/kg	135	4.84 ± 1.43/6 h	–	–	7.1 ± 1.2/6 h	[521]
							IP 6 mg/kg		8.0 ± 0.6			81.5 ± 10.7	[522]
							IV 3 mg/kg	377 ± 109	31.6 ± 5.2	2.76 ± 1.08	0.25 ± 0.21	3/5 h 9/2 weeks	[226]
							IV 6 mg/kg	266.4 ± 51.9	56.5 ± 7.0	0.007/kg	6.1 ± 0.7/46 h	357	
							IP 3 mg/kg	338 ± 60	6.6 ± 1.8/4 h	–	0.13 ± 0.07	77 ± 21	[226]
Teicoplanin	95	41–62	0.84–1.13	5–10	124	<2	IP 20 mg/L	508	9	2.5	–	–	[296]

Table 9.8 Pharmacokinetic studies with quinolones, aminoglycosides, trimethoprim-sulfamethoxazole, and miscellaneous antibiotics

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Ciprofloxacin	40	3–4	2.8	652	16.8	300	O 750 mg (n = 6)	16.8 ± 5.1	3.61 ± 1.56	373.5 ± 213.4	–	0.4–1.6/48 h	[523]
							O 4 ×250 mg	8.44 ± 3.23	–	–	–	1/48 h	[216]
							– perit						
							+ perit	7.19 ± 1.75	–	–	–	1.5/48 h	
							O 4 × 250 mg every 12 h	11 ± 1	2.3 ± 0.2	256 ± 47	4.16 ± 0.33	2/48 h	[524]
Ciprofloxacin		4.6 ± 0.9	7.33 ± 5.67	86.3 ± 43.8	11.1 ± 2.8	19.6 ± 7.6	O 750 mg	8.9 ± 3.1	3.36 ± 1.12	33.0 ± 28.6	8.8 ± 6.5		[299]
Fleroxacin	18	8.6	1.5	168	24.7	63	IV 100 mg SD	28.6 ± 6.7	–	0.58 ± 0.13/kg	0.05 ± 0.01/kg	7.8 ± 3.6/96 h	[525]
							O 400 mg SD	–	4.9 ± 0.06	–	–		
Fleroxacin		8.9–13.5		122–168	13–21							<10	[301]
Ofloxacin	25–30	6* ± 1.2	1.23* ± 0.11	180.5* ± 12.1	18.4* ± 12.1	68.4* ± 35.1	O 300 mg	25.1 ± 2.54	–	3.55 ± 0.43	–	4.2/24 h ± 0.5	[300]
							O 200 mg	26.8 ± 2.5	–	35.2 ± 8.2	4.0 ± 0.5	5.8/24 h	[526]
							O 250 mg	–	–	–	–	5/24 h	[527]
							O 200 mg SD IP 10 mg/L SD	35 ± 4.19	–	29.3 ± 11.2	4.5 ± 0.8	15/96 h	[528]
							– perit	–	–	–	–	81.9 ± 1.5/4 h	[529]
							4 × 20 mg/2 L MD IP 10 mg/L SD	–	0.57 ± 0.07/24 h	–	–	–	
							– perit	–	–	–	–	84.7 ± 1.5/3 h	
							4 × 20 mg/2 L MD	–	17.8 ± 0.17	–	–	–	
Ofloxacin	25–30	6 ± 12	1.23	180.5	18.4 ± 12.1	68.4 ± 35.1	IP 200 mg	22.1	3.55	35.9	2.15	<10	[307]
Pefloxacin	25*	8*	1.9*	137*	12.1* ± 1.7	117*	O 400 mg SD	19.2 ± 3.3	–	1.0 ± 0.2 (mL/min/kg)	0.06 ± 0.01	–	[530]
							IV 400 mg SD	17.4 ± 2.3	6.4 ± 0.4	–	–	–	
Pefloxacin							IP 200 mg/L	–	3.5 ± 0.8/65 kg	1.3 ± 0.3 (mL/min/kg)	0.09 ± 0.02	–	
							O 400 mg SD	19 ± 5.8	5.6 ± 1.3	39.1 ± 11.1	2.7	2.3–3.7/24 h	[531]
Gentamicin	<10	2	0.24	95	60	2	IV 1 mg/kg	27.4 ± 11.7	4.5 ± 1.0	–	–	0 in 3/5 patients	[532]
							IP 1 mg/kg	27.9	3.64 (6 h)	–	–	84/6 h	
							IP 50 mg/L	36 ± 9	3.9 ± 1.5 (6 h)	–	2.94 ± 0.4	20.2 ± 9/24 h	[533]
							IP 7.5 mg/L – perit	–	0.6 (6 h)	–	5.7 ± 0.4 mass transfer	64/6 h	[229]
							+ perit	–	0.8 (6 h)	–	16.4 ± 1.9	79.3/6 h	
							0.6 mg/kg	35.8	–	7.36 ± 1.49	5.74 ± 1.5	–	[250]
Tobramycin	<10	2.5	0.23	80	60	3	IV 1.1–15 mg/kg	34.6 ± 7.4	–	8.0 ± 1.0	3.8 ± 0.4	13–26/24 h	[534]
							IV 1.5 mg/kg	39.5 ± 18	–	7.6 ± 3.1	1.11 ± 0.8	–	[535]
							IP 1.5 mg/kg/2 L	35.1 ± 12	1.8	9.8 ± 4.0	1.96 ± 1.6	52/6 h	
							IV 2 mg/kg	25.7 ± 46.5	9.8 ± 3/0.3 h	7.3 ± 2 70 kg	3.4 ± 1 70 kg	30/48 h	[536]
							IP 2 mg/kg/2 L CCPD 2 L cycles/h	–	5.6 ± 2/6 h	–	–	73 ± 10.6 h	

Table 9.8 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IP 160 mg/2 L						
							– perit	–	5.9 ± 1.4/40 h	–	12.8 ± 1.2	4.4 ± 4.4/48 h	[230]
							+ perit	–	6.5 ± 1.3/40 h	–	17.4 ± 1.1	5.5 ± 3.6/48 h	
							IP 5 mg/L	–	1.3–2.1 ± 0.12/24 h	6.8	–	48/48 h	[473]
Tobramycin							IP 50 mg/L LD	–	4.3/6 h	5.6	–	85/6 h	
							IP 7.5 mg/L MD	–	3.7	–	–	50 ss	
							IP 1.93 mg/kg/2 L LD	38.7 ± 10.6	6.6 ± 1.1	6.9 ± 1.2	–	–	[537]
							IP 0.96 mg/kg/2 L						
							IP 20 mg/2 L						
							– perit	–	–	–	6.5 ± 3.1 mass transfer	–	[538]
							+ perit	–	–	–	18.5 ± 8.2 mass transfer		
Streptomycin	35	2.5	0.26	85	80	3	IP 100 mg/L LD	–	5.5/5 h	–	7.3	75/6 h	[539]
							IP 30 mg/L MD	–	4.8	–	–	–	
Amikacin	<10	2.5	0.25	90	70	3	IV 7.5 mg/kg	42.2 ± 14.2	18.6–26.8/24 h	3.9 ± 1.0/1.73 m^2	2.0 ± 1.0/1.73 m^2	–	[540]
							IP 7.5 mg/kg/2 L	37.2 ± 13.2	19.6 ± 6.1/5.6 h	4.6 ± 1.2	2.7 ± 0.4	53 ± 14/5 h	
Netilmicin	<10	2.0	0.25	88	40	5	IV 100 mg						[217]
							– perit	18.1 ± 3.7	–	16.8 ± 2.3	3.38 ± 0.37	23 ± 2.7/48 h	
							+ perit	19.6 ± 2.0	–	18.5 ± 3.2	4.9 ± 1.1	27.9 ± 5.2/48 h	
Netilmicin							IP 1.5 mg/kg followed by IP 40 mg/day	–	1.9 ± 9.9	1.4 ± 9.0	–		[541]
Kanamycin	<10	2	0.23	95	80	2	IP 50 mg/L						
							– perit	–	3.1 ± 0.3	–	11.4 ± 0.9 mass transfer	67 ± 4/4 h	[542]
							+ perit	–	4.3 ± 0.4	–	17.2 ± 2.1 mass transfer	83 ± 2/4 h	
Trimethoprim	40–70	13	2	125	25	65	O 80 mg	24	–	–	2.32 ± 0.39 (night) 4.65 ± 1.25 (day)	–	[543]
Sulfamethoxazole	40–90	10	0.2	30	35	10	O 400 mg	15	–	–	1.64 ± 0.58 (night) 4.29 ± 0.95 (day)	–	
Trimethoprim							O 320 mg	27.7	–	31.1	0.88	2.75/24 h	[544]
							IV 320 mg	28.6 ± 10.6	–	29.3 ± 11	0.77 ± 0.36	2.7/24 h	
							IP 320 mg	27 ± 8.8		39.1 ± 20	0.77 ± 0.35	73	
Sulfamethoxazole							O 1,600 mg	12.8 ± 1.9		11.9 ± 3.2	0.62 ± 0.25	5.24/24 h	
							IV 1,600 mg	13.0		11.8 ± 3.1	0.62 ± 0.25	5.17/24 h	
							IP 1,600 mg	11.8 ± 2.2		15.3 ± 5.0	0.53 ± 0.08	65	
							IP	–	–	–	14 ± 2.5	60/3 h	[545]
Fosfomycin	<10%	1.5–2	–	–	4.88	–	IV 1 g	38.4 ± 8.7	32.6 ± 2.8/4 h	7.0 ± 1.4	3.2 ± 0.2	37.2 ± 3.6	[546]
							IP 0.5 g	– /5 h	34.7 ± 2.3	–	–	68.4 ± 6.0	

Table 9.8 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Roxithromycin		10–14	–	–			O 300 mg	20.6 ± 8.7	2.3–6.8	37–118	0.9–1.8	1.0–3.1	[315]
Aztreonam	50–60	1.8	0.2	80	7.2	22	IV 1 g	–	–	23.8 ± 2.5	2.1 ± 0.29	9/48 h	[547]
							IP 500 mg/L		30 ± 3.3/3 h	–	–	72.9 ± 2.4/6 h	
							IP 500 mg/L		42.5 ± 12.4/6 h	–	10.05 ± 3.7	90.8 ± 3/8 h	[548]
							IP 1.5 g/L single LD + pert	9.3 (6–14)	83 (61–92)/2 h	30.4	–	86–95	[310]
Metronidazole	20	7	0.7	82	7	82	IV 750 mg	10.93 ± 2.01	–	50.17 ± 18.6 (mL/kg/h)	4.49 ± 0.88	10/48 h	[322]
Metronidazole		6.0–8.8	0.53–1.1	68–87	6.1–9.5	55–183	IV 500–800 mg single dose	5.6				10	[324]
		6.1–14.7	0.52–0.96	68–81	7.0–2.1	–	O 250–2,000						
Ornidazole							IV 500 mg	11.8 ± 0.9		47.9 ± 6.3	3.0 ± 0.4	6.2 ± 1.1/48 h	[323]

Table 9.9 Pharmacokinetic data with antiviral and antifungal drugs in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Acyclovir	15	2–3	0.6	300	19.5	25	IV 200 mg/kg ($n = 1$)	14.7	–	48.6	3.6	7.3/24 h	[549]
							IV 5 mg/kg ($n = 1$) SD	17.1	7.7	48.3	4.4	5.7/24 h	[550]
							IV 1 g ($n = 2$) IV 0.5 g ($n = 2$)	13.2 ± 4.7	–	39.7 ± 10	3.4 ± 0.2	–	[551]
							IP 1 g/2L	10.8 ± 2.9	–	64.6 ± 7.5	–	61 ± 10	
Ganciclovir					6.3	35.5	5 mg/kg IV					Probably not relevant	[331]
Foscarnet		4.5						41.4–45.8		8.8–9.8	4.5–5.8	5–30	[336]
Zidovudine							O 200 mg SD				0	0	[552]
Zidovudine							O 200 mg ($n = 5$) SD	1.8 ± 0.5	5.3 ± 2.4	1,059 ± 511	5	<1/24 h	[552]
GZVD*								–	–	–	15	20/24 h	
Zidovudine	30	1.1	1.4	1,500	1.4	737	SD 200 mg						
							SD 200 mg O ($n = 1$)	7.9	1.36	856	4.2	0.5/14 h	[337]
							SD 100 mg O	26	0.2	2,079	5.8	0.14/14 h	
							SD 200 mg ZVD	19.9	9.06	–	3.6	8.5/14 h	
							100 mg ZVD	7.1	6.78	–	3.7	4/14 h	
Didanosine		1.56 ± 0.43		13.0 ± 1.6	3.6 ± 0.8	3.4 ± 1.2	300 mg IV	3.11 ± 0.88	9.17 ± 4.54	3.2 ± 1.2	?		[339]
		1.54 ± 0.38					300 mg per os	3.88 ± 1.26	2.16 ± 1.32				
Amphotericin B	90–95	24	0.46	15	40	9	50 mg IV/4 h	S: 10* D: 0.1–0.2*					[553]
							10 mg IV	S: 0.2 (1–12 h) D: 0.2					[554]
Fluconazole	11	33	0.71	–	98	–	O 100 mg	85	S:1,439 ± 246 D: 1,050 (6–24) 790 (24–48 h)	–	5.53 ± 1.03	18/48	[348]
							IP 150 mg/2 L	80	S: 2,123 ± 360	8.75 ± 22	4.3 ± 0.4		[555]
							IP 50 mg/2 L	72	S: 885 ± 136	7.63 ± 1.2	4.41 ± 0.49		
Fluorocytosine	4	5	0.7	113	85	7	LD 30–40 mg/kg 4 days		S ?				[556]
							MD 15 mg/kg O		D ?				

Table 9.9 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							LD 3.5 g 2 days 2.5 g 2 days		SSs: 24–86				[557]
							MD 1 g day IP 100 mg/L		SSs: 25–33				
							– perit	–	1.78	–	16.1 ± 2 Mass transfer	81 ± 2/4 h	[558]
							+ perit	–	–	–	19.0 Mass transfer	93/4 h	
							LD O 2 g + IP 100 mg/2 L		S: 25–33 D: 29–43				
Itraconazole	99.8	21–38	–	–	25		O 200 mg SD	–	S: 0.08	–	0	0	[351]
Ketoconazole	99	3	–	–	–	–	O 400 mg/day ($n = 1$)	3.51	–	–	–		[559]
							O 200 mg/day for 4 days		SC_{max} 2.0 ± 11.3 $DC_{max} < 0.1$				[560]
							O 400 mg/D for 4 days		SC_{max} 1.6 ± 0.5 $DC_{max} < 0.1$				
							O 200 mg SD – perit + perit		DC_{max} 0.021 (ND–0.073) DC_{max} 0.015 (0.010–0.019)				[561]
Ketoconazole	99	3	–	–	–	–	400 mg SD – perit + perit		C_{max} D: 0.029 (0.014–0.056) D: 0.074 (0.032–0.115)				
							O 400 mg SD	2.4 ± 0.8	C_{max} 2.3 ± 1.7		<1		[260]

Table 9.10 Pharmacokinetic data with H_2-antagonists, metoclopramide and cispramide

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Cimetidine	13–25	1.5–2	0.8–1.2	313–808	3–5	193	IV 300 mg	6.9 ± 0.18	–	167.1 ± 8.06	3.01 ± 0.57	1.6 ± 0.23/24 h	[354]
							IV 300 mg	4.3	–	191 ± 55	4.2 ± 3.1	2.2 ± 1.4/24 h	[353]
Ranitidine	15	1.5–3	1.1–1.9	568–709	6–9	103–230	IV 50 mg	7.06 ± 0.96	–	126 ± 67.5	3.2 ± 0.7	1.3/24 h	[355]
							O 150 mg	10.02 ± 1.71	904 ± 529/4.2 h		2.6 ± 0.6	0.9/24 h	
Famotidine	15–20	2.5–3.5	1.1–1.4	412	9–18	40–60	IV 20 mg	15.5 ± 4.0	–	–	–	4.5 ± 1.1/24 h	[352]
Cisapride	98*	7–10*	2.4*	–	15*	385*	O 30 mg every 6 h	–	0.031–0.04 (serum)	–	–	–	[358]
							IV 10 mg every 6 h	–	0.007–0.008 (dialysate)	–	–	–	
							IP 5 mg/L every 6 h	–	0.028–0.053 (serum)	–	–	–	
Cisapride	98	36,440	2.4		9.6 ± 3.3	380 ± 161	O 20 mg		Probably not altered				[359]
Metoclopramide	–	3	3.4	916	14	196	O 15 mg (n = 1)	34.65	66.4	–	3.54	–	[562]
							IV 15 mg (n = 1)	30.13	329	61.6	1.47	3/6 h	
							IP 15 mg/2 L (n = 1)	30.13	146.2	–	–	97/6 h	
Lansoprazole	96	1.2–2.9					O 15–30 mg	1.6	Probably not altered				[356,357]
Pantoprazole	98	0.9–1.9	0.15–0.17	60–130	Not altered				Probably not altered				[563]
Omeprazole	95	0.7–2.1			0.7–2.1				Probably not altered				[356]

*Adapted from [495, 496].

Table 9.11 Pharmocokinetics of intravenously administered erythropoietin in peritoneal dialysis

PD regimen	Dose	C_{max} (U/L)	T_{max} (h)	$t_{1/2}$ (h)	AUC (U/1 h)	V_d (L)	Cl_{tot}	Percentage dose lost	References
6 CAPD	300	7,688 ± 1,103	0.5	11.2 ± 0.4	81,004 ± 9,523	5.0 ± 1.0/24 h	0.52 ± 0.008 mL/min/kg	2.63 ± 0.45/24 h	[564]
9 CAPD	100	1,595 ± 104 (11–145)	0.4 ± 0.1	8.7 ± 1.0	16,909 ± 1,217	4.9 ± 0.6	6.7 ± 0.5 mL/min	–	[565]
10 CAPD	100	2,000	–	5.1 ± 0.6	–	–	–	–	[566]
7 CAPD	100	1,440 (1,088–1,994)	–	8.3 (6.6–13)	14,623 (10,286–19,562)	4.5	6.0 (4.7–9.7) mL/min/1.73 m^2	–	[567]
12 IPD	100	1,923 ± 197	0.3	5.6 ± 0.3	–	3.7 ± 0.6	8.1 ± 1.4 mL/min	–	[361]
8 CAPD	120	3,959 ± 758	0.25	8 ± 2 (6.2 ± 10.2)	45,102 ± 11,405 (0–24 h)	0.033 ± 0.013 1/kg	0.047 ± 0.017 mL/min/kg	2.3/24 h (1.7–3)	[568]
6 CAPD	100	1,602	–	6.1	13 592	–	–	–	[569]

Table 9.12 Pharmocokinetics of subcutaneously administered erythropoietin in peritoneal dialysis

PD regimen	Dose	C_{max} (U/L)	T_{max} (h)	AUC (U/1 h)	Bioavailability (%)	References
6 CAPD	300	484 ± 75	24	8,230 ± 1,312 (0–24 h)	10.2 ± 1.0/24 h	[564]
9 CAPD	100	81 (11–145)	12	–	14/24 h; 31/72 h	[566]
12 IPD	100	32 ± 4	28 ± 5	–	14.9 ± 4.8	[361]
8 CAPD	120	176 ± 75	18	9,610 ± 4,862 (0–24 h)	21.5 (11.3–36)	[568]
6 CAPD	100	114	–	3,316	24.0	[569]
10 CAPD	50	81 ± 13 mU/L	24	1,492 ± 165 mU/1 h	-	[570]

Table 9.13 Pharmocokinetics of intraperitoneally administered erythropoietin in peritoneal dialysis

	Dose (U/kg)	Vol dialysate	Dwell (h)	C_{max} (U/L)	T_{max} (h)	AUC (U/1 h)	Bioavailability (%)	References
6 CAPD	300	2	4	108 ± 18	8–12	1,981 ± 271 (0–24 h)	2.5 ± 0.2	[564]
3 CAPD	300	2	12	170 ± 13	12	2,933 ± 413 (0–24 h)	3.6 ± 0.5	
9 CAPD	100		12	52 ± 14	12 ± 0.2	1,426 ± 366	8.5 ± 1.9	[565]
3 CAPD	100	2	10	80	12	56% of AUC after SC inj.	–	[566]
7 CAPD	100	2	12	23 (18–55)	14 (6.3–18)	808 (426–1,652)	6.8 (2.2–12)	[567]
12 IPD	100	dry cavity	–	213 ± 27	17 ± 2.3	–	41.4 ± 7.2	[361]
8 CAPD	50,000 U	1.5–2	8	375 ± 123	12	6,432 ± 2,150 (0–24 h)	2.9 (1.2–6.8)	[568]
10 CAPD	50	2	8	36 ± 4	12–24	803 ± 67 mU/1 h	–	[570]
6 CAPD	400	50 mL of (saline undiluted)	8	1,500 (estimated)	12	52,399 ± 6,865 mU/mL/h	>9-fold increase vs diluted	[360]
6 CAPD	400	2 diluted	8	300 (estimated)	12	5,739 ± 1,292 mU/m/h	–	

24-h period for both drugs. A model was developed to examine serum and dialysate concentrations after intermittent IP administration of 15 mg/kg cefazolin and 0.6 mg/kg tobramycin. The model-predicted IP cefazolin provides adequate serum and dialysate concentrations for 24 h. Intermittent IP tobramycin doses must be 1.5 mg/kg for one exchange during the first day and then given as 0.5 mg/kg thereafter. It was concluded that the current empiric dosing recommendations for PD-related peritonitis may be adequate for cefazolin (15–20 mg/kg); however, tobramycin doses must be changed to 1.5 mg/kg IP on day 1, then to 0.5 mg/kg IP thereafter in APD patients.

Ceftazidime

After IP administration of 1 g ceftazidime, serum concentrations reach therapeutic levels within 30 min and are maintained for more than 24 h. A V_d of 16 L was found. Overall, use of 1–1.5 g once daily or 15 mg/kg body weight has been recommended [279, 280]. The pharmacokinetics and dynamics of ceftazidime in CAPD peritonitis were recently explored in Thai patients [281]. In accordance with the ISPD 2000 recommendations, the antibiotic regimen comprised continuous IP cefazolin and once-daily IP ceftazidime. Cefazolin was administered as loading and continuous maintenance doses of 500 and 125 mg/L dialysate, respectively. Ceftazidime (20 mg/kg body weight) was given IP once daily. Duration of treatment was 96 h. Following ceftazidime administration, serum ceftazidime levels were above 8 μ/mL, the recommended MIC throughout 24 h. Dialysate ceftazidime levels were below the MIC for total periods of 4.19 and 6.26 h in day 1 and day 4, respectively. The clinical response rate to the empiric regimen was 90%. It was concluded that once-daily IP administration of ceftazidime according to the ISPD 2000 recommendation could not provide adequate therapeutic levels of ceftazidime in dialysate throughout 24 h. Despite this finding and the poor post-antibiotic property of ceftazidime, the empiric regimen including once-daily IP ceftazidime yielded good clinical outcome The objective of the recent study of Sisterhen et al. [282] was to determine whether a continuous maintenance

Table 9.14 Pharmocokinetics of miscellaneous drugs in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Ethosuximide	0	60	–	10	–	–	0.3 × 400 mg CCPD (child)	–	–	–	–	50/24 h	[373]
Phenobarbital	66	70	0.75	9	100	6	O 2 × 250 mg day 6 CCPD (child)	-	21	–	–	40/24 h	[373]
Phenytoin	87–93	18	0.57	25	9	125	O 3 × 100 mg	–	16.6 mm/L SS	–	1.77	–	[571]
							O 3 × 200 mg	–	22.6 mm/L SS	–	1.70	–	
							O 4 × 100 mg	–	26.1	–	1.60	–	
1.25 di–OH vit D								O 27.4	O 116	O 15.3	–	–	[572]
								IP 19.2	IP 121	IP 18.4	–	–	
1-alpha-OH-vit D							80 mg/kg	IV 109.4 ± 129.5	NM ?				[384]
Clodronate							300 mg IV	182 ± 138	26.0 ± 19.3	2.4 ± 0.6	7		[392]
Mycophenolate-Mofetil								O 2 × 1 g			14.6 ± 3.4	6.5 ± 1.6	[223]
Alprazolam	68.4	10–14.5	0.72–1.05	44–67	11.5	70	O 1 mg				–		[378]
Triazolam		2.56 ± 4.06	1.31 ± 0.1	330 ± 110	2.29	–	O 0.5 mg						[378]
Midazolam		1.36 ± 2.29	0.38–1.14	323–645		680	O 5–20 mg		680				[378]
	95–97.5				–	–	–						[573]
Loprazolam		6.3–14.8		230			O 0.5–2 mg						[378]
Zolpidem	92	1.5–2.4	0.54–0.68	15.7	3–4.8		O 5–20 mg		probably as in ESRD				[380]
Ethinyl estradiol		3.4 ± 1.6		1,007 ± 754				8.4 ± 4.1	9.3 ± 0.7	518 ± 3.7			[376]

dose of IP ceftazidime (125 mg/L) in the absence of a loading dose would maintain adequate serum and dialysate concentrations to be effective in the treatment of peritonitis. Mean serum concentrations at completion of the short rapid cycles and at 24 h were 28.92 ± 13.64 and 23.92 ± 11.93 μg/mL, respectively. Serum bioavailability at 24 h was 74 ± 6%. Mean dialysate concentrations at completion of the short rapid cycles and at 24 h were 87.43 ± 19.18 and 32.06 ± 6.27 μg/mL, respectively. All patients achieved serum and dialysate ceftazidime concentrations greater than the MIC within 4 h.

Cefotaxime

Cefotaxime is metabolized in the liver to an active metabolite, which is primarily excreted by glomerular filtration and tubular secretion. However, dose reduction is necessary only when the CrCl falls below 5 mL/min. Several studies explored the pharmacokinetics of cefotaxime in CAPD [283]: a high proportion of the IP administered cefotaxime is absorbed into the circulation and therapeutic serum levels can be obtained after IP administration; no further dose adaptation is needed for patients on CAPD.

Cefepime

The clearance of cefepime, a third-generation cephalosporin, is 15 mL/min in CAPD patients, with a peritoneal clearance of 4 mL/min [284]. For IV administration, 1–2 g every 48 h is recommended [285]. It has a low protein binding value, and a relatively low V_d; therefore, a once-daily IP administration is probably not recommended, and the IV route should be preferred. Elwell et al. [286] recently determined the pharmacokinetics of IP cefepime in six APD patients. All patients were administered a single IP dose of cefepime (15 mg/kg) over a 6-h dwell. Patients then underwent a fixed APD regimen consisting of the first 6-h dwell, followed by an 8-h dialysate-free period and a subsequent series of three overnight APD exchanges. One hour after IP administration, serum cefepime levels exceeded the MIC (8 mg/mL) for susceptible organisms. The mean serum and dialysate concentrations at 24 h were 15.8 ± 3.6 and 6.2 ± 2.3 mg/mL, respectively. Bioavailability was 84.3 ± 6.2%, V_d 0.34 ± 0.07 L/kg, and serum $t_{1/2}$ was 13.8 ± 3.2 h. Total, peritoneal, and renal clearances were 16.5 ± 4.4, 4.3 ± 0.7, and 3.5 ± 2.5 mL/min, respectively. It was concluded that IP cefepime dosed at 15 mg/kg resulted in adequate serum concentrations in APD patients at 24 h post dose. Pharmacokinetic predictions suggest that most APD and CAPD patients would achieve adequate serum cefepime concentrations if treated with standard doses of 1,000 mg given IP once daily.

Cefpirome can be administered both IP and IV. Dialysis clearance by PD is negligible.

Moxalactam is a semisynthetic β-lactam antibiotic with activity against a broad range of Gram-positive and Gram-negative aerobic and anaerobic bacteria. This antibiotic exists as two stereoisomers with different antimicrobial activities. Several pharmacokinetic studies in CAPD patients have shown that, after IV administration, dosage adjustment to account for loss of moxalactam via the peritoneal cavity is not necessary. It appears further that there are no significant differences between R-Mox and S-Mox kinetics in CAPD patients [287].

Piperacillin

For piperacillin, whether or not in combination with tazobactam, dose adaptations should be made according to RRF. During CAPD, 5.5% of piperacillin and 10.7% of tazobactam are removed by dialysis over 28 h [288]. Another study [289] assessed the pharmacokinetics of IP administration of the combination piperacillin/tazobactam (PIP/TAZ) to patients on CAPD with and without *Pseudomonas* peritonitis. All patients were given an IP loading dose of 4 g/0.5 g PIP/TAZ. Twenty-four hours after the initial dose, a maintenance dose of 0.5 g/0.0625 g PIP/TAZ was administered with each dialysate exchange for a period of 1 week. After the loading dose, the highest plasma Cmax was 51.6 ± 21.25 μg/mL and appeared at 1.5 ± 0.45 h. During the maintenance period plasma PIP concentration was 5.2 ± 4.75 μg/mL. Tazobactam was detected in the plasma of one patient only. The concentration of TAZ in the dialysate fluid during the maintenance period was 2.3 ± 0.5 μg/mL. It was concluded that piperacillin administered IP at 4 g reached plasma concentrations comparable to IV administration and were considered therapeutic (above the MIC90 for *Pseudomonas aeruginosa*) in CAPD patients with or without peritonitis. The maintenance dose, however, should be augmented. Tazobactam could not be detected in the plasma of most patients and the therapeutic implications of IP administration of TAZ cannot be directly correlated to IV administration.

The pharmacokinetics of IV piperacillin in APD patients were recently studied [290]. Eight patients received a single IV dose of piperacillin (35 mg/kg actual body weight). GFR and piperacillin clearance values were normalized to 1.73 m2. Dwell times used in the patients on APD were 2.25 ± 0.06 h on cycler and 7.26 ± 0.14 h off cycler. Piperacillin $T_{1/2}$ was not statistically different on or off the cycler (on cycler 1.99 ± 0.39 h, off cycler 4.39 ± 5.4 h) and remained

insignificant. Piperacillin total Cl was 31.29 ± 6.02 mL/min. Renal Cl and PD Cl accounted for 8.8 and 16.8% of total clearance. Mean piperacillin serum and dialysate end-of-dwell concentrations were above MIC of susceptible organisms (8 μg/mL) for the three cycler exchanges only. The predicted serum and dialysate concentrations, using a one-compartment model, suggest that IV piperacillin 4,000 mg would provide adequate concentrations for susceptible organisms over a 12-h period. Thus, the current IV piperacillin dosing recommendations of 4,000 mg every 12 h for PD-related peritonitis are appropriate for patients on automated PD, but intermittent IP piperacillin is not recommended.

Glycopeptide Antibiotics

The two major drugs in the class of glycopeptide antibiotics are vancomycin and teicoplanin. *Staphylococcus aureus* and *Staphylococcus epidermidis* are almost always susceptible to vancomycin. Concentrations of 5 μg/mL or less are inhibitory although some strains require 10–20 μg/mL. Vancomycin is a large molecule (around 1,500 Da) and has a low serum protein binding. In ESRD its $T_{1/2}$ is very prolonged [200–250 h]. Pharmacokinetic studies after IV administration in CAPD patients show a low peritoneal clearance, which, however, increases during peritonitis. Although it has been claimed that CAPD does not require dose adjustment, serum drug levels should be followed in patients with substantial RRF [291]. As the *V*d of vancomycin (0.5 L/kg) is large in comparison with the IP volume, there remains a high concentration gradient between dialysate and plasma after IP administration (Fig. 9.12 from [291]). Therefore, vancomycin is rapidly absorbed into the circulation. When the dialysate is drained, and new dialysate is instilled, it rapidly becomes saturated with vancomycin from the blood, and adequate IP levels of vancomycin are obtained. Because of this phenomenon, a single high dose (15 mg/kg) of vancomycin is sufficient to obtain adequate dialysate levels. Whether, from a microbiological point of view, vancomycin is still the antibiotic of first choice in the treatment of PD-related peritonitis, is a matter of debate. The growing concern on the emergence of vancomycin-resistant enterococci in the United States has forced the Ad Hoc Advisory Committee to classify vancomycin from agent of choice to agent to be avoided (see Chapter 19 in this book). Other centers, however, having a high incidence of methicillin-resistant staphylococci (MRSA), have recommended a center-tailored therapeutic approach of peritonitis where vancomycin is still regarded as the first choice [292].

There are few studies of the pharmacokinetics of vancomycin and gentamicin in PD patients and the influence of antibiotic concentrations on treatment outcome. Concerns about resistance to ceftazidime and potential of aminoglycoside toxicity make the choice of empiric antibiotics difficult. Blunden et al. [293] retrospectively collected data from 613 patients on PD between 1 June 2002 and 31 December 2005 and adopted a protocol that minimized aminoglycoside exposure to patients with RRF and carefully monitored serum antibiotic concentrations. There were no statistical differences in mean day-5 vancomycin concentrations for CAPD versus APD and for anuric versus not-anuric patients. However, low levels (<12 mg/L) were recorded for 12.8% CAPD and 15% APD patients. These remained low at day 10 in 16% patients (25% if not anuric), despite incremental dosing. Vancomycin concentration did not predict cure or relapse of Gram-positive or culture-negative peritonitis. Gentamicin concentration (>2 mg/L in >50% patients) did not predict outcome of Gram-negative and culture-negative peritonitis. Moreover, cure rates were the same irrespective of whether gentamicin was continued for 14 days or was switched to ceftazidime after 5 days.

This important study concluded that the International Society for PD (ISPD) dosing guideline for vancomycin in CAPD and APD patients produces adequate serum concentrations of the antibiotics in the vast majority, but that large incremental dosing of vancomycin is needed if day-5 levels are low; especially for not-anuric patients. While evidence of gentamicin toxicity in PD remains controversial, ISPD dosing regimen resulted in high levels for >50% patients. High gentamicin concentrations did not correlate with treatment success, but switching gentamicin to ceftazidime at day 5 appeared safe and limited aminoglycoside exposure. Increasing vancomycin and gentamicin concentrations do not appear to improve cure rates and alternative strategies (such as combination treatment) should be considered for future research.

The pharmacokinetics of a single dose of IV vancomycin (15 mg/kg total body weight) were recently studied in 10 APD patients [294]. Dwell times were 2.3 ± 0.1 h on cycler and 7.3 ± 0.1 h off cycler. Vancomycin $T_{1/2}$ was significantly different on-cycler than off-cycler (11.6 ± 5.2 h versus 62.8 ± 33.0 h). Vancomycin total Cl was 7.4 ± 2.0 mL/min. Renal Cl and PD Cl accounted for 23.6 and 28.0% of total Cl, respectively. Mean vancomycin serum and dialysate end-of-dwell concentrations were above MIC of susceptible organisms (5 mg/mL) for the first cycler and the second ambulatory exchanges only. This study suggests that, to provide adequate concentrations for susceptible organisms over a 24-h period, current intermittent vancomycin dosing recommendations for PD-related peritonitis need to be changed to 35 mg/kg IP on day 1, then 15 mg/kg IP thereafter (i.e., once daily) in APD patients.

Little information is available on the disposition of vancomycin during chronic PD in children. This problem was recently studied [295] following IP administration of vancomycin in children receiving short-dwell APD and long-

dwell CAPD. A 6-h exchange containing vancomycin 500 mg/L, using an exchange volume of 1,100 mL/m^2 body surface area (BSA), was followed by 4-, 6-, and 8-h antibiotic-free exchanges. The 8-h exchange was followed by three to four 90-min antibiotic-free exchanges. The bioavailability of vancomycin during a 6-h IP exchange was 70 ± 5%, resulting in a delivered dose of 12.0 ± 1.8 mg/kg, and a 6-h serum vancomycin concentration of 23.3 ± 7.2 μg/mL. Total body vancomycin clearance measured 10.72 ± 4.52 mL/min/1.73 m^2 BSA, while PD clearance measured 2.78 ± 1.08 mL/min/1.73 m^2 BSA and accounted for 29 ± 11% of total vancomycin clearance. Dialysis clearance during long-dwell (CAPD) and short-dwell (APD) regimens was similar accounting for 25 ± 13% and 32 ± 12% of total body clearance, respectively. It was concluded that IP absorption and dialysis clearance of vancomycin in children receiving PD are similar to those reported in adult dialysis patients. In contrast, total body clearance of vancomycin was increased and the $T_{1/2}$ decreased in children, due to increased elimination by nonrenal nondialysis routes. For intermittent IP vancomycin therapy in children with peritonitis, an IP load containing vancomycin 1,000 mg/L (or 30 mg/kg), followed by a single full-fill (1,100 mL/m^2 BSA) daily exchange, containing vancomycin 250 mg/L (or 7.5 mg/kg), from day 2 until the end of treatment will maintain a vancomycin dialysate concentration of >4 μg/mL.

Teicoplanin is a glycopeptide that is mainly excreted via the renal route and has a prolonged terminal $T_{1/2}$ in renal failure. In PD patients with peritonitis the serum $T_{1/2}$ was 508 ± 193 h, and the V_d was 0.48 L/kg [296]. A recent pharmacokinetic study with teicoplanin was performed in anuric CAPD patients [297]. One single IV dose of 10 mg/kg teicoplanin was administered and blood and dialysate were sampled at regular time intervals for 48 h post drug infusion. Teicoplanin serum levels above 10 μg/mL, the level desired to treat systemic infections, were detected for 24 h after administration. All dialysate concentrations were very low. Teicoplanin presented two phases of elimination: an early first phase and a late second phase. Mean Cmax was 75.56 μg/mL, mean $T_{1/2}$ of the early elimination was 3.34 h, mean $T_{1/2}$ of the late elimination was 61.68 h, mean AUC-time curve was 1,491.92 mg × h/L, mean clearance rate was 10.68 mL/min, mean apparent V_d was 0.80 L/kg, and mean V_d at steady state was 0.22 L/kg. The mean dialysate excretion was only 3.16% and the peritoneal clearance was 0.023 mL/min. Teicoplanin can thus be administered at 10 mg/kg every 24 h for the therapy of systemic infections in patients undergoing CAPD. However, its IV administration should be avoided in the treatment of peritonitis, because the achieved dialysate concentrations are very low.

Table 9.8 summarizes the data with quinolones, aminoglycosides, trimethoprim-sulphamethoxazole, and miscellaneous antibiotics. Pharmacokinetic data in CAPD of some of these antibiotics have been reviewed by us [217]. Fluoroquinolones have a large antibacterial spectrum, including Gram-negative bacteria and staphylococci. Most fluoroquinolones are well absorbed after oral administration and have a favorable pharmacokinetic profile. Janknegt [298] has summarized the pharmacokinetic and clinical studies with ciprofloxacin, ofloxacin, pefloxacin and fleroxacin in CAPD patients. Fractions of dose of quinolones removed by CAPD range between 1 and 2% at 24 h after dosing [299–301], probably due to the large V_d of these agents. As the IP levels of quinolones are reportedly low during the first 24 h of oral therapy, an IP loading dose is recommended [302]. It is of note that the concomitant administration of antacids significantly reduces the gastrointestinal absorption of the quinolones.

Although in CAPD therapy with quinolones requires dose adjustment as for patients with ESRD, high drug IP concentrations can be achieved after IV or oral administration, making these substances, at least theoretically, attractive alternatives to conventional treatment of CAPD peritonitis (for review and dose recommendations see refs [298, 302]. An additional study with oral ofloxacin in peritonitis was performed by McMullin et al. [303] in CAPD patients who received once-daily 400 mg oral ofloxacin for 7 days for the treatment of bacterial peritonitis. Ofloxacin, desmethyl ofloxacin, and ofloxacin-N-oxide accumulated over the course of therapy and could still be detected in serum and dialysate 5 days after the end of therapy. The mean elimination $T_{1/2}$ of ofloxacin in serum was 32 ± 7 h, desmethyl ofloxacin 45 ± 26 h, and for ofloxacin-N-oxide 44 ± 15 h. The total mean recovery of ofloxacin and its metabolites from the dialysate was 15.4%. This regimen results in serum and dialysate concentrations likely to be effective for the treatment of infection for at least 10 days.

Ciprofloxacin pharmacokinetic data in APD (CCPD) patients after administration of two doses of ciprofloxacin 750 mg orally every 12 h were recently studied by Yeung et al. [304]. The following results were obtained: serum $T_{1/2}$ 10.1 ± 1.2 h, Cmax 2.7 ± 0.5 mg/L, T_{max} 1.6 ± 0.1 h after the first dose, and peritoneal clearance 1.2 ± 0.1% of the total body clearance. While all patients achieved serum AUC-time curve above the MIC for *Escherichia coli* and *Klebsiella* species after the first dose, only two patients achieved this goal for *Pseudomonas aeruginosa*. End-of-dwell dialysate concentrations were above the MIC for *E. coli*, *Klebsiella* species, and *P. aeruginosa* after the second dose. Ciprofloxacin in an oral dose of 750 mg every 12 h in CCPD patients may thus be useful for empirical Gram-negative coverage of CCPD peritonitis and for treatment of documented peritonitis caused by sensitive *E. coli* or *Klebsiella* species.

A recent open-label, parallel-group study determined the pharmacokinetics after a single oral 600-mg dose of garenoxacin in subjects with severe renal impairment, including patients on CAPD [305]. Compared with healthy controls, garenoxacin, AUC, and Cmax were increased by 51% and lowered by 20%, respectively, in subjects with severe renal impairment. The terminal $T_{1/2}$ was prolonged in subjects with severe renal impairment compared with

healthy controls (26.5 ± 7 vs. 14.4 ± 3 h, respectively). In subjects receiving HD or CAPD, removal of garenoxacin from systemic circulation was relatively inefficient (HD, 1.5–11.5%; CAPD, 3%), suggesting no need for a supplemental dose of garenoxacin after dialysis.

The pharmacokinetics after IP administration in CAPD have been studied for ofloxacin, pefloxacin, and ciprofloxacin; the latter has also been studied in CCPD [306]. During CAPD, the half-lives of ciprofloxacin, pefloxacin, and ofloxacin are 10, 17–21, and 25 h, respectively. Adequate peritoneal ofloxacin levels were reported in the second and third exchanges after a single IP dose of 200 mg in the first exchange [307]. For fleroxacin, a mean dialysate to plasma concentration ratio of 0.5–0.6 can be expected after a short dwell of 4 h [301]. Therapeutic concentrations in the peritoneal fluid can be achieved in CAPD patients using an oral loading dose of 800 mg fleroxacin and a daily maintenance dose of 400 mg.

Aminoglycosides

After systemic administration of aminoglycosides a substantial fraction of the administered dose is removed over 24–48 h. The peritoneal clearance adds approximately 20–30% to the total removal from the body and clinically relevant concentrations in the dialysate are achieved after IV administration. This significant peritoneal clearance is due to the low protein binding and the small V_d of these drugs. It is recommended that plasma levels should be measured regularly, especially in repeated usage [250]. For all aminoglycosides tested, an important absorption has been observed after IP administration; there is a significantly higher systemic bioavailability in peritonitis compared to nonperitonitis patients. Continuous IP administration of aminoglycosides in patients with peritonitis leads to more or less constant plasma levels and carries the risk for ovotesticular toxicity and further decrease in RRF [308]. In order to decrease this potential ototoxicity and nephrotoxicity, once-daily administration seems to be preferable. Once-daily dosing with aminoglycosides is possible due to their important post-antibiotic effect. After IP administration of 0.6 mg/kg gentamicin, $T_{1/2}$ was 35.8 h, and V_d was 0.23 ± 0.08 L/kg [250]. A higher dose, 1 mg/kg, was recommended to obtain sufficient plasma and dialysate levels during 24 h.

Kim et al. [309] found that in peritonitis, the blood levels of netilmicin after a loading dose of 100 mg IP were the same irrespective whether the maintenance dose was either 0.6 mg/kg IP once daily, or 15 mg/2 L IP, four times daily. This study suggested thus that once-daily IP or continuous IP netilmicin may be empirically recommended to CAPD peritonitis patients but that the once-daily IP method may be the most convenient method. As mentioned earlier, aminoglycoside pharmacokinetics, in particular tobramycin, have in recent years been studied in association with cephalosporins (see above).

Aztreonam, a monobactam is effective against Gram-negative bacteria, with greater safety and a more predictable action in dialysate compared to aminoglycosides. The pharmacokinetics of aztreonam have been studied after both IV and IP administration in CAPD patients. Based on these data, several authors have described favorable results in Gram-negative peritonitis, including some *Pseudomonas* infections, with the IP route of aztreonam alone [310, 311], or in combination with cefuroxime [312] or vancomycin [313, 314].

The pharmacokinetics of roxithromycin were determined following a single oral dose to patients on PD. Serum elimination $T_{1/2}$ was doubled compared to healthy individuals. Less than 5% of the dose was recovered in dialysate over 48 h, and dialysate concentrations were low. Administration every 48 h is recommended [315].

It is of note that macrolides can inhibit metabolization, and thus affect the plasma levels of many other drugs. Serious adverse interactions are therefore possible, and dose adaptations for these medications (e.g., cyclosporin, oral contraceptives) are necessary when macrolides are administered.

Azithromycin is an azalide antibiotic with a similar antibacterial spectrum to erythromycin but with greater Gram-negative activity, a more favorable pharmacokinetic profile, and with improved absorption and higher sustained tissue concentrations compared with erythromycin. The pharmacokinetics and PD clearance of azithromycin were studied following a single 500-mg oral dose of azithromycin in eight CAPD patients without peritonitis [316]. Cmax concentrations occurred at 2–3 h with 0.35–1.35 μg/mL .The mean elimination $T_{1/2}$ was 84.55 h, and plasma clearance was 21.93 L/h. This compares with values of greater than 40 h and 40.8 L/h reported in healthy volunteers. After 8 h, the mean dialysate concentration was 0.07 μg/mL; the PD clearance was only 0.06 L/h. Azithromycin is thus not substantially removed by CAPD in the absence of peritonitis and cannot be recommended for widespread use in this setting at present.

Linezolid

Only rare case reports have described the use and limited pharmacokinetic data with linezolid, an antibiotic that is indicated in vancomycin-resistant enterococci (VRE) and vancomycin-intermediate-susceptible or -resistant

staphylococci (VISA and VRSA, respectively). After either IV [317] or oral [318] administration of 600 mg of linezolid, the $T_{1/2}$ ranged between 8.7 and 8.3 h, which is longer than given by the company information. A good penetration into the peritoneal cavity was observed.

Fusidic Acid

Because fusidic acid is metabolized and excreted by the liver, it is generally assumed that renal impairment has no effect on serum concentrations. Patients on CAPD were given the same dosage regimen for seven doses [319]. Accumulation was seen and, in the majority of patients, steady-state pharmacokinetics had not been achieved by the third day. The mean Cmax values for the first dose and for the seventh dose were 16.0 and 33.9 mg/L, respectively. Fusidic acid concentrations of 1.0–2.3 mg/L were detected in PD fluid in six of the seven CAPD patients. There was a tendency towards increased $T_{1/2}$ with repeated dosing. Protein-binding of fusidic acid in patient serum samples was 87.6–94.6%.

Anti-Tuberculosis Medication

An extensive in-depth review on anti-tubercular therapy in renal failure, including the pharmacokinetic aspects of these drugs in PD, has recently been published by Launay-Vacher et al. [320]. This review should be consulted for recommendations of dosing of the common and more recently developed antitubercular drugs.

Ahn et al. [321], administered nine patients on CAPD a conventional oral dose of antituberculosis medications and plasma and peritoneal fluid concentrations of isoniazid and rifampicin and pyrazinamide were measured. Average Cmax levels of isoniazid, rifampin, and pyrazinamide were 3.3, 6.5, and 30.9 mg/L, respectively, all of which much exceed the MIC for *Mycobacterium tuberculosis*. Peritoneal fluid concentrations of isoniazid and pyrazinamide were maintained well above the MICs for *M. tuberculosis*; however, the dialysate concentration of rifampicin was below the therapeutic range most of the time. Thus, for the treatment of systemic or pulmonary tuberculosis in CAPD patients, no dose adjustments are required for isoniazid, rifampicin, or pyrazinamide but for the treatment of tuberculous peritonitis, oral rifampin therapy is not expected to be effective because of its low peritoneal fluid concentration.

The two agents used in anaerobic infections, metronidazole and ornidazole, have a low peritoneal clearance and only 10 and 6% of the dose, respectively, are removed by the peritoneum [322, 323]. The dosage in CAPD patients is therefore the same as in undialyzed, uremic patients [324].

Table 9.9 summarizes the data for antiviral and antifungal drugs. An extensive recent review of antiviral drug therapy, including pharmacokinetic data in renal failure and dialysis is available [325].

Acyclovir has significant activity against HSV-1, HSV-2, and Varicella zoster virus (VZV). Acyclovir seems to have a three-compartment pharmacokinetic profile in CAPD patients [326]. Mean total plasma clearance was 46 mL/h/kg, 12% of which was due to PD. Acyclovir has an apparent V_d of 62.5 L, with a protein binding of less than 20%. It was found [327] that the doses recommended for ESRD patients (1,600 mg) led to supratherapeutic levels of acyclovir in CAPD patients, increasing the risk of neurotoxicity, which was reported in two patients [328]. Based on computer modelling, a daily oral dose of 600–800 mg is recommended [327].

As mentioned above, acyclovir-induced neurotoxicity is reported to be associated with high serum drug levels even when following the recommended reduced doses for this renal failure population. In view of the high oral bioavailability of valacyclovir (the L-valyl ester of acyclovir), the risk of neurotoxicity becomes more prominent [329]. In 12 CAPD patients who were administered a single oral dose of 500 mg valacyclovir, acyclovir was analyzed. High interpatient variations were observed with acyclovir apparent total clearance values of 7.238 ± 4 L/h and $T_{1/2}$ values of 22.27 ± 16.82 h. However, dosage simulations confirmed supratherapeutic acyclovir concentrations for all participants when following the recommended dose of 1,000 mg valacyclovir/24 h for varicella-zoster infections.

Ganciclovir is extensively used as an antiviral agent for cytomegalovirus (CMV) infections in immunocompromised patients. Sommadossi et al. [330] reported higher, although highly variable, values for V_d in patients with renal failure (V_d 0.41 ± 1.5 L/kg) compared to normal volunteers. Ganciclovir has a low molecular weight and a low protein binding (1–2%) and is thus effectively cleared by HD. However, due to the large V_d compared to the dialysate volume, removal of ganciclovir by PD is negligible, and the doses should be adapted as for patients with renal failure. It is of note that, due to an important tubular secretion, CAPD patients with RRF have a ganciclovir clearance higher than the creatinine clearance [331].

Izzedine et al. described the pharmacokinetics of ritonavir and nevirapine in a CAPD patient suffering from HIV infection [332]. Ritonavir does not appear in the peritoneal dialysate, but like in the study by Taylor et al. [333], the dialysate concentration of nevirapine was almost 50% of the plasma concentration so that monitoring of plasma levels during therapy with this drug in CAPD patients with HIV is recommended. In the study by Taylor et al. [333] the

pharmacokinetics of nelfinavir (1,250 mg bid) were also described. Nelfinavir, like ritonavir, does not cross the peritoneal membrane due to its large size and high protein binding.

Cidofovir

Brody et al. [334] found that in patients receiving cidofovir that the mean cidofovir clearance in subjects with normal renal function was 1.7 ± 0.1 mL/min/kg, which decreased with declining renal function as indicated by the regression equation. The mean V_d at steady state did not change significantly in subjects with kidney disease and cidofovir serum elimination $T_{1/2}$ was significantly increased in subjects with severe renal impairment. Cidofovir was not significantly cleared during CAPD. It was concluded that in patients with varying degrees of renal insufficiency aggressive dosage reduction of cidofovir is necessary.

Oseltamivir is an antiviral drug used in prophylaxis and therapy for influenza and its dose reduction is recommended for patients with ESRD. However, dosing recommendations are not available for treatment or prophylaxis of influenza in these patients. Robson et al. [335] assessed the pharmacokinetics and tolerability of oseltamivir in patients undergoing HD and CAPD. In this open-label, multiple-dose study, patients received 30 mg oral oseltamivir suspension over 6.5 weeks. This dose was predicted to be suitable for ESRD patients based on a two-compartment model. CAPD patients received six doses given once weekly after a dialysate exchange. In CAPD patients, mean Cmax after the first and sixth doses were 885 and 849 ng/mL, respectively. The mean AUC values for days 1–6 and days 36–43 were 33,400 and 32,400 ng h/mL, respectively. Oseltamivir was well-tolerated. In conclusion, a 30-mg dose of oseltamivir given once weekly in CAPD provides sufficient exposure to oseltamivir carboxylate to allow safe and effective anti-influenza treatment and prophylaxis.

No pharmacokinetic data for PD patients are available for foscarnet, and dose adaptations are recommended as in ESRD. One case report described a serum $T_{1/2}$ of 45.8 h for a patient on CAPD (normal renal function 4.5 h). CAPD clearance of foscarnet was calculated to be 4.5 mL/min with a total clearance of 8.8 mL/min [336].

Studies in a limited number of CAPD patients treated with zidovudine suggest that no further modification from the renal failure dosage regimen is necessary [337, 338]; however, great interpatient variability in its pharmacokinetics was noted [338].

Didanosine is an antiretroviral agent used for treatment of HIV infections. In patients with renal failure, elimination $T_{1/2}$ was reported to be prolonged to 3.6 ± 0.8 h as compared to 1.5 ± 0.5 h in normal renal function. CAPD has little effect on the removal of didanosine; dose reduction to one-fourth of the daily dose is thus recommended (a single administration), in patients on CAPD as well as in nondialyzed end-stage renal failure patients [339].

Antifungal Drugs

Information on the pharmacokinetics of antifungal drugs in PD patients is disappointingly scarce. Most studies are limited to occasional measurements of serum and/or dialysate levels during treatment for fungal peritonitis.

Amphotericin (AmB) is highly protein-bound and circulates in the blood in a complex of high molecular weight (200,000–300,000). It penetrates very poorly in the peritoneal fluid after systemic administration. The data are, however, conflicting [340–342]. Chemical peritonitis causing abdominal pain after IP administration of AmB B has been observed [252–255]. It has been proposed that for IP use the dialysate should be adjusted to a neutral pH to prevent aggregation [343]. AmB has been used in an IV dose of 0.5 to 1 mg/kg body weight, combined with an IP dose of 2–3 mg/L dialysate [344]. AmB induces the formation of pores and channels in the cell membrane, causing leakage of potassium and magnesium. This is probably the reason why the drug increases transcapillary ultrafiltration (see Part I, above); however, the chemical drug-induced peritonitis may also play a role in this phenomenon [345]. Studies of the absorption of AmB B after IP instillation are lacking, although the large V_d and the high protein binding are expected to favor its transfer to the blood stream.

Systemically administered fluorocytosine penetrates well into the peritoneal fluid [341]. The usual loading dose of 20–30 mg/kg in uremic patients is followed by a maintenance doses of 15 mg/kg. Serum levels of fluorocytosine should be monitored since toxicity is expected when serum levels exceed 100–125 μg/mL. This has mainly been tried with IP administration of 100–200 mg/2 L, together with IV AmB B [255, 346] or in a dose of 150 mg/L in combination with oral ketoconazole 400 mg daily [347].

Fluconazole is effective for both superficial and systemic fungal infections. The pharmacokinetic profile of orally administered fluconazole shows a low plasma protein binding, and a long plasma $T_{1/2}$, allowing once-daily dosing. The bioavailability is excellent. A good penetration of fluconazole into the dialysate after a single oral dose of 100 mg in

CAPD patients has been found [348]. When given systemically the dose should be the same as in undialyzed patients [349]. With IP administration the recommended dose is 150 mg in a single 2 L dwell, every 48 h.

Dahl et al. [350] investigated the pharmacokinetic characteristics of IP fluconazole in APD (CCPD). Five patients received a single dose of IP fluconazole 200 mg during their long daytime dwell. The bioavailability of IP fluconazole was $96 \pm 2\%$ over a 12-h dwell, absorption $T_{1/2}$ was 2.5 ± 1.2 h, serum elimination $T_{1/2}$ was 71.65 ± 12.76 h, and V_d was 0.66 ± 0.13 L/kg. Peritoneal clearance was 5.96 ± 0.93 mL/min and proportional to the total dialysate volume. Renal clearance was proportional to renal creatinine clearance. Current treatment guidelines for fungal peritonitis suggest fluconazole 200 mg intraperitoneally every 24 h. These data suggest that this dose, administered every 48 h, is more than sufficient to maintain serum and peritoneal concentrations above the MIC for most *Candida* species.

A single-dose pharmacokinetic study of itraconazole has been performed in patients with ESRD, including five CAPD patients [351]. The systemic pharmacokinetics of itraconazole were not affected by CAPD and the drug could not be detected in the dialysate. Oral administration of ketoconazole in CAPD patients revealed extremely low peritoneal clearances [253, 260]. After oral administration of 400 mg ketoconazole, Johnson et al. reported mean serum concentrations of 2.3 μg/mL, while the D/P ratio was only 0.03 after 5 h.

Table 9.10 covers the drugs used in gastroenterology. H2 antagonists are frequently described in dialysis patients. Studies have been performed with cimetidine, ranitidine, and famotidine [352–355]. Dosage reduction necessary for undialyzed patients, should be applied for patients on PD. No pharmacokinetic data on nizatidine or roxatidine in CAPD are available and it can be presumed that these drugs have a negligible peritoneal clearance.

To our knowledge omeprazole, a proton-pump inhibitor, has not been studied in CAPD patients. In patients with ESRD its pharmacokinetics are not significantly different from those in healthy subjects and the drug is not detected in dialysis fluid during HD [356]. One can therefore expect that omeprazole could be administered in uremic and CAPD patients at the usual dose of 20 mg/day. Lansoprazole and pantoprazole are also completely metabolized. The elimination $T_{1/2}$ of lansoprazole seemed to be prolonged in patients with moderate, but not in those with severe renal dysfunction. HD did not seem to influence the plasma concentrations of lansoprazole, probably due to a very high protein binding (97–99%) [357]. Lansoprazole also has some renally cleared active metabolites. The data with pantoprazole in patients with renal impairment are difficult to interpret, and further studies are required to clarify the controversial observations made until now [356].

With cisapride, a gastrokinetic drug, in a dose of 5 mg/L dialysate four times per day, excellent results were obtained in two diabetic CAPD patients suffering from gastroparesis. The IP dose produced the same plasma levels as the oral or IV doses of 30 and 10 mg, respectively [358]. In HD patients the terminal $T_{1/2}$ of cisapride was 9.6 ± 3.3 h and the V_d was 4.8 ± 3.3 L/kg. Cisapride was not found in the dialysate, in contrast with its metabolite norcisapride. The authors conclude that dose adaptation is not necessary [359].

Table 9.11 summarizes the data of IV erythropoietin (Epo)(11a), subcutaneous Epo(11b), and IP Epo(11c). A number of interesting pharmacokinetic studies have been performed with Epo in PD. With subcutaneous (SC) administration, Epo is slowly absorbed with a Tmax around 20–24 h. The SC bioavailability compared to IV dosing ranges between 10 and 36%. PD itself has no significant effect on the removal of Epo.

Human pharmacokinetic studies on IP administration of Epo show a very low bioavailability (ranging from 2.5 to 8.5%) when diluted in 2 L of dialysate, but this increased to $41.4 \pm 7.2\%$, when administered into a dry abdomen [360, 361]. The problem of low bioavailability of IP Epo when diluted in dialysate, can be overcome by using high dosages of Epo or low volumes of dialysate. Frenken et al. [362] utilized 100 U/kg intraperitoneally, diluted in 1 L of dialysate over a 9 h dwell thrice weekly and observed a slow but significant increase in hematocrit; Nasu et al. [363] reported an excellent hematocrit response when Epo in a high dose of 300 U/kg, diluted in 2 L dialysate, was given.

Bioavailability is further improved by instilling the dose into a dry peritoneum [364]. The pharmacokinetics of a single 100-U/kg IP Epo alfa in eight CAPD patients was studied after the instillation into a dry peritoneum and allowing a dwell for 8 h. CAPD was then resumed. A 14-h effluent dialysate sample was collected to determine Epo alfa recovery. The extent of Epo alfa absorption was significantly greater than previously reported for a 4-h dry dwell. The mean dose-normalized AUC using the 8-h dry dwell dosing technique was $6{,}331 \pm 2{,}536$ mIU · h/mL which was significantly greater than the value of $2{,}589 \pm 1{,}450$ mIU · h/mL from a previous study using a 4-h dry dwell. The absorption of Epo alfa administered by IP route is thus improved by extending the time the dose resides in a dry peritoneum.

To establish the effectivity of administration of IP Epo in a small amount of fluid in children with renal anemia on CAPD, it was found [365] that administration of Epo in a specially designed bag containing 50 mL NaCl 0.9%. leads to a decrease in the required dose from 262 to 194 U/kg/week while hemoglobin levels remained stable.

To compare the efficacy of IP and SC administration of Epo alfa, a 32-week prospective, randomized, crossover study was designed [366]. Twenty adult PD patients receiving stable doses of SC Epo alfa were enrolled in the study and were randomly assigned to receive either SC or IP Epo at the start of the study. Dose adjustments were made to

maintain baseline hematocrit ± 3%. Following 16 weeks of treatment, patients crossed over to the other route for an additional 16 weeks. IP Epo alfa was administered into an empty peritoneal cavity for approximately 8 h before resuming dialysis. End-of-study IP Epo alfa doses required to maintain target hematocrit were given twice weekly ($n = 1$), once weekly ($n = 11$), or once every other week ($n = 1$). The AUC for IP Epo alfa was larger than for SC administration and the slope of the 16-week dose-requirement curve was greater for IP administration, suggesting greater dose stability for SC administration. Paired analysis indicated greater IP intrapatient dose requirements. The mean difference in SC versus IP doses was 5,000 ± 1,510 U/week. It was concluded that IP Epo alfa may be a suitable alternative for some patients for whom SC dosing is undesirable. Darbepoetin (DarbEpo) is a hyperglycosylated analogue of recombinant human Epo which has an increased terminal $T_{1/2}$ in animal models. Macdougall et al. [367] extended these observations to humans. The single-dose pharmacokinetics of Epo alfa (100 U/kg) and an equivalent peptide mass of DarbEpo were compared following IV bolus in 11 stable PD patients. This was followed by an open-label study to determine the single-dose pharmacokinetics of an equivalent peptide mass of DarbEpo by SC injection in six of these patients. The mean terminal $T_{1/2}$ for IV DarbEpo was threefold longer than for IV Epo (25.3 versus 8.5 h), a difference of 16.8 h. The AUC-time curve was significantly greater for DarbEpo and the clearance was significantly lower (1.6 ± 0.3 versus 4.0 ± 0.3 mL/h/kg). The V_d was similar for both preparations. The mean terminal $T_{1/2}$ for SC DarbEpo was 48.8 h. The Cmax of SC DarbEpo was approximately 10% of that following IV administration, and bioavailability was approximately 37% by the SC route.

To characterize the pharmacokinetics of DarbEpo alfa and covariate relationships in HD and PD patients, Takama et al. [368] recently collected data from 63 HD and 68 PD patients who received IV DarbEpo alfa and applied pharmacokinetic modelling to them. The results of this analysis suggest no dosage regimen change is warranted for DarbEpo alfa in HD and PD patients over the range of distribution of covariates included in this study.

IP administration of iron dextran leads to an efficient absorption of iron. However, severe toxicity to the peritoneal membrane was found, precluding the use of concentrations higher than 2 mg/L [369]. Until now, intraperitoneal administration of iron dextran seems not to be recommendable.

Recombinant Human Growth Hormone (GH)

GH therapy is effective in the treatment of growth failure related to GH resistance among children with chronic renal failure. Recombinant human GH (MW 21,000) was intraperitoneally instilled and showed an immediate absorption with peak serum GH levels obtained between 4 and 8 h following administration [370]. It is highly probable that this drug is, at least partly, transported via the lymphatics. However, the traditional route of administration of GH is SC injection. A study [371] explored the effectiveness and tolerability of IP administration of GH in prepubertal PD patients. Peak serum GH was achieved 4 h after administration and serum $T_{1/2}$ was 4.6 h. The mean height velocity increased from a baseline of 4.6 to 8.5 cm/yr in year 1 and 6.1 cm/yr in year 2. This study suggests, thus, that the IP route of administration of GH can be utilized in the treatment of short stature among children requiring PD therapy.

Relevant to IP therapy with Epo and growth hormone is the study by Schroder et al. [372] who performed an in vitro study in which radiolabeled Epo and recombinant human growth hormone were added to small-volume (50- and 250-mL) dialysis bags. Recovery was measured after 15-min dwells. It was found that the adsorption of Epo and growth hormone was minimal (less than 7%). This finding provides another argument in favor of IP therapy in pediatric PD.

Table 9.12 summarizes data for miscellaneous drugs. An interesting observation was made on the removal of ethosuximide and phenobarbital in an epileptic child by PD [373]. During a peritonitis episode, the daily dialysis time of 8 h (CCPD) was increased to 24 h and the patient developed convulsions. Apparently, a substantial amount of both anticonvulsant medications was removed via the peritoneal dialysate and supplementary doses of both drugs were needed to stabilize the patient.

Leakey et al. [374] described a 3-year-old asthmatic boy who developed acute renal failure, necessitating acute PD. His plasma theophylline concentrations remained therapeutic; yet the child developed the symptoms of theophylline toxicity while undergoing PD. Excessively high plasma concentrations of the principal theophylline metabolite, 1,3-dimethyluric acid, were found. The high concentrations decreased only when renal function recovered. Apparently PD is not able to remove this theophylline metabolite.

In a pharmacokinetic study of flurbiprofen, CAPD patients were used as representative patients with ESRD. Neither flurbiprofen nor its metabolites were detected in the dialysate [375].

PD patients have a decreased clearance of ethinyl oestradiol, leading to slightly higher serum concentrations compared to women with normal renal function [376]. Serum $T_{1/2}$ was 8.4 ± 4.1 versus 3.4 ± 1.6 h in PD patients and normal individuals, respectively, after a single oral dose, and 15.7 ± 3.3 vs. 14.3 ± 2.3 after multiple dosing.

Data on the pharmacokinetics of benzodiazepines in PD are scarce but CAPD patients had longer serum half-lives than controls and HD patients [377]. There were also higher free fractions of the drug. CAPD patients should thus be monitored for side-effects and the dose should be adjusted accordingly. Dose modification may not be necessary in renal failure for midazolam [378], but some reports of sustained activity of midazolam due to accumulation of metabolites in renal failure were reported in ICU patients with renal failure [379]. Zolpidem is an imidazopyridine that differs in structure from benzodiazepines and is approximately 92% protein bound. The free fraction increases to 14.9% in uremic patients, while the V_d increases, and elimination $T_{1/2}$ doubles [380]. Although exact data are not available, dose reduction in CAPD patients seems to be prudent.

Morphine

Conjugation with glucuronic acid represents the major route of biotransformation of morphine and the glucuronides, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), are eliminated via the kidneys. Chronic renal failure should thus affect the disposition of M3G and M6G. Some patients undergoing long-term PD require pain treatment with morphine and the pharmacokinetics of morphine and its metabolites in CAPD patients after a single IV dose of 10 mg morphine-hydrochloride were investigated [381]. While the systemic clearance of morphine (1,246 $\pm$ 240 mL/min) was in the range observed in patients with normal kidney function, both M3G and M6G showed substantial accumulation. The AUC ratio of M3G:morphine and of M6G:morphine was 5.5 and 13.5 times higher than in patients with normal kidney function. Renal clearances of morphine, M3G, and M6G and dialysate clearances were extremely low. Therefore the accumulation of M6G and M3G in kidney failure is not compensated by CAPD.

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil is a prodrug of the immunosuppressive agent mycophenolic acid (MPA). It is rapidly converted to MPA following oral ingestion. MPA is metabolized to MPA glucuronide (MPAG), which is renally excreted. After initiation of PD in patients with a GFR $<$ 10 mL/min, the AUC substantially decreased. The calculated clearance increased from 8.1 mL/min/kg in nondialyzed patients to 14.6 mL/min/kg in CAPD patients. MPA itself was found in only trace amounts in the dialysate. However, MPAG was found to be removed by PD for up to 2 g/12 h, representing removal of 1.2 g of MPA [223]. MacPhee et al. [382] examined the pharmacokinetics of MMF after an overnight fast of a single oral dose of 1 g in patients on HD or on PD. Plasma concentrations of MPA and MPAG were measured from 0 (predose) to 36 h after administration. The mean AUC for MPA was 55.7 $\pm$ 32.6 mg/L/h for HD patients and 44.7 $\pm$ 14.7 mg/L/h for PD patients, which is similar to the expected values for subjects with normal renal function. The mean Cmax for MPA was lower than would be expected for subjects with normal renal function (16.01 $\pm$ 10.61 mg/L for HD, 11.48 $\pm$ 4.98 mg/L for PD). MPAG clearance was prolonged with AUC approximately five times what would be expected in subjects with normal renal function. No MPA was detectable in HD or PD fluid, but small amounts of MPAG were detected in PD fluid in 3 out of 10 subjects. The accumulation of MPAG may be responsible for the poor gastrointestinal tolerance of this drug in dialysis patients and probably limits the maximum dose of MMF that can be tolerated.

Vitamin D Analogues, Bisphosphonates, and Cinacalcet

A recent excellent comparative review on the pharmacokinetics of vitamin D analogues in patients treated with HD and PD was published by Bailie and Johnson [383]. This review summarizes also the studies performed with the vitamin D analogues in CAPD patients, discussed in the previous edition of this book.

CAPD treatment is associated with peritoneal losses of vitamin D metabolites, contributing to the low serum levels of 25-OH-D3 and 25-OH-D binding capacity; losses of 1,25(OH)2D3 and 24,25(OH)2D3 in the dialysate average 6–8% of the plasma pool per day [384, 385].

IP calcitriol (CT) raises serum calcium and depresses serum PTH more effectively than increasing dialysis fluid calcium [386]. The CT and alfacalcidol should, however, be injected directly through the catheter port and not into the dialysate, as a substantial amount is otherwise adsorbed to the PVC bags [387, 388]. Salusky et al. [388] have studied the pharmacokinetics of CT after IV, oral, and IP administration of 60 ng/kg in CAPD and CCPD patients. The serum CT levels were similar after 24 h for the different routes of administration. The bioavailability of CT (AUC 0–24 h) was 50–60% greater after IV than after oral or IP administration. Comparable results were obtained by Joffe et al. [384], who determined appearance of 1,25-OH vitamin D3 after oral, IV, and IP administration of alfacalcidol [384].

Murakami et al. [389] recently investigated whether transperitoneal absorption of maxacalcitol (22-oxacalcitriol ; OCT) inhibited intact parathyroid hormone (i-PTH) in CAPD patients when the OCT was added to the PD fluid.

After injection of 20 μg of OCT into the peritoneal cavity of CAPD patients, the mean concentration of OCT in PD fluid rapidly decreased, from 25,268 pg/mL at 0 h to 1,694 pg/mL at 2 h and 44.9 pg/mL at 4 h. In contrast, the mean serum OCT level increased from the pretreatment level, which was below the detection limit of the assay, to 656 pg/mL at 0.5 h and a peak of 759 pg/mL at 1 h, and thereafter gradually decreased, to 713.8 pg/mL at 2 h and 555.8 pg/mL at 4 h. Mean i-PTH significantly decreased, to 83.9% of the baseline level at 1 h and thereafter stayed at around 90%. No consistent trends in calcium and phosphate levels were observed in these patients. Injecting OCT into the peritoneal cavity can thus significantly decrease i-PTH levels. Hamada et al. [390] evaluated the stability of physiological activities of CT and OCT in PD bags and to determine the CT or OCT dosage for IP administration: CT 1.5 μg or OCT 10 μg were added to different PD solutions, contained in different containers. Although the levels of CT and OCT in PD bags made of polyvinyl resins decreased by 70–75% immediately after injection, levels in PD bags made of polypropylene resins decreased only slightly. The concentration of CT mixed into the acidic solution in glass containers was stable; the decreased concentration of CT in the PD solution might be due to adsorption onto polyvinyl resins. The results showed good peritoneal transport of OCT but not rapid disappearance, unlike after IV administration. If peritoneal administration of vitamin D derivatives is contemplated, it is important to select the composition of the PD bag resins, the type of vitamin D analog, and time lag to use when deciding the dosage of injectable vitamin D preparations, such as OCT or CT. It appears that IP administration in overnight dwells might be useful for PD patients as a complementary vitamin D preparation.

Biphosphonates are becoming increasingly popular for treatment of osteoporosis, morbus Paget, and hypercalcemia. An excellent review on the use of these drugs including PD patients has been published by Rodd [391]. In general it must be remembered that these drugs are poorly eliminated across the peritoneal membrane after IV administration and that the doses should be reduced as in patients with ESRD without PD.

The major route of elimination of clodronate is renal excretion. Hence, the dose of clodronate should be reduced in renal failure. In one study [392], CAPD removed clodronate poorly from the circulation (7% of administered dose over 24 h), and most of the clearance was attributed to skeletal deposition of the drug. This uptake was related to parathormone levels. Clearance of clodronate after a single IV injection was 2.4 ± 0.6 mL/min. The V_d was 0.49 ± 0.34 L/kg, and elimination $T_{1/2}$ was 16.9 ± 4.7 h. D/P for clodronate was approximately 0.4 after a 6-h dwell. Data on pamidronate in PD are not available, but most probably the same recommendations as for clodronate can be made, and dose adaptations as in patients with severe renal failure should be made.

The pharmacokinetics and dynamics of cinacalcet in ten CAPD patients were recently studied [393]. Following single-dose administration of cinacalcet, there was no evidence of increasing exposure with increasing degree of renal impairment, and the pharmacokinetic profile was similar for all subjects regardless of whether they were receiving HD or PD. Protein binding of cinacalcet was similar in all groups and the level of renal function did not affect the pharmacodynamics (as determined by intact parathyroid hormone and calcium levels). No serious adverse events occurred during either study. Therefore, the dose of cinacalcet does not need to be altered for degree of renal impairment or dialysis modality.

Insulin

Insulin is one of the most commonly administered IP drugs in PD patients. Earlier studies demonstrated that IP insulin is absorbed into the portal venous circulation [394] and that IP insulin leads to a persistent positive portal–systemic difference [395]. A substantial portion (50%) of the portal venous insulin is degraded during first passage through the liver. Such IP treatment appears to improve glucose control and glucose stability without increasing the risk of hypoglycemia [396–400]. The intrapatient variation of the plasma-free insulin was markedly lower with continuous IP than with continuous SC or intramuscular insulin administration [401, 402]. This could be attributed to the considerably smaller insulin depot after IP administration. IP insulin administration is most effective in patients on PD if it is given into an empty peritoneal cavity, at least 30 min before the dialysate is instilled [403]; this creates a high peritoneum to plasma concentration gradient and avoids the adsorption of insulin to the peritoneal fluid bags. When radiolabeled insulin was added to the 2-L dialysate bags only 35% of the dose entered the peritoneal cavity [404]. In contrast, about 84% of 16 U of unlabeled insulin added per bag reached the peritoneal cavity when administrated directly through a port on the Tenckhoff catheter [405]. IP insulin is rapidly absorbed and is detected in the peripheral blood within 15 min of administration, and peak serum insulin levels are observed 30–45 min after administration into an empty peritoneal cavity [235]. These peak values are delayed until 90–120 min when insulin is added to the dialysate [406]. However, due to the partial hepatic inactivation of IP insulin, absorption kinetics and efficacy of IP and systemic insulin are difficult to compare by measurement of peripheral blood insulin levels. Wideroe et al. [235] found that fluid volume and osmolality of the solution in the peritoneal cavity decrease the transport rate of insulin, but not its bioavailability. A better blood glucose regulation after 120 min was found with IP administration in

dialysate as compared to administration into an empty abdomen [235]. A recent review [407] has covered the most important aspects of insulin administration to PD patients.

Peroxisome Proliferator-Activated Receptor (PPAR)γ Agonists

Pharmacokinetic profiles of PPARγ agonists make these drugs potentially suitable for their use in patients with type 2 diabetes and patients with chronic renal failure with and without dialysis (for review see [408]). Furthermore, the available glitazones have an adequate oral bioavailability and are extensively metabolized by the liver. Rosiglitazone is mainly metabolized by cytochrome P450 (CYP) 2C8 into inactive metabolites. Less than 1% of the parent drug appears in the urine in unchanged form [408, 409]. Both total and unbound plasma concentrations of rosiglitazone after a single 8-mg oral dose were not affected by the presence of mild, moderate, and severe renal insufficiency, thus indicating that the starting dose of rosiglitazone needs not be adjusted in patients with renal impairment [410]. Moreover, similar values of AUC–time curve, maximum Cmax concentrations, and $T_{1/2}$ were observed in a group of ten HD patients (nondialysis day) in comparison with a group of healthy individuals after a single 8 mg oral dose of rosiglitazone. Metabolites of pioglitazone are more active and are excreted predominantly in the bile. Both pioglitazone as its metabolites do not accumulate in chronic renal failure. The pharmacokinetic profile of pioglitazone was similar in healthy subjects and in patients with moderate and severe renal failure [411].

PPARγ agonists therapy in dialysis patients has shown adequate safety and tolerance profiles. In the study of Manley and Allcock [412], there were three hospitalizations for new or worsening congestive heart failure (CHF) in a group of 40 HD patients with type 2 diabetes treated with glitazones. Interdialytic weight gain significantly increased, 0.3 kg in rosiglitazone-treated patients. Rosiglitazone therapy has been well tolerated in both diabetic and nondiabetic uremic patients on CAPD. Edema in lower extremities and weight gain in approximately 2% of the patients have been reported [413, 414]. Altogether, these results suggest that PPARγ agonists might be an adequate alternative in the antihyperglycemic therapy of diabetic patients with CRF, regardless of the treatment used for renal failure. According to the American Heart Association and the American Diabetes Association recommendations, in patients without clinical data of CHF, but with one or more risk factors for its development, as it is the case in CRF patients, therapy with glitazones should be initiated at low doses, i.e, rosiglitazone 4 mg/day and pioglitazone 15 mg/day. The increases in dose should be gradual, with tight monitoring for signs of excessive weight gain, peripheral edema, and/or CHF [415].

Heparin

Heparin has an average MW of 15 kDa and consists of a heterogeneous group of anionic mucopolysaccharides, called GAGs (see Part I of this chapter). Heparin is the most frequently used drug in PD, for the purpose of preventing fibrin formation and catheter obstruction. Furman et al. [416] performed a pharmacokinetic study of IP heparin, assayed as the activated-partial-thromboplastin time (APTT) of dialysate added to control plasma. The $T_{1/2}$ of disappearance from the peritoneal cavity ranged between 8.26 and 12.77 h. Systemic blood coagulation was unaffected by a single IP dose of 10,000 U of heparin. Other investigators [417, 418] showed that heparin did transfer across the rabbit peritoneal membrane and, to a slight extent, in CAPD patients [419]. In a CAPD patient with deep-vein thrombosis, long-term IP application of low-molecular-weight (LMW) heparin in a dose of 8,000 antifactor Xa units/2 L, resulted in adequate and therapeutic plasma levels as measured by antifactor Xa units [420]. IP administration of heparin (1,000–2,500 U/L) without addition of ATIII is sufficient for prevention of IP fibrin formation in CAPD patients [419, 421].

Enoxaparin

Brophy et al. [422] studied the pharmacokinetics and pharmacodynamics of enoxaparin in healthy volunteers and HD and PD subjects. Antifactor Xa activity estimated the pharmacokinetics, whereas thrombin generation time (TGT) estimated the pharmacodynamics. Enoxaparin 1 mg/kg was given SC to all subjects. Antifactor Xa max and AUC(0-12) were similar between groups, but the TGTmax was significantly greater in the dialysis groups. The TGT remained significantly more prolonged throughout the 12-h study period, and there was a trend toward greater TGT AUC (0–12) for both dialysis groups. These results suggest that in dialysis patients, there may be accumulation of active heparin metabolites that are undetected by the antifactor Xa assay. Therefore, these subjects exhibit greater thrombin generation time prolongation despite similar antifactor Xa exposure.

Thrombin Inhibitors

Ximelagatran is an oral direct thrombin inhibitor and may be used as an anticoagulant for the prevention and treatment of thromboembolic disease. After oral administration, ximelagatran is rapidly absorbed and bioconverted to its active form, melagatran. Eriksson et al. [423] studied the pharmacokinetics of this drug in volunteers with norma and impaired renal function. All volunteers received, in a randomized sequence, a 3-mg SC injection of melagatran and a 24-mg immediate-release tablet of ximelagatran. In renal failure, the AUC and the $T_{1/2}$ of melagatran were significantly higher than in the group with normal renal function. This result was related to the decreased renal clearance: 12.5 and 81.3 mL/min after SC administration of melagatran and 14.3 and 107 mL/min after oral administration of ximelagatran, respectively. Ximelagatran and melagatran were well tolerated in both groups. It was concluded that after administration of SC melagatran and oral ximelagatran, subjects with severe renal impairment had significantly higher melagatran exposure and longer $T_{1/2}$ because of lower renal clearances of melagatran compared with the control group with normal renal function. These results suggest that a decrease in dose and/or an increase in the administration interval in patients with severe renal impairment would be appropriate. Pharmacokinetic studies in PD have not yet been performed with these drugs.

Desferrioxamine

A pharmacokinetic study of desferrioxamine and its iron and aluminium chelates has been performed in CAPD patients [424]. Desferrioxamine (10 mg/kg) was administered either intramuscularly or intraperitoneally. The AUC calculated from 0 to 12 h was about 20% lower after the IP than after the intramuscular administration. An advantage of the IP administration was, however, the progressive increase in plasma concentrations, without an unduly high peak. The fact that 8–12 h after administration the concentrations of desferrioxamine in plasma and peritoneal fluid were approximately the same, is consistent with the low binding of desferrioxamine to plasma proteins.

Desferrioxamine was given IV and IP in a CAPD patient in order to remove iron. Forty-five percent of the total amount instilled was recovered in the outflow dialysate [425]. An IP dose of 750 mg/day or 1,250 mg on alternate days led to removal of 73 and 39.6 mg iron, respectively, as compared with 75 mg removal per week after an IV dose of 1,500 mg thrice weekly. Several authors have used IP desferrioxamine successfully to remove aluminium in PD patients [426–428]. IP doses of 40 mg/kg were used over a 10-h dwell in one study [427] and 0.5 g into each 2 L dialysate to a total dose of 6 g was applied in another study [429]. In the latter study the aluminium clearance with desferrioxamine was 3.1 versus 2.5 mL/min without desferrioxamine. The enhanced removal of aluminium by PD persists for several days after a single administration of the chelator.

Anticancer Drugs

For cancers that have disseminated to the peritoneal surfaces, IP chemotherapy results in high drug concentrations locally with low systemic toxicity. Using a rat model, Mohamed et al. [430] compared the pharmacokinetics and tissue absorption of paclitaxel infused intraperitoneally in two isotonic carrier solutions: 1.5% dextrose PD solution and hetastarch (6% hydroxyethyl starch), a high-molecular-weight solution. The mean total quantity of drug remaining in the peritoneal cavity was significantly greater with hetastarch at 12 and 18 h. There was a 105% increase in the AUC ratio of peritoneal fluid to plasma paclitaxel concentrations with hetastarch versus PD. The use of IP paclitaxel with hetastarch carrier solution provides a pharmacologic advantage for a local-regional killing of residual tumor cells with decreased systemic toxicity. Similar results were obtained with docetaxel [431].

Melphalan

The use of heated intraoperative IP melphalan may provide a pharmacokinetic and clinical advantage in a group of gastrointestinal cancer patients who cannot be made cancer-free with cytoreductive surgery. Thirteen patients with residual disease following cytoreductive surgery for peritoneal carcinomatosis received IP melphalan (70 mg/m^2) in 3 l of 1.5% dextrose PD solution at 41–42°C for 90 min [432]. During the 90 min of treatment 87.2 ± 4.3% of the drug was absorbed from the perfusate/peritoneal fluid and 11.9 ± 2.1% was excreted in the urine. The AUC ratio of peritoneal fluid to plasma was 33.3 ± 11.8 with an average peak plasma concentration of 0.82 ± 0.24 μg/mL occurring at 28.5 ± 13.1 min. Concentrations of melphalan in tumor nodules on the peritoneal surface were approximately ten times higher than in plasma with an average peak concentration of 7.2 ± 4.2 μg/g. It was concluded that approximately 90% of the drug was absorbed during the 90-min procedure with a 30 times greater exposure of drug at the peritoneal

surfaces than in the blood. These data demonstrate that heated intraoperative IP melphalan could have a significant impact on the treatment of peritoneal surface malignancies.

PD and Removal of Contrast Media

To examine the elimination of iomeprol, its safety in clinical use, and its peritoneal permeability in CAPD patients with variable degrees of RRF, a nonrandomized comparative study was undertaken in CAPD and HD patients [433]. In all CAPD patients, plasma iomeprol clearance was markedly slow, with a biological $T_{1/2}$ of over 32 h. Over 80% of plasma iomeprol was eliminated during the 4-h HD. The plasma iomeprol elimination rate was significantly higher from 4 h after the iomeprol administration in CAPD patients with RRF (creatinine clearance of 3.8 mL/min), compared to those with a creatinine clearance of 0.6 mL/min. However, $T_{1/2}$ in patients with RRF was over 24 h. D/P creatinine was significantly correlated with D/P iomeprol. In view of the prolonged elimination rate of iomeprol in CAPD patients both with and without RRF, a HD procedure or intensive PD just after the use of iomeprol may be advisable to promptly remove circulating iomeprol.

Another contrast medium, gadodiamide was studied by Joffe et al. [434] in patients with severely reduced renal function (GFR, 2–10 mL/min), patients on HD, and patients on CAPD. Gadodiamide injection caused no changes in renal function. In patients with severely reduced renal function, the elimination $T_{1/2}$ of gadodiamide was prolonged (34.3 h $\pm$ 22.9) compared with data in healthy volunteers (1.3 h $\pm$ 0.25). An average of 65% of the gadodiamide injected was eliminated during a HD session, but only after 22 days of CAPD, 69% of the total amount of gadodiamide was excreted, reflecting the low peritoneal clearance. It was concluded that gadodiamide is dialyzable and can safely be used in patients with severely impaired renal function or those undergoing HD or CAPD.

Homocysteine and Vitamins

The amount of total homocysteine eliminated by PD and its relationship to peritoneal transport characteristics in CAPD have been explored by Vychytil et al. [435]. A significant influence of plasma total homocysteine concentrations, of the daily dialysate effluent volume and of the D/P creatinine on peritoneal elimination of total homocysteine was found. The daily peritoneal excretion of total homocysteine was 5.27 $\pm$ 2.81 mg. There was a positive linear association of the daily total homocysteine elimination with plasma total homocysteine concentrations. A significant linear correlation was observed between D/P creatinine and D/P total homocysteine, D/P free homocysteine, as well as D/P protein-bound homocysteine. The peritoneal elimination of total homocysteine primarily depends thus on the plasma total homocysteine concentration and elevated total homocysteine plasma levels cannot be reduced efficiently by PD.

Boeschoten et al. [436] have summarized earlier studies on vitamin status and vitamin losses in the dialysate in IPD and CAPD patients. They have performed a more complete analysis of plasma and 24 h dialysate losses of vitamin A, B1, B2, B6, B12, C, folic acid, E, and β-carotene in 44 CAPD patients. Vitamins B12, A, and E and carotenoids were not detectable in dialysate. In contrast, vitamins B2, B3, B6, C, and folic acid were excreted in the 24 h dialysate in amounts higher than in 24 h urine of individuals with normal renal function. The loss of vitamin B1 in dialysate was low. The authors recommend vitamin supplementations in CAPD patients for vitamins B1, B6, C, and folic acid.

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Chapter 10
Peritoneal Dialysis Connectology

N.V. Dombros and V. Liakopoulos

Conventionally, term *connectology* refers to the body of available information and accumulated experience on the various systems of transfer sets, connecting devices, etc., that are used during the process of peritoneal dialysis (PD). This chapter will cover connectology as it refers to continuous ambulatory peritoneal dialysis (CAPD), with only a brief discussion of automated peritoneal dialysis (APD). Acute peritoneal dialysis is not discussed.

Following the initial rapid evolution of the various systems and connections, which accompanied the development of PD as a treatment of chronic renal insufficiency, there is a relative deceleration of the evolution of PD connectology. This fact could be attributed, on one hand, to the drastic decrease of the frequency of peritonitis, but, on the other hand, to a decline of PD expansion. Lack of evidence-based information or double-blind studies on connectology reflects this stagnancy.

Short History

Georg Ganter was the first who tried to put PD in clinical practice [1]. Back in 1923, in Germany, he used a sterile solution containing electrolytes and dextrose. This solution, placed in large boiled glass bottles, was instilled into the peritoneal cavity through a simple hollow needle, with a rubber tubing serving as the conduit between the bottle and the needle. Later, in the mid-1940s in Holland, P.S.M. Kop used porcelain containers for the dialysis solution, latex tubing, and a glass catheter to instill the solution into the patient's peritoneal cavity [2]. A couple of years later, in Massachusetts, A. Seligman, J. Fine, and H. Frank improved this system by using two catheters, one for the inflow and one for the outflow procedure [3]. In 1952, Arthur Grollman described for the first time a method for intermittent PD using 1-L glass containers with a cap that connected to plastic tubing attached to a flexible polyethylene catheter with very small holes in its distal end [4].

Morton Maxwell took one step further, by developing the "Maxwell Technique." He used two custom-made 1-L glass bottles with plastic tubing and a polyethylene catheter for the inflow. After a 30 min dwell, the fluid was drained back into the two original bottles placed lower than the patient's abdomen. This system simplified PD and made it more easily available [5].

In 1960, Fred Boen, working with B. Scribner in Seattle, introduced home PD, when he developed an automated unit using 40-L "carboy" containers equipped with an automatic device that would open and close a switch to lead the fluid in and out of the peritoneum during the 24 h of dialysis. These containers were filled and sterilized at the University of Washington and then delivered to the patient's home. Peritoneal access was achieved by placing a new catheter before each dialysis (once a week at that time) and removing it afterwards [6]. Boen's system was simplified by Henry Tenckhoff, working in the same center in 1963. He used a reverse osmosis water purification system mixed with a concentrated peritoneal fluid and a simple automatic PD machine. Later, Tenckhoff improved the silicone catheter originally developed by Russell Palmer [7] and completed an intermittent PD system [8]. During the same time, Norman Lasker in New Jersey introduced the first peritoneal cycler that used 2-L glass bottles and instilled warm dialysate in the peritoneal cavity [9].

In 1975, in Austin, Texas, Jack Moncrief and Robert Popovich conceived the method of CAPD using two 1-L glass bottles, plastic tubing, and Tenckhoff's catheters [10, 11]. However, a high incidence of peritoneal infections was the major drawback of their method (Fig. 10.1).

N.V. Dombros (✉)
Professor of Internal Medicine/Nephrology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
e-mail: ndombros@med.auth.gr

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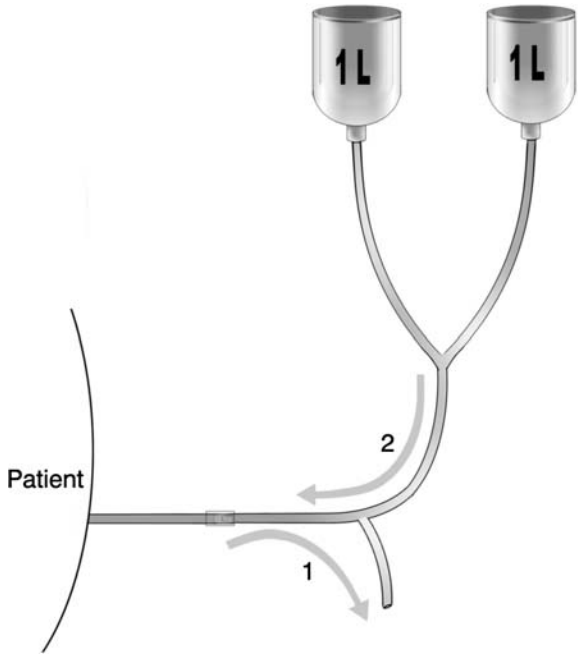

Fig. 10.1 The original CAPD system by R. Popovich and J. Moncrief

In the early 1970s, Dimitrios Oreopoulos had established a 70-patient intermittent PD program in Toronto Western Hospital, using Lasker's cyclers and Tenckhoff's catheters. He was using collapsible 2-L bags. Adopting the idea of CAPD, Oreopoulos developed a tubing with a spike on the one end, to fit into the bag, and a male press fitting on the other, to fit into the catheter. The empty dialysate bag was rolled up and remained attached to the patient's body until the next bag exchange. At that time, all 70 patients in the Toronto Western Hospital intermittent PD program were converted to CAPD. This gave a major push to the then newborn method, particularly because the peritonitis rate was reduced drastically from one episode per 10 weeks to one episode per 8–11 months [12]. "Peritoneal dialysis was here to stay" [13].

Ideal PD Delivery Systems

A PD system should be characterized by reliability, simplicity, ease of use, and acceptable cost. Its materials should be durable, biocompatible, easily disposable, and recyclable. Furthermore, the connection system should not add to the aesthetic drawback of the presence of the peritoneal catheter in the patient's abdomen. Most importantly, a PD system should be safe and effective in preventing PD-related infections.

Description of Various Delivery Systems

CAPD delivery systems include:

Nondisconnecting systems:

- Collapsible bags with simple spike (or Luer lock)
- Collapsible bags with simple spike and germicidal ultraviolet (UV) chamber
- Collapsible bags with simple spike and thermoclave
- ANDY® system (Y-set system)

Disconnecting systems:

- Y-set systems
- O-set systems (a subclass of the Y-set systems)
- T-set systems (a subclass of the double-bag systems)
- Double-bag (or twin-bag) with Y-set systems
- UV flash® system (Y-set sterilized by UV light)
- Safe lock®
- Safe lock 5F®
- ANDY-disc® system (double-bag Y-set system)
- Stay-Safe®
- UltraBag®
- Delta 4 system
- Gemini
- Gambrosol® Trio

The first PD delivery system that made the wide clinical application of CAPD possible was the wearable bag system introduced by Oreopoulos in the late 1970s [12] (Figs 10.2a–10.2c). In this "wearable" system, referred to as the "standard" system for many years, the catheter is connected to the bag *via* a titanium adaptor, which replaced the male press fitting and a piece of tubing and a spike or a Luer lock device. During each bag exchange procedure, the spent dialysate is drained from the peritoneal cavity to the empty bag, which is then disconnected and discarded. The next step is the connection of a new bag to the patient's catheter and the fresh dialysate is introduced into the peritoneal cavity. The empty bag is rolled up and remains attached to the patient until the next bag exchange (nondisconnecting system). This system achieved a significant drop in peritonitis rate. However, this rate was stabilized at approximately one peritonitis episode every year, mostly due to touch contamination.

A major improvement was the introduction of the Y-set system by Buoncristiani [14] (Fig. 10.3). A Y-shaped transfer set filled with disinfectant during the dwell time is connected permanently to the catheter. During the bag exchange procedure, one of the two free limbs of the Y transfer set is connected to a new bag containing the fresh dialysate and the other to an empty drainage bag. At the beginning of each exchange, the spent dialysate is drained from the peritoneal cavity into the empty bag. The Y-connecting tubing is then flushed with a small volume (~100 mL) of fresh dialysate drained from the new bag directly into the drainage bag (flush before fill). After that, the fresh dialysis solution is introduced into the patient's abdomen and the Y-set, along with the bags, is disconnected from the catheter (disconnecting system). With this technique, micro-organisms that happen to be inadvertently introduced into the system during the connection are flushed into the drainage bag.

A number of variants of the original Y-set have been introduced into clinical practice[15–17]. The most widely used are the long Y-set (a Y with two long free limbs) and the O-set (named from the shape it takes when the two free limbs are connected to each other during the dwell phase) (Figs 10.4a and 10.4b). In both systems the prosthesis is disconnected after each exchange. In some versions, the Y- or O-set is filled with disinfectant during the dwell time and reused in the next exchange.

The **double (or twin)-bag system,** introduced by Bazzato et al. [18], is similar to the Y-set system, but both bags (the one containing the fresh solution and the empty-drainage bag) are already connected to the Y-shaped tubing by the manufacturer. The Y-set lies on the bag side. Therefore, only one connection is required by the patient, that of the catheter to the free branch of the Y-set via a catheter extension (Fig. 10.5).

A modification of the double-bag system is the T-set, which consists of a catheter extension equipped with a very short lateral limb, through which, at the end of the exchange, before the disconnection of the bag, a disinfectant is injected, filling the catheter extension [19] (Fig. 10.6).

In the early years of the various Y-set systems, the tubing was rinsed with a hypochlorite disinfectant during bag exchange. However, a danger of accidental infusion of the disinfectant into the peritoneal cavity was always present. Many studies have confirmed that the "flush before fill" is the main preventive characteristic of the Y-sets [20–23]. Therefore, the use of the disinfectant has been abandoned by most manufacturers. In a recent position paper, Buoncristiani et al. [24] propose a double Y-set consisting of one Y-shaped connector mounted on the catheter and a second mounted on the distal end of the down flow tube of the fresh dialysate bag equipped with a special slider (manual or electromechanical) in order to overcome the injection of disinfectant into the peritoneal cavity.

Double-bag systems are currently the mainstay of treatment and they are considered as the "standard" PD delivery system.

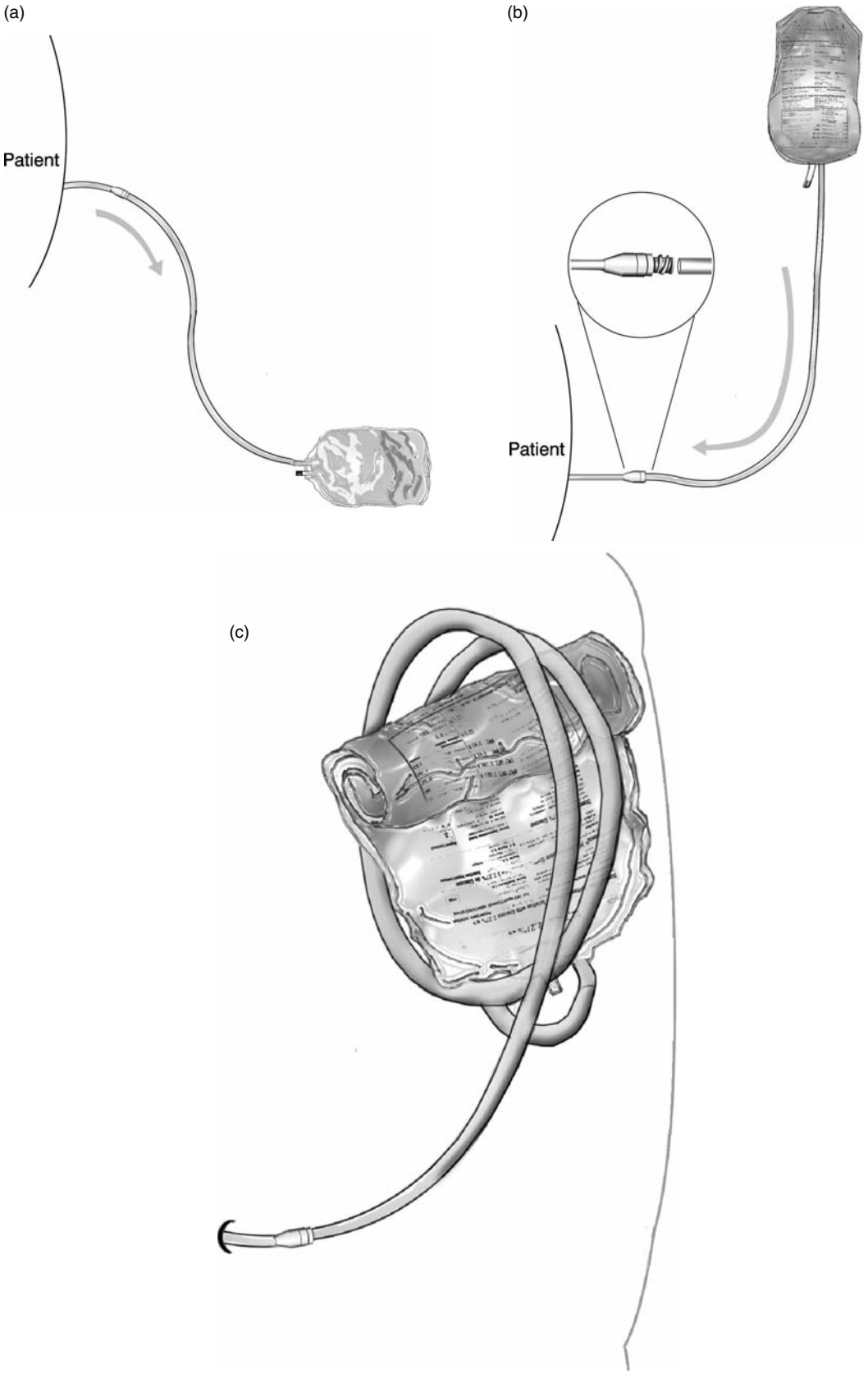

Fig. 10.2 The Oreopoulos wearable or "standard" CAPD system. (**a**) drain, (**b**) fill, (**c**) dwell

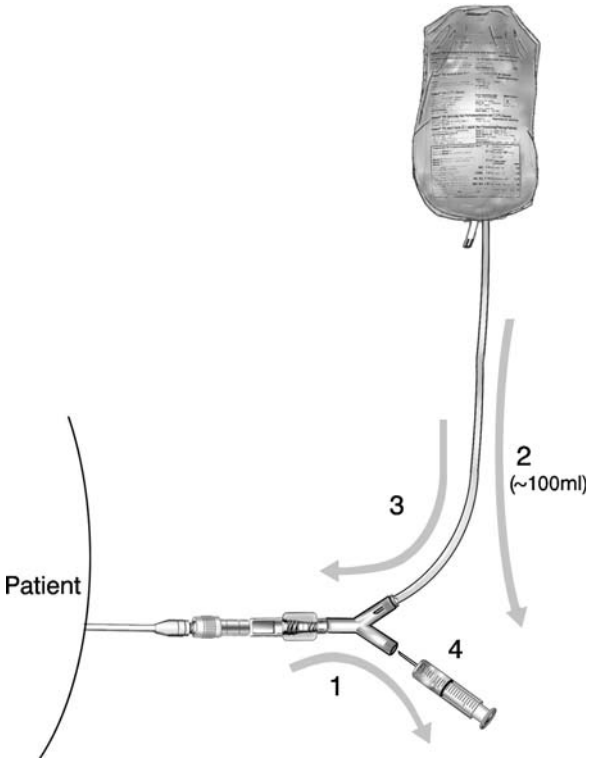

Fig. 10.3 The Y-set CAPD system. (1) drain, (2) flush before fill, (3) fill, (4) fill with disinfectant

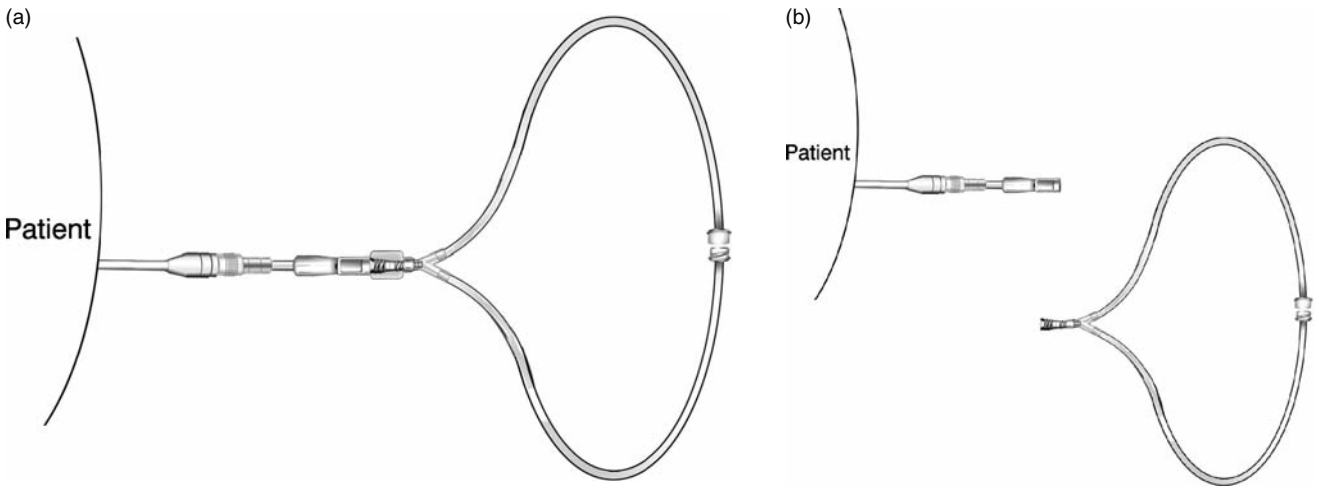

Fig. 10.4 The O-set CAPD system. (**a**) connected, (**b**) disconnected

Connection Devices (Connectors)

In the nondisconnecting systems era, a long transfer set, which consisted of a PVC tubing, was used to connect the catheter with the dialysate bag. The proximal end of this transfer set was connected through a male press fitting to the permanent peritoneal catheter. Frequent accidental disconnections at this point were accompanied by a high incidence of dialysate leak. The introduction of titanium adaptors (Fig. 10.7), which replaced the male press fitting connectors, reduced significantly these accidents and, consequently, peritonitis rates.

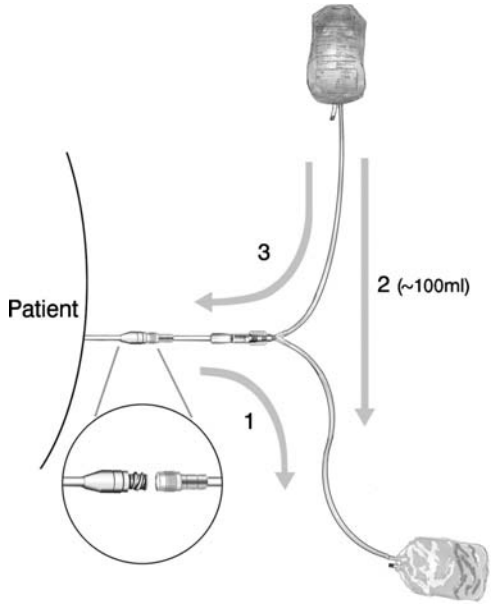

Fig. 10.5 The double-bag CAPD system. (1) drain, (2) flush before fill, (3) fill

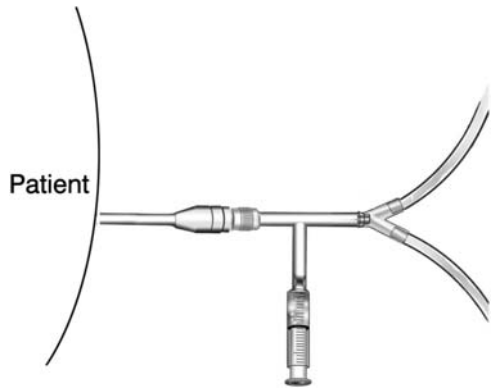

Fig. 10.6 The T-set CAPD system

The distal end of the transfer set was connected to the fresh dialysate bag via a spike (rigid pointed hollow plastic tube) (Fig. 10.8) or a Luer lock connector during each bag exchange procedure (Fig. 10.9). This procedure is associated with a high peritonitis risk due to touch contamination and, therefore, is not recommended [25]. In nondisconnecting systems, transfer sets were initially changed every week and later every month.

In disconnecting systems, a catheter extension tubing is securely screwed onto the titanium adaptor and is connected with the tubing of the dialysate bag at every bag exchange via a connection device that differs from one manufacturer to the other, as described below under "Internationally Available CAPD Delivery Systems". Material improvements have allowed catheter extension changes to be performed approximately every 6 months.

One type of connector was the Safe-lock®, consisting of a cone and a press-fit of the cone, which was deeply recessed, so that the path of the dialysate could not be touched. The Safe-Lock 5F® contained a spring-operated sealing valve inside the catheter, which regulated the dialysate flow in five steps. No extension sets were required and

Fig. 10.7 The titanium adaptor

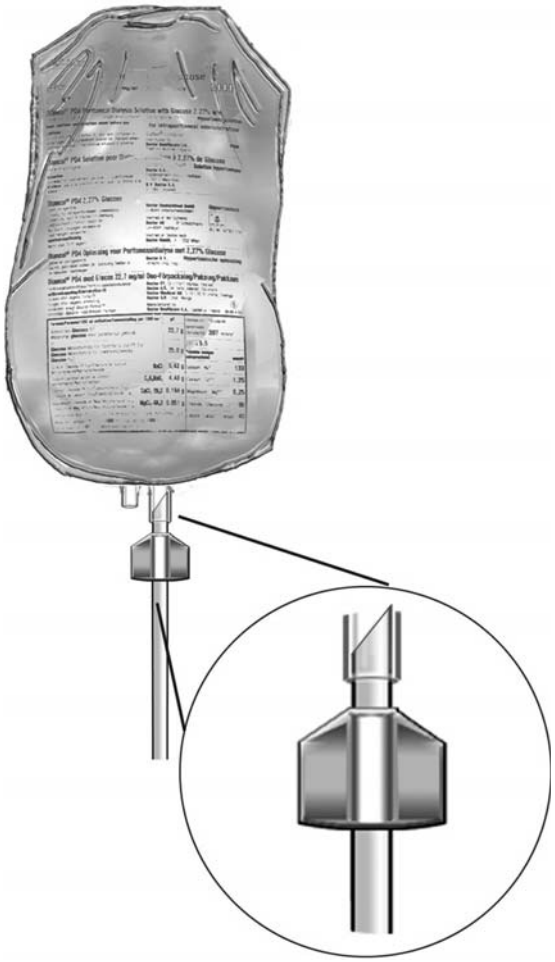

Fig. 10.8 A spike connector

between exchanges only the connector remained attached to the catheter. These two connectors were sprayed with an antiseptic solution both before and after the connection [26].

The Freeline® was a Y-set system where instead of the use of a disinfectant, the extension was closed with a cap containing an iodine impregnated sponge [26].

Another variation was the ANDY® system (nondisconnecting system), where, after the bag exchange, the Y-set was closed with an irreversible clamp and remained attached to the catheter acting as a cap until the next exchange [27].

Disinfecting Devices

In the era of "wearable" systems, the use of devices that could sterilize connecting surfaces was tempting. Ultraviolet (UV) light sterilization as well as heat sterilization, achieved with either electrical resistance or microwaves, were tested.

In a large randomized study by Nolph et al. [28] the UV-flash® disinfecting device did not prove effective in reducing peritonitis rate The authors recommended its use in less-skilled patients experiencing technique problems. Higher peritonitis rates were found in patients using UV-assisted "wearable" systems compared to patients using disconnecting systems [16]. However, these devices could prove useful in patients with impaired dexterity or vision, according to a retrospective multicenter study from Japan [29]. In vitro studies supported the germicidal effectiveness of these devices [30], but the results of a subsequent study by the same investigators, who quantified bacterial removal in disconnecting (Y-set and double-bag) systems, attribute the safety of these systems to the protective action of the design of the fluid path flow and the "flush before fill" [21].

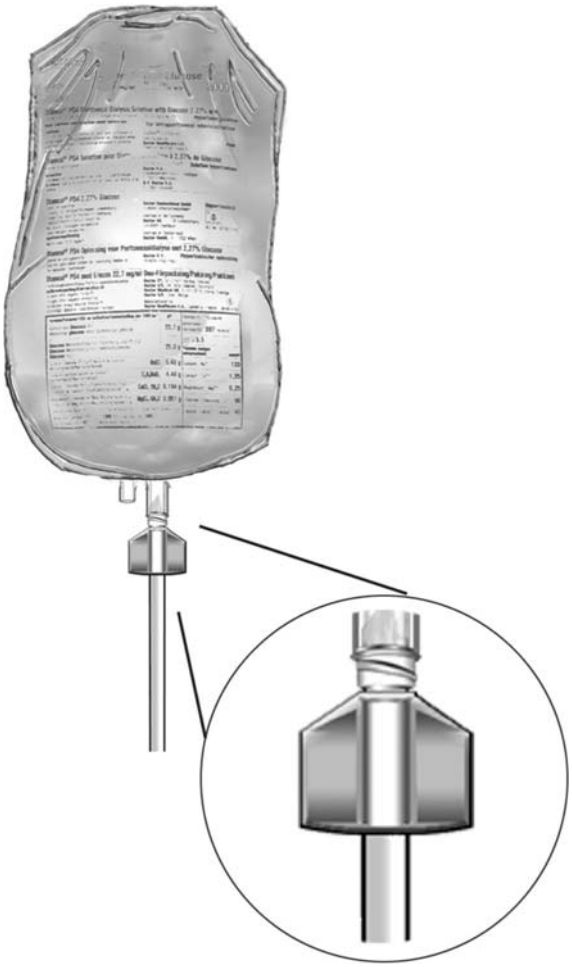

Fig. 10.9 A Luer lock connector

Other devices used heat for sterilizing the connection site. The Terumo Flame-Lock system used heating over a flame and ceramic connections with good results in reducing peritonitis rates [31]. The Fresenius Thermoclave device was used with the Safe Lock 5F® connector and gave good results, as well [32]. Low incidence of touch contamination and high patient acceptance was also reported with the use of the Sterile Connection Device, which used a heated blade to cut through parallel placed tubing of transfer set and fresh dialysate bag [33]. Another heat sealing device, although safe and simple, included the danger of serious burns for the patient or the caregiver and was very large and bulky [34]. Microwave moist-heat devices showed good in vitro results but did not prove practical [35, 36].

However, PD is considered a simple and patient friendly method without the complicated equipment of hemodialysis. All these devices added to the complexity and increased the cost of the method without substantial benefit for its safety and, therefore, their use has been mostly abandoned.

Internationally Available CAPD Delivery Systems

CAPD systems available internationally today, excluding locally manufactured and used ones, are, in alphabetical order of their manufacturers, the following (data provided by manufacturers after personal communication):

Baxter: The UltraBag® system is a double-bag system with a Luer lock connector. Different PD solutions are available (standard glucose, lactate/bicarbonate in dual-bag chambers, amino acid solutions, icodextrin solutions). Dialysate containers are made of PVC. Moreover, a special device for assisting patients during the bag connection (EZ-AIDE®) and a disinfecting device using UV light (UV flash® germicidal exchange device) are also available.

Bieffe: The Delta 4 system is a double-bag system with a Luer lock connector and a catheter extension cap containing povidone iodine. The dialysate container is made of Clear Flex®. The Clear Flex® has three layers. Starting from the outer layer these are made of polypropylene, polyamide, and polyethylene.

Fresenius AG: Stay-safe® and ANDY-disc® are both double-bag systems incorporating a special connector, the disc. After the initial connection of the disc to the extension set, all exchange phases are performed by turning the knob of the disc. At the end of the exchange an automatically introduced pin seals the lumen of the catheter extension. The tip of the extension is protected with a disinfectant-containing cap. Stay-safe® is the newer system of the two, offering more solution options (standard glucose, bicarbonate solutions, and dual chamber bags). The dialysate container is made of Biofine®, while the ANDY-disc® system uses PVC containers. Biofine® is made of polymers constructed exclusively from hydrogen and carbon atoms, the polyolenes.

Gambro: The Gambrosol® trio system is a double-bag system incorporating a special three-barrier connector and a prefilled tubing. The PVC containers have three compartments. An iodine containing cap is used for closing the catheter extension set.

Delivery Systems and Peritonitis

From the literature available so far, it becomes clear that disconnecting (Y-set and double-bag) systems are associated with lower peritonitis rates, compared to "standard" systems. All but one randomized controlled trial (RCT) or quasi-RCT comparing Y-set delivery systems to the "standard" systems showed that the number of CAPD patients who experienced at least one episode of peritonitis was significantly less for patients using the Y-set [37–43]. The exception was a study by Cheng et al. where this difference did not reach a statistically significant level ($p = 0.08$) [17]. All studies showed a significant improvement in peritonitis rates (episodes per patient-months) in favor of the disconnecting systems. These results are supported by a number of retrospective or observational studies [15, 44–47]. The length of the branches of the Y-set system, in one study, was not related to the incidence of peritonitis [48].

Three controlled studies where the "standard" system was compared to the double-bag systems showed a significantly reduced incidence of peritonitis with the latter systems [43, 49, 50]. Moreover, five controlled studies [43, 49, 51–54], where the two newer methods, that is, the Y-set and the double-bag systems were compared, consistently reported greater numbers of months per episode of peritonitis with the latter system. The superiority of Y-set or double-bag systems over "standard" systems and of double-bag over Y-set systems was confirmed by two meta-analyses of RCTs [55, 56].

Finally, two RCTs compared two double-bag systems: Stay-Safe® with UltraBag® and Andy-Disc® with Ultra-Bag®. The first study concluded that the two systems had similar incidences of peritonitis and exit-site infections [57]. The second study showed a trend towards greater peritonitis risk on the Andy-Disc® arm [58].

The Italian group that first described the Y-set reported a very low peritonitis rate (as low as one episode every 63 patient-months) [48]. Although such impressive results were not verified by others, a much improved peritonitis rate of one episode every 21–28 months was found in randomized studies comparing the new disconnecting systems with the "standard" [40, 50, 59]. Today, peritonitis rates are around one episode every 30 patient-months [60].

The routes through which an infectious agent can enter the peritoneal cavity and cause peritonitis are transluminal (touch contamination), periluminal (around the catheter), transmural (through the intestinal wall), hematogenous, and ascending (vaginal) [61]. The use of disconnecting systems led to a significantly lower danger of touch contamination. This is supported by the fact that the reduction observed in peritonitis rates after the introduction of disconnecting systems is mainly attributed to the reduction of infections with skin-related micro-organisms, like *Staphylococcus epidermidis*, while infections caused by *Staphylococcus aureus* or *Pseudomonas* species remained unchanged [40, 47, 49, 50, 62].

Delivery Systems and Exit-Site Infection

Two retrospective studies demonstrated a better exit-site infection rate in patients either on a Y-set [47] or a double-bag system [63], compared with patients on the "standard" system. However, in almost all randomized prospective controlled studies, the incidence of exit-site or tunnel infection is not related with the type of delivery system used. In particular, four studies comparing the Y-set with the "standard" system [17, 40–42], two studies comparing the double-bag with the Y-set [53, 54], and one study comparing a double-bag system with a "standard" one [50] demonstrated no significant difference in the rates of exit-site or tunnel infections. Similar results were published by Burkart et al. in two prospective, nonrandomized trials for Y-set versus "standard" systems [59, 64]. Only the study by

Kiernan et al. showed a trend towards lower exit site infection rate in patients using double-bag system compared with those using a Y-set (one episode per 12.5 patient months versus one episode per 28.5 patient months, respectively), but, again, the difference did not reach statistically significant levels [52]. Another RCT showed similar exit-site infection rates with two different double-bag systems (Stay-safe® and Ultrabag®) [57].

Delivery Systems and Ease of Use

Ballocchi et al. concluded that a double-bag system was rated as easy to use by the majority of their patients [65]. In a randomized study comparing double-bag systems versus Y-set systems, the former were considered more convenient and easier to handle [54], while the same group failed to find any differences in patients' acceptance between two different double-bag systems, at least after the first introductory month [57].

Delivery Systems and Technique Survival

It is difficult to assess the impact of a particular delivery system on technique survival, since so many other factors like ultrafiltration failure, peritonitis, catheter malfunction, etc., could play a decisive role. From the limited literature available, Tarchini et al. showed that the use of Y-set reduced the number of dropouts from the method, mainly due to the reduction in peritonitis rate [66], results that were confirmed by Port et al. in U.S. patients [46]. In another study, no difference in technique survival was found between patients using the "O" system and the "standard" system [17]. Finally, in a recent study comparing two double-bag systems, Wong et al. also showed no difference regarding technique survival [58].

Cost Effectiveness of Delivery Systems

Cost is a major concern for health systems, the cost of providing dialysis being a financial burden for insurance organizations, governments, and patients. Li et al. found that the extra cost required for the Y-system could be offset by other expenses required for infection-related morbidity of patients on the standard system [42]. In a Canadian study, Dasgupta et al. showed that the more expensive double-bag system resulted in significant savings due to reduction in peritonitis episodes and hospitalization rates compared to Y-sets [67]. Two randomized prospective trials proved that double-bag systems were more cost effective, compared with single-bag systems [43, 53].

CAPD Delivery Systems in Children

The data concerning the impact of delivery systems in children on PD are very limited. Some studies included children but made no special reference to this age group [41, 58, 59]. One retrospective study in children undergoing CAPD manifested a significantly lower peritonitis rate by the use of disconnecting (O- or Y-set) systems, compared with a nondisconnecting "standard" system [68]. Today, most children are on automated peritoneal dialysis (APD), a method more suitable to their lifestyle and special needs.

Comparison of CAPD Delivery Systems with APD

Automated PD machines (cyclers) are outside the scope of this chapter. However, the connections described here are also used for connecting the catheter extension with the tubing of the dialysate containing bags of a cycler.

In two studies where disconnecting systems had a lower peritonitis rate, as compared to "standard" ones, the former group included 259 APD patients out of a total of 968 patients on disconnecting systems [64, 69]. Comparisons of infectious complications between APD (by design a disconnecting system) and CAPD disconnecting (Y-set and Double-bag) systems are limited. In a randomized prospective study by de Fijter et al., APD patients had improved peritonitis rates but similar exit-site infection rates to patients on Y-set CAPD [70]. Another randomized study in a small number of patients (17 in each group) by Bro et al. failed to confirm these results [71]. In a nonrandomized prospective study from a Spanish center, APD resulted in lower peritonitis rate and similar exit-site infection rate,

compared with a Y-set CAPD system [72]. Retrospective or observational studies gave conflicting results. Two studies supported a lower incidence of peritonitis in CAPD patients using double-bag systems versus patients on APD [73, 74], while another found the two methods equal [75]. Finally, a study by Huang et al. showed a trend (with marginal statistical significance) towards lower peritonitis rates in APD patients [76].

Guidelines and Recommendations

Recommendations regarding PD delivery systems or connectology are made by only some of the guidelines published in the English language. In alphabetical order, these are:

British Renal Association [77]: *The use of disconnect systems should be standard unless clinically contraindicated (Evidence level A).*

Caring for Australians with Renal Impairment [78]: *Disconnect systems of CAPD result in lower rates of peritonitis than standard systems ("spike" or Luer lock) and the standard system should no longer be used (Evidence level A). Twin bag systems have lower rates of peritonitis than Y-disconnect systems and are recommended as the preferred CAPD technique (Evidence level A).*

European Best Practice Guidelines [79]: *Double-bag systems should be preferred, because they are more efficient in preventing peritonitis in CAPD patients. If double-bag systems are not available, any alternative Y-set system prevents peritonitis more effectively than any spike system (Evidence level A). Disinfecting devices have not demonstrated any significant reduction of peritonitis rates obtained by double-bag or Y-set systems (Evidence level A).*

International Society of Peritoneal Dialysis Guidelines [25]: *Spiking of dialysis bags is a high risk procedure for contamination of the system. "Flush before fill" reduces the risk of contamination (Evidence).*

The **Kidney Disease Outcomes Quality Initiative** [80] and the **Canadian Society of Nephrology** [81] have made no recommendations in their guidelines on the matter of PD connectology.

Glossary

Automated PD machine An electrical appliance specifically designed to perform peritoneal dialysis automatically, also known as a "cycler."

***Biofine*®** A material made up by polyolenes, which are polymers constructed from hydrogen and carbon atoms.

Catheter Refers to the permanent peritoneal catheter.

Catheter extension A piece of tubing connecting the catheter to the PD delivery system.

Clear flex® A registered trademark of Bieffe-Baxter. The Clear-Flex® bag is a three-layer laminate. Its inner layer is composed of polyethylene, the middle of polyamide, and the outer of polypropylene.

Connecting device A device of different designs (exclusively specific for each PD delivery system) used for the connection of the catheter or its extension to the delivery system. Synonym to connector.

Connector See connecting device

Cycler See automated PD machine

Dialysate The peritoneal dialysis solution.

Dialysate container The bag containing the dialysate, also known as "peritoneal dialysis bag."

Dialysate fresh The unused dialysate.

Dialysatespent The used dialysate, after its dwell into the peritoneal cavity.

Disconnecting system Also known as disconnect system, refers to those CAPD delivery systems that are disconnected from the patient between bag exchanges.

Disinfectant Any solution used for the disinfection of any connection site of a PD delivery system.

Disinfecting device A device of different designs using various sources of energy (heat, UV light) in order to disinfect the connection site of a PD delivery system.

Double-bag system A CAPD delivery system where both bags (the one containing the fresh dialysate and the empty drainage bag) are already connected to the Y-shaped tubing by the manufacturer.

Drain The action of outflow of the spent dialysate from the peritoneal cavity.

Drainage bag The bag into which the spent dialysate is drained.

Dwell The period during which the dialysate remains in the peritoneal cavity.

Fill The action of the inflow of the fresh dialysate from its container into the peritoneal cavity.

Flush before fill The action of flushing the tubing with a small volume (~100 mL) of fresh dialysate drained from the new bag directly into the drainage bag, followed by the fill.

Luer lock A type of tubing connector with threaded fittings for a secure connection and added leverage for seal disconnect. The concept for these connectors and adapters was developed by a German instrument maker whose name, Luer, still defines this unique design.

Nondisconnecting system Also known as nondisconnect system, refers to those CAPD delivery systems where the dialysate bag remains connected to the patient between bag exchanges.

O-set A variant of the original Y-set, named from the shape it takes when the two free limbs are connected to each other during the dwell phase.

Peritoneal dialysis bag See dialysate container

Peritoneal dialysis connectology A conventional term referring to the various systems of transfer sets, connecting devices, containers, adapters, etc., that are used during the process of PD.

Peritoneal dialysis delivery system A system incorporating all necessary parts and actions required for the process of bag exchange in peritoneal dialysis. Synonym to "peritoneal dialysis system."

Peritoneal dialysis solution See dialysate

Peritoneal dialysis system Synonym to "peritoneal dialysis delivery system."

PVC Polyvinyl chloride.

Spike A rigid, pointed, hollow plastic tube.

Standard PD system The nondisconecting or wearable PD system.

Titanium adaptor The Luer lock adaptor, made of titanium, connecting the catheter to its extension.

Transfer set The tubing connecting the catheter to the dialysate bag in the nondisconnecting system.

T-set A variant of the double bag system, which consists of a catheter extension equipped with a very short lateral limb, through which, at the end of the exchange, before the disconnection of the bag, a disinfectant is injected, filling the catheter extension.

Twin-bag system Synonym to "double bag."

Y-set A Y-shaped connecting tube. During the bag exchange procedure the main (vertical) limb of the Y-shaped connecting tube is connected to the catheter extension, while the second limb is connected to an empty (drainage) bag and the third one to a new bag containing the fresh dialysate.

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Chapter 11
New Peritoneal Dialysis Solutions and Solutions on the Horizon

M. Feriani and R.T. Krediet

This chapter discusses 1) the effects of alterations in electrolytes, 2) amino acids, 3) icodextrin, and 4) biocompatible peritoneal dialysis (PD) solutions.

Effects of Alterations in Electrolytes

Magnesium

Magnesium is an important cation involved in several enzymatic reactions. The serum concentration of magnesium in dialysis patients depends on dietary intake and on the concentration of the cation in the dialysis solution. Normal values of total serum magnesium range from 0.65 to 0.98 mmol/L, while its diffusible fraction is about 55–60% of the total. Commercially available continuous ambulatory peritoneal dialysis (CAPD) solutions contain 0.25–0.75 mmol/L of magnesium. In such conditions, when 0.75 mmol/L magnesium and 1.5% glucose solutions are used in CAPD, a slight magnesium uptake from the dialysis solution usually occurs by diffusive gradient [1]. Kwong et al., however, have reported a negative dialytic balance with the same solution [2].

When ultrafiltration is increased by a 4.25% dextrose solution, convective removal counteracts diffusive uptake, yielding a negative magnesium mass transport in most patients [1]. Not only is peritoneal transport of magnesium influenced by diffusion gradients and ultrafiltration rates, but also by dwell time and peritoneal permeability because of the large hydrated radius of the molecule [1].

In most papers [3–6] the use of 0.75 mmol/L magnesium solutions resulted in elevated levels of magnesium in the serum. Hypermagnesemia is a common finding in dialysis patients [7]. While it is almost impossible to show abnormalities related to modestly elevated magnesium concentrations, when serum magnesium increases above 2 mmol/L symptoms of neuromuscular and cardiovascular toxicity are present [8]. Controversial reports concerning beneficial or deleterious effects of hypermagnesemia in dialysis patients have been published. Potential harmful effects include pruritus [9], altered nerve conduction velocity [10], and contribution to osteomalacic renal osteodystrophy by inhibiting bone remodeling [11]. Other authors pointed out that hypermagnesemia does not result in any clinical complication and, on the contrary, a protective role on soft tissue calcifications has been suggested [12]. A suppression of parathyroid hormone (PTH) [13] has also been suggested. This latter effect has recently been hypothesized to have a pathogenetic role in adynamic bone disease [14]. Despite such frequent hypermagnesemia, the muscle content of magnesium is generally not altered [15]. Therefore, the relationship of serum magnesium to intracellular magnesium concentration and total body magnesium in CAPD patients is unclear. Dietary magnesium intake is a function of protein intake. On the other hand, magnesium removal with standard 0.75 mmol/L magnesium solutions is negligible. In spite of these observations, CAPD patients do not display a continuous increase of serum magnesium levels, and stool magnesium losses may play a regulatory function [16].

To achieve a correct balance, Nolph et al. suggested lowering dialysate magnesium to 0.25 mmol/L [4]. The use of this solution did not cause hypomagnesemia, and most patients experienced a normalization of magnesium serum levels [4, 17]. In a more recent report, however, 64% of the studied CAPD population using the low magnesium containing CAPD fluid showed a reduction in serum magnesium levels [18]. Since hypomagnesemia has been associated with cardiac arrhythmias [19, 20] and various electrocardiographic abnormalities [21], serum magnesium levels should be monitored during treatment with these solutions. In addition, the use of an ion-selective electrode for

M. Feriani (✉)
Ospedale Umberto 1°, Reparto di Nefrologia e Dialisi, Mestre-Venezia, Italy
e-mail: Mariano.Feriani@ulss12.ve.it

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the measurement of the ionized magnesium, the active fraction of this cation, has shown that the correlation between total serum and ionized magnesium is less strong in CAPD patients than in normal subjects due to hypoalbuminemia and the increased complexed fraction of magnesium often present in dialysis patients [22]. This could imply that significant magnesium depletion can be present despite a normal serum value [23].

The use of lower or zero magnesium dialysate has also been investigated to permit oral treatment of hyperphosphatemia with magnesium salts as a calcium-free phosphate binder [24]. This, however, frequently results in a laxative effect, requiring careful monitoring of compliance to therapy and serum magnesium levels [25, 26].

Calcium

In the past, peritoneal dialysis fluids (PDF) contained 1.75 mmol/L of calcium. This concentration was chosen in order to ensure a positive calcium balance since, in uremic patients, the active vitamin D deficit leads to a reduction in calcium absorption from the gastrointestinal tract. In this condition serum calcium concentration is low, PTH is high, and a high-turnover bone disease often occurs. In addition, PTH was considered one of the most harmful "uremic toxins" because of its deleterious effects on several organs and functions.

While a negative balance may result from the use of 1.5 mmo/L dialysate calcium [27], kinetic studies suggest that CAPD solutions with 1.75 mmol/L of calcium (three exchanges with 1.5% glucose and one exchange with 4.25% glucose) generally lead to peritoneal calcium absorption and rapidly normalize total and ionized calcium serum levels [1–3, 28]. This was suggested to be beneficial in order to prevent progression of uremic osteodystrophy and calcium losses from the bone [6–29]. However, clinical studies did not confirm such a positive effect [27, 30–31].

Since normal serum concentration of diffusible ionized calcium ranges from 1.15 to 1.29 mmol/L, calcium is absorbed from PDF or lost into PDF depending on diffusive gradient direction [1]. In CAPD solutions, 30% of calcium is not ionized being "chelated" by lactate [2]. Ionized calcium probably crosses the peritoneum faster than chelated calcium. As a consequence, ionized calcium gradient is rapidly dissipated. The rapid increase in dialysate pH further contributes to this phenomenon decreasing calcium ionization in the solution [2]. A significant correlation between positive calcium balance and dialysate/serum gradient for ionized calcium has been found by using 1.75 mmol/L calcium solutions [2]. Blumenkrantz et al. have also reported that net dialytic calcium uptake inversely correlates with total serum calcium [32]. When ultrafiltration increases in hypertonic exchanges, calcium uptake tends to decrease [1] or even to become negative [2, 28]. Different rates of ultrafiltration may help to explain discrepancies among different studies. Convective removal counterbalances diffusive uptake and decreases dialysate/serum gradient because of a dilution effect [33].

Overall calcium mass-balance is also affected by gastrointestinal absorption. In CAPD patients, an empirical relationship has been found between dietary intake and gastrointestinal absorption [32]. One study found that 720 mg/day of dietary calcium intake resulted in an estimated average gastrointestinal absorption of 25 mg [32].

When new attention was paid toward the deleterious effects of the high phosphate serum levels often encountered in dialyzed patients, and the danger of aluminum toxicity contained in the aluminum-containing phosphate binders was recognized [34–37] (osteomalacia and encephalopathy), the calcium salts of carbonate and acetate were introduced as phosphate binders. Block et al. [38] have recently pointed out that hyperphosphatemia but also moderate to severe hyperparathyroidism and hypercalcemia are associated not only with bone disease but also with cardiovascular disease and greatly affects mortality in dialyzed patients. Calcium-containing phosphate binders were aimed to both reduce serum phosphate levels and hyperparathyroidism through an increase in serum calcium levels. However, if oral calcium supplementations are administered as phosphate binders, significantly greater amounts of calcium are absorbed from gastrointestinal tract. Assuming a daily phosphate intake of 1,000 mg in CAPD patients [39], 70% of this should be bound in the intestinal tract to maintain the balance [28]. This goal can be achieved with 6.25 g of calcium carbonate supplementation (2,500 mg of elemental calcium), which leads to an average gastrointestinal calcium absorption of 700 mg/day [40, 41]. Hence, in a standard patient, total calcium absorption from the diet and calcium carbonate is approximately 725 mg/day. In such conditions, a large number of patients may encounter an increased risk of hypercalcemia and soft tissue calcification [42].

A solution to this puzzle has been found by using a lower dialysate calcium concentration. This approach has been suggested to avoid the risk of calcium carbonate–related hypercalcemia [1]. Martis et al. [43] have calculated on theoretical bases that a calcium concentration of 1.25 mmol/L in peritoneal fluid would lead to a calcium removal of 160 mg/day when serum ionized calcium is 1.3 mmol/L and to a greater removal in the case of hypercalcemia. In a prospective clinical study, Hutchison et al. [17] have demonstrated that a 1.25 mmol/L calcium dialysate allowed the administration of larger doses of calcium carbonate with good control of serum phosphate, and maintained serum

ionized calcium near to the upper limit of the normal range. Parathyroid hormone was suppressed in the majority of patients and bone histology improved. Similar results have been achieved in a large multicentric study in which 1 mmol/L calcium solution has been used and low doses of vitamin D and calcium carbonate as phosphate binders have been orally supplemented [44]. However, in the long term, a great percentage of patients with low calcium dialysis fluid (23%) as compared to patients with 1.75 mmol/L calcium dialysis fluid (10%) experienced worsening of the preexisting hyperparathyroidism [45].

Low calcium PD fluids have been extensively studied by several investigators and the results confirm the benefit of this approach on uremic osteodystrophy [46–50]. Long-term usage of lower calcium dialysate by large numbers of patients raises the question of safety in cases of poor compliance to oral calcium carbonate supplementation. In 12 patient treated with 1.5% glucose and 1.25 mmol/L calcium solution, a net gain of calcium was demonstrated when the serum ionized calcium level was less than 1.25 mmol/L. This observation seems to prove that a very low risk of hypocalcemia is present in these patients [17]. However, there is a tendency to lose calcium regardless the serum-ionized calcium in patients treated with 4.25% glucose and low calcium solutions. Since a rapid exacerbation of hyperparathyroidism in some patients converted to low calcium dialysate without adequate oral calcium supplementation has been documented [51] in CAPD patients using two or more hypertonic bags per day and a low calcium solution, a careful surveillance of the mineral metabolism is needed.

In the last decade, the prevalence of type of bone lesions in PD patients has changed and adynamic bone disease has been increasingly recognized [52]. The term "adynamic bone disease" indicates a reduced activity of the physiologic process of bone remodeling with reduced synthesis of bone matrix, osteoblastic and osteoclastic activity, and a lack of osteoid accumulation. In this condition, patients are predisposed to the risk of poor healing of microfractures and to an increased incidence of fractures. In addition, since the calcium buffering effect of bone is diminished [53–55], patients with a positive calcium balance from calcium-containing phosphate binders and/or high-calcium PDF can be exposed to frequent episodes of hypercalcemia with calcium deposition in the vascular bed and myocardium that increase cardiovascular mortality [56]. In a large number of bone biopsies in an unselected end-stage renal disease (ESRD) population in Toronto, the percentage of adynamic bone disease was 61% in PD patients as compared with 36% in HD patients [57]. More recent observations confirmed these data (63% of adynamic bone disease in PD patients) [58].

The etiology of adynamic bone disease is unknown but several risk factors have been suggested [59–61], the most important probably being the oversuppression of PTH secretion and/or the lack of physiologic fluctuations in secretion. High calcium serum levels, positive calcium balance from calcium-containing phosphate binders, or high calcium PDF and vitamin D administration are the main factors involved in the PTH oversuppression. The role of the positive calcium balance in this condition is confirmed by the increase of serum PTH levels in patients treated with low calcium PDF and switched from calcium-containing phosphate binders to non-calcium-containing phosphate binders such as sevelamer [52].

The concerns about adynamic bone disease have changed the previous views on maintaining calcium serum levels of PD patients at the highest value of the normal range in order to reduce PTH secretion. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [62] recommend PTH values from 150 to 300 pg/mL and a serum calcium $<$9.5 mg/dL. Recognition of the high prevalence of the adynamic bone disease in PD patients and the understanding of its supposed pathophysiology have added new indications to the use of low calcium PDF so that the formulation containing 1.25 and 1 mmol/L are now suggested by guidelines on PD.

Several studies have been performed comparing the effect on bone diseases of the high and low calcium PDF in adynamic bone disease PD patients. In the study of Sanchez et al. [63], no significant histological changes were recorded in the low calcium group (1.25 mmol/L) as compared with standard 1.75 mmol/L calcium PDF. As expected, PTH increased in the study group and calcium-containing phosphate binder medication was increased while no changes in serum calcium and phosphate levels were recorded.

A recent randomized study [64] comparing the effects of standard versus low calcium (1 mmol/L) PDF for an extended period of 16 months in CAPD patients with biopsy-proven adynamic bone disease showed in the study group an increase in bone formation rate to normal range being suppressed at baseline and no changes in the control group. Serum-ionized calcium significantly decreased despite an increase in calcium carbonate supplementation and PTH rose of about 300% in the low-calcium PDF group. Again, no changes in the standard calcium PDF were observed. Bone mineral content did not decrease during the study in either group, demonstrating no calcium loss from bone. In addition, in the study group hypercalcemic episodes decreased significantly while asymptomatic hypocalcemia occurred infrequently. Some patients in the low-calcium PDF did not change the bone histology due to an insufficient bone formation rate increase. The authors hypothesized that the relatively high doses of calcium carbonate were still able to maintain a positive calcium balance and the new calcium-free phosphate binders could add a further benefit in this condition.

The commercially available solutions for automated peritoneal dialysis treatments are substantially similar to those for CAPD. Andersen [65] reported that a positive calcium transfer from dialysis fluid can be obtained with a 2.16 mmol/L calcium concentration in dialysate both during 1.5% and 4% glucose 30 min dwell-time exchanges, while in automated peritoneal dialysis, the low-calcium dialysis solution (1.25 mmol/L) could result in a negative calcium balance [66]. Although there are no specific studies of calcium mass balance and calcium mass transfer in automated peritoneal dialysis (APD), it seems reasonable that, since larger volumes of fluid are utilized with greater ultrafiltration and shorter dwell times, the calcium balance would be negative or at least less positive than in CAPD [67]. This implies that a bigger dose of calcium containing phosphate binders and vitamin D supplementation could be used with less risk of hypercalcemia and PTH suppression. The major mineral metabolism problem could be the hyperparathyroidism. The new calcium mimetics or vitamin D analogues could be of value for treating this condition.

Low Sodium

Most commercially available dialysis solutions have a sodium concentration of 132–134 mmol/L, which is an average of about 5 mmol/L lower than the plasma sodium concentration. Because of this small concentration gradient, the transport of sodium is mainly determined by convection [68]. The magnitude of net convective transport is dependent on the balance between transcapillary ultrafiltration and the peritoneal absorption of the dialysate.

The diffusion of sodium can be increased by lowering the sodium concentration of the dialysis fluid. However, when this is done without raising the dialysate glucose concentration, keeping the osmolality constant, the increased diffusional transport is counteracted by a decreased removal by convection. [69]. The diffusion of sodium is dependent on the concentration gradient between plasma and dialysate, and on the mass transfer area coefficient. The latter has yielded values that are dependent on the experimental setting in which it was calculated. Using a conventional 3.86% glucose-based solution, an average value of 4 mL/mm has been reported during a period of isovolemia [70]. Values of 7–8 mL/min have been found using experimental dialysis solutions with a sodium concentration of 102–105 mmol/L [71, 72].

Single dwell studies have shown that sodium removal can be increased three-fold when a dialysate sodium concentration of 100 mmol/L is used [71]. This was confirmed in the only clinical study in which six overhydrated patients were treated with such a solution once daily for seven consecutive days [73]. Other significant effects included decreases of body weight and blood pressure. Clinical studies performed after these initial cases have only published in abstract form. Low or ultralow sodium-containing dialyis solutions have never been produced on a large scale and are currently not available.

Amino Acids

A high percentage of patients treated with peritoneal dialysis present different degrees of malnutrition [74]. Since CAPD patients absorb a substantial amount of glucose from the peritoneal dialysis solution and many of them become obese [75], it seems that protein rather than caloric deficit is the major problem for these patients. Continuous losses of amino acids (3–4 g/day) and proteins (8–15 g/day) into dialysate greatly contribute to this nutritional derangement [75, 76].

In the late 1960s, Gjessing suggested supplementing peritoneal dialysis solutions with a mixture of amino acids to correct serum amino acid abnormalities and to prevent obligate protein losses with dialysate [77]. More than 10 years later, Oreopoulos et al. proposed an amino acid solution in peritoneal dialysis both for nutritional supplementation and as an alternative to glucose as the osmotic agent. Experiments in a uremic rabbit model [78] and in peritoneal dialysis patients [79, 80] underlined the advantages of substituting glucose in the solution and improving nutritional support.

Osmotic Efficacy

Molecular weights of different amino acids range from 75 to 214 daltons. Since amino acid mixtures for PD usually contain a higher proportion of small-molecular-weight compounds, the average molecular weight represented in these solutions is approximately 100 daltons [81], which is lower than that of glucose. Nevertheless, the absorption rate of amino acids is not significantly faster than that of glucose. Since, at the fresh dialysis solution pH, some amino acids

are electrically charged, the hydration shell increases the relative Einstein-Stokes radius of the molecules. As a consequence, diffusion coefficients are smaller in comparison to uncharged molecules with equivalent molecular weight, and absorption velocity is reduced. It has been demonstrated that the D/P ratio for creatinine is near to that of glutamine (a near neutrally charged amino acid with almost the same molecular weight) but significantly higher than that of glutamic acid (negatively charged) and of lysine (positively charged), both with the same molecular weight of creatinine [82].

Several studies have been performed to evaluate the ultrafiltration capacity of amino acid solutions. A 2% amino acid solution was compared to a 4.25% glucose solution in an acute study on 6-h exchanges [80]. The two solutions induced equivalent amounts of ultrafiltration and similar amounts of urea, creatinine, and potassium removal. The initial dialysate osmolality was similar for the two solutions and similar dialysate osmolality changes during dwell time were observed. At the end of the exchange, 90% of the administered amino acids were absorbed. Later, the same group [83] reported a short-term study in which the ultrafiltration obtained with a 1% amino acid solution (osmolality 364 mmOsm/kg) was intermediate between that of 1.5% (osmolality 346 mmOsm/kg) and 2.5% (396 mmOsm/kg) standard glucose solution. Goodship et al. confirmed the observation of smaller but not statistically different ultrafiltrate volumes, comparing a 1% amino acid solution with a 1.5% glucose solution [84].

A comparison of ultrafiltration profiles and solute mass transfer between a 4.25% glucose (478 mmOsm/kg) and a 2.76% amino acid (501 mmOsm/kg) solution showed that intraperitoneal volume profiles were equal during the first 180 min of dwell. Later, the volume of amino acid solution tended to decrease more rapidly than that of glucose solution, leading to a nonsignificant decrease in net ultrafiltration at the end of the 6-h dwell time exchange [85]. The diffusive mass transport coefficient tended to be higher with amino acid solutions, but the difference was not statistically significant . Young et al. [86] studied ultrafiltration and D/P ratios of several proteins in an 8-h dwell time exchange using a 1% amino acid solution in comparison with 1.5% glucose standard solution. Volumes of dialysate at the end of the exchanges were significantly less after amino acid exchanges, although the osmolality decreased comparably during the dwell time. At the end of the study period (12 weeks), amino acid absorption and protein losses were increased as compared to the beginning of the study. The clearances of the studied proteins expressed as D/P ratios showed a 18–34% increase, respectively, at the beginning of the amino acid use and after 12 weeks. D/P ratios for creatinine showed a 7–10% increase, respectively, while no differences were observed for urea. The increase of the peritoneal permeability during the use of amino acid–based solution was attributed to an activation of complement by amino acids or their metabolites to produce C5a [87] and the generation of prostaglandin E2 [88]. The peritoneal permeability increase was reversed when standard glucose solutions were resumed [86].

Douma et al. [89] have reported a study on the peritoneal membrane permeability when a 1.1% amino acid solution is used: the mass transfer area coefficients of low-molecular-weight solutes (creatinine, urea, and urate) were significantly greater with amino acid solution compared to glucose solution. The clearances of the macromolecules were also greater with the amino acid solution, but the increase of albumin and IgG clearances was small and not significant. The transcapillary ultrafiltration rate was higher during the amino acid treatment, but no significant difference in net ultrafiltration was found. These data indicated a vasoactive effect of the amino acid solution: the increased peritoneal blood flow and the effective peritoneal surface area were probably caused by vasodilation. This was not associated with changes in intrinsic permeability to macromolecules or increased protein loss. This study also demonstrated that these effects were not due to nitric oxide activity (L-arginine contained in the amino acid solution could serve as a substrate for nitric oxide synthesis) nor to the peritoneal release of prostaglandins.

Despite the contradictory results of kinetic studies, in clinical practice amino acid solutions deliver ultrafiltration and small molecule clearances equivalent to those achieved with 1.36% glucose solutions. The differences among various studies probably reflect the difference in concentration and composition of amino acids in the employed solutions. The osmotic power produced by different solutions is not only expressed by the osmolality, calculated or measured, but also depends on the degree of absorption and metabolization of each amino acid [90].

Nutritional Efficacy

Nutritional value, changes in serum amino acid profile, amino acid absorption, and the effects on lipids and glucose metabolism of CAPD amino acid solutions have been evaluated in clinical studies. During the 30 years of experience and attempts to find out the best composition for the amino acid solution, several amino acid formulations of the CAPD solutions have been proposed and tested. Table 11.1 reports the amino acid composition of some of the most used. Clinical results were often conflicting because different amino acid composition solutions were used, different parameters were taken into account as markers for nutrition, different CAPD population were studied (malnourished

Table 11.1 Amino acid composition (mg/dL) of different solutions (see references in the text)

Category	Amino acid	Solution A	Solution B	Solution C	Solution D
EBCAA	Valine	46	126	139.3	123
EBCAA	Leucine	62	92	101.9	85
EBCAA	Isoleucine	48	77	84.9	70
EAA	Threonine	42	59	64.5	54
EAA	Tyrosine	4	6	30	27
EAA	Phenylalanine	62	75	57	47
EAA	Lysine	58	86	76	55
EAA	Hystidine	44	65	71.4	59
EAA	Tryptophan	18	25	27	23
EAA	Methionine	58	77	84.9	36
NEAA	Arginine	104	97	107.1	68
NEAA	Serine	–	46	50.9	55
NEAA	Proline	42	54	59.5	49
NEAA	Glycine	213	46	50.9	42
NEAA	Alanine	213	86	95.1	77
NEAA	Aspartic acid	–	–	–	65
NEAA	Glutamic acid	–	–	–	65

EBCA: Essential branch-chained amino acid; EAA: Essential amino acid; NEAA: Nonessential amino acid

versus nonmalnourished, different caloric intake), different CAPD schedules were used (amino acid solution used in the overnight exchange versus in exchanges close to a meal).

The clinical results with solution A in Table 11.1 were rather discouraging, showing insufficient effects on nutritional parameters and some unwanted effects such as increased levels of blood urea nitrogen (BUN) (with symptoms of uremia), loss of appetite, and moderate to severe metabolic acidosis [83, 91–93]. The authors concluded that the amino acid formulation, the timing of administration, the patients' low caloric intake, or the patients' sufficient nutritional state could be responsible for the ineffectiveness of the amino acid solution and that the intraperitoneal supply of amino acids was probably used as a source of energy [94].

Following the these experiences, a new 1% amino acid solution was proposed and tested (solution B in Table 11.1). This solution was designed specifically for patients with renal insufficiency and its related amino acid derangements [95]. Thus, the essential amino acid proportion was increased and the lactate concentration was increased to 35 mmol/L.

The studies using the improved 1% amino acid solution demonstrated more beneficial effects than the previous solution in patients with signs of protein malnutrition and low dietary protein intake. Some nutritional parameters such as serum transferrin [96, 97], albumin [98], estimated nitrogen balance (99–100), and serum amino acid profile [93, 94] improved during the study. In all these reports, lipid metabolism improved, BUN increased, and acidosis remained a commonly concern. This was most likely due to the acid load delivered by salts of basic amino acids (lysine hydrochloride) and that arising from metabolism of sulfur amino acids to sulfate (methionine) [101].

In order to further improve the clinical efficacy, a new formulation of the amino acid solution has been proposed and tested (solution C in Table 11.1). Essential amino acid concentrations were increased as well as lactate concentration (from 35 to 40 mmol/L). Total amino acid concentration was increased to 1.1% in order to provide the same osmotic effect as the 1.5% standard glucose solution. This is the formulation now commercially available. A short-term crossover multicentric study in CAPD patients with signs of protein malnutrition has been performed [102]. The nitrogen balance, serum transferrin, and total protein increased in 19 malnourished patients using one or two 1.1% amino acid solution for 20 days. Dietary protein intake of 0.8 g/kg/day and caloric intake of 25–30 kcal/kg/day was prescribed to all patients. Because of the amino acid absorption from dialysis fluid, a total protein intake of 1.1–1.3 g/kg/day was achieved in all patients. Protein anabolism was positive, as directly determined from ^{15}N-glycine studies and indirectly from the plasma phosphate and potassium decrease. The amino acid pattern in plasma tended toward the normal range during the treatment phase and serum triglycerides and HDL cholesterol increased. Plasma total CO_2 significantly decreased, showing a tendency toward a metabolic acidosis mainly in patients treated with two exchanges per day of this solution.

A clinical evaluation of this amino acid solution was performed in a second study [103]. This was a 3-month prospective crossover study in 15 stable CAPD patients not necessarily malnourished. Only one exchange with amino acid was prescribed at lunchtime to couple amino acid absorption with energy intake. Serum albumin and transferrin

significantly improved both in patients with and without malnutrition. Plasma amino acid profile and total proteins did not change. Plasma bicarbonate levels also remained stable.

A prospective randomized study was also performed in order to compare the nutritional effects of the 1.1% amino acid solution with the conventional glucose solution in 54 malnourished patients [104]. After an initial significant increase in serum albumin, transferrin, prealbumin, and total protein, after 3 months of treatment these parameters did not achieve the statistical significance as compared with those of the 51 patients in the control group. However, in the tertile with the lowest albumin levels at the baseline, serum albumin and prealbumin remained significantly increased. In the tertile with the highest albumin levels at the baseline, the mid-arm muscle circumference increased significantly after 3 months of treatment. In the whole population treated with the amino acid solution, circulating insulin-like growth factor 1 (IGF-1) increased, while it slightly decreased in the control group.

In an acute study the amount of amino acids delivered by this amino acid solution was quantified [105]. It has been shown that the gain of amino acid during one exchange largely exceeded the daily losses of amino acid and proteins. This effect was independent of the peritoneal membrane transport type. Skeletal muscle amino acid uptake was increased after 6 weeks use of this solution in 10 CAPD patient [106] and, in an acute study using the ^{3}H-phenylalanine kinetics as indicator, muscle protein synthesis increased by 20% [107].

A short-term use of amino acid solution was also effective in improving net protein balance and converting nitrogen balance from negative to positive in patients on automated PD [108]. Other studies could not demonstrate an improvement in nutritional parameters in well-nourished CAPD patients treated with 1.1% amino acid solution [109, 110]. The longest experience with this amino acid solution was performed by Li et al. [111]. Sixty malnourished Chinese patients were randomized to receive either the amino acid or the conventional solution for 3 years. Normalized protein equivalent of nitrogen appearance (nPNA) and dietary protein intake increased while triglycerides decreased in the study group, Albumin and cholesterol remained stable in the treated group and decreased in the control group. No differences were recorded in mortality, hospitalization, drop out, and composite nutritional index between groups. The last report on the 1.1% amino acid solution is an observational study in 46 malnourished Korean patients [112]. After 1 year of treatment, mean serum value of blood urea, creatinine, lean body mass, nPNA, serum IGF-1 level, back lift strength and SGA score increased significantly. The other studied nutritional parameters (albumin, hand grip strength, anthropometry, and dietary intake) did not change and serum bicarbonate statistically decreased.

In conclusion, in malnourished CAPD patients a dialysis solution with a more appropriate amino acid composition may improve their protein nutrition and metabolic status. However, increased BUN levels and the tendency toward acidosis remain problems to be solved. The last point has been addressed by Jones et al. [113]. They tested a modified amino acid solution formulation (solution D in Table 11.1) in which acidogenetic amino acid concentrations (lysine, arginine ,and methionine) were reduced in comparison with the 1% amino acid solution (solution C in Table 11.1). In addition, aspartic and glutamic acids, two dicarboxylic acids that generate alkaline equivalents during their metabolism, were added. A substantially better acid-base status was achieved during the treatment with the modified amino acid solution as compared to the conventional amino acid solution.

Icodextrin

History

Icodextrin is the only high-molecular-weight osmotic agent that has been approved for use in peritoneal dialysis patients. The name icodextrin is derived from the Greek word *icosa* ("twenty") and the chemical name *dextrin*, describing a glucose polymer obtained by the partial hydrolysis of starch with a molecular weight of about 20,000 dalton [114]. Dextrins are polymers in which the glucose molecules are linked at the α1–4 position. This is different from dextran, where α1–6 linkages are present. The difference in the linkages is crucial in relation to the manner in which these polymers behave in the body. There are a number of enzymes that can attach themselves to the α1–4 polymer and break this bond, producing oligosaccharides, maltose, and eventually glucose. This is different from the α1–6 bond, which is more resistant to enzymatic cleavage.

Icodextrin as used for PD is prepared by hydrolysis of corn (maize) starch and purified enzymatically to maltodextrin. Using a number of filtration steps, the low-molecular-weight fractions are removed. This results in a dextrin preparation with a molecular weight range from 1,640–45,000 daltons. The average molecular weight is 16,800 daltons, and >90% of the bonds are of the α1–4 type.

The first clinical study using a single 6- and 12-h dwell with a 5% icodextrin solution was published in 1987 [115]. A comparison with a 1.36% glucose solution showed that net ultrafiltration at the end of the 6-h exchanges was greater

with the polymer, despite the lower osmolality of the polymer solution. For glucose, increasing the exchange time to 12 h led to absorption of the intraperitoneal volume in all patients, resulting in negative ultrafiltration; with the glucose polymer solution, ultrafiltration continued throughout a 12-h exchange. The absorption of the polymer averaged 14.4% of the instilled quantity after 6 h and 28.1% after 12 h, probably by uptake into the lymphatic system. Because α1–4 bonds are degraded by circulating α-amylase, the absorption causes a rise of the plasma maltose concentration of 0.79 mmol/L (about 0.3 g/L) after 12 h [115].

This initial observation resulted in a number of issues: 1) the use of the glucose polymer during the long exchange, 2) restriction of its use to one exchange per 24 h to prevent extensive maltose accumulation and allow peritoneal removal of maltose during the other exchanges, and 3) the concept of its action by colloid osmosis, similar to that of albumin [116]. This process is based upon the principle that fluid flow across a membrane permeable to small solutes occurs in the direction of relative excess of impermeable large solutes, rather than along the osmolality gradient.

The final preparation used for subsequent studies consists of a 7.5% icodextrin solution, lactate-buffered, with an osmolality of 285 mOsm/kg water. Its composition is given in Table 11.2.

Pathophysiology

The concept of colloid osmosis, leading to fluid transport mainly through the so-called small pores, has been confirmed by showing the absence of sodium sieving [117]. Using dextran 70 as a volume marker, the intraperitoneal volume showed a linear increase during at least 8 h [118], as shown in Fig. 11.1. The absorption of icodextrin averaged 21% after a 4-h dwell, suggesting uptake into the lymphatics similar to that of other intraperitoneally administered macromolecules [117]. The high and persistent fluid flux across the small pore system causes an increase in convective transport, leading, for instance, to an increase in the peritoneal transport of beta-2-microglobulin [117, 119].

Many studies have found a relationship between peritoneal solute transport rates and the efficacy of ultrafiltration on icodextrin [117, 118, 120]. The higher the D/P ratios or mass transfer area coefficients, the better the net ultrafiltration. The explanation is obvious: high D/P ratios suggest a large peritoneal vascular surface area, so more small pores are available for fluid transport. This relationship has been supported by the results of computer simulations [121] and by observations during peritonitis where more, instead of less, ultrafiltration was found [122, 123]. It appeared possible to adequately predict fluid kinetics on icodextrin with a modified three-pore model [124].

Kinetic studies with icodextrin in rats suggested intraperitoneal breakdown of icodextrin during the dwell, both in a stable situation and during peritonitis [125, 126]. However, this could not be confirmed in PD patients [127] and is probably due to the extremely high amylase concentrations in rats. This makes the rat unsuitable for performing kinetics studies with icodextrin.

The presence of a fast peritoneal transport status, reflecting a large peritoneal surface area, leads to a reduction in ultrafiltration with glucose-based solutions due to a high diffusion rate of glucose. As discussed above, icodextrin is especially potent in this situation, because the colloid osmotic pressure gradient remains stable for several hours. This has led to the use of icodextrin as salvage therapy in chronic PD patients with ultrafiltration failure. Some retrospective studies reported that icodextrin enabled patients who would otherwise have been transferred to hemodialysis to continue PD [128, 129]. This has been confirmed in a prospective study [130].

Table 11.2 Composition of 7.5% icodextrin compared to a 3.86% glucose solution

	Glucose	Icodextrin
Na + (mmol/L)	132	133
Ca++ (mmol/L)	1.25/1.75	1.75
Mg++ (mmol/L)	0.25/0.75	0.25
Cl– (mmol/L)	102	97
Lactate (mmol/L)	35/40	40
Glucose (g/L)	38.6	0
Dextrin (g/L)	0	75
Osmolarity (mOsmol/L)	486	285
pH	5.5	5.8

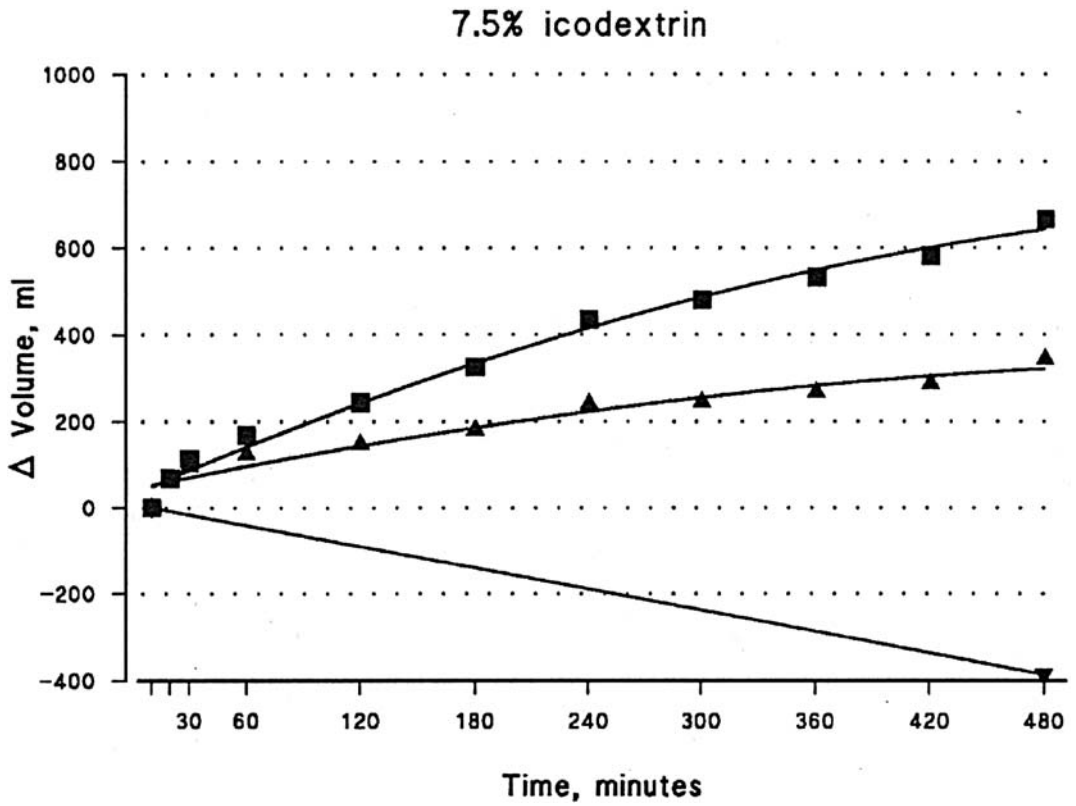

Fig. 11.1 The time course of peritoneal fluid kinetics during an 8-hour dialysis dwell using 7.5% icodextrin. The upper line represents the volume increase due to transcapillary ultrafiltration, the lower line represents the decrease in intraperitoneal volume caused by the effective lymphatic absorption rate. The middle line shows the almost linear increase in the in situ intraperitoneal volume. Taken from ref [118] with permission of the author and of Blackwell Scientific Publishers

Biocompatibility of Icodextrin

The following factors can contribute to the bioincompatibility of PD solutions: acidity, buffer, hyperosmolality, glucose, and glucose degradation products (GDP). Icodextrin contains no glucose, isosmolar, and the concentrations of GDPs are lower than those in a 1.36% glucose solution [131]. The first in vitro study of the biocompatibility of icodextrin showed no improvement compared to glucose-based solutions [132]. However, at neutral pH the secretion of interleukin (IL)-6 by monocytes was superior to that after exposure to a 1.5% glucose-based solution [133]. Improved phagocytosis by peripheral polymorph nuclear cells and monocytes has been described after stimulation with icodextrin compared to standard solutions [134]. Ex vivo studies have shown improved phagocytosis of peritoneal macrophages when isolated from icodextrin effluent, compared to those from glucose effluent [135]. Similarly, the proliferation capacity of mesothelial cells on icodextrin was better [136]. The cancer antigen 125 (CA125) appearance rate in peritoneal effluent probably reflects mesothelial cell mass and is used as an in vivo biocompatibility marker for new dialysis solutions [137]. This parameter was not influenced by acute [138] or chronic treatment with icodextrin [139], probably because it is always combined with other osmotic agents for the short dwells.

Randomized Controlled Trials with Icodextrin

Two large randomized controlled trials (RCT) have been published on the efficacy and safety of icodextrin in prevalent PD patients [140, 141]. The MIDAS study, performed in the United Kingdom, was done in CAPD patients and had a follow-up of 6 months [140]. Icodextrin for the long dwell was compared with glucose. Icodextrin showed superior ultrafiltration after an 8 h dwell than 1.36% glucose and similar to 3.86% glucose. Mean serum sodium decreased from 140 to 136 mmol/L, probably because of slightly increased serum maltose levels that remained stable throughout the

study. An overall CAPD-related symptom score was better for icodextrin, compared to glucose. The RCT performed in the United States comprised CAPD and APD patients, and had a follow-up of 1 year [141]. The results were similar to those of the MIDAS study. Mean net ultrafiltration was higher on icodextrin compared to 2.5% dextrose for the long dwell. Body weight was stable on icodextrin but increased in the 2.5% glucose group and less icodextrin than glucose patients reported edema. The beneficial results on long dwell ultrafiltration in APD were similar to those described in other studies [142, 143].

The effects of icodextrin on net ultrafiltration, especially in patients with fast transport rates of low-molecular-weight solutions (see the section on pathophysiology) have prompted more RCTs in this patient group. A multicenter RCT in APD patients with a fast average or fast transport status showed superiority of 7.5% icodextrin for the long dwell compared to 4.25% dextrose [144]. Another double-blind RCT in CAPD and APD patients with fast average or fast transport status and a urine production <750 mL/24 h, comparing 7.5% icodextrin with 2.2.7% glucose for the long dwell, showed a decrease in body weight, total body water, and extracellular fluid in the icodextrin group during a follow-up of 6 months [145]. The beneficial effects of icodextrin on volume status were also found by Konings et al., who additionally reported a reduction of left ventricular mass, assessed by echocardiography [146].

General Effects and Side Effect of Icodextrin

The better control of volume status achieved with icodextrin could lead to better control of blood pressure. This was indeed found in one study [147], but could not be confirmed in another [145]. A beneficial effect on lipids has also been reported [148], but this could also not be confirmed in a larger study [145]. Improvement of diabetic control has been reported as assessed from Hb1Ac levels and insulin requirements [149]. One study reported some better preservation of residual urine production [145], and in another small retrospective analysis better preservation of residual creatinine clearance was found in APD patients [150]. Confirmation of these unexpected findings is required.

The use of icodextrin has effects on some laboratory investigations. All studies have shown a decrease of plasma sodium of on average 3 mmol/L. It is likely to be caused by the increased plasma maltose concentrations, as a compensatory mechanism to avoid hyperosmolality. A significant discrepancy has been reported between glucose measurements using glucose dehydrogenese-based methods and methods obtained in the laboratory using a reference method, like hexokinase [151, 152]. These methods overestimate plasma glucose levels due to the presence of oligosaccharides (mainly maltose) in the circulation and are therefore unsuitable for use in patients on icodextrin.

Dialysis with icodextrin also interferes with the measurement of plasma amylase activity resulting in a reduction of amylase levels. Plasma amylase activity may be reduced by 90% [153, 154]. Consequently, because icodextrin does not affect lipase activity, lipase measurement should be used for the diagnosis of suspected pancreatitis in dialysis patients on icodextrin. Skin rashes are the most frequent side effect of icodextrin [144]. Their prevalence varies from 0–6% to 15% [155–157]. An incidence of 1 per 60 patients-years has been found in a large post-marketing survey [158]. The occurrence is not related to the presence of circulating dextran antibodies [159]. The rash is usually not severe and is self-limiting.

An epidemic of culture-negative peritonitis in icodextrin patients was first described in 1999 [160]. It was followed by many other reports [161–165]. The incidence peaked in spring 2002. It appeared to be due to contamination by peptidoglycans, which are components of the bacterial cell wall [166]. The problem disappeared after adjustment of the production process, leading to peptidoglycan levels below the detection limit. It should be appreciated, however, that peritoneal effluent cell counts in stable patients are higher on icodextrin than on glucose-based conventional solutions [167]. The meaning of this is unknown.

The Place of Icodextrin in Modern Peritoneal Dialysis

The use of icodextrin for the long dwell both in CAPD and APD is well established because of its superior ultrafiltration profile and reduced exposure to glucose and glucose degradation products. A skin rash is the most important side effect, but it is usually mild and its occurrence is relatively rare. It should, however, be appreciated that plasma sodium levels are on average 3 mmol/L lower compared to glucose and that a low plasma amylase activity is present. Self-assessment methods for blood glucose determinations will have to be checked for interference of maltose. When these precautions are taken into account, icodextrin is currently the preferred osmotic agent for the long dialysis dwells.

Mixing icodextrin with other osmotic agents, for instance, a small amount of glucose, has been investigated [168–170], but this solution has not been taken into production. More recently, an experimental solution consisting

of 6.8% icodextrin, 2.86% glucose, and a sodium concentration of 121 mmol/L reported superior ultrafiltration and sodium removal during a 15-h dwell, but its applicability is not known [171]. The use of icodextrin in a glucose and amino acids mixture has been investigated in short APD dwells and was associated with only moderate increases in plasma levels of icodextrin metabolites, while leading to a marked reduction in the absorption of glucose [172]. However, this approach is also experimental.

Biocompatible PD Solutions

The bioincompatibility of conventional PD solutions, as discussed in Chapter 27, has led to the development of dialysis solutions that were different in one or more of the following: buffer, pH, and glucose degradation products (GDPs). No changes were made in the concentrations of glucose. The rationale for focusing on buffer, pH, and GDPs lies in the results of in vitro biocompatibility studies. The most important ones have been summarized in [173]. The combination of a low pH with lactate caused a partly irreversible decrease of the intracellular pH [174]. Heat sterilization of dialysis solutions leads to the formation GDPs and to marked toxicity of cultured mouse fibroblasts [175]. GDPs consist of aldehydes and dicarbonyl compounds [176], of which 2,3-dideoxyglucosone might be the most toxic one. They also promote the formation of advanced glycosylation end products at a faster rate than glucose itself.

Based on the above considerations, four dialysis fluids have been developed and are available in Europe and parts of Asia. These are Trio® (Gambro), Physioneal® (Baxter), Balance® (Fresenius), and Bicavera® (Fresenius). Their characteristics are summarized in Table 11.3. The reduction in the content of GDPs and the use of bicarbonate as a buffer can only be achieved by the use of dialysis bags with two compartments, which are mixed just before inflow. To reduce the formation of GDPs, glucose should be sterilized at a low pH, e.g., pH = 3, and in a high concentration. In Trio® and Balance®, glucose is sterilized separately.

It is evident from Table 11.3 that the solutions are different with regard to pH and buffer. The amount of GDP is somewhat higher in Physioneal®, but still less than half of that in Dianeal®. When bicarbonate only is used as a buffer, supraphysiological concentrations (35–40 mmol/L) are required. In vitro studies, however, showed no adverse effect of this excess [133, 177–180] with the exception of one [181]. The results with the bicarbonate buffer were similar to those obtained with lactate after adjustment to a normal pH [178].

In Vitro -and Animal Studies

All biocompatible solutions showed superiority in in vitro studies, when compared with conventional PD solutions [133, 177–180, 182–185]. This has also been shown for their effects on cultured mesothelial cells, where the bicarbonate buffer did better than the lactate buffer [186]. The in vitro studies have been reviewed in [180, 187, 188].

Animal studies have mainly focused on direct effects of exposure on peritoneal vessels, on changes in imprints of liver mesothelium, and on effects of long-term exposure of the peritoneal membrane. Intravital microscopy of mesenteric vessels in the rat showed that a conventional 4.25% glucose dialysis solution induced maximal vasodilation of mesenteric arteries, resulting in doubling of the arterial flow [189]. A reduction in the bicarbonate content reduced this effect, and it was absent when a bicarbonate buffer was used. The same model was used to study leukocyte recruitment [190]. The inhibition of lipopolysaccharide (LPS)-stimulated recruitment by conventional PD fluids was lower when Bicavera® was used.

Replacement of lactate by bicarbonate caused less damage of murine liver mesothelial cells [191], but this was not confirmed in trypsin washout experiments in a rabbit model [192]. The presence of GDPs in the dialysis solution caused marked mesothelial toxicity after 10 weeks exposure [193]. Exposure of Physioneal® in rats for 12 weeks showed a reduction in the peritoneal content of advanced glycosylation end-products (AGE), but not in peritoneal pentosidine [194]. Morphological changes after 10 weeks exposure in rats also showed a reduction in angiogenesis [195]. This

Table 11.3 Characteristics of biocompatible PD solutions

	pH	Buffer	3-DG (μmol/L)	Source
Trio	6.3	Lactate	65	Gambro
Physioneal	7.4	Bicarbonate/lactate	253	Baxter
Balance	7.0	Lactate	–	Fresenius
Bicavera	7.4	Bicarbonate	42	Fresenius

3-DG: 3-desoxyglycosone

reduction in the number of vessels by Physioneal® was even 50% after exposure for 20 weeks [196]. In the latter study, less peritoneal fibrosis was also found. A lower number of peritoneal vessels and a reduction in peritoneal fibrosis, in combination with a reduction in the staining for endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), picosirius red (stains fibrillary collagen), and AGE have later been confirmed, together with less mesothelial damage on Physioneal® [197]. The results of various animal studies have been reviewed in [198]. It can be concluded that the animal studies, also after long-term exposure, showed superiority in the preservation of peritoneal morphology and function of the biocompatible PD solutions compared to the conventional ones.

Ex Vivo Studies

Ex vivo studies have focused on functions of macrophages isolated from peritoneal effluent, on the properties of mesothelial cells cultured from the dialysate, and on substances that can be determined in effluent and that reflect some properties of peritoneal tissues. Peritoneal macrophages isolated after a 30 min dwell showed impaired secretion of tumor necrosis factor alpha (TNF-α) on conventional lactate buffered solutions [199]. This was unchanged after isolation from a bicarbonate solution but improved after a dwell with a bicarbonate/lactate fluid. Treatment with Physioneal® for 6 months resulted in a sustained improvement in peritoneal macrophage function [200]. The use of Balance® led to a reduction of epithelial-to-mesenchymal transition of mesothelial cells cultured from effluent when compared with a conventional solution [201].

Biocompatible dialysis solutions when used in prevalent patients have all been associated with an increase in the CA 125 concentration in effluent. This has been shown for Trio® [202], Physioneal® [203], Balance® [201, 204], and Bicavera® [205]. It is remarkable that these solutions, which are different with regard to buffer and pH, all show this phenomenon, suggesting an increase in mesothelial cell mass [137]. The data could be interpreted as a consequence of the reduced amount of GDPs present in all solutions, but this is still speculative.

Some studies showed a decreased effluent concentration of hyaluronan [202–204] while treated with biocompatible solutions. This substance has been suggested as a marker of inflammation and tissue remodeling in the peritoneal cavity. The results of studies of dialysate procollagen peptides have been equivocal [202, 203]. No consistent effects were found for effluent VEGF.

Clinical Studies

Clinical studies with biocompatible PD solutions have focused on inflow pain, correction of acid/base balance, effects on peritoneal transport, serum levels of AGEs, and whether or not an effect on residual renal function and patient survival is present.

A reduction of inflow pain on biocompatible solutions has been reported, which was statistically significant for Physioneal® [206] and just did not reach significance for Trio® [202]. This effect is likely to be due to the higher pH compared to conventional lactate buffered solutions [202]. The effect of a pure bicarbonate-based solution was less pronounced [206].

Replacement of lactate by bicarbonate resulted in a small increase in plasma bicarbonate in adult CAPD patients [207] and also in children treated with Bicavera® [205]. It appeared that the net bicarbonate gain was dependent on the ultrafiltration rate, plasma bicarbonate, and the bicarbonate content of the dialysis solution [208]. A comparison of a bicarbonate/lactate buffer with bicarbonate showed no differences in plasma bicarbonate or lactate concentrations [209, 210]. A randomized controlled clinical study comparing Physioneal® with the conventional solution showed that both solutions were equivalent with regard to plasma bicarbonate level and peritoneal solute transport [211]. A somewhat better ultrafiltration and a lower peritonitis incidence were also reported in that study, but these data have not been confirmed in other studies [212]. In general, no marked acute effects on peritoneal transport are present [213].

Glucose degradation products are low-molecular -weight solutes that are almost completely absorbed during a dialysis dwell. As stated above, GDPs lead to the formation of AGEs at a faster rate than glucose itself. It is therefore interesting that some clinical studies reported a reduction in the serum concentration of some AGEs while on biocompatible solutions. This has been described for total AGE and carboxymethyllysine in patients on TRIO® [214], and for imidazolone and carboxymethyllysine in the Eurobalance trial [204]. However, the decreases are small and the clinical relevance is unknown.

An unexpected effect of Balance® was found on residual renal function, which was better preserved than with the control solution [204]. These results will have to be confirmed to be sure that this effect has not been caused by chance. Another unexpected finding comes from the retrospective analysis done in Korea, where patient survival on Balance® was reported to be higher compared to treatment with conventional dialysis solutions [215]. However, the study has some methodological flaws, making the interpretation difficult. Obviously, more studies are required.

The Place of Biocompatible Solutions in Modern Peritoneal Dialysis

In vitro data, animal studies, and ex vivo data have shown beneficial effects of solutions with a reduced content of GDPs, often in combination with a higher pH and the inclusion of bicarbonate as a buffer. Clinical studies have not shown inferiority compared to the conventional solutions, and have shown some benefits, like less pain on infusion and lower serum levels of advanced glycosylation end products. It is noteworthy that, at present, the authors are not aware of any patient who developed encapsulating peritoneal sclerosis after treatment with biocompatible solutions exclusively. However, the results of more long-term studies will have to be known before determining their place in routine peritoneal dialysis.

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Chapter 12
Automated Peritoneal Dialysis

P. Kathuria and Z.J. Twardowski

Automated peritoneal dialysis (APD) is a term used to refer to all forms of peritoneal dialysis that employ a mechanized device to assist in the delivery and drainage of dialysate. Automated cyclers are used in intermittent peritoneal dialysis (IPD), nocturnal intermittent peritoneal dialysis (NIPD), continuous cyclic peritoneal dialysis (CCPD), tidal peritoneal dialysis (TPD), and continuous flow peritoneal dialysis (CFPD) [1–3]. In addition, some patients on continuous ambulatory peritoneal dialysis (CAPD) may receive one or more nocturnal exchanges with a night exchange device [4].

Automated PD is a fast growing modality for renal replacement therapy. The growth of APD has been facilitated by the development of new smart machines and increasing physician knowledge and patient acceptance. These machines have easy-to-use interfaces and incorporate microchips and computer technology enabling choice of therapies, safety features, and modalities to optimize therapy. Individualized therapies can be delivered to meet the lifestyle needs of the patient while ensuring adequacy of dialysis and ultrafiltration. Automation has dealt with some of the limitations of CAPD, including ultrafiltration failure, complications of increased intra-abdominal pressure, treatment fatigue, and failure to achieve clearance goals, and to some extent with noncompliance. Furthermore, in the new millennium, APD is poised to deliver a dose range beyond conventional dialysis and has the potential to deliver biocompatible solutions with specific compositions to meet individual needs by online preparation or regeneration of dialysate [5].

There has been a steady increase in APD utilization over the years: in 1998, only 21% of global PD patients were on APD and this number has increased by 1–2% annually [6] to approximately 30% at the end of 2004 [7]. Peritoneal dialysis grew by 6% between 2003 and 2004, largely driven by a 10% increase in utilization of APD. Mexico, the United Kingdom, and Korea are countries with the highest utilization of peritoneal dialysis, wherein treatment with APD modalities accounted for 21%, 32%, and 5% patients, respectively, in 2004 [7]. The French peritoneal dialysis registry reported the use of APD increased from 23% in 1995 to 36% in 2005 [8].

In the United States, even though the prevalent patients on peritoneal dialysis increased to 25,825 in 2003, there has been an overall decrease in the utilization of peritoneal dialysis for incident patients (USRDS 2005 Annual Data Report) [9]. The number of new peritoneal dialysis patients peaked at 8,530 in 1995 and declined to 6,690 patients in 2003. Of these, 2,100 (31.3%) patients were started on CCPD. Fifty-six percent of prevalent PD patients were on APD [9]. An industry report evaluating dialysis trends in the United States looked at four large cohorts of patients initiating peritoneal dialysis in 2000–2003 and found that majority of patients selected APD as their modality with a trend towards greater utilization from 58% in 2000 to 64% in 2003 [10]. This aberrancy from the USRDS Data Report may be due to inaccuracies in reporting of PD modality and a number of patients being reported with unknown modality. A prior report from the same group found that the proportion of patients on APD was over 60% in all age groups except those above 80 years of age [11].

CCPD was the modality of choice for 26% for all incident end-stage renal disease patients of age from 0 to 19 years, per the 2005 USRDS Data Report [9]. The North American Pediatric Transplant Cooperative Study Registry reported that APD was the modality at initiation and as well as throughout peritoneal dialysis follow-up for almost 70% of incident pediatric dialysis patients between 1992 and 1998 [12].

P. Kathuria (✉)
University of Oklahoma College of Medicine, Tulsa, Oklahoma
e-mail: Pranay-Kathuria@ouhsc.edu

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History of APD

The first peritoneal cycler was described by Fred Boen et al. in the early 1960s [13, 14]. This device used a sterile dialysate prepared in the hospital and delivered to the bedside in 40-L carboys. Therapy consisted of multiple 2-L exchanges delivered over a 10-h period. An automatic solenoid device controlled delivery of the dialysate into the peritoneal cavity. In 1966, Norman Lasker and co-workers [15] described an automated cycler that became the forerunner of modern cyclers. This gravity-based machine utilized 2-L bottles of dialysate and disposable tubing. A preset volume of dialysate was delivered to the patient and was drained after a prescribed dwell time. At the same time as Lasker, Tenckhoff et al. [16] designed an automated system that mixed dialysate concentrate with distilled water processed by a "miniature still." This system proved to be expensive, bulky, and time consuming to use, and was soon abandoned. After the development of reverse-osmosis water, Tenckhoff et al. [17] adapted the technology to develop a new cycler. This cycler used reverse-osmosis water and a proportioning system to mix treated water with dialysate concentrate. Large amounts of dialysate could be easily prepared at a relatively lower cost. Higher glucose concentrations were achieved by adding hypertonic glucose to the mixture.

Cyclers were initially used for intermittent peritoneal dialysis (IPD). IPD was popular between 1970 and 1976 because the simplicity of the procedure permitted patients to perform home dialysis with or without the help of a partner [18]. Patients on IPD also enjoyed relative freedom between treatments to carry out other activities. However, IPD fell out of favor by the late 1970s because of poor outcomes due to inadequate dialysis and malnutrition [19–21]. In 1976, Popovich and co-workers [22, 23] described the concept of equilibrium peritoneal dialysis, moving the focus away from cycler-dependent treatments. They proposed that fluid left in the abdominal cavity over 4 h would equilibrate with blood urea. Five exchanges of 2 L each and 2 L of ultrafiltration would be required for controlling uremia. This method came to be called continuous ambulatory peritoneal dialysis (CAPD) [23]. The real revolution for CAPD came with the development of collapsible plastic bags for dialysate [24].

Interest in APD was revived by Diaz-Buzo et al. [25] and by Price and Suki [26]. They described the procedure called continuous cyclic peritoneal dialysis (CCPD), which is a form of automated equilibrium peritoneal dialysis. Patients receive three or four exchanges automatically at night and an additional exchange that remains in the abdomen through the day. The catheter is capped during the day and the patient starts the nocturnal exchange by emptying the peritoneal cavity.

A dialysis procedure that combined intermittent and continuous-flow technology was introduced in the late 1960s and early 1970s to increase the efficiency of IPD. This technique was initially introduced as recirculating peritoneal dialysis [27] and was later revived by Twardowski in 1989 and renamed tidal peritoneal dialysis (TPD) [28]. During this procedure, after an initial fill volume is instilled into the abdominal cavity, only part of the dialysate is drained and replaced by fresh peritoneal dialysis fluid with each cycle. The hypothesis behind this procedure is that leaving a "sump volume" in the cavity would improve clearances, as there would be constant contact between the peritoneal membrane and dialysate.

Peritoneal Dialysis Solutions

The traditional peritoneal dialysis solutions used for APD are the same as used for CAPD. The solutions are available in three different dextrose concentrations (1.5%, 2.5%, and 4.25% dextrose). The dextrose concentrations used for shorter dwells are generally 1.5% or 2.5%, while for the long dwell the preferable concentration is 2.5% or 4.25% to prevent excessive fluid absorption. The composition of the standard peritoneal dialysis solution is provided in Table 12.1. A problem occasionally seen in APD modalities using short dwells (NIPD, TPD) is the development of hypernatremia due to sodium sieving [29–32].

Several in vitro and in vivo studies have demonstrated the unphysiologic nature of conventional dialysis solutions [33–35]. Lactate, the low pH, high glucose, and glucose degradation products are likely the major determinants of

Table 12.1 Composition of standard solutions for automated peritoneal dialysis

Dextrose (%)	1.5, 2.5, 4.25
Sodium (mEq/L)	132
Potassium (mEq/L)	0
Calcium (mEq/L)	2.5–3.5
Magnesium (mEq/L)	0.5–1.5
Lactate (mEq/L)	35–40

bioincompatibility. Experiments by Breborowicz suggest that the cytotoxicity of peritoneal dialysis solutions is most evident immediately after instillation of dialysate and gradually declines within minutes of the dwell [35]. This decline in cytotoxicity occurs due to the residual intraperitoneal fluid and a rapid equilibration process in the peritoneal cavity. Since the impact of fresh peritoneal dialysis solutions is maximum at the beginning of the dwell time, there has been concern that the larger volumes of solution and more frequent exchanges during APD would cause a more rapid deterioration of the peritoneal membrane when compared with CAPD [36]. Comparison of CAPD and CCPD in an in vitro system showed no short-term detrimental effects on biocompatibility parameters indicative for peritoneal host defense, mesothelial cell integrity, and peritoneal fibrosis [36]. On the other hand, ex vivo studies on peritoneal macrophages have shown impaired local phagocytic and opsonic capacity with shorter dwells [37, 38].

With glucose-based therapies, the incidence of negative ultrafiltration during the long dwell is high [39]. This therapeutic failure with glucose-based solutions increases the requirements for enhanced ultrafiltration in the cycler-based nocturnal component of the therapy, resulting in the use of higher glucose tonicities and consequently greater glucose exposure [40]. Icodextrin is an alternative osmotic agent, which provides sustained ultrafiltration during the long dwell and is low in glucose degradation products [41–44]. It has a high molecular weight, which results in a sustained colloid osmotic gradient. Icodextrin is absorbed from the peritoneal cavity at a much slower rate than dextrose and consequently provides superior ultrafiltration per gram of absorbed carbohydrate [43]. Reduction of carbohydrate absorption may help reduce the metabolic complications of peritoneal dialysis [45]. In a computer-generated three-pore model, Rippe and Levin predict that ultrafiltration will keep increasing with icodextrin even after a 15-h dwell [46]. Most clinical studies in APD patients have shown that ultrafiltration with icodextrin is around 168–270 mL [41–44]. However, Finkelstein et al. in a study comparing icodextrin and 4.25% dextrose in high and high average transporters showed mean ultrafiltration with icodextrin in APD patients to be >500 mL with a dwell period of 14–16 h. Between 33 and 38% of patients in this study had negative ultrafiltration with 4.25% dextrose and none after 2 weeks of randomization to icodextrin [40]. A recent study showed maximum ultrafiltration with icodextrin dialysis solution in APD patients is achieved at 10 h, beyond which, increasing the dwell time does not lead to any significant increase in ultrafiltration [47]. Overall ultrafiltration with icodextrin during the day exchange in APD appears to be less than in the night exchange on CAPD. An upright posture and physical activity produce greater intraperitoneal pressure, resulting in increased lymphatic reabsorption during a daytime dwell [48].

A benefit of increased ultrafiltration with icodextrin is an increase in small solute clearances and sodium removal [40–43, 49]. The increase in sodium removal has been demonstrated to improve control of fluid balance [43, 49, 50]. Impact of icodextrin on blood pressure control on APD patients needs to be studied in a systematic manner with only one of the current studies showing improvement in blood pressure control [50]. With improved ultrafiltration, it was initially feared that there would be a negative impact on residual kidney function. However, current studies suggest that the use of icodextrin could preserve urinary volume and clearances compared to conventional peritoneal dialysates [49, 51].

Another benefit of icodextrin is that it produces less glycation of protein and appears more biocompatible [52]. The European Automated Peritoneal Dialysis Outcomes Study (EAPOS) measured longitudinal membrane function (solute transport and ultrafiltration capacity) annually in a prospective but nonrandomized cohort of 177 functionally anuric patients. The whole cohort experienced an increase in solute transport and reduction in ultrafiltration capacity at 12 and 24 months. A subgroup analysis according to glucose exposure and icodextrin use at baseline found these changes were accelerated and more severe in patients using either 2.27 or 3.86% glucose. Icodextrin use in these circumstances was associated with less deterioration in membrane function [53].

The use of icodextrin may cause a decrease in serum sodium and chloride levels. There is a decline in serum α-amylase activity, which likely has no clinical significance. A skin rash and exfoliate dermatitis may develop with the use of icodextrin [43, 54].

An innovative development from the standpoint of APD has been the introduction of bicarbonate solutions. These solutions are packaged in dual chambered bags or potentially, in the future may be generated online. The dual-chambered bags separate calcium and magnesium from bicarbonate. These bags contain physiologic concentrations of bicarbonate and allow dialysate to be delivered at a physiological pH. Furthermore, the two chambers allow glucose to be sterilized at a very low pH, minimizing the generation of glucose degeneration products [55]. Currently marketed are peritoneal dialysis solutions contain 25 mmol/L of bicarbonate with either 10 or 15 mmol/L of lactate, allowing for flexibility in control of acidosis. An alternative solution contains only bicarbonate (34 mmol/L) as a buffer (Table 12.2). On-line production of dialysate was first described by Tenckhoff [16, 17]. More recently, a machine used for online production of a replacement fluid for hemofiltration was adapted to produce peritoneal dialysate [56]. The machine utilizes reverse osmosis water and a proportioning system to mix a standard acid concentrate with a bicarbonate bath. Such systems could potentially decrease costs associated with high-volume therapies and offer customization of dialysate to meet the needs of an individual patient.

Table 12.2 Composition of bicarbonate-based peritoneal dialysis solutions

	Bic/Lac 35	Bic/Lac 40	Bicarb 34
Sodium (mEq/L)	132	132	134
Calcium (mEq/L)	1.75	1.25	1.75
Magnesium (mEq/L)	0.25	0.25	0.5
Chloride (mEq/L)	101	95	104
Bicarbonate (mMol/L)	25	25	34
Lactate (mMol/L)	10	15	0
Dextrose %	1.5, 2.5, 4.25	1.5, 2.5, 4.25	1.5, 2.5, 4.25
Ph	7.4	7.4	7.0–7.6
pCO_2 (mm Hg)	48	48	60

Bicarbonate-based peritoneal dialysis solutions are more physiological, and are especially indicated for children in whom hepatic conversion of the buffer lactate to bicarbonate is rate-limited, in patients requiring dialysis for acute renal failure, or those with hepatic dysfunction [57]. These solutions are associated with lesser infusion pain and improvement in biocompatibility parameters including enhanced phagocytic activity of peritoneal macrophages, reduced constitutive inflammatory stimulation, reduced advanced glycosylation end products accumulation, and better preservation of the mesothelial cell integrity [58, 59]. Children dialyzed with conventional peritoneal dialysis solutions may need additional bicarbonate to correct acidosis; a switch to bicarbonate [59] or bicarbonate/lactate solutions improves acid-base balance and may even cause alkalosis [60]. Subtle changes in solute transport may be noted on peritoneal equilibration tests during bicarbonate dialysis with a less steep creatinine equilibration curve suggesting reduced peritoneal vasodilation [59].

Amino acid–based peritoneal dialysis solutions may be an option for the malnourished patient on APD. A 1.1% amino acid solution provides ultrafiltration roughly equivalent to a 1.36% dextrose solution [61]. Studies have established the benefit of amino acid peritoneal dialysis solutions in continuous ambulatory peritoneal dialysis [62, 63]. For adequate absorption on APD, the amino acid solutions would have to be used for the long dwell. An option to achieve adequate ultrafiltration would be to combine an amino acid solution with glucose or a glucose polymer [64]. In a crossover study, combined administration of dextrose and amino acid in the peritoneal dialysate improved protein anabolism in APD patients [65].

Peritoneal Dialysis Cyclers

The use of sophisticated software and hardware has made the present generation of cyclers safe, reliable, and easy to use while allowing these devices to become compact and portable. Most cyclers offer built-in programs with options for all the varied modalities of automated peritoneal dialysis, including CCPD, classical IPD, NIPD, TPD, and CFPD. These machines are programmable for dialysis modality, inflow volume, fill, dwell and drain times per cycle, last bag fill options, and additional daytime automated exchanges. Most cyclers automatically monitor infusion and drainage rates. They increase treatment efficacy by eliminating lag-time between exchanges after a predetermined volume has drained and the drain has slowed below a certain threshold. The cyclers are equipped with on screen displays, which provide instructional steps, including troubleshooting alarms.

Recent sophistications include flash memory cards and modems. The memory card serves two functions: To program the patient's prescription into the cycler and to collect information about treatments. The card is programmed at the center with the desired prescription and then uploaded into the cycler. In some machines, the card can contain information about several prescriptions and the patient could choose the most appropriate for a particular session. The card also records details of each treatment, including ultrafiltration, total volume, fill volume, drain time, cycle time, and any alarms, eliminating the need for paper records. Information regarding compliance such as shortened or missed treatments, changes in fill volumes, and bypassed therapy phases are recorded. This information is easily converted by software into easy-to-interpret charts and graphs allowing for quick identification of problems. The data card can be brought by the patient for their visit or be uploaded to the center through a modem.

Cyclers are equipped with easy-to-install disposable tubings. The tubing manifold has several prongs for spiking dialysate bags and a single prong leading to the patient. Some cyclers provide for automatic connection and bag identification using laser bar-readers. The use of large-volume dialysate bags has reduced the costs of treatment, as well as the number of required connections. The dialysate is moved from the dialysate bags to a reservoir bag and then instilled into the patient. After the designated dwell time is complete, the dialysate is either emptied into a bag or

drained directly. The movement of dialysate through the cycler and in and out of the patient is mediated by gravity, pump-driven systems, or a combination of the two. Fluid is preheated in the reservoir bag, which is placed on a heater cradle. The preheating of the fluid is done more for the patients' comfort rather than to prevent hypothermia. Integrated scales allow accurate delivery of the fill volume and measurement of drainage and ultrafiltration volumes. Cyclers with pediatric treatment options can deliver volumes as small as 50 mL with the option of 10-mL increments [66].

Ronco et al. [66, 67] predict that, in the future, cyclers will be capable of optimizing therapy and delivering appropriate solutions. Machines will be equipped with sensors capable of measuring intraperitoneal pressure in addition to flow sensors. Segmental bioimpedance measurements may be incorporated to measure intraperitoneal fill volumes and ultrafiltration during rapid APD therapy. These devices will allow for detection of catheter malfunction as well as allow the machine to tailor make the next dialysis exchange with regards to osmolality, dwell time, and cycle volume. A fine control of ultrafiltration could be achieved by altering sodium and glucose concentrations in the dialysate. These futuristic machines will monitor pO_2, pCO_2, and pH in the effluent to perfect on-line production of bicarbonate-based dialysate with intelligent feedback. Measurement of urea and creatinine in the spent dialysate will permit assessment of adequacy. Biosensors capable of detection of white blood cells will help with the early diagnosis of peritonitis.

Physiology of Solute and Fluid Transport

Physiological principles of solute and water transport are discussed extensively in Chapter 6. APD modalities introduce a biphasic profile for both clearances and ultrafiltration behavior by the use of short dwell exchanges during the night and a day dwell that may be much longer than the overnight dwell in CAPD.

Solute Transport

Solute transport across the peritoneal membrane is dependent on diffusion and convection.

Solute Transport by Diffusion

The diffusive transport of solutes is a function of the membrane transport characteristics, dialysate flow rate, peritoneal capillary blood flow rate, concentration gradient, and time allowed for transport [68].

The membrane transport characteristics can be assessed by a variety of clinical tests. The most commonly used technique to evaluate the peritoneal transport characteristic is to measure the dialysate to plasma solute concentration (D/P) for particular solutes during an exchange with conventional peritoneal fluid. This procedure has been standardized by Twardowski et al. [69, 70], and named the peritoneal equilibration test (PET). Patients are classified into four membrane categories: high, high average, low average, and low. Other measures of peritoneal transport are the mass transfer coefficients (MTC) and the peritoneal permeability analysis [71–73]. The MTC is the solute clearance rate that would be achieved across the peritoneum in the absence of both ultrafiltration and solute accumulation in the dialysate. Various numerical models have been described to calculate the MTC. The standard peritoneal permeability analysis (SPA) is a modification and extension of the PET: glucose1.36% dialysate is used, to which dextran 70 is added for the calculation of fluid kinetics. Mass transfer area coefficients (MTAC's) of low molecular weight solutes, clearances of proteins and the change in intraperitoneal volume (IPV) are assessed.

High or rapid transporters tend to equilibrate small solute concentrations between dialysate and blood early in a dwell. These patients also absorb glucose early in the dwell. Once the osmotic gradient has dissipated, ultrafiltration ceases, and the dialysate returns are reduced because of reabsorption of fluid. These patients are best served by short dwell treatments. On the other hand, patients with low transport rates achieve peak ultrafiltration late during the dwell, and D/P ratios increase almost linearly over a long dwell. These patients benefit from continuous regimens, as the total dialysis time is crucial for adequate clearances [74]. These principles are illustrated in Fig. 12.1 and recommended peritoneal dialysis modalities are suggested in Table 12.3.

Several factors affect the MTC; important from the APD standpoint are the position during dialysis and the dialysate exchange volume (V_{ip}). Using the same V_{ip}, the MTCs for urea and creatinine were increased 24% and 19% in one study [75], and 15% and 9%, respectively in another study [76] in the supine position when compared with the upright position. In the supine position, the dialysate layers throughout the entire abdominal cavity, while in the upright position dialysate pools in the subumbilical region of the abdomen. The increase in the MTC is caused by increased contact of dialysate with

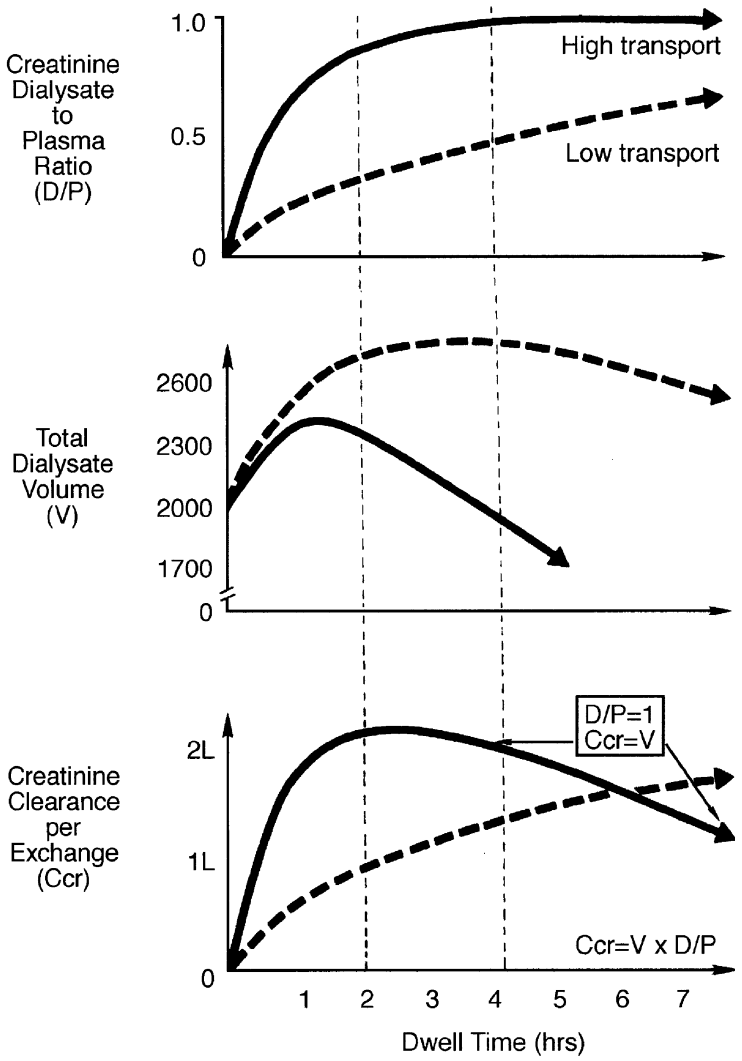

Fig. 12.1 Idealized curves of creatinine and water transport during exchange with 2 L of 2.5% glucose dialysis solution in patients with extremely low and high peritoneal transport characteristics. Upper panel shows dialysate to plasma ratio (D/P); middle panel shows total dialysate volume (V), which is the sum of infusion volume and ultrafiltration; lower panel shows creatinine clearance per exchange (C_{cr}). The curves in the lower panel are derived from those of the upper and middle panels. ——, high peritoneal transport; - - - -, low peritoneal transport. From Ref. [74] with permission

the peritoneal membrane. Additionally, in the supine position, dialysate is more accessible to the peritoneal membrane around the liver [76]. The peritoneal membrane around the liver accounts for up to 45% of the total MTC for the entire peritoneal cavity [77]. Portal blood flow also increases in the supine position [78].

An increase in the V_{ip} increases solute clearances by an increased plasma to dialysate concentration gradient and/or to an increased effective peritoneal area [79]. Schoenfeld et al. [80] observed a strong linear relationship between the peritoneal transport constant and V_{ip}. These correlations occurred over a range of 1–3.8 L of V_{ip}. Keshaviah et al. [81] found that the V_{ip} associated with peak MTC increased with increasing body surface area, and a fill volume of approximately 1,500 mL/m^2 body surface area provides a maximal MTC. Higher fill volumes do not improve dialysis efficiency further. A study using computerized tomography to assess the effect of increased dialysate volume from 2 to 3 L found an 18% increase in peritoneal surface area in contact with dialysate and consequently enhanced the MTC. In spite of a 50% increase in fill volume, the larger volume does not make contact with the entire peritoneal dialysis surface area [79]. Increasing the V_{ip} is a more effective means of increasing solute clearances than more frequent exchanges with lower V_{ip}. This practice also reduces dialysate transit time, or the non-dialytic period, and improves clearances. Increases in $V_{ip,}$ however, will increase the intra-abdominal pressure which may decrease ultrafiltration.

Table 12.3 Preferred peritoneal dialysis modality based on solute transport

Solute transport	Preferred modality
High	NIPD, CCPD, TPD
High-average	CAPD, CCPD, CCPD + CAPD, TPD + CAPD
Low-average	CAPD, CCPD, CAPD+ CCPD
Low	CAPD, HD

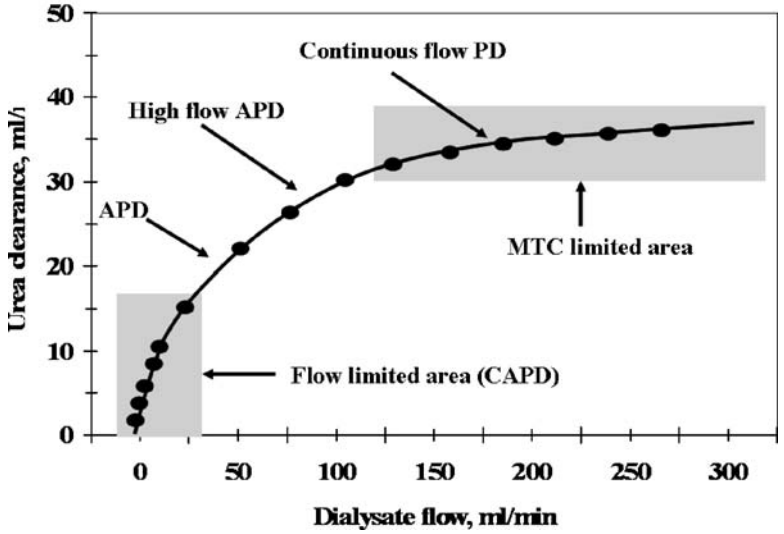

Fig. 12.2 Relationship between urea clearance in peritoneal dialysis and dialysate flow rate. From Ref. [82] with permission

The impact of dialysate flow on urea clearance is demonstrated in Fig. 12.2 [82]. The initial portion of the curve corresponds with the dialysate flow rates typical of CAPD (three to five exchanges per day). In this region of the curve, there is a steep correlation between urea clearance and dialysate flow rates. CAPD is, therefore, dialysate flow limited, and improved clearances may be achieved by increasing the number and/or the volume of exchanges. The second region of this curve is typical for APD. This region is affected by both the dialysate flow rate and MTC. As dialysate flow is increased in automated regimens, the dwell times become shorter, and an increasing proportion of exchange time is occupied by the inflow and drainage times [82, 83]. Although clearances may be improved by increasing dialysate flow, a point of diminished return will eventually be reached. Continuous flow peritoneal dialysis and tidal peritoneal dialysis try to address this issue by increasing contact time between dialysate and the peritoneal membrane. In tidal peritoneal dialysis, only part of the fluid is drained and replaced during an exchange [28]. Continuous flow peritoneal dialysis [84] through two catheters or a double-lumen catheter secures full contact of the dialysate with the peritoneal membrane, but at high flow rates, fluid channeling may restrict mixing [85].

The above illustrates that higher urea clearances can be achieved by increasing dialysate flow rates. Creatinine, urates, phosphates, and middle molecules equilibrate at a slower rate and hence clearances are lower than for urea. These kinetic characteristics of APD create adequacy discrepancies between Kt/V_{urea} and creatinine clearance [86]. The absorption of glucose is characterized by an exponential decay, shorter dwells reduce absorption of dextrose and improve ultrafiltration. Adequate ultrafiltration may be obtained while using low glucose concentrations in conjunction with high dialysate flow rates [86].

Solute Transport by Convection

Solutes accompany the bulk flow of water from the peritoneal capillary blood into the peritoneal membrane by convection (solute drag). For high-molecular-weight solutes, the convective transport is more important than the diffusive one. The magnitude of convective transport is determined by the ultrafiltration rate for the peritoneal membrane, the average solute concentrations within the membrane [87] and the sieving coefficient (S, describing the fraction of solute that passes through the membrane with water flow: $0 \leq S \leq 1$) [29, 30].

Although the sieving effect influences each solute, the important clinical consequence of sieving is related to sodium. The ultrafiltrate is usually low in sodium. Thus, dialysate sodium concentration is initially reduced in the dialysate and tends to increase late in the dwell due to diffusion of sodium into the dialysate and diminished ultrafiltration in longer dwells [29–32, 69]. During APD with shorter dwells, the net electrolyte removal per liter of ultrafiltrate remains far below the extracellular fluid concentration and severe hypernatremia and hyperosmolality may develop [88]. Ortega et al. [89] compared sodium removal in 36 patients undergoing CAPD and APD. Average peritoneal sodium removal was 195 mmol/day in CAPD and 87 mmol/day in APD, a difference attributed to lower ultrafiltration provided by APD. Part of the differences in ultrafiltration and sodium removal between CAPD and APD may be due to overfill of dialysis bags. In CAPD, the overfill is drained into the same bag submitted for laboratory analysis leading to an overestimation of ultrafiltration and sodium removal. The cycler patients use a single, smaller-volume flush that is discarded at the time of set-up and the cyclers provide fairly accurate estimates of instilled and drain volumes [90]. In a

larger study, Rodríguez-Carmona and Fontán [91] reported that total sodium removal was 210 mmol/day for CAPD and 91 mmol/day for APD, after taking into consideration overfill. Sodium removal of less than 100 mmol/day was present in 7.1% of CAPD patients and 56.4% patients on APD in their study. The use of icodextrin, supplementary diurnal exchanges, and longer nocturnal dwell times improves sodium removal in APD. An alternative is to reduce the dialysate sodium concentration. Since commercially available dialysis solutions do not offer this option, one may mix a 5% glucose solution (D5W) in appropriate proportions to achieve lower dialysate sodium concentrations [74].

Fluid Transport

Ultrafiltration

The net ultrafiltration is determined by the difference between the transcapillary ultrafiltration (TCUF) and absorption of fluid from the peritoneal cavity. The latter consists of transcapillary back-filtration and fluid uptake into the lymphatic system. The transcapillary ultrafiltration gradient is dependent on the hydraulic permeability of the peritoneum, its effective surface area, and the hydrostatic and the osmotic (colloid and crystalloid) pressure gradients [92, 93].

The transperitoneal crystalloid osmotic gradient is established by dextrose. The dissipation of dialysate/plasma glucose gradient during peritoneal dialysis is nonlinear, with a rapid initial decline followed by a slow decrement. The shorter nighttime cycles in APD take advantage of the high initial ultrafiltration rate. Further, the shorter the dwell time, the more preserved is the osmotic gradient and lower the difference for ultrafiltration across different membrane transport types. On the other hand, during the long daytime dwell, there is dissipation of the osmotic gradient and hence loss of the stimulus for ultrafiltration. High and high-average transporters are at most risk for negative ultrafiltration. This is best addressed by shortening the day dwell, or the use of higher dialysate tonicities or icodextrin [94].

The hydrostatic pressure in the peritoneal capillaries may be assumed to be 17 mm Hg [95]. The opposing hydrostatic pressure in the peritoneal cavity (intraperitoneal pressure) varies depending on the V_{ip} and posture and activities and may range from 5 mm Hg in the supine position, to over 20 mm Hg while standing and over 200 mm Hg with certain activities [96, 97]. In the supine position, the intraperitoneal pressure (IPP) is the least. However, with the use of larger volumes to augment clearances, the IPP will rise and impact transcapillary ultrafiltration and more so increase back filtration and lymphatic absorption [98].

Lymphatic Absorption

Along with ultrafiltration, there is a constant absorption of fluid from the peritoneal cavity. Fluid and solutes are reabsorbed directly by the lymphatics and also by a process of back-filtration into the peritoneal interstitium [99–101]. Fluid and solutes entering the peritoneal interstitium are taken up by the local lymphatics and capillaries. The IPP is a major determinant of egress of fluid from the abdominal cavity into the tissues lining the peritoneal membrane [100–102] and consequently the IPP influences the lymphatic absorption rate [98].

The subdiaphragmatic lymphatics account for the major portion of the fluid reabsorbed by lymphatics [99]. Lymphatic absorption is dependent on diaphragmatic movements and contact of fluid with the diaphragm. There is an increased contact of fluid with the subdiaphragm in the supine position and enhanced fluid absorption [103, 104]. Thus, in supine APD, two conflicting variables affect lymphatic fluid reabsorption: one, the lower IPP and two, the increased contact of fluid with the subdiaphragm.

Relationship Between Intraperitoneal Volume and IPP

Physical characteristics such as gender, body size, abdominal muscle tone, duration on peritoneal dialysis, and infused dialysate volume influence IPP. The empty peritoneal cavity has an IPP of 0.5–2.2 cm H_2O. The IPP rises in direct proportion to the amount of fluid infused into the abdominal cavity. Studies from APD show increases in IPP from 3.76 to 6.11 cm H_2O per liter of intraperitoneal fluid in the semi recumbent position [105–107]. Durand et al. demonstrated a rise in the IPP of 2 cm H_2O per liter of infused dialysate in the supine position [108]. A study measuring IPP in CAPD patients in the supine position found a strong inverse relationship between the dialysate volume/BSA ratio and IPP. This inverse relationship means that for any given fill volume, patients with smaller body size have a higher IPP than do patients with larger body size [109].

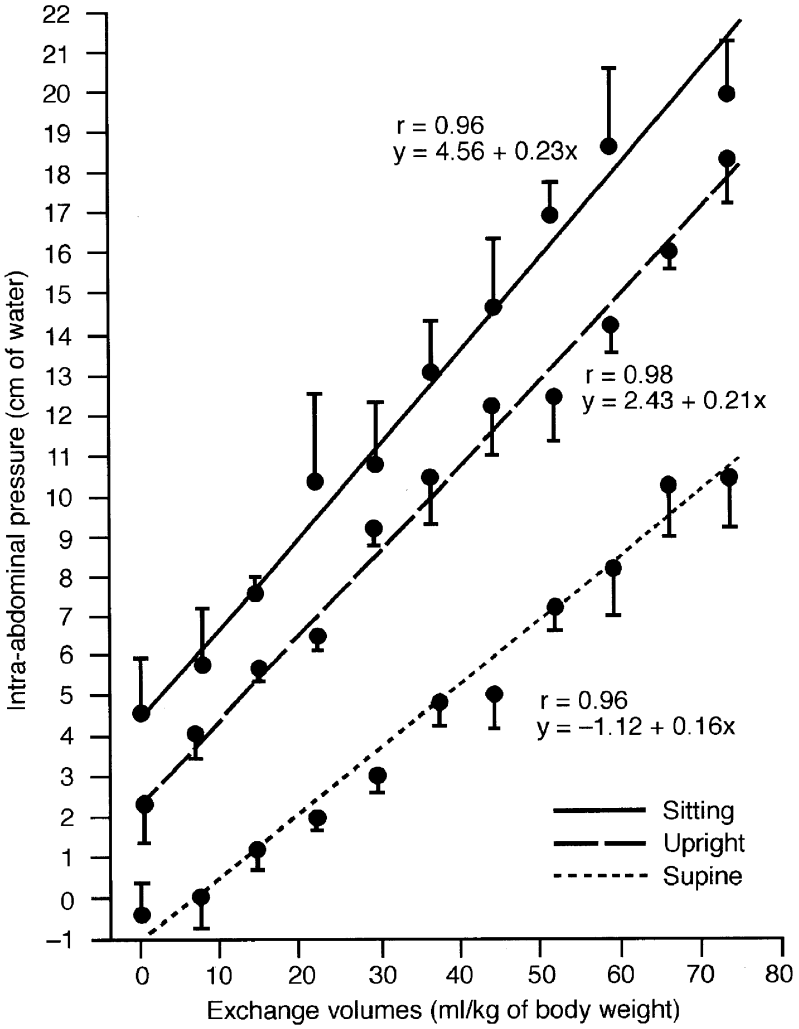

Fig. 12.3 Comparative effect of dialysate volume and patient position on intra-abdominal pressure. From Ref. [97] with permission

The relationship between IPP and V_{ip} is maintained regardless of the patient's position, but the slope of the curve does shift with changes in position. For any intraperitoneal volume, IPP is minimized by assuming the supine position; sitting leads to the highest pressures, and standing results in intraperitoneal pressures between those seen with sitting and lying down (Fig. 12.3) [96, 97, 107].

An increase in the IPP can cause a decrease in the net ultrafiltration [110]. A change in posture from supine to upright was associated in one study with a small increase in lymphatic absorption (+8%) and a decrease in transcapillary ultrafiltration (–5%), largely attributable to change in the IPP [104]. In another study, an increase in the IPP by 1 cm of water was found to cause a decrease in ultrafiltration of 74 mL at 2 h [111].

Dialysate Fill and Drain Profiles

It is generally known that dialysate fill rate is a function of fill height and patient position. The lower IPP in the supine position facilitates a higher fill rate for dialysate than in the upright position. Increasing drain height can also shorten the drain rates. Larger-bore catheters do not provide better fill rates, but may decrease the drain time [75].

The characteristic drain profile shows a bimodal pattern with high drain rate (>200 mL/min) for the initial 5–7 min, during which time over 80% of the dialysate is drained; followed by a very abrupt transition to a very slow drain rate (<50 mL/min) (Fig. 12.4) [75, 112]. A variable intraperitoneal volume is left at the breakpoint ranging from 0 to 1,200 mL, with an average of 500 mL [113]. This abrupt transition between outflow rates may happen due to bowelloops

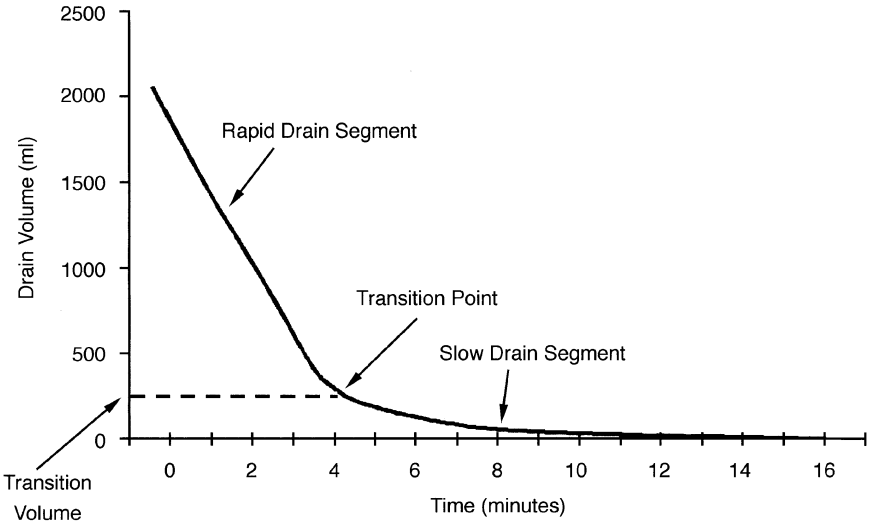

Fig. 12.4 Representative dialysate drain profile. From Ref. [75] with permission

collapsing on the catheter as the transition volume is approached, causing a significant reduction in outflow [75]. An alternative explanation is that the breakpoint may be due to a sudden drop in the conductance of the hydraulic system – when a critical intraperitoneal volume is reached, outflow from the abdomen becomes restricted [112]. The IPP is the force behind the drainage phases and at breakpoint, an equilibration between the V_{ip} and the IPP is possibly reached.

From the above discussion it is clear that a majority of the drain time during each cycle in APD is spent removing a small percentage of the total dialysate. Tidal peritoneal dialysis, wherein a tidal volume is exchanged in each cycle, utilizes only the rapid drain segment and obtains maximal benefit of this mechanism. A further refinement is breakpoint APD that refers to a tidal PD characterized by a variable reserve volume determined by the breakpoint allowing for optimization of drainage times. The effects of optimizing drain cycles are discussed subsequently in this chapter.

Factors Influencing Selection of APD

APD is the fastest-growing modality of peritoneal dialysis worldwide. However, there is a high variance in the use of APD in different areas of the world. Medical limitations, physician education and biases, availability and cost of equipment and supplies, patient preferences, social reasons, and reimbursement concerns impact the selection of dialysis modality [114].

The choice of APD over CAPD should initially be based on the patient's preference. The increased convenience of these treatments makes them more suitable for patients who have work commitments during the day. APD is the modality of choice in children and adolescents. The main reasons for these are the following: peritoneal diffusion is higher in children [115], freedom from bag exchanges in the daytime, no need for venipunctures, and no major effect on the work schedule of their parents [116, 117]. Elderly patients and those with manual or visual impairments who are dependent on assistance from others opting for peritoneal dialysis are best treated by APD to prevent overwhelming their partners or helpers [117, 118]. Patients, especially children who develop psychosocial problems due to distortion of body image by a protruding abdomen, should also be treated by APD [116].

From a physiological standpoint, the choice of peritoneal dialysis modality is best guided by the nature of the peritoneal membrane transport characteristics. Optimum therapy is achieved by matching modality and dwell times to the transport type of the patient [70, 74] (Table 12.3). Patients with high peritoneal transport characteristics and minimal residual kidney function (RKF) are best treated with APD to maintain adequate ultrafiltration. APD may need to be considered as a modality for patients with ultrafiltration failure. Larger patients and those with declining RKF needing higher fill volumes to achieve adequacy are candidates for APD as they may be more comfortable with doing these exchanges while supine. APD is a viable option for patients with complications due to increased intra-abdominal pressure (hernias, dialysate leaks, hemorrhoids, uterine prolapse, and back pain) [6]. From our earlier discussion, IPP is much lower in the supine position for the same dialysate exchange volume. Tidal peritoneal dialysis is indicated for patients who have drain problems or patients with infusion pain or pain at the end of a drain. APD may be offered to patients feeling burnout from CAPD [67].

However, APD is not an option for all patients. Higher costs due to the need of a cycler, disposable tubing, and generally larger dialysis volumes serve as a deterrent. Some patients may not accept the prolonged restriction to bed for the duration of overnight cycles or the dependence on a machine. There is a potential for sleep disturbances by machine alarms [118]. Sodium sieving may lead to hypernatremia, increased thirst, and poor blood pressure control [88].

Different Regimens of APD

Classical Intermittent Peritoneal Dialysis

Intermittent peritoneal dialysis (IPD) is a term used for dialysis regimens wherein periods on dialysis alternate with those when the peritoneal cavity is dry [3]. During classical IPD the patient receives several short dwell exchanges over 12–24 h with a dialysis dose between 40 and 60 L, several times a week but usually not every day. Though the procedure can be performed manually, automated cyclers or systems with on-line generation of dialysate are more practical. Treatments may take place in-center or at home.

Classical IPD is no longer used as a modality of chronic renal replacement therapy because of poor clearances and high morbidity and mortality [19–21]. However, the procedure continues to be used in countries where there are few alternatives for dialysis [119]. IPD may serve as an alternative to hemodialysis in patients needing immediate dialysis after peritoneal catheter placement. Small-volume supine dialysis is recommended during this period of catheter break-in. Cheng et al. [120] reported a higher incidence of pericatheter leaks, especially among diabetics started on IPD during the break-in period. IPD may be used as a transient therapy for patients who have hernias or leaks or those who have recently undergone abdominal surgery [121]. Some leaks may spontaneously seal off with lower intra-abdominal pressures on supine IPD. Another area of application of IPD is refractory heart failure on maximal medical therapy. Several studies have documented the reduction in morbidity days, and improvement in functional status [122–124]. Peritoneal ultrafiltration has not been shown to improve survival in most studies [125].

Nocturnal Intermittent Peritoneal Dialysis

Nocturnal intermittent peritoneal dialysis (NIPD) is an intermittent dialysis regimen performed every night, and may be considered to be similar to CCPD with a dry day (Fig. 12.5) [3]. NIPD treatments are performed overnight on a cycler. The dialysis usually lasts between 8 and 12 h. Dialysate volumes of 8–12 L are typically used for therapy per night, though larger volumes of dialysate and extended dialysis may be required for some patients.

The dry days eliminate 10–20% of small solute clearances achieved in a patient who is an average transporter on nightly cycles plus a wet day [126, 127]. Treatment of patients with NIPD has a greater impact on the clearance of middle molecules. The clearance of middle molecules is a time-dependent process, and dry days reduce clearances by 50% [126–128].

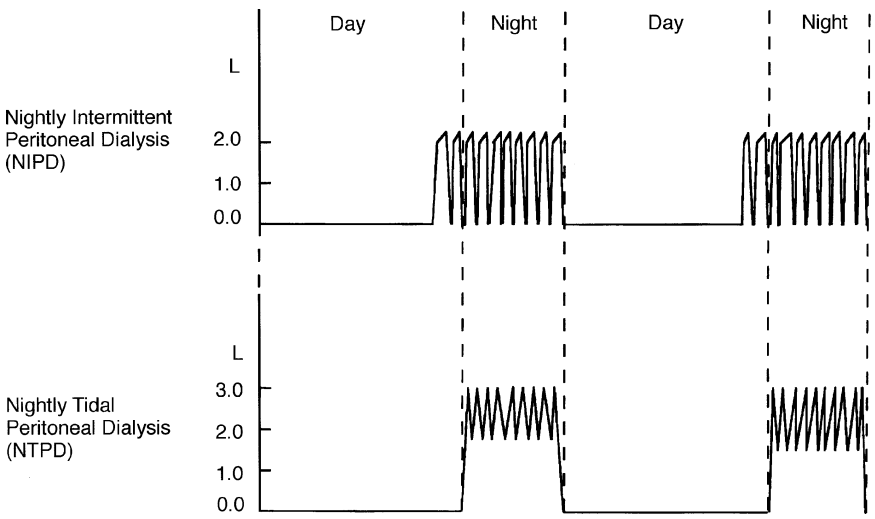

Fig. 12.5 Nightly peritoneal dialysis. Upper panel shows nightly intermittent peritoneal dialysis; lower panel shows nightly tidal peritoneal dialysis. From Ref. [3] with permission

NIPD may be an optimal modality for those with complications due to elevated intraperitoneal pressure, who are unwilling, or are not candidates for hemodialysis. Patients with high transport characteristics and those with type I ultrafiltration failure may also be treated with NIPD [74, 127]. Those patients with high levels of RKF may initially be treated with NIPD. This modality is not an option for subjects with large body surface area and those with average or below average transport characteristics with minimal or no RKF as adequacy parameters cannot be met [126]. NIPD does offer the psychosocial advantage of a better body image and lower glucose absorption leading to a better appetite. The costs of treatment run higher than with CAPD, and patients often do not accept the prolonged confinement to bed. Additionally, sodium sieving and the consequent low sodium in the ultrafiltrate may lead to hypernatremia, increased thirst, and worsening hypertension [88].

Continuous Cyclic Peritoneal Dialysis

Continuous cyclic peritoneal dialysis (CCPD) is a continuous automated peritoneal dialysis regimen [3] (Fig. 12.6). The technique is essentially a reversal of CAPD where the shorter exchanges are automatically provided at night while the longer exchanges are performed during the day. After the last nocturnal cycle the cycler is programmed to deliver a final exchange (last bag fill) of hypertonic dialysate or an alternative osmotic agent like icodextrin.

Small solute clearances are slightly lower in CCPD than in CAPD for the same dialysate flow [129, 130]. The total weekly clearances of middle molecules are the same as CAPD. The solute clearances may be improved by increasing the delivered intraperitoneal volume, increasing the number of nightly exchanges and duration on the cycler. A hybrid modality to increase adequacy and ultrafiltration is called PD Plus or CCPD + CAPD, wherein additional daytime exchanges are performed in addition to CCPD [131]. These daytime exchanges may be performed manually or by hooking back to the cycler.

This regimen is best suited for schoolchildren and employed patients who are frequently unable or unwilling to perform multiple daytime exchanges. Patients requiring assistance in performance of dialysis are better served by CCPD than CAPD. Connections and disconnections may be minimized to two, reducing burden on the provider. This is obviously an ideal choice for institutionalized patients.

Tidal Peritoneal Dialysis

Tidal peritoneal dialysis is a regimen combining intermittent and continuous-flow technology. The procedure attempts to increase efficiency by maintaining a reserve volume in the peritoneal cavity at all times, providing for uninterrupted solute clearance [28, 132]. In classical TPD, after an initial fill of the peritoneal cavity, only a portion of dialysate is drained and replaced by fresh dialysate (tidal volume) leaving the rest of the volume (reserve volume) in the peritoneal cavity (Fig. 12.5). Often the tidal volume is expressed as a percentage of the initial fill volume. For example with a 50% TPD with an initial 2L fill, subsequent tidal volumes would be 1L. Prediction of ultrafiltration is important to assure the reserve volume

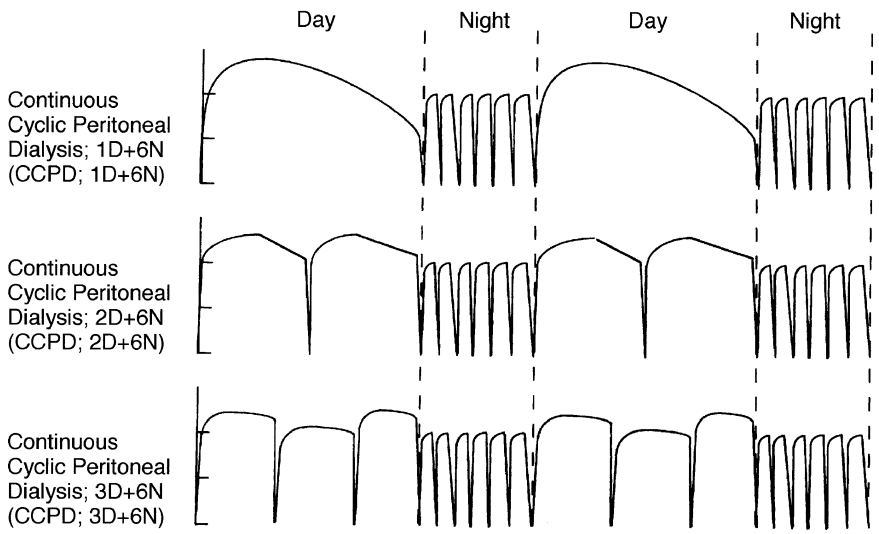

Fig. 12.6 Continuous cyclic peritoneal dialysis (CCPD). Upper panel shows standard CCPD with last bag fill; middle and lower panels show CCPD combined with additional daytime exchanges. From Ref. [3] with permission

remains unchanged. If ultrafiltration volumes are overestimated, the reserve volume would gradually be depleted. If ultrafiltration volumes are underestimated, the reserve volume will gradually increase leading to abdominal discomfort.

The initial studies comparing TPD and other APD modalities utilized much higher dialysate flow rates in TPD and found improved solute clearances. Among these studies was one by Flanigan et al. [132], which showed that utilizing 16 L of dialysate in TPD over 8 h provides equivalent clearances to 9.5 L for CCPD over 10 h. Protein losses were not increased on TPD. In another study, comparing CAPD, CCPD, 50% TPD, and 25% TPD, therapy with 50% TPD plus wet days was found to be most efficient, but once again had the highest dialysate flow [133].

Studies utilizing roughly similar amounts of fluid have found no benefit of TPD in increasing solute clearances. For example, in the Spanish Multicenter Study [134], patients were treated with CAPD, CCPD, and TPD for 2 months each. The treatment volumes were comparable between CCPD and TPD and ranged from 14 to 15 L/night and 1.8 to 2.0 L/daytime. CAPD was found to have the lowest creatinine and urea clearances. CCPD had the highest urea clearances and creatinine clearances were comparable for CCPD and 50% TPD. A study comparing solute clearances and ultrafiltration on TPD and traditional IPD found with dialysate flow rates of 18.5 mL/min, solute clearances and ultrafiltration volumes were higher on IPD than on TPD. With flow rates of 25.9 mL/min, the ultrafiltration volume was higher on IPD, but no difference was found for solute clearance. At flow rates of 44.4 mL/min there was no difference in ultrafiltration or solute clearances between the two modalities [135]. Piraino et al. [136] in a small study using a dialysate flow rate of 3.7 L/h for IPD and 3.8 L/h for TPD found no difference in small molecule clearances. Quellhorst et al. [137] reported that TPD to be more efficient than IPD using a treatment volume of 60 L/day.

Middle molecule removal is a function of time and TPD has not been shown to impact clearances of β_2-microglobulin [138]. Sodium sieving is more marked in short dwell therapies, but the few studies analyzing sodium removal in TPD have found little differences from other APD modalities [86, 139, 140]. Quellhorst et al. [137] have documented better blood pressure regulation with TPD than IPD, while Balaskas et al. [141] found no difference.

In conclusion, TPD does not increase small solute clearances above those obtained with other APD therapies. The advantage of TPD with a continuous contact between the peritoneal surface and dialysis fluid may be offset by the negative influence of a smaller concentration gradient between dialysate and blood. It has been suggested that inadequate mixing of the tidal volume with the reserve volume may cause this. TPD may be indicated for patients experiencing pain at the beginning of inflow and/or the end of drain. It may also be used in patients with mechanical outflow problems such as due to adhesions or improper catheter placement [142, 143]. In such instances, a high initial fill volume with low tidal volumes may allow PD to continue sans problems. TPD may be the preferable modality for patients with ascites wherein controlled drainage of fluid can be achieved rather than draining the entire abdominal cavity with each cycle [144].

Breakpoint APD

Breakpoint APD is a TPD modality characterized by a variable reserve volume determined by the point at which the drain rates transition into a slow drain rate as discussed above in a previous section. The breakpoint may vary for an individual patient from cycle to cycle and with change in position, intraperitoneal pressure, and catheter function besides other factors. By transitioning from a drain phase to a fill phase at the "breakpoint," the time spent draining a limited quantity of dialysate would be eliminated, improving efficiency. Computerized modeling as well as clinical studies have shown improved clearances with this modality [86, 145]. In one study, shortening the total drain time to include only the initial high outflow period increased urea clearance by nearly 10% during an 8-h APD treatment with six cycles and a total dialysate flow of 12 L in a patient with average membrane permeability (urea MTC approximately 15 mL/min). The increase in urea clearance was the result of increased dwell time with maximal dialysate volume. There was also improved sleep quality due to decreased alarms [145]. In another study comparing NIPD, 50% tidal PD, and breakpoint APD, Amici found a 10% improvement in clearances with breakpoint APD compared to tidal [113].

Continuous Flow Peritoneal Dialysis

Continuous flow peritoneal dialysis (CFPD) is a futuristic modality to augment small solute clearances by maintaining a fixed intraperitoneal volume with a constant flux into and out of fresh or regenerated dialysate through the peritoneal cavity. This system allows the use of high dialysis flow to improve clearance values close to the MTC (Fig. 12.2). There is no time wasted during inflow and drain and a continuous concentration gradient generates a solute flux that is maintained during the whole dwell time [146, 147].

CFPD would offer an option a patient to remain on peritoneal dialysis after failure of CAPD or standard APD to provide adequacy. Cruz et al. [148] have demonstrated peritoneal clearances of 42 mL/min for urea and 33 mL/min for

creatinine using a dialysate flow rate of 200 mL/min and a 2-L initial fill volume. They obtained a mean ultrafiltration of 16 mL/min with a 1.5% dextrose solution. Raj et al. [149] using a single lumen catheter with a "Y" adapter and a lower dialysate flow rate of 141 mL/min obtained mean urea and creatinine clearances of 26.5 and 24.1 mL/min, respectively. An ultrafiltration of 3 mL/min was obtained with a mean dextrose concentration of 0.73 g/dL. Thus, an added advantage of CFPD is the ability to use lower dextrose concentrations as the system continuously adds dextrose to the system. Consequent reduction in glucose absorption may prevent complications attributable to high glucose concentrations in the dialysate. Because of the high efficiency of the treatment, patients could dialyze during the night and be dry during the day. Though this would potentially allow the peritoneal membrane to regenerate, there would be a loss of middle molecule clearances whose removal is time dependent and not flow dependent.

CFPD requires large amounts of fluid (200–300 mL/min) to achieve maximal efficiency. The use commercially available peritoneal dialysis solutions would be associated with enormous cost and storage issues. Recirculating a moderately sized batch of dialysate until it saturates, though an option, would limit clearances. Another approach is the online production of dialysate as done for hemofiltration, which would allow individualization of therapy. The most viable option may be the use of a commercial dialysate followed by continuous extracorporeal regeneration of the spent dialysate by either a hemodialysis filter or adsorption using a sorbent column or a combination of the two. The protein in the dialysate would be concentrated and returned to the patient in the final exchange [147]. This may be complicated by loss of middle molecule clearances since these are extensively protein bound [146].

Two catheters or a double-lumen catheter would be needed to provide such high flow rates of dialysate, with special designs to prevent streaming. Another issue that needs to be addressed with current cyclers is the inability to assess and control ultrafiltration. With CFPD, the ultrafiltered volume needs to be matched by removal of extracorporeal fluid. A mismatch would lead to either abdominal overdistension or underfilling. Segmental bioimpedance coupled with intraperitoneal pressure measurements with closed-loop feedback in intelligent machines may provide an answer in the future.

Nighttime Exchange Device

The nighttime exchange device (NXD) allows CAPD patients one or more nighttime exchanges while reducing patient burden and improving clearances (Fig. 12.7). Though several patients on four or less exchanges may opt for this device as a lifestyle choice, the NXD is extremely helpful for patients prescribed five or more exchanges [4].

There is a physiological and kinetic advantage to using this system. Equilibrium of urea between peritoneal dialysis solutions and plasma occurs within 3–6 h of dwell. Dwell times longer than 6 h do not contribute any further to the removal of small solutes and require higher concentrations of dextrose to maintain ultrafiltration. In terms of efficiency, four exchanges every 6 h are more effective than three short and one long dwell. The supine position for

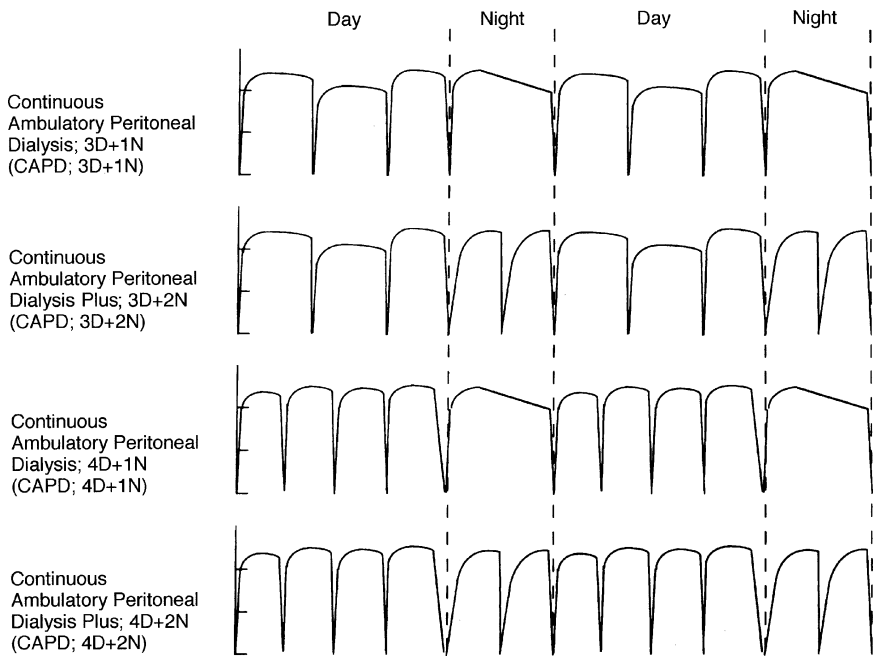

Fig. 12.7 Continuous ambulatory peritoneal dialysis (CAPD) and the use of the night exchange device (NXD). Panel 1 shows CAPD – three daytime exchanges and one bedtime exchange; panel 2 shows CAPD Plus – three daytime exchanges, one bedtime exchange, and an additional exchange delivered by the NXD; panel 3 shows CAPD – four daytime exchanges and one bedtime exchange; panel 4 shows CAPD Plus – four daytime exchanges, one bedtime exchange and an additional night-time exchange delivered by the NXD

the nighttime exchange(s) offers an opportunity to use higher V_{ip} maximizing the MTC without an increase in the IPP. Furthermore, patients retaining fluid due to the longer dwell at night on CAPD may also benefit from using the NXD. Patients switching to NXD only for lifestyle reasons, with no change in the number of exchanges, experience only a slight improvement in their solute clearances over baseline. In patients advised an additional exchange, the clearances increase significantly [150]. However, higher clearances may also be achieved by increasing the V_{ip} without changing the number of exchanges [81].

In summary, the major advantage of NXD is to help achieve adequacy in CAPD, as well in achieving net negative ultrafiltration in patients retaining fluid overnight [151].

Adequacy of Automated Peritoneal Dialysis

Background

Survival on dialysis is determined by the removal of nitrogenous waste products, correction of electrolyte and acid-base imbalance, and fluid removal to maintain normal volume status [152]. Adequate dialysis is defined as the dose of dialysis below which one observes a significant worsening of morbidity and mortality. The National Cooperative Dialysis Study (NCDS) [153] on hemodialysis gave rise to the concept that small solute clearances influence patient morbidity and mortality significantly, and these data were extrapolated to the peritoneal dialysis population.

Small solute clearances in peritoneal dialysis are conventionally quantified in terms of either urea clearance [Kt, (L/week)] normalized to total body water [V, (L)] and/or total creatinine clearance (C_{cr}) normalized to standardized body surface area (BSA).

A series of observational studies reported the importance of small solute clearances in defining adequacy among peritoneal dialysis patients [154, 155]. In 1997, the Kidney Disease Outcomes Quality Initiative (K/DOQI) Peritoneal Dialysis Work Group published a guideline for the adequacy of dialysis dose [156]. The K/DOQI recommended a weekly Kt/V of 2.0 in CAPD, 2.1 in CCPD, and 2.2 on NIPD. The initial creatinine clearance guidelines of 60 L/week/1.73 m^2 for all transport types were modified in the 2000 update of the guidelines to 50 L/week/1.73 m^2 for low and low-average transporters [157]. These guidelines were largely based on the results of the Canada-USA (CANUSA) study [155]; a reanalysis of this study showed that RKF predicted survival and not the peritoneal clearance [158]. Since then two randomized controlled studies in CAPD patients evaluating adequacy have been published. The ADEMEX (ADEquacy of peritoneal dialysis in MEXico) [159] found no difference in survival between groups having a mean total Kt/V of 2.27 and 1.80. Patients receiving a lower prescription had more deaths from congestive heart failure, uremia, and hyperkalemia. The Hong Kong study [160], a prospective randomized multicenter study, comparing three groups with total weekly Kt/V 1.5–1.7, 1.7–2.0, and >2.0 also did not find any difference in survival based on small solute clearances. The group with Kt/V of 1.5–1.7 had more anemia, inadequate dialysis, and ultrafiltration.

Observational studies in anuric CAPD patients suggest a minimum Kt/V urea of 1.7 as a minimum target. The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), using time-dependent analyses of peritoneal clearances after achievement of anuria ($n = 130$) found no dose-response relationship between weekly Kt/V_{urea} and outcomes. Analyzing the data as a dichotomous variable, the investigators reported that a weekly $Kt/V_{urea} < 1.5$ was associated with an increased risk for death [161]. In an observational study from Hong Kong, patients at the onset of anuria with a baseline Kt/V_{urea} of less than 1.67 (based on a Kaplan-Meier analysis) had a significantly poorer patient survival, mainly confined to female patients [162].

No randomized controlled study addressing adequacy in APD has been performed. In a retrospective study involving a small sample of anuric CAPD and APD patients there was a trend to reduced mortality, although not statistically significant, in patients with peritoneal Kt/V urea above 1.85 [163]. Another study of 763 patients in which 34% of patients were on CCPD found that neither peritoneal Kt/V_{urea} nor peritoneal creatinine clearance were predictive of 1-year mortality [164]. The European Outcomes APD Study (EAPOS) [152] was a prospective multicenter study evaluating the feasibility and clinical outcomes of anuric APD patients ($n = 177$). Time-averaged creatinine clearance and baseline solute transport had no effect on patient or technique survival. Time-averaged analyses showed that age, subjective global assessment, and diabetic status predicted patient survival. Baseline ultrafiltration below 750 mL/day was predictive of poorer survival.

The above data establish the limitations of peritoneal small solute clearances in predicting outcomes of PD patients. Further, measured Kt/V_{urea} is not always the delivered Kt/V_{urea}. Nonadherence with exchanges, changes in timing of exchanges, variations in ultrafiltration volume, urinary output, and GFR may affect solute clearances. In addition, during automated peritoneal dialysis, the shorter nighttime exchanges provide a higher urea clearance than creatinine clearance.

Besides small solutes, protein-bound uremic toxins and middle-molecular-weight uremic toxins are important in the uremic syndrome. The removal of middle molecules is a function of the membrane area, membrane permeability, and time. Since time is the only variable, the total duration of dialysis is critical for the removal of middle molecule waste. Long dwells during the day contribute significantly to the clearance of middle molecules. The clearance of middle molecules in CCPD appears to be similar to CAPD. However, in NIPD with dry days, the time available for dialysis is reduced by 50%, and this dramatically reduces the clearance of middle molecules [126].

Several studies have demonstrated that peritoneal dialysis patients are overhydrated compared to hemodialysis and transplant patients [165, 166]. Furthermore, patients on APD have lower sodium removal and ultrafiltration than CAPD patients and consequently are more volume expanded [89, 91]. Some of the studies have been biased against APD because of not considering overfill of dialysis bags in their estimates [90]. The fluid status is associated with diastolic blood pressure, left ventricular hypertrophy, and mortality. The benefit of blood pressure and volume control has been demonstrated by Lameire [166]. Ates et al. [167] have demonstrated that better total sodium and fluid removal are factors effecting survival in peritoneal dialysis. In the EAPOS analysis, anuric patients on APD with baseline ultrafiltration below 750 mL/day had a poorer survival, but the effect of ultrafiltration disappeared in the time-dependent analysis [168]. Though greater fluid removal may indicate better volume control, it may also indicate a higher fluid intake. A higher fluid intake is more likely to be seen in healthier patients and the better outcomes with higher ultrafiltration and sodium removal may just be reverse causation [169].

Adequacy Recommendations

Guidelines from Kidney Disease Outcomes Quality Initiative (K/DOQI)

For patients with RKF (urinary volume >100 mL/day), the K/DOQI has recommended the minimum delivered dose of total small solute clearances (peritoneal and kidney), expressed as Kt/V_{urea}, should be at least 1.7 per week. Total solute clearances should be measured within the first month after initiating therapy and at least once every 4 months thereafter. If the patient has greater than 100 mL/day of urinary output, and RKF is being considered part of the total weekly clearance goal, a 24-h urine collection for urine volume and solute clearance should be obtained at a minimum of every 2 months. In patients with no RKF (urinary volume $\leq$100 mL/day), the minimum delivered dose of total small-solute clearance should be a peritoneal Kt/V_{urea} of at least 1.7 per week, measured within the first month of starting dialysis and at least once every 4 months thereafter [170]. Determination of creatinine clearance is no longer recommended for adequacy measurements by K/DOQI [164].

An emphasis on preserving RKF and maintenance of euvolemia is also incorporated into the guidelines. Important in preservation of RKF are the use of ACE inhibitors and angiotensin receptor blockers and avoidance of nephrotoxic exposure. Implementation of the goal of euvolemia involves close monitoring of urine volume, ultrafiltration, and physical examination including blood pressure. Restriction of salt and water intake, adjustment of the dialysis prescription as necessary, and use of loop diuretics to preserve or increase urinary volume are some suggested methods [170].

Other Guidelines

The International Society of Peritoneal Dialysis has made recommendations similar to the K/DOQI for small solute removals. Also recommended in APD patients is an additional target of 45 L/week/1.73 m^2 of creatinine clearance [171]. The European Best Practice Guidelines for PD recommend achieving a minimum Kt/V_{urea} of 1.7, a creatinine clearance of 45 L/week/1.73 m^2, and a net ultrafiltration of 1.0 L per day in anuric patients [172]. The Australian PD Guidelines advise the weekly Kt/V target should be =1.6/week. The minimum weekly corrected creatinine clearance (Ccr) target would be 60 L/week in high and high-average peritoneal transporters, and 50 L/week in low-average and low peritoneal transporters [173]. The Canadian Guidelines indicate that Kt/V_{urea} should be maintained at a minimum of 1.7 when the residual GFR is less than 4 mL/min. In patients with residual GFR greater than 4 mL/min, peritoneal Kt/V_{urea} may be maintained between 1.0 and 1.7.

The Automated Peritoneal Dialysis Prescription

The peritoneal dialysis prescription should take into consideration patient's body surface area (BSA), peritoneal membrane permeability properties, and amount of RKF. The presence of RKF makes it easier to achieve clearance

guidelines. Each 1 mL/min of corrected residual kidney creatinine clearance (C_{cr}) adds approximately 10 L/week/1.73 m^2 of creatinine clearance to the total C_{cr}. Similarly, for each 1 mL/min of urea clearance, 0.25 is added to the total weekly Kt/V for a 70-kg male. As the RKF declines with time the peritoneal dialysis prescriptions should be adjusted to maintain adequacy criteria.

The peritoneal transport characteristics are determined by the PET [69, 70], by mass transfer coefficients [71, 72], or by the standard permeability analysis [73]. The effect of peritoneal transport in influencing dialysis adequacy is both direct via solute clearance, and indirect via influencing ultrafiltration. A study assessing peritoneal transport characteristics of 1,229 patients found the group consisted of 15% low transporters, 33% low-average transporters, 37% high-average transporters, and 15% high transporters [94]. Low transporters are difficult to treat with APD unless they have substantial RKF. Body surface area and body weight affect the requirements for dialysis. Among the U.S. dialysis population, 75% of patients have a BSA >1.71 m^2 and a median BSA of 1.85 m^2.

The variables that may be manipulated in achieving adequacy are the dialysis modality, fill volume, number of exchanges and spacing, and duration of exchanges [129]. Computer-assisted kinetic modeling programs are available to help evaluate membrane transport characteristics and assist in writing prescriptions. Three major programs are available in the market: PD-Adequest® (Baxter Healthcare Corporation, Deerfield, Illinois, USA) [174], Patient-online (POL®) (Fresenius Medical Care, Bad Homburg, Germany) [175] and Personal Dialysis Capacity Test (PDC®) (Gambro, Lund, Sweden) [176]. These programs have user-friendly interfaces and use a mathematical model describing the peritoneal dialysis system. Data from a specific peritoneal function test needs to be entered for each patient [86, 177]. Even though prescriptions generated by the computer programs have reasonably close correlation with the actual measurement of 24-h urine and dialysate clearances, they are subject to errors. The errors relate to intraindividual biologic variability, population variability, lab errors and the use of peritoneal transport models that oversimplify the physiology of the peritoneal membrane. Furthermore, modeling expects a perfect performance of exchanges, which very often is not the case in real life [86]. Kinetic modeling is not meant to replace the actual measurement of clearance.

For a patient initiating APD with a residual GFR > 2 mL/min, the initial fill volume should range between 800 and 1,500 mL/m^2. The number of exchanges at night should be between three and five and the time on the cycler should range between 7 to 10 h. Dry days are not recommended except in patients with substantial RKF and in high transporters with small BSA. In anuric patients, higher doses of dialysis are required and low and low-average transporters with BSA exceeding 2.0 m^2 may not achieve adequacy with APD. Recommendations for initial therapy are summarized in Table 12.4, adapted from the National Kidney Foundation K/DOQI clinical practice guidelines for peritoneal adequacy: update 2000 [157]. General principles for APD therapy are summarized in Table 12.5.

The adequacy of the initial prescription must be assessed within the first month after initiating dialytic therapy and at least every 4 months thereafter. If the patient has a RKF that is being included in adequacy calculations, the RKF should be measured at a minimum of every 2 months. Inadequate dialysis may happen due to the dialysis prescription not being matched to the membrane transport characteristics, loss of RKF, insufficient time on the cycler or noncompliance, and a poorly functioning PD catheter.

The dialysis prescription can be optimized by increasing fill volumes. There is a theoretical linear relationship between body surface area and the volume of dialysate needed for optimal contact with peritoneal capillaries reaching a maximal at a fill volume of approximately 1,500 mL/m^2 [81]. Multiple studies have demonstrated that clearances rise as volume of dialysate is increased. In a study of 20 patients on either CAPD or APD, increasing fill volume by 1 L per

Table 12.4 Possible initial empirical dialysis prescriptions for CCPD

For patients with an estimated underlying GFR >2 mL/min	
BSA <1.7 m^2	4 × 2.0 L (9 h/night) + 2.0 L/day
BSA 1.7–2.0 m^2	4 × 2.5 L (9 h/night) + 2.0 L/day
BSA > 2.0 m^2	4 × 3.0 L (9 h/night) + 3.0 L/day
For patients with an estimated underlying GFR ≤2 mL/min	
BSA < 1.7 m^2	4 × 2.5 L (9 h/night) + 2.0 L/day
BSA 1.7–2.0 m^2	4 × 3.0 L (9 h/night) + 2.5 L/day
BSA > 2.0 m^2	4 × 3.0 L (10 h/night) + 2 × 3.0 L/day[a]

Source: NKF-K/DOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy: update 2000 [157]

GFR = glomerular filtration rate; BSA = body surface area

[a] Consider combined hemodialysis/peritoneal dialysis or transfer to hemodialysis if the clinical situation suggests the need. These empirical prescriptions are based on modeling for patients with dialysate-to-plasma creatinine concentration ratio on PET of 0.71 at 4 h, BSA in the range above, and corrected residual kidney function of 2 mL/min or 0 mL/min

Table 12.5 General guidelines for APD therapy

1. Dialysis modality should be based on the ability of the regimen to provide adequate dialysis, the patients' preference, and their ability to perform the procedure.
2. APD prescriptions should be individualized based on membrane permeability, RKF, and BSA.
3. Computer prescription programs may be useful in designing prescriptions. Kinetic modeling, however, cannot replace actual clinical measurements of clearance.
4. Nightly intermittent peritoneal dialysis regimens should be avoided in all patients except high transporters with small body surface area or substantial RKF.
5. Anuric patients with low or low-average membrane transport characteristics should not be offered less than 24-h dialysis.
6. Delivered dose of dialysis and RKF must be periodically monitored. Prescriptions should be modified for a decline of RKF.
7. Clearances may be maximized by increasing the V_{ip} and/or the number of exchanges, minimizing drain time, and adding daytime exchanges.
8. Icodextrin may be used for the long dwell to improve clearances and ultrafiltration.
9. Compliance with prescriptions must be verified periodically.

RKF = residual kidney function; BSA = body surface area; V_{ip} = intraperitoneal exchange volume; IPP = intraperitoneal pressure

exchange increased urea and creatinine clearances by 26% [178]. In another study of CAPD patients, an increase in the dialysate fill volume of 1.5 L over 24 h increased peritoneal Kt/V_{urea} and creatinine clearance by 12% and 10%, respectively, and drain volumes by 20% [179].

Durand has recommended that fill volumes be optimized by monitoring of the IPP measured from the mid-axillary line, targeting a maximal of 18 cm H_2O [108]. These measurements should be done at atmospheric pressure. Whilst this is not a concern in disconnect systems, an air inlet is required for non-disconnect systems (such as APD) to negate the counter-pressure in the line and the empty bag. This is best achieved by introducing a trochar at the injection sit of the bag. On the other hand, Twardowski et al. [97, 180]. have demonstrated that there is poor correlation between IPP and tolerance of increased intraperitoneal volume. The best correlation of volume tolerance was with pulmonary function [97, 180]. Patients with the poorest tolerance of increased volume had a significant drop of the forced vital capacity at increased intraperitoneal volume with only small increase in IPP (Fig. 12.8). In a study from Mexico, even though

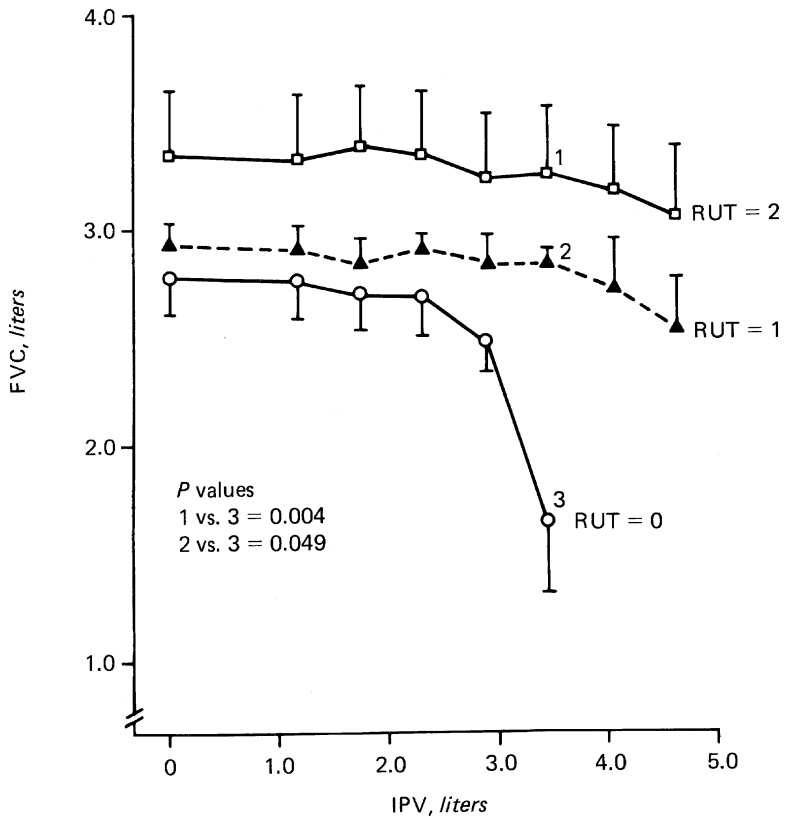

Fig. 12.8 Forced vital capacity (FVC) in the supine position in relation to intraperitoneal volume (IPV) in three groups of patients. Routine use of 3-L exchanges (RUT) = 2, patients routinely using 3-L volume exchanges; RUT = 1, patients occasionally using 3-L volume; RUT = 0, patients never using 3-L volume. From Ref. [97] with permission

larger dialysate volumes caused more discomfort, there was a lack of correlation between the discomfort score and the IPP [109]. The discomfort score was determined by asking patients to mark on a visual analog score their level of discomfort. When a 2.0-L dialysate volume was infused, the discomfort score for 86% of the patients was lower than 10, and that for 93% was lower than 50. With a 2.5-L dialysate volume infusion, 64% of patients had a discomfort score lower than 10 and 83% lower than 50. With a 3.0-L dialysate volume infusion, 44% of patients had a discomfort score lower than 10 and 64% lower than 50 [109]. Sarkar et al. [178] have shown that few patients are capable of discriminating between 2.0-, 2.5-, and 3.0-L dialysate volumes when infused blindly in random order. Most patients did not complain of discomfort in the face of a documented increase in their abdominal perimeter when 3.0 L of dialysate was infused. Thus, a majority of patients will be asymptomatic with higher fill volumes.

An alternative to increasing the fill volume is increasing the number of exchanges. More frequent cycling theoretically increases the time spent in filling and draining. A study by Perez et al. [140] evaluated this issue by comparing four different APD regimens for 1 week each. The prescriptions were for 9 h each and were all based on 2-L dwell volumes, but differed in the frequency of exchanges. They were 5 × 2 L, 7 × 2 L, and 9 × 2 L, as well as a 50% tidal peritoneal dialysis (TPD) prescription using 14 L. Higher dialysate flow rates achieved a higher small solute clearance across all membrane transport types as well as better ultrafiltration and sodium removal. The peritoneal urea clearance was significantly higher using 9 × 2 L exchanges as compared to the other three prescriptions. The peritoneal creatinine clearance was the lowest, with 5 × 2 L, and comparable between 7 × 2 L and 9 × 2 L therapies. The urea and creatinine clearances on TPD exceeded only those obtained with 5 × 2 L and were comparable to the 7 × 2 L regimen. Juergensen [181] has also reported that peritoneal Kt/V_{urea} and peritoneal creatinine clearance increase significantly when the frequency of exchanges and the total volume are increased across all transport types. Frequent cycling may negate the effects of lost time by the benefits of more frequent replenishment of the peritoneal cavity, with fresh dialysate maximizing diffusive clearance and the better-maintained osmotic gradient leading to better ultrafiltration. Such a regimen increases the cost of therapy and may be useful in some patients who cannot do a day exchange or tolerate a higher fill volume.

The use of daytime exchanges is more advantageous and cost effective. Based on kinetic modeling, Blake et al. [130] have demonstrated that in CCPD, addition of a daytime exchange is superior to further increases in the nightly dialysate volume (Fig. 12.9). In anuric patients, one to two daytime exchanges are required to meet the adequacy guidelines [152] unless one uses "high-flow" APD [182]. Increasing the time on the cycler is another option to achieve adequacy. The patient's lifestyle must be kept in consideration prior to modifying duration on the cycler. Compliance typically decreases if the total cycle time exceeds 9 h per session [183].

Management of Ultrafiltration

Volume overload is associated with congestive heart failure, left ventricular hypertrophy, and hypertension and is a predictor of poor survival [170]. It is therefore important to achieve a desirable target weight in a peritoneal dialysis patient where the patient is euvolemic. The edema-free state can be considered the minimum bracket for euvolemia. The weight below which undesirable clinical signs and symptoms such as hypotension and cramps develop can then be viewed as the maximum bracket for fluid removal. The weight range between these defined limits constitutes the

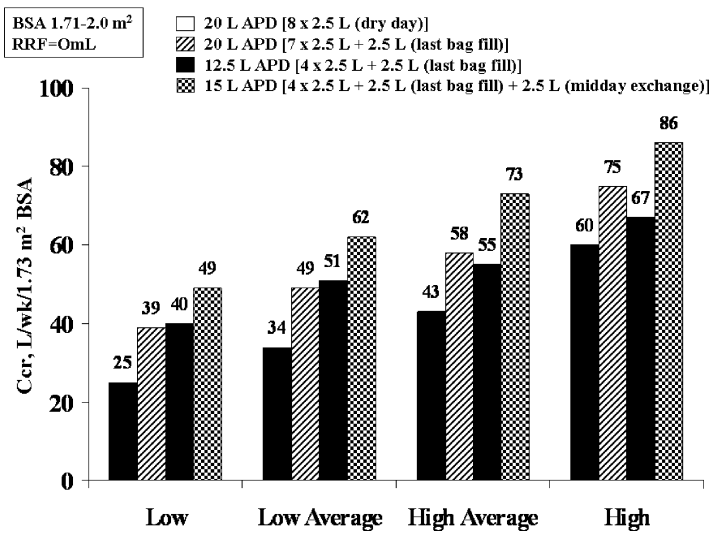

Fig. 12.9 The effect on creatinine clearance of wet days, increasing the number of exchanges, and adding a midday exchange to APD therapy prescriptions. The difference compared with a dry day is illustrated clearly in the first two bars of each membrane transport type. The effect of a midday exchange is shown in the last bar. From Ref. [130] with permission

clinical definition of desired weight – a highly variable and often complex target [184]. Maintenance of euvolemia requires attention to the peritoneal transport characteristics, protection of RKF, dietary counseling and enhanced compliance, use of loop diuretics, and control of hyperglycemia [94]. APD creates a biphasic profile for clearance and ultrafiltration with short nocturnal exchanges and a long daytime dwell. The shorter dwells provide for higher ultrafiltration rates because of a higher initial dextrose concentration. The membrane transport characteristics have a minimal effect on ultrafiltration with short dwells, while in the long dwell fast transporters have negative ultrafiltration [94]. Attention to the long dwell is essential in achieving euvolemia. If inadequate or negative ultrafiltration is seen, a midday exchange or switch to icodextrin must be considered [151]. Use of hypertonic glucose-based solutions that may cause peritoneal membrane damage should be minimized.

As regards the short dwells, frequent cycling could increase the inactive time and decrease net ultrafiltration but this has not been borne out in clinical studies [140, 181]. APD offers a unique ability to alter the tonicity of the dialysate by using bags of different tonicities since the cycler draws proportionally on all bags selected for a given

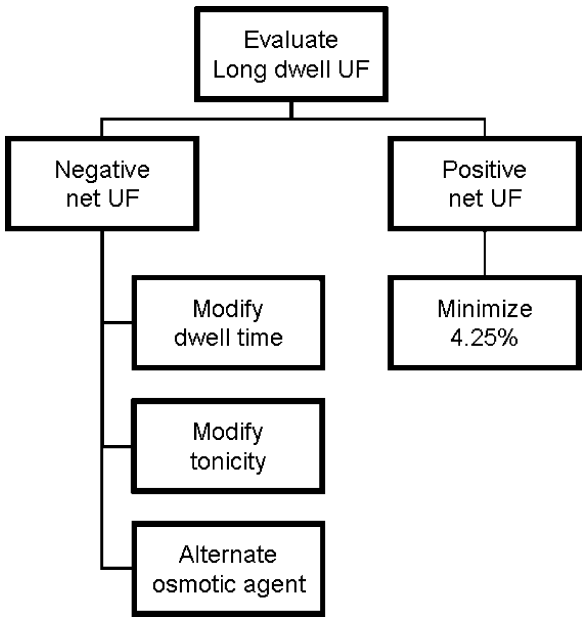

Fig. 12.10 Algorithm for fluid management in patients on PD: Management of the long dwell. UF: ultrafiltration. Modified from Ref. [151] with permission

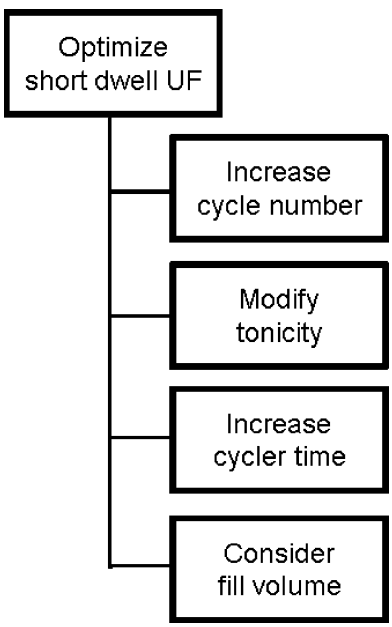

Fig. 12.11 Algorithm for fluid management in patients on PD: Management of the short dwell. UF: ultrafiltration. Modified from Ref. [151] with permission

therapy. For example, equal mixing of a 1.5 and 2.5% dextrose solution can create a 2% dextrose solution. The caloric cost per milliliter of ultrafiltration is lower with the use of higher tonicities of dextrose [151]. An increase in the fill volume helps increase ultrafiltration because of a higher total glucose mass in the peritoneal cavity [185]. However, increasing fill volumes increases IPP and may enhance net fluid absorption [110], though the effects are likely to be modest with short dwell times in APD [151]. An algorithm for fluid management in APD is detailed in Figs 12.10 and 12.11.

Incremental Peritoneal Dialysis

The decision to initiate dialysis was until recently based on the development of uremic symptoms or complications. It is becoming conventional now to start dialysis earlier to have a healthy start and avoid malnutrition and uremic complications. It is suggested that one could initiate dialysis with a "full-dose" prescription, ignoring the residual kidney component, or alternatively, one could "incrementally" increase the dialysis component of solute clearance as RKF decreases, maintaining minimal total solute clearance goals at all times [170].

APD offers an option for incremental peritoneal dialysis. Patients with significant RKF may be initiated on NIPD. With decline in RKF clearances may be augmented by switching to high-dose NIPD or to CCPD. Later, clearances may be improved by combining APD with CAPD (Fig. 12.12) [186]. Theoretically, such an approach could protect the peritoneal membrane from 24-h glucose exposure. Early start of peritoneal dialysis is associated with some risks. These risks include infection and a quicker loss of RKF. There is also the possibility that increasing the length on peritoneal dialysis may contribute to eventual patient "burn out". The reduced interference with daily routine, lower work burden, and fewer complications with APD make this a preferable procedure for early start.

Monitoring of Treatment

Patient compliance with therapy may be monitored by use of removable memory cards, teledialysis, reviewing order histories, and by frequent home visits. Catheter malfunction may be suspected if there are frequent alarms and by observing the fill/drain profiles. Changes in serum creatinine should make one suspect a change in RKF, changes in peritoneal transport characteristics, or noncompliance. Direct measurements of RKF are mandated by guidelines every 2 months and of peritoneal clearances every 4 months [170]. Since APD treatments are intermittent in nature, a fluctuation in plasma concentrations predialysis versus postdialysis may be seen. These differences are more marked for urea than creatinine and postdialysis samples will overestimate Kt/V [187]. To standardize measures of Kt/V, the blood sample should preferably be obtained at a time equidistant from the previous and subsequent nocturnal APD session.

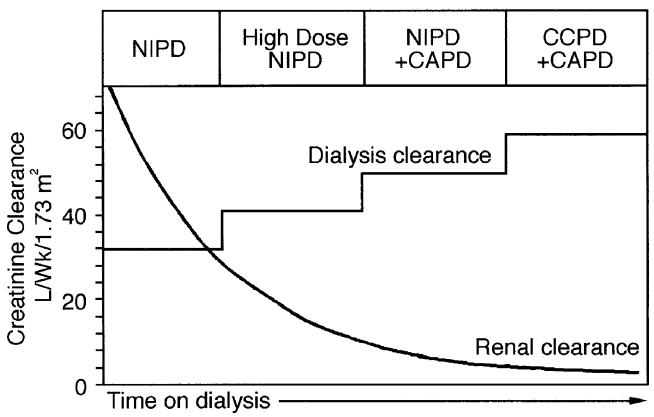

Fig. 12.12 Schematic drawing showing the adaptation of APD to change in residual kidney function. From Ref. [186] with permission

Complications of APD

Qualitatively, the complications of APD are similar to those encountered with CAPD. However, quantitative differences may exist in the incidence of these complications in the two modalities. Here, we will discuss selective complications of APD.

Peritonitis

Although the incidence of peritonitis in patients treated with peritoneal dialysis has decreased during recent years, it remains a major complication and frequent cause of hospitalization and discontinuation of peritoneal dialysis. The incidence of peritonitis in the earlier years of APD was significantly lower than CAPD [26, 188–190]. With the introduction of disconnect systems, the incidence of peritonitis has markedly decreased on CAPD. Some studies continue to demonstrate a benefit of APD over CAPD. In a randomized prospective study, de Fijter and associates [191] observed that peritonitis occurred significantly less often in those patients receiving CCPD than in those on CAPD with Y-connectors (0.51 compared with 0.94 episode per patient-year; $p = 0.03$). The median time to the first episode of peritonitis was 11 months for patients receiving CAPD with Y-connectors compared with 18 months for CCPD patients ($p = 0.06$). Patients on CAPD with Y-connectors developed their second episode of peritonitis in 6 months compared to 25 months for CCPD patients ($p = 0.18$). Rodriguez-Carmona [192] also reported on the superiority of APD over CAPD in regards to peritonitis. The adjusted difference was 0.20 episodes/patient/year.

In contrast, Burkart et al. [193], in another prospective study, found no difference in the incidence of peritonitis between patients on APD (0.58 episode per patient-year) and patients on the Y-set (0.61 episode per patient-year). Their patients using the standard spike system developed peritonitis at a significantly higher rate of 1.62 episodes per patient-year. Williams and co-workers [194] reported the incidence of peritonitis on APD to be similar to CAPD with disconnect systems with one episode occurring every 31 months and 29 months, respectively. The incidence of peritonitis for CAPD without disconnect systems was one in 13 months. Yishak et al. [195] reported peritonitis rates of 0.57 per patient-year and 0.55 per patient-year on APD and CAPD, respectively. A report of the French Peritoneal dialysis registry [8] reported a lower incidence of peritonitis on APD. However, the data is hard to interpret since the patient populations were somewhat different. Patients needing nursing assistance, overall a sicker population, more often received CAPD with nondisconnect systems and a majority of autonomous patients received APD. Oo and colleagues [196] in a recent retrospective analysis of the USRDS database between 1994 and 1997 found CAPD to be associated with a lower risk of development of a first episode of peritonitis after 9 months of peritoneal dialysis therapy as compared to CCPD. Even though this data set did not include information on connectology, it is likely that most patients would have been on a Y-system (with or without a twin-bag).

In studies showing benefit of APD over CAPD, the reduced numbers of connections to, and disconnections from, the abdominal catheter have been thought to be significance [191, 192]. Furthermore, most of these connections in APD occur between two sterile surfaces (a new connection line and a new bag); while in CAPD, most connections are between the new set and a reusable transfer line and peritoneal catheter. Improved patient technique due to performance of all connections in the same environment, less patient fatigue due to performance of fewer connections, and assistance of a helper may help reduce peritonitis rate. Most APD systems now employ flush-before-fill technology, further reducing infection by touch contamination. In addition, peritoneal immune function may be better preserved in patients with dry days in NIPD or having long dwells on CCPD [37, 197].

Patients with peritonitis usually present with cloudy fluid and abdominal pain. A dialysate white blood cell count $>100/mm^3$, with more than 50% polymorphonuclear cells, is supportive of the diagnosis, as is a positive Gram stain. The number of cells in the effluent will depend in part on the length of the dwell. Patients on APD with a day dwell who present during the day generally have cell counts similar to those of CAPD patients and are not difficult to interpret. However, APD patients without a daytime exchange who present with abdominal pain may have no fluid to withdraw. In this case, 1 L of dialysate should be instilled and allowed to dwell for at least 1 h, and then drained and examined for turbidity and sent for cell count, differential, and culture. In equivocal cases, or in patients with systemic and abdominal symptoms in whom dialysate appears to be clear, a second exchange is performed with a dwell of at least 2 h but preferably 3–4 h. On occasions, the initial drain of stagnant fluid present in the abdomen all day in patients with only partial daytime exchanges or dry days will appear cloudy in the absence of peritonitis. The white blood cell count may exceed $100/mm^3$, but

mononuclear cells will predominate. More important, dialysate rapidly clears with the initiation of peritoneal dialysis. Clinical judgment should guide initiation of therapy [198].

For patients on APD who present during their nighttime treatment, the dwell time is much shorter than with CAPD; in this case, the clinician should use the percentage of polymorphonuclear cells rather than the absolute number of white cells to diagnose peritonitis. The normal peritoneum has very few polymorphonuclear cells; therefore, a proportion above 50% is strong evidence of peritonitis, even if the absolute white cell count does not reach 100/mL [198].

The diagnosis of peritonitis in APD may often be delayed in patients using cyclers that dispose of dialysate directly without a drain bag [199]. To avoid those problems, patients should be trained to collect a small amount of the dialysate from the initial drain at the start of the night therapy and inspect it for cloudiness. If abdominal pain is experienced, a manual exchange for inspection and possible cell count with culture is recommended.

The organisms causing peritonitis in APD are similar to CAPD [191, 195, 200]. *Pasteurella multocida* has been identified as the cause of peritonitis in a few patients. This infection is caused by cats biting into the cycler tubing [201].

Intraperitoneal antibiotics, used intermittently or continuously, are preferred to intravenous antibiotics for treatment of peritonitis. Most antibiotics have enhanced absorption during peritonitis. For successful intermittent intraperitoneal therapy, high concentrations of the drug must be achieved in the systemic circulation, of sufficient magnitude that enough drug will diffuse back into the dialysate in subsequent drug-free exchanges [202]. With rapid exchanges in APD, there may be inadequate time to achieve therapeutic intraperitoneal levels with subsequent exchanges using intermittent antibiotics. Little is known about the pharmacokinetics of antibiotics and treatment outcomes in APD. Further, most of the studies performed in APD have been done on uninfected patients with intravenous administration of antibiotic, which makes it hard to extrapolate the data to intraperitoneal treatment of peritonitis [203–205]. The data show the clearance of antibiotics is largely dependent on dialysate flow as well as the RKF [202].

Among the data available, cefazolin, cefepime, and ceftazidime used once daily do not provide an adequate minimum inhibitory concentration of antibiotic during short nighttime cycles for most organisms [206–208]. Similarly, vancomycin in a dose of 15 mg/kg given intravenously also does not provide adequate intraperitoneal levels [205]. Oral ciprofloxacin in a dose of 750 mg twice a day provides dialysate concentrations that exceed the MIC for *Escherichia coli* and *Klebsiella* sp, but below those needed for *Pseudomonas aeruginosa* [209]. In spite of this pharmacokinetic data, clinical studies using intermittent antibiotics on APD have provided cure rates between 73 and 88%, catheter removal rates of 7.5–17.5%, and peritonitis-related deaths of 2–10%, which is not different than CAPD [210].

The International Society of Peritoneal Dialysis in its recommendations for treatment of peritoneal dialysis infections: 2005 Update [198] has suggested that vancomycin, cefazolin, tobramycin, fluconazole, and cefepime may be administered intermittently while continuing APD. The recommended doses are mostly higher than those for CAPD and a minimum 6-h dwell time for the antibiotic containing dialysate is advised. The committee also acknowledged the inadequacy of data backing these recommendations. Given this lack of knowledge, alternative options for treatment are switching patients to CAPD, using longer cycles on APD, or continuous antibiotics. Each institution should consider modifying the guidelines for initial antibiotic therapy based on their data on common organisms and sensitivities. In addition, patients may require adjustment of the APD prescription to account for the increased permeability of the peritoneal membrane during peritonitis.

Catheter Infections (Exit Site and Tunnel)

Catheter-related infections are an important cause of morbidity, peritonitis, and catheter failure. There appears to be little difference in the incidence of catheter-related infections on APD in comparison to CAPD. In data reported by Burkart et al. [193], the incidence of exit-site infections was 0.41 episode per patient-year for APD, 0.32 per patient-year for patients on Y-sets, and 0.62 per patient-year for patients on a standard spike. Statistical significance was only seen for the comparison between Y-set and standard spike ($p = 0.01$). de Fijter et al. [191] and Rodriguez-Carmona et al. [192] reported a similar incidence of exit site infections between APD and CAPD. Holley and coworkers [211], on the other hand, reported a significant decrease of exit-site infections for cycler patients (0.5 episode per patient-year) in contrast to CAPD patients using disconnect systems (0.86 episode per patient-year). Patients on nondisconnect systems developed exit-site infections at an incidence of 1.2 episodes per patient-year. Overall, disconnect systems, including APD, have fewer catheter infections than nondisconnect systems. It may be

postulated that, by disconnecting, the exits are subject to lesser trauma, tension, torque, or pulling [193]. The assessment and management of exit site and tunnel infections in APD is no different from CAPD.

Complications of Increased IPP

Hernias and Dialysate Leaks

The most common anatomic complication of peritoneal dialysis is hernias. The usual sites for these are sites of previous abdominal incisions and the umbilical, inguinal, and pericatheter regions [212]. The incidence of hernias on CAPD ranges between 10 and 25%, while on IPD the incidence is 2–5%; for CCPD the incidence is approximately 9% [213, 214]. The higher pressures in sitting and standing as against in the supine position may be partly responsible for this difference [97]. However, in spite of the fact that IPP rises proportional to the infused volume, there is no consensus between studies whether higher fill volume increases the incidence of hernias and leaks. In a survey of 75 dialysis units, representing 1864 dialysis patients across the United States and Canada, Van Dijk et al. [212] found no association between the volume of dialysate and the time of the largest exchange with the development of hernias. Similarly, Del Paso et al. [215] and Hussain et al. [216] found no association between fill volume and hernias. Furthermore, Durand et al. [217] found no relationship between IPP and mechanical complications. It may be possible that the IPP required to cause hernias are much higher than achieved under usual clinical conditions, and patients who develop hernias have structural weakness of the abdominal wall. Susceptible patients include older multiparous females, patients with autosomal dominant polycystic kidney disease, those with prior hernias or dialysate leaks, and prolonged corticosteroid treatment [212, 215, 218]. Susceptible patients should receive smaller diurnal dwells. Surgery is recommended for most hernias because of the risk of bowel or omental incarceration and strangulation. Post-surgery, once patients return to peritoneal dialysis, low volume and/or supine dialysis should be used.

Dialysate leaks are another frequent complication and occur more often in CAPD than APD. Risk factors for development of leaks are the median insertion of the peritoneal dialysis catheter, increased intra-abdominal pressure, and a weak abdominal wall. Leaks are characterized by dissection of fluid through tissue planes and may or may not be associated with hernias. These may present as abdominal or genital edema, pericatheter pseudohernias, and rarely as a vaginal leak of dialysate. Leaks may be a cause of ultrafiltration failure and weight gain [219]. Fluid leaks may be detected by radionucleotide imaging, MR peritoneography, or by computerized tomography scans with contrast in the dialysate [220]. Sometimes, leaks without associated hernias resolve by utilizing low-volume supine dialysis or a temporary transfer to hemodialysis. Surgical repair may eventually be required.

Respiratory Function

The presence of fluid in the abdomen and elevated IPP impact on pulmonary indices. There is a greater decline in pulmonary indices in the supine position compared to the upright or sitting positions [97]. CAPD patients generally have better pulmonary indices than patients do on APD. A good measure of the tolerance of intraperitoneal volumes is the forced vital capacity (FVC) in the sitting position [97, 180] and supine position [97, 217] (Fig. 12.8). Thieler et al. [221] described that the FVC in the supine position declined by a mean of 3.4% after the infusion of 2 L of dialysate into the peritoneal cavity. Pulmonary indices were not significantly affected by the presence of 2 L of fluid in the sitting or upright positions. In a study by Durand et al. [108], vital capacity decreased linearly by 4.42% per liter of V_{ip} in the supine position. During sleep, the drop in vital capacity is reflected by a reduction in the pulmonary reserve volume. Decreases in vital capacity by 20% or more may affect blood oxygenation. It has to be stressed that some patients may feel discomfort and shortness of breath at lower intraperitoneal volumes, possibly due to the reduced strength of the diaphragm [96, 111]. Caution needs to be exerted in increasing fill volumes on APD in patients with lung disease. The ultimate guide of the appropriate intraperitoneal volume is the subjective assessment of the patient [97, 180].

Hydrothorax

Hydrothorax is another pulmonary complication. Hydrothorax usually develops on the right side. Patients may range from being asymptomatic to having severe respiratory compromise. Most patients developing hydrothorax are females; multi-parity confers an additional risk. Fluid transverses the diaphragm through lymphatics or through defects in the diaphragm [219]. This complication occurs very rarely on NIPD and may be treated by low-volume supine dialysis, pleurodesis, or surgical repair [222].

Back Pain

Back pain is another complication related to increased IPP. The increased IPP can pull lumbar vertebrae into a more lordotic position and increase the stress on the spine. Poor muscle tone, osteoporosis, and degenerative joint disease can worsen the process. The treatment is aimed at reducing IPP by switching to APD, preferably with dry days [214].

Residual Kidney Function

The RKF contributes significantly to the adequacy of dialysis and the excretion of middle and large molecules. Survival on peritoneal dialysis has been linked to the RKF [158, 164]. Various studies have explored the loss of RKF in APD patients. An analysis of the Dialysis Morbidity and Mortality Study (DMMS) found no difference in the decline of RKF between APD and CAPD although ultrafiltration rates were not reported [223]. Hamada et al. [224]. reported better preservation of renal function in APD patients in a small study with a two-year follow-up. A prospective, nonrandomized study of 53 new CAPD and 51 APD patients followed for at least 1 year found a faster rate of loss of RKF in APD patients, despite controlling for PET results. This difference may have been negated by the role of ultrafiltration in determining loss of RKF and may have been influenced by prescription alterations once PET results were known [225]. In a small nonrandomized study of new dialysis patients, Hiroshige et al. [226] found that RKF declined more rapidly in APD patients over a 6-month period. For the eight patients on NIPD, the rate of decline in creatinine clearance was -0.29 mL/min/month and for the four CCPD patients -0.34 mL/min/month. These rates were significantly higher compared to the authors' own CAPD data, as well as the data of others. In another prospective, small nonrandomized trial of 36 consecutive unmatched new PD patients followed over 1 year, there was a faster rate of decline in the APD group. The APD group consisted of both CCPD and NIPD patients without any difference in the rate of loss for each therapy, although the numbers were small [227]. It is suggested that the acute changes in volume status and osmotic load induced at each nightly PD session could potentially accelerate deterioration of RKF.

Technique and Patient Survival in APD

Peritonitis and catheter related infections are the leading cause of technique failure on peritoneal dialysis. Other causes include mechanical catheter problems, inadequate dialysis including ultrafiltration failure, and psychosocial problems. In 1984, Diaz-Buxo et al. [19] had reported the technique survival for CCPD to be 80%, 62%, and 56% at 1, 2, and 3 years, respectively. A more recent study by Mujais et al. [10] examined the profile of PD practice in the United States by following four large inception cohorts of patients starting PD in the years 2000–2003. This study found that transfer to HD was lower in APD than CAPD for any cause of technique failure. This difference was most evident in the first year on PD and tended to disappear during the second year of therapy. Overall technique survival in APD was 81% in the first year and 67%, 55%, and 46% in each of the 3 subsequent years in this study. Patients on CAPD had a significantly higher rate of technique failure in the first 6 months and stabilized thereafter. Overall, technique success was 75% in the first year and 63%, 53%, and 44% in each of the 3 subsequent years for CAPD [10]. Patients treated with APD have a survival advantage over CAPD in the first 6 months of therapy. A younger age, selection bias of patients for APD, or better compliance with therapy may have influenced patient survival on APD in this study. The overall trend is of improving patient outcomes and technique success with time. The European APD Outcome Study was a prospective multicenter study of outcomes on APD in anuric patients. Patient survival was 78% and technique survival 62% and combined patient and technique survival was 49% at 2 years. The predictors of poor survival were age >65 years, malnutrition, diabetic status, and ultrafiltration <750 mL/day [152]. Peritoneal membrane transport had no effect on survival, though the study excluded low transporters [152].

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Chapter 13
Peritoneal Dialysis Program Organization and Management

The Nurse's Role

M. Luongo and B. Prowant

Peritoneal dialysis (PD) has been a successful mode of renal replacement therapy with a positive response from patients [1]; however, there has been a progressive decline in patient recruitment for this self-care modality and in the total number of PD patients in the United States [2, 3]. This has contributed to a lack of clinical experience and expertise in PD, and loss of the infrastructure crucial for successful implementation of PD therapy. This is both a cause for concern and a distinct challenge.

As a renal replacement therapy, PD can be individualized for each patient's specific clinical and psychosocial needs [4, 5]. Also, the patient who assumes responsibility for self-care can benefit from the flexibility and freedom that PD offers.

The success of PD as a renal replacement modality in an ever-changing healthcare arena is dependent on the commitment and efforts of all members of the PD healthcare team [6]. This chapter will discuss the development and organization of a PD home program [7, 8] and the nursing roles in providing care to PD patients [9–13].

Structure and Function of a PD Program

Establishing the foundations of the PD program should be the shared responsibility of the medical director and PD nurse manager. Defining each team member's responsibilities and writing the position description is one of the first steps in program development. Clarifying the specifications of the physical environment and ordering the necessary equipment is often the next step [14, 15]. Other critical elements include creating policy and procedures and training protocols, developing quality outcome management strategies, and financial planning [7, 8, 16–18].

The Healthcare Team

The clinical care and support of the self-care PD patient is a team effort. The team is comprised of a central core of healthcare providers and a peripheral group of specialty consultants (Table 13.1) [19–22]. Core members of the PD healthcare team include the nephrologist, access surgeon, PD nurse, advanced practice nurse [22], dietitian, and social worker. Some larger PD programs have successfully integrated a technician role [19, 20]. The core team members collaborate with the patient's primary care physician and other healthcare professionals who contribute to the care of PD patients. It is often the PD nursing staff who coordinate the efforts of the team to provide home care for the PD patient [12, 13].

The Physical Environment

Developing a safe, functional environment for a PD program requires strategic planning. The PD nurse needs to be involved throughout this process to provide the necessary nursing perspective. Table 13.2 lists essential elements of the physical plan for a PD home program [7, 8, 14, 16, 17].

M. Luongo (✉)
Massachusetts General Hospital, Boston, Massachusetts
e-mail: Mluongo@partners.org

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Table 13.1 Healthcare team members

Core PD team members
• Patient
• Nephrologist
• Peritoneal dialysis nurse
• Dietitian
• Social worker
• Renal fellow
• Access surgeon
• Advanced practice nurse
Consulting physicians
• Primary care physician
• Infectious disease specialist
• Diabetologist
• Gerontologist
• Psychologist/psychiatrist
• Hospitalist
• Vascular surgeon
Other care providers
• Transplant team
• Research staff
• Hospital nursing staff
• Extended care facility staff
• Rehabilitation facility staff
• Hemodialysis staff

Table 13.2 Physical requirements for the peritoneal dialysis program

• Waiting room or reception area
• Training room(s)
• Clinic rooms
• Conference room
• Staff office(s)
• Restrooms for patients and staff
• Clean utility room
• Dirty utility room
• Supply storage area
• Secured area for patient records, computerized records, printers, copy and fax machines

Planning should focus first on safety for patients and staff. Hallways and training rooms need to be large enough to accommodate wheelchairs, stretchers, and emergency equipment. Training rooms must be large enough to accommodate the nurse, patient, and family members. A larger room may be constructed for group training.

To prevent falls, the floor covering should not be slick or slippery; it should have some texture to promote safe footing. If part of the unit is carpeted, the carpet fibers should be short to prevent tripping and to allow effective cleaning. Light-colored, washable paint should be used to reduce glare. Large windows will need shades or adjustable blinds to filter sunlight and prevent glare. The training room needs to have a thermostat so the temperature can be adjusted to the comfort level of the individual patient [23].

Table 13.3 outlines equipment required for a PD program. Sturdy furniture should be selected to provide comfortable seating for patients and family members. Wheeled chairs should have locking wheels to prevent falls and to provide secure seating. Each training room must have a table where the patient can sit comfortably to practice dialysis procedures. Additional counter space may be available to organize dialysis supplies and equipment. These surfaces must be constructed of a material that can withstand frequent disinfection with approved cleaning solutions.

Another concern regarding the physical environment is the ability to protect the patient's privacy and confidentiality. Training rooms and clinic rooms need doors rather than just curtains. The PD nurse needs an office or private

Table 13.3 Equipment requirements for the peritoneal dialysis program

- Chairs and table top working areas
- Cabinets for supply storage
- Sinks for hand washing
- Wall-mounted soap dispensers and hand sanitizers
- Portable IV poles or ceiling-mounted hooks for solution bags
- Patient scales
- Scales for weighing dialysis solution bags
- Wall-mounted clocks
- Wall-mounted sphygmomanometer
- Automatic sphygmomanometer
- Dialysis cycler
- Device(s) to heat dialysis solutions
- Refrigerator
- Computers, printers, copy machine, fax machine
- Wheelchair

area to provide patient counseling and to make confidential phone calls. The area where medical records are stored must be able to be locked when not in use. Electronic medical records must be protected with passwords and security screen locks. Fax machines must also be located in a restricted area and a confidentiality statement must be included on the first page of all faxed transmissions that include patient information.

Policy and Procedure Development

Federal regulations mandate that each PD program have a policy and procedure manual. This manual should include all patient care procedures, written patient education materials, position descriptions, and strategies for outcome management. Table 13.4 outlines components of a policy and procedure manual. The initial effort of developing a procedure manual will be outweighed by the long-term benefits.

Policies and procedures should be evidence-based whenever possible. Several evidence-based practice guidelines have been published in recent years [24–26]. These provide detailed information describing which practices and procedures are supported by scientific data, the level of the scientific evidence, and key references. The International Society for Peritoneal Dialysis (ISPD) and national societies have also published guidelines and recommendations for clinical care [27–29]. Reviews of controlled clinical trials [30–32] and best demonstrated practices [33, 34] have also been published.

After the PD program is successfully underway, periodic review and revisions to the policies and procedures are mandated by regulatory guidelines. Typically, the policy and procedure manual is reviewed and revised annually to reflect current practice and to meet regulatory requirements; however, individual sections may require updates between annual reviews.

The medical director and PD nurse manager will also need to develop mechanisms to review clinical outcomes, and note changes in regulatory mandates, insurance parameters, and current standards of care. The review of clinical outcomes may be accomplished through weekly dialysis rounds, monthly summaries of care, an annual report of program outcomes, and the continuous quality improvement program. The clinical outcomes should be compared to regional and national benchmarks [35–39] and recently published data.

Patient and staff education materials are essential for successful home dialysis. Patient education materials are available from equipment and supply manufacturers, others have been published or are available on the internet [40, 41]. Patient education materials should be available in a variety of formats and media [42]: written and illustrated [43], audio [44] and video, “hands-on” [45], and interactive [46]. Besides unit-specific procedures and education materials, patients should be given a list of resources including websites [41]. The nursing staff will also need reference books (e.g., drug manuals, nephrology, dialysis, and nursing textbooks), current journal subscriptions and resource lists including websites.

A copy of the patient’s bill of rights should be included in the patient’s home training manual and posted in the dialysis unit. Some home dialysis units also include a list of patient responsibilities.

Table 13.4 Components of a peritoneal dialysis program policy and procedure manual

- Mission statement
- Goals and objectives
- Role descriptions for the peritoneal dialysis team members
- Description of the CKD patient education program
- Content outline for the initial interview process
- Catheter insertion protocol
- Procedures
  - Care of the newly inserted catheter
  - Care of the established catheter
  - Hand washing
  - Daily hygiene
  - Exit site care
  - Management of exit site infection
  - Management of peritonitis
  - Obtaining dialysate specimens
  - Manual CAPD
  - Automated PD
  - Capping of catheter
  - Changing transfer set
  - Addition of medications to dialysis solutions
- Fluid balance guidelines
- Use of heparin and nonheparin alternatives
- Recognition of complications
- Problem solving techniques
- Obtaining vital signs in the home setting
- Home records
- Protocols
  - Development of patient care plan
  - Assessment forms
  - Obtaining consent
  - Advance directives
  - Confidentiality protection
  - Incident reports
  - Training sessions
  - Home visits
  - Clinic visits
  - Telephone follow-up
  - Annual retraining
  - Travel
  - Disaster preparedness
  - Emergent and non emergent hospitalizations
- Samples of all program-specific educational materials
- Procedures for routine monitoring of quality indicators

Patient Safety

All electrical equipment in the PD unit must be checked for electrical hazards, approved for use, and routinely maintained.

Appropriate emergency equipment and medications must be available and all members of the nursing staff will need to maintain certification in cardiopulmonary resuscitation (CPR). Some institutions require that support staff also be certified in CPR. Emergency drills should take place periodically to provide the staff with education and experience in how to function in a life-threatening emergency.

To protect all patients, visitors, and staff, a unit-specific fire plan must be developed. A written fire plan should be posted and emergency contact numbers need to be in view for easy accessibility. All staff must know the location of fire alarms, fire doors, fire extinguishers, and evacuation routes. Periodic fire drills are mandatory.

Infection Control

Practices in the Peritoneal Dialysis Unit

A number of practices recommended to reduce the transmission of disease in hospitals, ambulatory care settings, and hemodialysis units are appropriate of peritoneal dialysis units [47–51]. These are summarized in Table 13.5 and discussed below.

Handwashing

Effective handwashing remains one of the most effective strategies to prevent the transmission of diseases in health care facilities. The Centers for Disease Control and Prevention (CDC) recommends handwashing after removing gloves and between patient contacts [47]. Handwashing procedures must be developed for both the dialysis unit and for the patient in the home environment. Many units promote the use of an antibacterial liquid soap in a pump dispenser in the home when many family members are using the same sink(s) for handwashing. This may prevent sharing of bacteria that might accumulate on bar soap. The current guideline for hand hygiene in healthcare settings reviews studies and provides recommendations to improve hand hygiene practices [52]. This document also summarizes recent studies related to alcohol-based hand rubs. These "waterless" disinfectants have been shown to remove microorganisms effectively and take less time than conventional handwashing [53]. Studies have shown that there is less irritation to hands [53, 54] and increased compliance with hand hygiene among healthcare workers [53, 55].

Although we found no studies specifically related to use of alcohol-based hand cleansers in peritoneal dialysis, these are being used both in the clinics and by patients and partners dialyzing at home. They could be used routinely when PD procedures call for handwashing, instead of soap and water (when hands are not visually soiled). This would eliminate the problem of increased transfer of microorganisms when hands are washed but not thoroughly dried [56]. Waterless cleansers could be also be used when the patient is connected to the cycler and may not be able to reach a sink, and whenever a continuous ambulatory peritoneal dialysis (CAPD) patient is performing procedures in a

Table 13.5 Recommendations to reduce disease transmission [47–51]

Immunizations
• Routine serologic testing for hepatitis B and C
• Vaccination for all patients susceptible for hepatitis B
• Test for anti-HBs 1–2 months after series is complete
• Retest annually and give booster immunization if necessary
Injections
• Use single-use syringes and needles
• Use single-dose medication vials or prefilled syringes whenever possible
• Perform hand hygiene before preparing and administering an injection
• Prepare injections in a designated medication room or area
• Use aseptic technique to prevent contamination of sterile equipment and medications
• Dispose of syringes and needles in an approved container at the point of use
Venipuncture
• Use barriers when drawing blood to prevent blood from contaminating surfaces
• Perform hand hygiene before donning gloves and after removing gloves
Equipment
• Handle equipment that might be contaminated with blood in a way that avoids contact with skin and mucous membranes
• Evaluate equipment and devices for the potential for cross-contamination
• Establish procedures for safe handling and effective cleaning
• Maintain physical separation between clean and contaminated equipment and supplies
Exposure to blood
• Wear gloves for procedures that might involve contact with blood
• Perform hand hygiene after inadvertent blood contamination
Other
• Clean and disinfect training and clinic rooms between patients
• Routine infection surveillance
• Infection control education

location where there is not access to running water. It is also possible that the use of waterless hand cleansers might increase compliance with handwashing by PD home patients.

Immunizations

Pneumococcal pneumonia and influenza vaccines are recommended for patients with chronic illnesses, and the hepatitis B vaccination series is recommended for patients on dialysis therapy [49]. Each dialysis unit should be prepared to provide these immunizations or refer patients to a local health department, if the immunizations are not given in the physician's practice. All immunizations must be documented in the patient's medical record, including the date of immunization, location of injection, drug lot number, and occurrence of any unusual reaction. A copy of the documentation should be given to the patient.

Dialysate Disposal

Another aspect of patient safety is the disposal of infectious waste. The procedures for disposal of peritoneal dialysis effluent will vary depending on the physical layout of the PD unit. Waste maybe disposed in a designated waste sink in the training room or in a central waste disposal area. When transferring dialysate to the central disposal area, it must be handled in a manner that prevents contact with clothing, skin, and mucous membranes. Some units use plastic bags designated for infectious waste for this purpose. The PD nurse must use standard precautions to protect him/herself and other members of the staff when emptying the dialysate bags. A face shield, gloves, and protective gown or apron should be worn when handling the dialysate. A mask might also be worn when handling dialysate from patients with known tuberculosis, as transmission has occurred from inhaling aerosolized mycobacteria [47]. The bags and tubings should be discarded in a designated hazardous waste receptacle. Spills of effluent must be cleaned with an approved bactericidal/virucidal solution.

At home, dialysis patients typically discard dialysate in the toilet or a sink. Patients who use dialysis cyclers with an open drain line should be instructed to ensure that the tip of the drain line is not submerged below the water level in the toilet or drain [47]. Procedures for dialysate disposal at home should include warnings against splashing, instructions regarding how to clean spills, and how to clean the sink or toilet used for dialysate disposal, and appropriate cleaning solutions. If a family member or someone other than the patient is disposing of the dialysate, they should use the protective garb similar to that recommended for the staff.

Quality Improvement Program

The quality improvement program provides data collection, evaluation, and outcome management for an interdisciplinary team effort [57] in promoting excellence of care. In many countries, establishing a quality improvement program is not optional, but is a regulatory requirement. All quality improvement efforts monitor and assess clinical outcomes and make changes in the processes of care with the ultimate goal of providing efficient, effective, and safe patient care, which will result in improved patient outcomes [8, 58].

Table 13.6 provides examples of outcomes that may be monitored in a quality improvement program. At a minimum, PD-related infections [27], catheter survival [59, 60], patient survival, and technique survival (proportion of patients remaining on PD therapy) should be monitored. Data may be collected and analyzed on a monthly, quarterly, or annual basis, depending on the size of the program and the frequency of the outcome. Outcomes can be compared to data from national registries and published reports [35–39]. Review of the literature, particularly abstracts from nursing and multidisciplinary meetings, and networking with other programs are helpful when initiating a quality improvement program in order to obtain ideas about data collection strategies and experiences in making timely changes to improve outcomes.

Each program needs to adopt or develop a system to routinely collect information. Designing a tool to collect the information on a monthly basis is often a simple, effective method of documenting outcomes. This may be a simple tool to manually enter the data or a computer program to collect and analyze the information. Reports can also be generated by the program's Medical Information System (MIS) of computerized patient records. The data collection may be a shared responsibility of all the team members or it may be the sole responsibility of one nurse.

Inherent in the continuous quality improvement (CQI) process is the need for several members of the interdisciplinary team to meet periodically, discuss the outcomes, analyze the contributing factors (root cause analysis), and plan strategies to improve outcomes. Typically, it is a nurse who coordinates the quality team; however, multidisciplinary participation,

Table 13.6 Outcomes for continuous quality improvement projects

- Adequacy of dialysis
- Technique survival (time on peritoneal dialysis)
- Access
  - Catheter demographics
  - Catheter survival
  - Catheter-related infections
    - Exit site infection
    - Tunnel infection
    - Peritonitis
  - Catheter complications
- PD complications
- Hospitalizations for dialysis complications
- Fluid balance and hypertension
- Nutrition
- Metabolic parameters
  - Serum albumin and protein
  - Anemia management
  - Calcium/phosphorus balance
  - Electrolytes
  - Glucose management and control
  - Secondary hyperparathyroidism
- Effectiveness of patient education program
- Psychological adjustment to PD

including that of a committed physician, is critical to its success [57]. The team process facilitates the implementation of changes required to achieve excellent outcomes and promote PD as an effective renal replacement modality.

Another component of quality assessment and improvement is to solicit feedback from the patients regarding the care they receive [1, 61]. Patient satisfaction surveys that guarantee anonymity and are returned to an address or individual separate from the home dialysis program can provide surprisingly candid feedback pointing out problems in delivery and effectiveness of care. It has been suggested that the process of care has a strong impact on retention of chronic PD patients [62], so responding to patients' concerns may improve patient retention.

CQI efforts in PD programs have resulted in increasing the number of patients who choose PD therapy [63–65], reducing infections [66–80] and amputations [81], changing procedures for home care interventions [67, 68, 72–74, 76, 80], and identifying strategies to improve dialysis adequacy [77, 82–84], fluid balance [85], nutrition [86], bone health [87, 88], and anemia [89]. The CQI effort also promotes the development of a team identity and, in some instances, may improve communication and reduce adversarial relationships.

Financial Considerations

Fiscal responsibility is important for the long-term success of the PD program. Prudent use of supplies and medications can be achieved through staff and patient education and an organized approach to inventory levels. Each program will have a unique approach to cost effectiveness based on methods of supply ordering, vendor contracts, and available storage space.

A technical assistant or secretary can be taught to participate in supply inventory, computerized billing, tabulating monthly charges, and staff payrolls, with supervision from the nurse manager. A dialysis technician can also participate in these activities and save personnel costs in large programs [19, 20].

Establishing a good working relationship with the home supply team is vital to insure that the patient has the appropriate home supplies but does not accumulate excess or outdated supplies, thus avoiding waste and expensive emergency deliveries.

The PD nurse may be supported by administrative staff in assessing PD program costs, but must take an active role in this process. Developing an internal communication process for transmitting information regarding patient training days, episodes of care, and billing for supplies and drugs is critical. Networking with the individuals who are responsible for the billing process also contributes to effective billing. Often, the nurse must educate the billing staff regarding aspects of clinical care to help them understand the often-complicated billing process for the home dialysis patient.

Table 13.7 Legal strategies to manage risk

Program is structured to comply with all state and federal regulatory requirements
Clinical care
• Consent for procedure(s) signed by patient or proxy
• Patient rights are posted and a copy given to patients
• Documentation of advance directives
• Physician orders for all treatments
• Patients and families are treated in a professional and caring manner
• Patient privacy and confidentiality are respected and documented
• All patient interactions and interventions are documented
• Patient plan of care signed by patient and team members
• Periodic review of patient's skills and knowledge and retraining if indicated
• Incident or unusual occurrence forms completed as necessary
Staff roles
• Position descriptions for all team members
• Competencies listed for each position
• Competencies are evaluated and documented for each staff member
• Team members must function within defined competencies
• Nurse should not dispense medications for home use

Cost accounting should be done by the PD nurse on a monthly basis so that the acquired revenue can be compared to the program's activities. This can include a record of clinic visits, training sessions, home visits, on-call activity, staff educational sessions, and supplies for the home patient and the dialysis unit. In some instances, the PD nurse is involved in the development of the annual budget. Insights from the budget planning process and monthly cost accounting can be very helpful in understanding the program's financial stability, and increases the nurse's investment in maximizing efficient supply ordering and effective billing [7, 17].

Legal Considerations

PD is a unique specialty within the practice of nephrology medicine and nursing. The PD nurse often functions in an autonomous role while providing quality care for the home dialysis patient. Providing legal protection of both the patient and staff must be a key part of the program's philosophy and policies [90]. The policy and procedure manual must be very specific in delineating the role of each core team member. Job descriptions need to be specific and current. The nurse must be careful not to exceed defined boundaries (e.g., in many countries, only a physician or pharmacist may dispense prescription medications) and must document patient care consistently and objectively.

The healthcare team should not hesitate to obtain professional legal advice for complicated patient situations [90]. Sources of assistance in the hospital setting or large dialysis organizations are the risk management team, designated patient advocates, and the ethics committee [91]. Table 13.7 summarizes strategies to manage legal risks in a home dialysis program.

Education of the Patient with Chronic Kidney Disease

One of the first tiers of education is that which is provided for the patient with chronic kidney disease. This takes place prior to the initiation of renal replacement therapy. The newly diagnosed patient with chronic kidney disease is faced with many life-altering changes that maybe both overwhelming and confusing. Efforts to provide excellent predialysis care include early detection, strategies to slow disease progression, prevention of uremic complications, education regarding therapy options, and the timely start of renal replacement therapy [92–100].

One key to successful predialysis management is the timely referral of the patient to a nephrology practice where a nephrologist or a nurse practitioner can individualize the patient's care and education. The newly diagnosed patient often focuses on the term *end-stage renal disease* and can become frightened and discouraged, so identification and regard for the patient's fears and anxieties must be foremost in the minds of the care providers. It is important to establish an atmosphere of trust.

Early interventions include nutritional counseling, hypertension education, and medication reviews. The patient may initially obtain the most information and education from the dietitian and the nephrology practice nurses; however, in some nephrology practices, specific education strategies and programs are in place that require participation of the PD nurse, hemodialysis nurse, social worker and transplant team. This allows the patient to meet and develop an early relationship with members of the renal replacement therapy team [1]. Other programs refer patients to predialysis education programs or dialysis education activities based exclusively in the home dialysis program [6].

Utilizing an integrated care approach to support the patient in choosing the right modality at the right time in the course of chronic kidney disease (CKD) is the responsibility of the both the nephrology and dialysis teams [101–103]. Timely education and decisions about dialysis modality also support PD, because often the CKD patient who develops uremia and starts hemodialysis emergently does not have the opportunity to then change to PD due to logistical barriers [5, 6, 104].

Providing predialysis education helps the patient understand the disease process, monitor and control hypertension, medications, strategies to preserve residual renal function, and renal replacement therapies. It should also create a supportive environment that allows the patient to ask questions and voice concerns. The patient then has the necessary information to make an informed choice of the mode of renal replacement therapy [5, 6, 101–103]. This early relationship and patient education may also help to promote adherence and the development of self-care management skills.

Renal replacement therapy options must be carefully presented without bias. All CKD patients should have the benefit of education about PD, hemodialysis, and transplant candidacy. Although PD is primarily a self-care therapy, patients who are not physically or mentally able to assume the responsibility for dialysis have done PD successfully with the assistance of family members, friends, or contracted care providers. Predialysis education can be accomplished by a variety of methods, but should be based on principles of adult education [105–110], with a chronic disease focus [111]. Individual counseling is appropriate for all patients, but group classes may also be helpful for the patient and family members, and classes utilize staff time more efficiently. For the patient who is unusually anxious, it is often helpful to provide an opportunity to meet with an established dialysis patient. The questions and information sharing are based on actual personal experience. These encounters are often rewarding and may be valuable for all prospective dialysis patients [112].

Participation in predialysis education is a valuable opportunity for the PD nurse and other PD team members. Their participation in early intervention and early education can contribute to recruitment of prospective PD patients. Key to retaining the interest of patients in PD is periodic follow-up and response to the patient's questions and concerns. The PD nurse must also communicate with the referring primary care physician and nephrologist.

Interviewing Prospective PD Patients

The interview process provides an opportunity to share information with the patient and family members about PD while establishing a relationship the prospective home dialysis patient. The interview may be part of the predialysis education program or take place later, after the patient has chosen PD. Knowledge of dialysis modalities and participation in the decision about type of renal replacement therapy promote the development of a sense of control early in the patient's dialysis experience. The patient learns to actively participate in his care. This can help to control fear, reduce anxiety and establish self-care skills. Developing this confidence may also promote adherence to the plan of care [113–115].

To prepare for the interview, the PD nurse should review the patient's medical history and prior experience with health care. Goals should be set for the interview and shared with the patient and family. Careful regard for cultural diversity and the patient's religious beliefs can aid in individualizing the process [112, 116, 117]. The patient with a language barrier must have the services of an interpreter. Whenever possible, this interpreter should not be a family member or friend so that unintentional bias or misinterpretation does not occur [116, 117].

The nurse must be competent in physical assessment, nursing diagnosis, and adult education and have good communication skills. Knowledge of chronic kidney disease management and renal replacement therapy options are also prerequisites. Utilizing this knowledge, the nurse then needs to individualize the information for each prospective patient. A successful interview will also depend on the nurse's compassion, understanding, and self-confidence [118, 119].

The physical environment is also important for a successful interview experience. The ideal setting would provide adequate lighting, a comfortable temperature, and comfortable seating for the patient and family in an environment that is free from distractions. Information should be directed to the patient with the family as the support system. The

nurse must also be a good listener and be ready to answer questions and validate the patient's fears and anxieties. The chronically ill patient will fatigue easily and the nurse must adjust the length of the interview based on the patient's tolerance. Allowing the patient to take a break and have refreshments may be helpful. Some patients may need a return appointment to complete the interview or to have time for questions and answers.

If the prospective patient has not had the opportunity to meet with a successful PD patient, this may be helpful. Asking questions of a fellow patient may not only provide information, but meeting a confident and successful PD patient may diminish stress and foster a positive approach to assuming self-responsibility [118].

Table 13.8 provides a sample outline for an initial interview. The nurse must be careful to select content that is important at the time of the interview. It may not be feasible to either obtain or offer as much information as desired, so it is important to individualize the interview. Using a written tool to collect information is recommended, and a documentation tool that follows the unit-specific interview outline can be developed.

There are additional issues related to interviewing the hospitalized patient. This patient is often sicker and under more environmental stress, and may need to make a more immediate decision about modality selection. Lack of privacy, lack of sleep, noise, and frequent interruptions can make the interview process challenging. If the PD nurse must interview the hospitalized patient, it is important to work with the hospital nursing staff to schedule an opportune time. Patients who are acutely ill and/or frankly uremic often must rely on family and significant others in making decisions, so they should be included whenever possible. The interview will need to be succinct and organized. Concise documentation of the content presented and the patient's response must be in placed in the hospital record to communicate with other healthcare providers [118].

Patients may also choose to transfer to PD later in the course of renal replacement therapy. The established hemodialysis patient may decide to switch to PD due to lifestyle issues, dissatisfaction with hemodialysis, or clinical complications of hemodialysis. The patient with recurrent problems with vascular access may need to change to PD in order to survive. Also the patient with a failed transplant may choose to resume dialysis as a home PD patient.

Table 13.8 Interview outline for prospective peritoneal dialysis patients

Patient information

- Employed/student/retired/disabled
- Family and community support
- Hobbies/interests
- Access to transportation
- Travel

Assessment of language and education

- Language
- Level of formal education
- Reading level
- Previous chronic kidney disease education

Review of health status

- Primary diagnosis
- Co-morbidities
- Prior experience with renal replacement therapies
- Prior experience with self-care

Assessment of physical limitations

- Sight
- Hearing
- Impaired ambulation
- Tactile impairment
- Hand strength
- Limitations in activities of daily living

Assessment of home environment

- Type of home; utilities
- Other individuals sharing home
- Appropriate area for dialysis procedures
- Space for supply storage
- Pets in household

Source: Adapted from [118] with permission.

PD Access

Effective management of the PD access is essential for successful PD. This includes catheter selection, preoperative, perioperative, and postoperative routines, chronic catheter care, and analysis of outcomes. The PD nurse will need to fulfill the roles of educator, coordinator and evaluator in establishing a PD access program with positive catheter outcomes [120, 121].

The first step is to identify and communicate with the team members who participate in access management. This includes the nephrologists, surgeons, operating room staff, recovery room staff, and the hospital unit staff. It may also include the interventional radiology staff and individuals who purchase supplies. The PD nurse may need to meet with each member individually or in small groups to achieve a collaborative approach to access management. Follow-up may be done by telephone and email. In some programs, an access coordinator or nurse may be designated to manage the scheduling of both hemodialysis vascular access and PD catheter placement and interventional procedures.

The group must choose the catheter(s) that will be utilized by the program. There is a variety of catheters to choose from: single or double cuffed, straight or coiled, presternal, and catheters with or without a swan neck configuration [122–124]. Implantation techniques vary and may include surgical dissection, laparoscopic placement, and burying the external segment for future externalization of the catheter [123, 125, 126]. The choices should be based on research of the available catheters, the current data in the literature, and the surgeon(s)' and program's experience.

The nephrologist or nurse practitioner will make the initial referral for PD and catheter placement, and will be responsible for the short- and long-term management of the patient's care. The surgeon will evaluate the patient for catheter placement, implant the catheter, and provide surgical follow-up. In some programs, the surgeon may also be involved in long-term outcome management by reviewing catheter outcomes data or participating in quality meetings. If catheters are routinely placed in an interventional radiology setting, the radiologist or interventional nephrologist would be part of the quality team.

Table 13.9 PD catheter management routines [60, 121, 122, 124, 127–130]

Preoperative routine

- Patient selects peritoneal dialysis as renal replacement therapy
- Patient referred by nephrologist for catheter placement
- Peritoneal dialysis nurse educates patient and family about catheter placement routines and initial catheter care
- Patient is evaluated by surgeon; catheter exit site evaluated in both upright and supine positions
- Proposed catheter insertion and exit sites are marked
- Culture nares (if done at this unit)
- Consent for procedure is obtained
- Bowel , bladder, and skin preparation
- Patient reports to either hospital pre operative admission area, to transient outpatient area or other designated location on day of catheter placement

Perioperative routine

- If catheter is placed by surgical dissection or by laparoscopy, the patient will be cared for by the operating room team during the procedure
- Antibiotics are given before the start of the procedure
- Catheter patency is tested by infusing and draining
- Catheter is capped or appropriate tubing or transfer set is attached
- Dressings are applied to incision site and exit site per program protocol
- Catheter is secured to prevent traction at the exit site
- Surgeon will recommend when the catheter can be first used for dialysis exchanges

Postoperative routine

- Patient will be monitored either in a recovery room or in a transient care setting
- Pain control is provided
- Surgeon will determine if patient may return home or will be admitted for overnight observation
- Peritoneal dialysis nurse may flush catheter either in the hospital or transient care setting or arrange for clinic follow-up in 24 to 48 h
- Initial dressing per program policy may be removed either by surgeon, peritoneal dialysis nurse, or designee
- Prophylactic antibiotics (systemic and/or local) continued per unit protocol
- Patient is provided with written instructions for catheter care, bowel regimen, pain medication prescription, and follow-up appointment
- Emergency telephone numbers are provided and reviewed
- Follow-up appointments are arranged with the peritoneal dialysis outpatient program

Table 13.10 Components of catheter evaluation at routine clinic visits

- Inspect catheter and adaptor for cracks, splitting and leaks
- Inspect catheter exit site for dialysate leak and signs of exit site infection
- Inspect the abdominal wall for evidence of subcutaneous leak and hernias
- Monitor the flow of effluent during infusion and drain
- Monitor effluent for color, clarity, and the presence of fibrin
- Observe the patient for unusual pain or discomfort
- Periodic review of home exit site care procedures

The PD team needs to identify the responsibilities of each unit or staff member (e.g., the operating room nurses often participate in testing catheter patency, capping the catheter, and placing the surgical dressings), develop written protocols for catheter care procedures, provide initial staff education, and identify resources for these care providers. Outlines of preoperative, perioperative, and postoperative routines are listed in Table 13.9 [60, 121, 122, 124, 127–130].

Each program must develop specific procedures for maintaining catheter patency, including nonheparin alternatives. There must also be protocols for catheter obstruction [131], daily exit site care, and strategies to prevent infection. Also, effective procedures for catheter "break-in" help to maintain patency, facilitate wound healing, and prevent early leaks [132].

Long-term management of PD catheters is a crucial to insuring the patient's longevity on PD. Early identification of catheter complications [133] and catheter-related infections and prompt intervention are critical to catheter survival. All team members must agree on and follow exit site procedures so that the patient has the benefit of consistent care. A routine catheter and exit site assessment should be part of each clinic visit and hospital admission. Table 13.10 summarizes elements of catheter assessment. Catheter-related queries can also be incorporated when assessing the PD patient by phone.

A quality program for PD catheter outcomes helps to insure consistent monitoring and evaluation of access management. The nurse acting as a facilitator can utilize the documentation from routine catheter and exit site assessments to effectively track catheter-related problems and infections.

The PD nurse must also monitor the literature for evidence-based practices for exit site and catheter care and benchmarks for catheter outcomes [24, 59, 60].

PD Patient Education and Training for Home Dialysis

The foundation of a successful PD program is the provision of effective home dialysis training [134–137]. PD nurses often do not have formal training in education theories, methods, and strategies [138–141]. To successfully develop a program and successfully teach patients, the nurse must acquire this knowledge and related skills. Attending a formal education course or seminars, networking with colleagues, and developing a relationship with a mentor can prove to be excellent sources of information [139]. Each nurse must then take responsibility to periodically enrich his/her knowledge of the adult learning principles. Regional or national conferences offer opportunities for learning, networking, and informal sharing of experiences. An important investment for any dialysis unit is the purchase of adult education texts and resources [105–110]. Also, nephrology nursing textbooks include chapters on patient education [142, 143].

Although there may be generic learning objectives (Table 13.11) and a recommended list of content (Table 13.12), the educational program for each patient must be individualized. The cultural and religious background of the patient must be regarded when individualizing the patient education plan [116, 144, 145]. Patients who speak a different language should have the benefit of an interpreter who can translate the information in an unbiased manner. Utilizing an interpreter will lengthen the training sessions or increase the number of sessions. In general, the length of the training session is determined by the patient's degree of uremic symptoms, endurance, and attention span. Transportation requirements may also affect the scheduling and length of the session.

The patient and family must be included in scheduling sessions, deciding who will attend with the patient and arranging transportation. The patient should be the focus of each patient education session with the family member(s) providing support. When family members are training as dialysis partners or to provide back-up support, they will almost always have mastered the content by the time the CKD patient has; however, they will need to practice the procedures. Documentation should include verification that each individual who will be performing dialysis procedures has participated in the training and identify which procedures they can safely perform.

Table 13.11 Objectives for the peritoneal dialysis instructor

The PD instructor will:

- Provide an environment for effective learning
- Present an overview of the PD course
- Prepare learners for what they will learn and how both the learner and instructor will know that learning has occurred
- Apply concepts of adult learning
- Restrict educational content to three or four messages per hour
- Use pairs to help learners differentiate between symptoms and concepts
- Help the learner problem solve by defining problems and listing possible solutions
- Recognize the learner's need to repeat new information in order to move it from short- to long-term memory
- Recognize that repetition is an important method of reinforcing learning
- Recognize that information memorized is easiest to forget
- Use questions to evaluate the learning process and guide the learner
- Evaluate the effectiveness of learning by tracking outcomes
- Understand that retraining or additional education may be required over time

In teaching procedures the instructor will:

- Understand the difference between learning motor skills and procedures
- Not teach theory during motor skill learning
- Demonstrate steps of procedures with consistency
- Prevent the learner from practicing procedures until all steps have been learned in order
- Supervise the practice of procedures until all steps have been mastered
- Encourage and support the learner through repetition and verbal clues
- Provide immediate feedback during practice

Source: Adapted from [138] with permission.

Table 13.12 Suggested content for the PD home training education program

- Review of normal kidney function
- How peritoneal dialysis works
- Principles of aseptic technique
- Preparation of home environment for peritoneal dialysis
- Handwashing technique
- Utilization of waterless hand sanitizer
- Preparation of exchange area
- Organization of supplies
- How to do CAPD exchange
- Problem solving with exchange procedure
- How to set up and program automatic cycler
- Problem solving with cycler/APD procedures
- Addition of medications to PD solution bags
- Warming of dialysis solutions
- Appropriate use of face mask
- Documentation on home record sheets
- Monitoring of weight, blood pressure, and heart rate
- Principles of fluid balance
- Recognition of hypovolemia and hypervolemia
- Guidelines for managing fluid balance
- Exit site care
  - Routine exit site care
  - Use of antibiotic cream/ointment at exit site
  - Recognition of signs/symptoms of exit site infection
  - Care of the infected exit site
- Methods of securing catheter
- Recognitions of signs/symptoms of peritonitis
- Specific instructions related to PD complications:
  - Obstruction to flow of dialysis solutions
  - Change in dialysate color

Table 13.12 (continued)

- Fibrin formation
- Utilization of heparin or non heparin alternatives
- Accidental disconnections
- Traumatic injury to catheter or exit site
- Reporting falls or accidents with suspected abdominal trauma

- Guidelines for utilization of different dextrose concentrations
- Development of individualized daily dialysis prescription
- Daily hygiene routine including showering and frequent handwashing
- Review of medications
- Sexuality and reproductive concerns
- How to contact nephrologist and peritoneal dialysis nurse
- Seeking emergency assistance
- Description of elective or emergent hospitalizations
- PET and adequacy monitoring procedures
- Storage and ordering of supplies
- Review of travel procedures
- Outline of follow-up appointments

The PD unit is typically the site for training; however, in special circumstances, the training may occur in a hospital, rehabilitation setting, or even in the patient's home [146–148]. A few programs have routinely trained patients in their homes; others have limited training in the home to patients with special needs. The patient who is unusually anxious, disabled, or dependent on others for care may benefit from exclusive training in the home [149]. Patient education outside of the dialysis unit typically requires more nursing time, so is costly [149]. Regardless of the site, it is essential to maintain a quiet environment with few interruptions.

Patients may be taught in a small group for at least part of their training. There is no evidence that this method is more or less effective than individual teaching sessions. Some patients find group training supportive; however, others find it too distracting.

Sample content for a PD education program is listed in Table 13.12. This is not all-inclusive, but provides a basic framework. The PD nurse will need to individualize the content for each patient and determine what should be accomplished in each session. Clear, consistent instructions are particularly important when teaching procedures and may foster patient adherence.

The number of training sessions will vary depending on the patient's learning needs and ability to learn; however, the number of patient education days or sessions may be limited by the reimbursement structure, and the nurse must be aware of the financial implications. One study found that older patients and those with more co-morbidity required more training sessions [150].

Patient education needs to be well-documented [151]. Although checklists are useful tools during the patient education process, most regulatory agencies do not consider a checklist alone to provide adequate documentation. A written narrative indicating not only what topics have been covered, but the patient's response may be required. This might include a description of the patient's ability to grasp concepts, remember sequences, perform procedures, and problem solve. Written quizzes or tests may be included as documentation of learning [152].

The patient preparing for home dialysis should also have sessions with both the dietitian and social worker. The dietitian will perform an initial assessment, outline both short- and long-term plans for adequate nutritional intake, and teach the patient and family about the dietary recommendations. Dietary counseling will need to be provided on a regular basis to help the patient maintain an adequate protein intake, control total caloric intake, and avoid excessive intake of phosphorus, sodium, and potassium [7, 153].

The social worker also performs an initial assessment and may assist the patient with community resources, billing issues, supplemental insurance, housing, and transportation issues [154]. The social worker may also help the patient to cope with CKD and dialysis therapy by discussing the patient's fears, anxieties, coping strategies, and support systems. Unusually anxious patients and those with mental health diagnoses will need more intensive psychosocial or psychiatric support during the initial training period or even throughout the course of home dialysis.

The learning process continues after the patient is dialyzing successfully at home [155]; therefore, patient education is never completed, but is a continual process of reinforcement and evaluation of the patient's adaptation and changing learning needs. Some programs have a formal continuing education program, which provides a review and updates for established home dialysis patients [156]. Others have a monthly education topic that is presented at routine clinic visits. Still others provide information on clinic bulletin boards or in newsletters.

Home Visits

Visiting PD patients in their homes may be done at the time the patient completes home training, after the patient is established at home, when dialysis-related problems occur (e.g., repeated infections, problems with fluid balance), or for follow-up of ongoing problems [157–159]. In some programs the home visit is an essential step in initiating PD at home. When the initial home visit is made at the completion of home training or shortly thereafter, it gives the nurse another chance to evaluation evaluate what the patient has learned and the readiness of the patient and family to assume the responsibility for home dialysis.

If necessary, additional education can be provided during the home visit. The home visit provides a critical opportunity to evaluate the patient's environment: where PD will take place, how supplies are stored, facilities for showering or bathing and handwashing, and the safety of the physical environment. The nurse can also observe the patient performing dialysis procedures and interacting with family members and others. Also, in the safety of his or her home, the patient may voice concerns, anxieties, or questions that were not discussed in the dialysis unit. Table 13.13 is a sample checklist for documentation of home visit activities and assessments.

Reinforcement of previous training and additional training of family members may also be accomplished at this visit. Other home health providers may also want to be included at this visit not only to acquire education but also to network with the home PD nurse.

The home visit can enhance the relationship between the nurse and patient, fostering a mutual respect. In response to a patient satisfaction questionnaire, both patients and caregivers responded that they valued home visits [160].

Table 13.13 Home visit assessments and documentation

Physical environment:
____home _____apartment _____nursing home
____shelter _____other
Bathroom facility _____private _____shared

Inspection of environment:

- Cleanliness _____hand soap/sanitizer available
  _____sink/water for hand washing
  _____overall cleanliness of home
- Supplies _____safely stored
  _____missing supplies
  _____inventory list
  _____appropriate quantity
- Medications _____safely stored
  _____refrigerated if needed
  _____location of syringes

Pets

- Type and number of pets
- Are pets restricted from the exchange area?

Designated area for exchanges:

- Are supplies organized for this area?
- Can patient safely do the exchange?
- Can the patient perform handwashing in this area?

Family involvement:

- Who are the significant others in the home setting?
- Are there small children in the home?
- Which family members participate in PD?
- If patient not able to do self-dialysis, who is the dialysis caregiver?
- Does the patient have a health care/medical proxy?
- Who is the emergency contact?

Note date of next supply order and delivery

Schedule follow-up appointments

The limitations of the home visit must be addressed as well. Home visits are time consuming and costly. There may be neighborhoods and physical environments that are not safe for visiting care providers. Also, patients may decline to participate in this activity.

The home visit may need to be repeated if the nurse suspects changes in the home environment that may contribute to increased incidence of infections, patterns of nonadherence, or changes in the family support system.

Observations of the home environment must all be documented in the patient's medical record [157–159]. A documentation tool that follows the unit-specific home visit outline could be developed (Table 13.13).

Long-Term Management

After training has been completed and home dialysis has successfully been initiated, there must be an organized approach to providing long-term nursing care. This includes routine clinic visits, additional visits for problems, telephone follow-up, periodic retraining, and coordination of care with other providers. Table 13.14 summarizes elements of follow-up care for home dialysis patients.

Routine Clinic Visits

Routine clinic visits (e.g., at monthly intervals) provide an opportunity for the team to evaluate the patient's clinical status and adjustment to home dialysis. Ideally, the patient is seen by the PD nurse and the nephrologist together; however, in some programs, the visit with the nephrologist takes place at a separate location. Also, the social worker and dietitian see the patient during clinic visits, either routinely, at intervals as indicated by regulations, or when there is a need or patient request. Elements of the clinic visit are summarized in Table 13.15, and include a physical assessment, review of the current dialysis regimen and medication prescriptions, evaluation of adherence, answering patient questions, providing encouragement and support to the patient and family, and outlining changes in interventions to improve care. All prescription changes and recommended interventions should be documented in the patient's medical record, and the patient should receive a written copy of the team's recommendations [105, 112, 161].

Detecting nonadherence to the plan of care in the home peritoneal dialysis setting is a complex process [113]. The patient is not routinely assessed or observed in the home environment. Unexplained clinical changes in serum chemistries, hemodynamic instability, signs and symptoms of uremia, repetitive infections, and frequent appointment cancellations may be indicators of nonadherence.

Compliance with home peritoneal dialysis has been studied by repeated inventories of home dialysis supplies [162, 163] and by reviewing treatment data recorded by dialysis cycler software [164, 165]. The studies that inventoried home dialysis supplies, one in the United States [162] and one in Brazil [163], found similar rates of compliance with dialysis exchanges: 74 and 70%, respectively. The U.S. study found that noncompliant patients had significantly more peritonitis and hospital admissions, significantly lower weekly Kt/Vs, and were significantly more likely to transfer to hemodialysis [162]. The Brazilian study also found that noncompliant patients had lower weekly Kt/Vs; however, the peritonitis rates were similar between compliant and noncompliant patients [163]. The studies of compliance as recorded by cycler software show relatively few missed treatments, but also measured compliance by the volume of dialysis solution delivered [165] and the total dialysis time [164]. One of these studies found that patient education improved compliance [165]; however, compliance may also have improved in this group because they knew compliance was being monitored.

Establishing a realistic home dialysis regimen that reflects the patient's culture, lifestyle, and psychosocial needs, and providing individualized support may also enhance adherence to the dialysis prescription. This continuum of education and support is essential to foster adherence, not only to the dialysis regimen, but to medications, and to diet and fluid restrictions. Finally, promoting patient adherence to the plan of care is the responsibility of all participating healthcare providers.

The patient who has difficulty adhering to the plan of care or who is experiencing clinical complications may benefit from more frequent visits. One group found that when patients were included in the discussion regarding dialysis prescriptions, they were more adherent to dietary salt and fluid restrictions and had better fluid balance [166].

13.14 Nursing care activities for PD home patients

Establish care plan including nursing diagnoses and associated short- and long-term goals

- Care plan is updated quarterly by the peritoneal dialysis nurse, nephrologist, social worker, and dietitian.
- Document follow-up of home dialysis patient in the clinic visit and telephone consultation notes.
- Recently hospitalized patients will have a discharge summary of care in the medical record coupled with a plan to resume home dialysis care.

Clinical management parameters for home peritoneal dialysis care include

- Hemodynamic stability
  - Assess fluid and electrolyte balance
  - Monitor blood pressure and review blood pressure control
  - Review antihypertensive medications
  - Adjust dialysis regimen as necessary
- Anemia therapy
  - Therapy with erythrocyte stimulating agents (ESAs) is initiated and monitored with appropriate patient education
  - Oral iron supplements and intravenous iron therapy, as indicated
  - Obtain and monitor associated laboratory tests
  - Obtain appropriate insurance authorizations
- Calcium and phosphorus balance; secondary hyperparathyroidism
  - Coordinate nutritional counseling
  - Monitor and adjust phosphorus binders and should be vitamin D therapy
  - Obtain and monitor associated laboratory tests
- Nutrition counseling
  - Coordinate periodic nutritional counseling for patient and family
  - Nursing support for the individualized nutritional plan
  - Refer for resources for nutritional supplements, if needed
  - Obtain and monitor associated laboratory tests
- Catheter management
  - Assess catheter and exit site
  - Review procedures for exit site care
  - Local care interventions when indicated
  - Prescribe/provide antibiotics, when necessary
  - Monitor catheter function
- Home peritoneal dialysis management
  - Monitor patient (and partner's) adjustment to self-care and home dialysis
  - Measure adequacy of dialysis per program policy
  - Explain laboratory and adequacy of dialysis test results to patient
  - Explain need for prescription changes and new dialysis orders
  - Provide option of home visit, if indicated
  - Provide periodic retraining, if indicated
- Development of patient competence and self-responsibility
  - Use team problem solving approach
  - Incorporate patient into decision making
  - Provide time for patient to discuss individual issues with team
  - Individualize patient care and support
  - Offer patient positive feedback on a routine basis
  - Evaluate patient adherence and strategies for accountability
  - Refer for psychological or psychiatric support when indicated
- Transplant evaluation
  - Support transplant education
  - Encourage/refer for transplant evaluation
  - Obtain blood samples for routine screening
  - Encourage patient-to-patient networking
  - Support development of self-care management behaviors
  - Document patient's adherence to self-care management

Table 13.15 Components of clinic visit assessment

Review current dialysis prescription and routine
Reinforce any changes in dialysis prescription
Inspect and evaluation catheter and exit site
Vital signs (including supine and upright blood pressure measurements), and weight
Assess fluid balance
Review prescribed and over-the-counter medications
Assessments including: • Cardiovascular system • Pulmonary system • Gastrointestinal system • Central nervous system • Skin integrity • Mobility/physical limitations • Social support system • Psychological adjustment • Any infections and treatment
Review patient's home records • Dialysis • Fluid balance • Blood glucose control
Review laboratory results
Query regarding any hospitalizations and results of visits to other healthcare providers since last clinic visit
Update nursing diagnoses and care plan as indicated
Schedule follow-up appointment(s)

Communication Between Visits

An important part of follow-up management is communicating with the patient between visits, by telephone, mail, or email. Some programs specify an interval for routine telephone calls for established PD patients (e.g., weekly or once between clinic visits). The frequency and length of these communications also depend on individual circumstances. More frequent communication and more intensive support are required for new PD patients. Communication between clinic visits may also be indicated when a patient has several co-morbid conditions or is acutely ill, when there are problems with adherence to the dialysis routine, and when there are laboratory results that require adjustments in medications or dialysis prescription. Telephone conversations also provide time for the nurse answer questions, provide instructions (e.g., for adequacy collections), and clarify future appointments. Communications between clinic visits a can strengthen the bond between nurse and patient and may help to prevent patient isolation and burnout.

The health assessment and plan of care need to be periodically updated. In some programs or states, monthly or quarterly care plans are mandated.

It is important to engender an atmosphere of trust and security. Developing a supportive environment encourages patients to be honest and open in their communications, to give accurate information about self-care activities, and to voice their questions and fears. Using several avenues of communication with both patients and families encourages active participation. Individual discussion, group meetings, follow-up phone calls, letters, posters, handouts, newsletters, and email are all effective methods of communication.

Retraining

Annual or more frequent retraining sessions are used to reinforce correct dialysis procedures and technique or to introduce new dialysis systems or procedures. Annual retraining can be incorporated into a monthly clinic visit or can be done with a group of patients in classes or a day-long PD patient education seminar. Topics that are frequently covered include review of dialysis procedures, introduction of a new system for CAPD exchanges or a new cycling device, addition of medications to the dialysis solution, strategies to prevent infection, maintaining good fluid balance, recognition of signs and symptoms of infection, basic problem solving, exit site and catheter care, and assessment of the

catheter exit site. Time can also be designated to review how to contact the PD nurse and/or nephrologist for questions, problems, or emergencies, and how to prepare for an elective or emergent hospitalization. Obviously, this list is not all inclusive, but it addresses elements that are critical to safe and effective home dialysis. If a retraining visit is scheduled to address a specific problem, the objectives and strategies for the retraining session will have to be individualized.

Methods of retraining include formal and informal presentations, written handouts, demonstrations, skits, and videos. Methods of assessment include verbal review, quizzes or having the patient fill out a written questionnaire [103, 105, 138, 167]. It is also critical to allow sufficient time for patient and family questions. If the review is done as a class or education day, there should be time for patients to meet and talk with one another. Also, a patient or patients may participate in the presentations. Patients can share helpful hints and strategies for long-term success on home dialysis [168]. As with other types of follow-up care, retraining can contribute to enhanced adherence, and help to prevent burnout.

This time also provides an opportunity to ask the patient and family for suggestions regarding improvement of services and the plan of care. The patient who experiences frequent infections or is having difficulty adhering to home procedures may need frequent retraining that should be focused on the individual patient needs.

Providing On-Call Coverage

In many programs the PD nurse provides "on-call" coverage. Providing this coverage reduces unnecessary emergency department visits and hospitalization admissions, and ensures a channel of communication for the patient on a 24-h basis. This support service is both emotionally reassuring and clinically correct for the home PD patient.

Depending on the particular program's policies, the "on-call" role may vary. The nurse may provide telephone consultation on a 24-h basis to answer patient's questions, assist with problem solving, and offer clinical direction and support. In other situations the nurse is also the provider who triages the patient's care by directing the patient to a physician or emergency department for appropriate care. The most common problem necessitating emergency department visits is peritonitis [169]. In some programs, for a dialysis-related complication such as peritonitis, the PD nurse may also meet the patient at the emergency department to facilitate care.

Other healthcare providers who may be involved in "on-call" coverage include nephrologists, clinical nephrology fellows, interns, and residents. Nurse practitioners and hemodialysis nurses may provide on-call services to PD patients. Standing medical orders and specific policies and protocols to manage clinical problems help to ensure that the care provided is safe and appropriate.

The Hospitalized PD Patient

The role of the home PD nurse in providing care or consultation for the hospitalized patient will vary with each program [170, 171]. The PD program that is either hospital based or hospital affiliated may routinely require direct involvement of the PD nurse. The outpatient PD nurse may provide periodic inservice education for hospital nurses and be responsible for written protocols and guidelines. The PD nurse would be available to direct clinical care of the PD patient in both acute and non acute care units. In other programs, the PD nurse may perform CAPD procedures or set up the cycler and initiate PD. Communication and consistency are vital when providing the direction necessary for safe patient care.

The PD nurse who is not involved in hospital consultation can still participate in providing support for the hospitalized patient. Educating the patient about how to prepare for an elective hospitalization can be incorporated into the initial training for home dialysis. Providing written transfer information for the hospital unit can be critical in assisting the hospital staff to safely provide PD (Table 13.16) [170]. Telephone calls to the patient's hospital unit and primary nurse can be a successful method of clinical support.

Anticipating the patient's needs for an elective admission is another nursing responsibility. Preparing the patient and family for the routine of hospital care can diminish the stress associated with any hospital admission.

When the patient is admitted to a hospital that is not affiliated with a PD program, discussing the patient's dialysis-related needs with the hospital's admitting service and the department of nursing can only help to make the experience safer.

Common issues the PD nurse encounters during hospitalizations are the need for appropriate supplies, identifying who will be responsible for the dialysis exchanges, problem solving with exchanges, prevention of infection, identification of dialysis-related complications, and documentation of the patient's dialysis routine and clinical outcomes. The

Table 13.16 Hospital transfer information for the PD patient

Pertinent medical history/reason for admission
Medication allergies
Other allergies, e.g., latex
Medication list
Peritoneal dialysis
○ Description of any dialysis-related problems
○ Type of catheter
○ Most recent exit site assessment
○ Membrane classification, e.g., PET results
○ Current dialysis prescription
○ Type of PD system or cycler used at home
○ Whether patient requires a partner to do dialysis
○ Most recent dialysis adequacy results
○ Target weight
○ Blood pressure range
○ Specific issues related to home dialysis that may affect discharge

PD nurse may also assist the staff nurses with accurate documentation of fluid balance, the infusion and draining of exchanges and consistent daily weights. Hospital nurses who are inexperienced with PD and CKD particularly need the support of the home PD nurse.

Often, attending physicians or hospitalist physicians are not familiar with the patient's dialysis routine and prescription. Providing a checklist or sample dialysis prescriptions can often improve the appropriateness of the dialysis prescription and diminish the anxiety of the physician who is not familiar with PD. A sample checklist of components of the PD prescription for the hospitalized patient is shown in Table 13.17.

Discharge planning needs to be coordinated between the hospital staff and the PD nurse. The discharge summary of care must be provided to the home dialysis program so that home care can be resumed safely. The list of discharge medications needs to be reviewed carefully by the PD nurse for new medications, intentional changes to the dialysis orders and accidental omissions.

The PD nurse should educate the patient to always call the home dialysis program the day before (or the day of) discharge to arrange for the next outpatient appointment, clarify the current home dialysis prescription, and determine if any additional supplies need to be ordered . In some instances, a visiting nurse may be utilized for nondialysis support. The visiting nurse may not be familiar with PD and may need education about the patient's home dialysis responsibilities.

PD in Long-Term Care Facilities

After a hospitalization or due to other clinical and psychosocial circumstances, the PD patient may not be able to perform home dialysis unassisted. The patient may then need either short-term or long-term care in order to continue PD safely and consistently. Or a rehabilitation facility may provide a bridge before to discharge to the home. If the patient requires rehabilitation, the PD nurse will need to network with the hospital case manager and staff of the rehabilitation facility to ensure that the rehabilitation staff can perform dialysis safely. The rehabilitation nursing staff will need educational programs, written procedures, and protocols to provide PD care and contact information for the PD unit or primary nurse. Weekly or more frequent communication with the rehabilitation facility will provide an opportunity to follow the patient's clinical course and also to consult with the facility staff regarding the PD. Consistent communication is a key to provision of safe dialysis in a rehabilitation facility and also fosters successful discharge planning and transition back to self-care at home.

PD can be provided in the long-term care facility or nursing home as well [172, 173]. The patient may be admitted for a short-term transitional period after hospitalization or may need long-term care. Prior to the patient's admission to the nursing home, the nurse may do preliminary visit to the facility to meet the nursing director, schedule PD education classes for the staff, and to assess the environment for cleanliness and room for supply storage. The nurse will need to provide educational programs, written protocols, and procedures. Specific physician orders for dialysis must be provided and periodically reviewed. Finally, depending upon the state or federal policies and the payers, the administrators of the PD program and the nursing home must develop a written financial contract and clarify billing procedures.

Table 13.17 Dialysis prescription checklist for the hospitalized PD patient

Fill volume

- 500–1,000 mL (new catheter, initial therapy)
- 2,000–3,000 mL (maintenance therapy)
- 3,500 mL or greater (for unusual circumstances)

Exchanges

- Frequency will depend on PET results
- CAPD: 4–5 exchanges per 24 h
- APD: 5–8 exchanges per 24 h (combination of APD cycles, last fill, daytime exchanges)

Dextrose concentration

- 1.5%
- 2.5%
- 4.25%

Icodextrin 7.5% (used for selected patients)

- CAPD: overnight exchange or longest dwell
- APD: longest daytime dwell
- Glucose monitor per manufacturer's recommended list

Heparin

- CAPD: 1,000–2,000 units per 2- or 2.5-L bag
- APD: 2,000–3,000 units per 5- or 6-L bag
- For heparin allergy, heparin alternatives, or tissue plasminogen activator (tPA)

Chronic exit site care

- Daily inspection of site for erythema, exudate, leakage
- Daily cleansing of site
- Application of antibiotic ointments to site if indicated
- Catheter must be secured firmly with tape
- Culture exudate for suspected infection

Antibiotics

- Per current ISPD recommendations and guidelines available at www.ispd.org
- Route may be either intravenous or intraperitoneal
- Dosing may be in each solution bag or in the longest daily dwell

Insulin

- Either subcutaneous or intraperitoneal
- IP should be added immediately before exchange
- Monitor serum blood glucose

Potassium

- Safest route is oral
- May be added to intravenous solutions
- May be added to dialysis solution bag, if necessary

Specimens for suspected peritonitis

- Cell count
- Culture and sensitivity
- Gram stain
- Fungal culture

The monthly clinic visit may be accomplished by transporting the patient to the PD unit or in some situations the PD nurse and nephrologist may elect to visit the patient in the nursing home. This allows for evaluation of the patient's clinical needs and also provides an opportunity to observe the nursing home setting. Care provided by the PD nursing staff must be carefully documented in the patient's medical record in the PD program on a consistent basis.

The PD nurse should also communicate with the family about their perception of the nursing home's ability to safely manage their family member's care.

Modality Transfers

Hemodialysis patients may decide to change their dialysis modality to PD. Unfortunately many patients begin hemodialysis before they are informed about renal replacement options. Some of these patients decide to change modalities when better informed [174, 175]. A hemodialysis patient may also select PD to assume more responsibility for self-care. Hemodialysis patients with vascular access complications may switch to PD due to lack of available access. Often, these patients may have had many attempts to create a vascular access, and a long history of access complications, infections, and hospitalizations. These patients may not have initially selected PD because of reluctance to manage self-care, but now must depend on PD to survive. Such patients are often discouraged, anxious, and without residual renal function. Managing these patients presents a distinct challenge to the entire PD team. Because they have minimal or no residual renal function and often have a history of infection and chronic inflammation, they must be followed closely.

The patient who has a failed kidney transplant may select PD as the modality of choice. This patient may have experienced a very difficult clinical course of rejection episodes, infection, and hospitalizations compounded by disappointment and depression. This patient will also be a challenge to the team due to both the emotional experience of transplant loss and the effects of chronic immunosuppression. The PD nurse will need to pay particularly careful attention to educating the patient about infection prevention.

Assessment and Classification of the Peritoneal Membrane

The policies of the program should include a specific plan for obtaining the first assessment of the dialysis membrane. This will provide information about the patient's individual membrane characteristics that will allow for accurate prescription planning. Recommended assessments include the peritoneal equilibration test (PET), standard peritoneal permeability analysis (SPA), and the peritoneal dialysis capacity test (PDC) [26]. This section focuses on the PET, as it is most widely used. The standardized PET consists of a single 4-h exchange with dialysate samples at 0, 2, and 4 h and a blood sample at 2 h [176–178]. Abbreviated procedures have also been described [179, 180].

It is recommended that the initial PET be scheduled at least 4 weeks after catheter placement and the start of PD. The PD nurse must provide the patient with both verbal and written instructions outlining how to prepare for the test. As the day for the test approaches, it is suggested that the nurse call the patient to review the instructions. On the day of the test, if the nurse suspects that the patient has not complied with the instructions, the PET should then be rescheduled in order to prevent erroneous data and subsequent conclusions. Detailed descriptions of the PET procedure have been previously published [181, 182]. Common errors include inadequate drainage of the prior long-dwell exchange or of the PET exchange; inadequate mixing of dialysate; samples not drawn at the appropriate times; dialysate samples are mixed up and incorrectly labeled; or the final sample is diluted with fresh dialysis solution. If there are problems with the PET or results that are not consistent with the clinical picture, the evaluation can be repeated in the clinic. Each sample should be labeled when drawn (errors can occur with prelabeled tubes), and all samples should be run at the same time.

Indications for repeating the PET are unexplained clinical changes, suspected nonadherence with dialysis, suspected changes in the peritoneal membrane or membrane failure, or if there is an apparent change in membrane function due to infections or surgical procedures. Some programs may choose to repeat the PET at standard intervals, but there is no conclusive evidence that this is necessary.

PD Adequacy

Provision of adequate dialysis is part of the foundation to achieving a successful PD program. The PD program must have policies and procedures to direct an organized approach to the assessment of dialysis adequacy, and to intervene with appropriate dialysis prescription adjustments. Typically, the PD nurse and the medical director collaborate to develop dialysis adequacy policies, procedures, and data collection tools. Careful review of the current evidence-based practice guidelines [24–26] is necessary to determine the standard of practice and set the program's adequacy goals. In some countries, regulatory agencies mandate evaluation of dialysis adequacy at specified intervals to insure the delivery of safe patient care.

Differentiating between the concepts of adequate dialysis and optimal dialysis is important when establishing program policies. Adequate dialysis is defined as the dose of dialysis associated with an acceptable morbidity and mortality. Optimal dialysis is defined as the dose of dialysis associated with no further improvement in symptoms and survival [183, 184].

One typical practice is to schedule the first adequacy testing with the initial PET. An alternate approach is to perform both the first PET and initial adequacy testing during training. Adequacy testing may be repeated according to practice guideline recommendations or specific program policy. Clinical reasons for repeating adequacy testing include diminished residual renal function, symptoms of uremia, evaluation of patient adherence to dialysis prescription, and validation of the effectiveness of major prescription changes [26, 178, 185–188].

Dialysis adequacy testing should always be accompanied by a careful clinical assessment of the patient. An individual who is adequately dialyzed will look well, be free of uremic symptoms, maintain appropriate physical activity, have adequate nutrition, and report a generalized sense of well being [183]. In contrast, the patient who is inadequately dialyzed will have uremic symptoms and difficulties with fluid balance and blood pressure control. Inadequately dialyzed patients may also be malnourished and anemic, and are more likely to have neuropathies and sleep disturbances [183, 187]. Eventually, patients who are not well dialyzed will have an increased incidence of cardiovascular events, hospital admissions, and deaths [189, 190].

Risk factors for inadequate dialysis include an inappropriate or inadequate dialysis prescription, loss of residual renal function, large body surface area, low membrane transport characteristics, poor tolerance of large exchange volumes, a pattern of noncompliance, and patient resistance to prescription changes [187, 188, 191].

Urea kinetic modeling of peritoneal dialysis [192] requires a 24-h collection of urine and dialysate. The adequacy assessment should be done when the patient is clinically stable, does not have an infection, and is in good fluid balance. Patients must receive specific written instructions, verbal explanations, and appropriate reminders to complete the adequacy study. Patients should also be interviewed when they bring in the collections to determine if the samples were collected and labeled appropriately. PD adequacy assessment collection procedures are outlined in Table 13.18 [182, 193, 194].

If working in a hospital-based or independent facility, the PD nurse may need to communicate with laboratory personnel to explain the purpose of adequacy testing and the collection procedures and to agree upon sample size, containers. and labeling.

Common problems with the PD adequacy assessment include patient errors in collection (incomplete drain, including too few or too many exchanges, inaccurate volume measurement), mislabeling of specimens, laboratory errors, and calculation errors. Dialysate collections with either too many or too few exchanges will yield erroneous results and cannot be used. Also, if the patient does not save all urine, or saves urine at a different time than the dialysis, the results will not be accurate. The PD nurse and the laboratory must follow specific written procedures to collect and label samples correctly and analyze the results accurately [181, 186].

The laboratory results may be reported as raw data or may be returned with adequacy calculations. If raw data is reported, the PD nurse may perform the adequacy calculations manually, or enter them into a computer program, which will automatically calculate the adequacy results.

The adequacy results can then facilitate prescription adjustments [4, 183, 184, 187, 188]. Prescriptions that are individualized in respect to the patient's membrane characteristics will be most effective [183, 195]. The patient with low transport rates will benefit from longer dwell times and larger exchange volumes. The patient with average and high average transport rates may need additional exchanges and larger exchange volumes. The patient with a high transport rate will need rapid cycles with an automatic cycler with one or more daytime exchanges [196]. The patient who is experiencing a decline in residual renal function may need adequacy monitoring and prescription adjustments more frequently to avoid inadequate dialysis.

All adequacy assessments and prescription changes need to be carefully documented in the patient's medical record. These data can then utilized by the quality management program focusing on the provision and documentation of adequate dialysis.

In summary, maintaining adequacy is dependent on the information that the membrane characterization and adequacy studies offer. This allows the PD nurse and team to make thoughtful and accurate dialysis prescriptions [178, 183, 188]. Careful explanation to the patient coupled with a positive supportive approach can foster the patient's cooperation with prescription changes and overall adherence [186].

Prevention of Infection

Another cornerstone of successful PD therapy is the prevention and treatment of infections. The PD nurse must be expert in educating the patient about safe home procedures, identification of infections, and the importance of adherence to procedures [184]. The nurse also must be aware of the most current infection guidelines and recommendations concerning the catheter exit site and peritonitis [27, 197–200].

Table 13.18 PD adequacy assessment collection procedures

CAPD batch method

- Collect all drain bags for 24 h
- Weigh/measure effluent to determine 24-h total volume
- Combine all drained effluent in one large container
- Mix well
- Take sample for urea, creatinine

CAPD aliquot method

- Collect all drain bags for 24 h
- Weigh/measure effluent bags individually and calculate total volume, for example:
  #1 2,700 mL
  #2 2,600 mL
  #3 2,750 mL
  #4 2,850 mL
  total 24-h volume: 10,900 mL
- Take 0.1% sample from each bag (the volume of the bag is recorded in mL, and the decimal point is moved three places to the left); for example, 0.1% of 2,700 mL is 2.7
- Combine all samples and send to laboratory for urea and creatinine

APD batch method

- Instruct patient to collect 24-h dialysate in drain bag
- Instruct patient to save drain bag and note treatment data from the APD machine (nighttime prescription volume, initial drain, and UF)
- Patient may bring entire drain bag or instruct patient to mix dialysate and take a sample from the drain bag
- Calculate 24 h drain volume
- Take an appropriate sample and send to laboratory for urea and creatinine

APD aliquot method

- Instruct patient to collect 24-h dialysate in drain bag
- Instruct patient to save the drain bag from the daytime exchange
- Instruct patient to bring 200 cc from the APD drain bag and the entire manual drain bag to the unit
- Instruct patient to note treatment date from APD machine (night time prescription volume, initial drain, and UF)
- Calculate 24 h drain volume from APD and manual exchange
- Agitate drained effluent in bag to mix well
- Take 0.1% sample from APD drain bag; for example, if total APD drain volume is 11,400 mL, 0.1% is 11.4 mL
- For the manual exchange, weigh/measure the dialysate volume
- Take 0.1% sample; for example, if bag volume is 2,600 mL, 0.1% is 2.6 mL
- Add the two samples together in one container and mix well
- Take an appropriate sample and send to the laboratory for creatinine and urea

Source: Adapted from [182] with permission.

The primary goal of exit site care is to prevent infection [27, 132, 201]. Chronic exit site infections lead to prolonged use of antibiotics, disruption in adequate nutrition, and possible catheter removal. A recent study by Hall and colleagues found that the use of a structured education program based on principles of adult learning resulted in improved exit site conditions [137]. The written procedures must be clear, concise, and reinforced at each clinic visit. The nurse must be careful to assess the exit site at each clinic visit, and if an infection is suspected, treatment must start immediately to prevent a tunnel infection that usually leads to catheter loss [202]. There are situations that predispose the patient to early exit site infections. These include *Staphylococcus aureus* nasal carriage, sutures at the exit site, excessive manipulation of a newly implanted catheter, early colonization of the exit site, malnutrition, and diabetes [132, 204]. High-risk patients must be identified and their exit sites must be consistently and carefully assessed [203, 204].

There is a variety of protocols for exit site care [205–208] and currently most recommendations are opinion- rather than evidence-based [27, 132]. However, there is general consensus about many aspects of exit site care [205–208]. The initial dressing(s) should be changed by the PD nurse or designee. The use of aseptic technique, gloves, and masks are commonly noted. Careful hand washing is mandated along with securing the catheter with tape or immobilization devices to prevent traction and disruption of the exit site and tunnel. Effective cleaning of the site can be accomplished with normal saline, hypertonic saline, dermal wound cleansers, or mild soap and water. Hydrogen peroxide and iodine preparations should not be used in the healing wound tissue but could be used on the surrounding skin. Patients are taught to sponge bathe until the site heals, then they can shower. The healing exit site should not be submerged in bath

water. This prevents contamination with water-borne organisms and maceration of the healing tissue in the sinus track [132]. Dressings should be of absorbent material.

Some programs will have the patient remove the dressing once the site is healed or only wear a loosely applied dressing as a means of mechanical protection for the site. Antibiotic creams and ointments may be prescribed for exit site care as well. The most commonly used agent is mupirocin applied in a thin smear to the site daily or less frequently [209]. Recently gentamicin cream has been used with reported success [210].

Treatment of an exit site infection must be prompt and thorough. Erythema, tenderness at the site, and the presence of exudates all indicate the presence of infection [27, 132, 202–204, 209, 210]. The exudate should be cultured when present, because cultures of the exit site and sinus track may grow resident flora, rather than the infecting microorganism. Exuberant granulation tissues should be cauterized with silver nitrate sticks. Local care may include the application of wet saline dressings to the exit site daily or more frequently, cleansing with a mild cleansing agent, and carefully securing the catheter with nonirritating tape [132, 201, 202, 205]. The ISPD has published guidelines for treatment of exit site infections [27] and these are also available online at www.ispd.org. The usual course of antibiotic therapy is a minimum of 2 weeks. Infections that do not resolve, or that recur, and fungal infections will need a longer course of treatment. Inadequately or ineffectively treated exit site infections may progress to tunnel infections, which are often chronic and may result in peritonitis, catheter loss and transfer to hemodialysis [27, 202].

Each program must develop as specific set of policies and procedures to prevent, identify, and treat peritonitis. These must be periodically reviewed with the team to assure awareness of and support for the policies. Effective patient education must be a part of peritonitis prevention and management. The success of patient education will depend on the education of the PD nurse. The nurse must know how peritonitis is defined (Table 13.19) and the routes by which it can be acquired (Table 13.20) [27, 211]. Most nurses will have completed a basic microbiology course, but the PD nurse must assume responsibility for the specific knowledge needed to classify causative organisms, understand antibiotic treatment, and provide appropriate follow-up. The PD nurse must be familiar with the latest protocols and guidelines (from the ISPD, current literature and from national and regional conferences). Protocols can be obtained from the ISPD website. Networking with colleagues can also help with anecdotal experiences. The medical director must support the PD staff in assessment of infected patients, provision of peritonitis treatment and follow-up.

Identifying the risk factors for peritonitis can guide the nurse in the routine monthly clinic assessment. These include chronic exit site infection, tunnel infection, nasal carriage of *S. aureus*, bacteremia, immunosuppression, history of hemodialysis access sepsis, poor adherence to dialysis procedures, and invasive procedures not covered with prophylactic antibiotics (e.g., dental work, colonoscopy, and biopsy). CAPD systems that require spiking bags are associated with higher peritonitis rates than double-bag systems.

The presentation of peritonitis is noted by cloudy fluid, tenderness of abdominal wall, pain, fever, chills, diarrhea, nausea, and vomiting. Collecting the specimens is very important to identify the organism in a timely way. Each program must have a specific strategy for specimen collection, laboratory cooperation, and retrieval of results.

Table 13.19 ISPD peritonitis definitions [27]

Peritonitis – inflammation of the peritoneum
Infectious peritonitis – inflammation of the peritoneum due to microorganisms
Refractory peritonitis – symptoms persist after 5 days of treatment
Relapsing peritonitis – infection recurs within 4 weeks of therapy completion with same organism
Recurrent peritonitis – infection that recurs within 4 weeks of therapy completion with a different organism
Re-infection peritonitis – infection that occurs more than 4 weeks after therapy completion with the same organism
Nosocomial peritonitis – infection that occurs during a patient hospitalization

Table 13.20 Routes of contamination responsible for peritonitis [27, 211]

Transluminal – contamination of the closed system
Periluminal – along the outer surface of the catheter
Hematogenous – blood-borne organisms
Transmural – migration of organisms from the bowel
Ascending – from the female reproductive tract

Table 13.21 Determining the time at risk for infection

Time at risk (in days) =
patients on PD for entire month × # days in month
Plus
days of PD for new patients who trained, transferred in or returned post-transplant
Plus
days on PD for patients who discontinued PD due to transplant, transfer or death
Total days at risk ÷ number of days in month = months at risk
Months at risk ÷ 12 = years at risk
Number of events ÷ years at risk = rate per year
To determine the interval of months between episodes:
Months at risk ÷ episodes
Months between episodes ÷ 12 = rate per year

Source: Modified from [58] with permission.

Part of the initial training time must be devoted to the prevention and treatment of infection. The PD nurse must work very closely with each patient to assess individual risk factors, personal hygiene, procedure technique and potential for adherence. The patient should be provided with instructions for accidental contamination and also what to do if symptoms of peritonitis occur. Infection prevention must be reviewed periodically, at the home visit, at a monthly clinic visit or during retraining. The patient's vision and fine motor control should be periodically evaluated. Multiple infections or suspected changes in the home environment may prompt an additional home visit [159].

Once the diagnosis of peritonitis is made, the nurse must insure that the specimens are collected correctly and antibiotic treatment is started. Antibiotics may be given by the intravenous, intraperitoneal or oral route. The current ISPD guidelines and recommendations provide extensive information for antibiotic treatment [27]. The patient may come to the clinic to receive treatment, but is typically taught to self-administer at home. Fluid balance and protein intake will need to be carefully monitored during this period of acute inflammation. If the patient is too ill to manage safely at home, hospitalization may be necessary.

It is important to discuss with the patient what may have contributed to the development of peritonitis, but at the same time it is important not to blame the patient. Supporting the patient during the infection is crucial to promote future adherence and to alleviate the patient of guilt and uncertainty [112, 113].

The evaluation of peritonitis must be part of the quality management program. Each infection must be documented along with the results of treatment. The PD nursing staff must participate in quality projects related to infection and are often responsible for determining the program's rates of exit site infection and peritonitis. Table 13.21 outlines one method of determining time at risk for infections [58], one of the steps in determining infection rates. This infection documentation should be done monthly and then collated yearly. The data and analysis is necessary to evaluate the program's management of infection.

Special Considerations

Employment

Working, either full time or part time, is important for many PD patients. Some patients choose PD therapy because it provides the flexibility of scheduling that enables them to continue working. Also, the sense of accomplishment and purpose, and the income attained by working contribute to the well being of the home dialysis patient. Vocational counseling by the social worker or by a specialized counselor can be helpful to the patient seeking employment.

For the patient who is already employed, the PD nurse and patient can adjust the home dialysis schedule to accommodate the work schedule. Flexibility and creative planning may be necessary. Rearranging supply deliveries, clinic visits, and timing of exchanges may help the patient to sustain employment and to also be adherent with the dialysis schedule. If the patient is able to do an exchange in the workplace, the PD nurse may, at the patient's request, make a visit the workplace to inspect the environment where the PD exchange will take place and offer suggestions and support to the patient. Also, if the patient requests, letters may be sent to the employer to describe the dialysis regimen and provide education for the employer. The PD nurse should monitor the patient's adjustment to work, ability to do dialysis safely in the work setting, and to maintain an acceptable dialysis routine [8].

Exercise

Routine exercise is important to maintain cardiovascular health. The nephrologist and PD nurse must assess the patient's capacity for exercise and make recommendations regarding how to exercise safely. In all cases, the exercise program must be individualized. Care must be taken not to put pressure or traction on the PD catheter. It is important that the integrity of a healed tunnel remain intact in order to prevent exit site infection and dialysate leaks. Low impact exercises that avoid high intraabdominal pressure, such as walking and the use of a treadmill device at low speed and minimal platform elevation, or riding an exercise bicycle with minimal resistance [212–214] are safe for the majority of PD patients. Sports that involve physical contact, jumping, and weight lifting are riskier and need to be carefully evaluated. In all instances, the nephrologist must be involved in this assessment and the plan for the patient needs to be documented.

Warming Dialysis Solutions

Dialysis solutions should be protected against extremely hot temperatures during shipping and storage. High temperatures cause the glucose to break down, forming glucose degradation products (GDPs). The level of cytotoxic GDPs can double within a few hours; however, the concentration of GDPs gradually returns to normal when the dialysis solution temperature is lowered, and returns to baseline within 40 days [215].

Dialysis solutions should be warmed to body temperature shortly before use. Most manufacturers recommend using dry heat with temperature regulation to provide a safe heating mechanism for the home PD patient. Often a heating pad device is used; this is included in the initial home supply shipment. Other commercially available devices that employ dry, temperature-regulated heat (e.g., a heating cabinet or incubator) may be used in the dialysis unit or purchased by patients. Home patients have warmed bags by placing them in the sunshine or on a home heating vent or radiator. Regardless of the warming mechanism, the temperature of the solution should be approximately 37°C, and the bags should feel tepid to the touch. Heating solution bags in warm water is not recommended due to the potential exposure to water-borne organisms. If necessary, a dialysis solution bag that is at room temperature can be infused slowly to avoid excessive abdominal cramping.

Microwaving PD solution bags is controversial. Microwave devices may heat solutions unevenly, creating hot spots that may not be noticeable to the touch. This then exposes the patient to the risk of thermal burns. Also, due to differences in wattage and efficiency, different microwave ovens will require different time settings to achieve the same final temperature. Although microwaving PD solutions does not alter the pH or chemistries of the solution [216, 217], it is less clear whether microwaving PD solution bags causes leaching of plasticizers and chemicals into the dialysis solution.

Although manufacturers may not recommend microwaving their PD solutions, this has been widely practiced. Each program must make an informed decision whether it will allow microwave warming of PD solutions. Specific policies and procedures for microwaving PD solutions must be developed. Overheating of solutions can be avoided by measuring the warming time required for each size bag to reach 37°C in each microwave used to warm solutions. Inverting the heated bag several times will mix the solution and help to dissipate hot spots [177, 216].

Swimming

There are a number of anecdotal opinions regarding the risks and benefits of swimming for PD patients; however, many agree that swimming is an acceptable form of exercise for the PD patient. The patient with an exit site that has not healed or is infected should avoid swimming until healing has occurred [8, 201, 214]. The patient who has a healed exit site may swim but will need to protect and care for the exit site per program procedures. There are a variety of recommendations to consider. Some programs advocate covering the exit site and catheter with occlusive dressings while swimming, and then performing exit site care immediately after swimming. Others recommend changing into a dry bathing suit or clothing after swimming to prevent prolonged moisture at the exit site. There is more consensus that swimming in lakes and ponds poses the greatest risk for infection due to stagnant water with high bacteria counts. There is also general consensus that swimming in clean, chlorinated pools poses the least risk, and that the risks associated with swimming in ocean waters depends on the proximity of the beach to sewage outlets and highly populated areas [8, 214].

Table 13.22 Checklist for patient traveling on peritoneal dialysis

Travel details
Destination
Travel dates
Mode of transportation
Type of lodging
Back-up PD unit
-Unit name
-Individual contact name
-Contact information
-Billing policy
-Required diagnostic tests
-Required medical records
Shipping of dialysis supplies
Patient education
Letter of medical necessity
Supplies and equipment to carry on
Medications
Diabetic supplies
Performing dialysis procedures while traveling
Traveling with a cycler
Disposal of dialysate
Contacting the back-up unit
Paying for dialysis expenses while traveling
Tips for international travel

Source: Abstracted from [220] with permission.

Travel

PD patients may travel for pleasure or business; regional, national, and international travel can all be accomplished while performing PD safely; however, the dialysis unit must assist the patient in preparing for dialysis while traveling [218–226]. A detailed resource for both the nurse and PD patient is the "PD Tool Box" [220]. Information abstracted from this reference is included in Table 13.22.

When making travel plans, the patient needs to inform the PD nurse of the destination, and dates of departure and return. A dialysis unit at the patient's point of destination must be identified as an emergency contact for short trips; however, the designated unit may assume the role of the primary dialysis unit during a prolonged stay.

The patient should travel with letters of medical necessity, a description of medical supplies, a list of medications, copies of the current information from the medical record (similar to the information for hospital admission, Table 13.16), and the telephone numbers of emergency contacts and the destination dialysis unit.

Often, dialysis supplies are delivered to the travel destination. Arrangements with the home dialysis supplier must be made well in advance to prevent disruption of service and additional charges. All administrative and financial details must be reconciled before the patient arrives at his destination. Dialysis services provided in other countries may not be covered by health insurances and may require private payment by the patient.

If the patient is traveling to a remote area and is not able to reach a dialysis unit in a reasonable amount of time, a supply of antibiotics may be given to the patient to self administer in an emergency situation.

Disaster Preparation

Recently, we have witnessed natural disasters that have included hurricanes, tornados, earthquakes, tsunamis, fires, and extreme temperature changes. Political and religious tensions have resulted in conflicts and terrorist attacks. These events have raised awareness of the potential for future disasters and the necessity of disaster planning. The PD nurse must help the patient and family prepare to continue dialysis during a disaster, when there may be disruption in communications and dialysis-related services [227–229], but must do so without unnecessarily alarming them.

Patients who use a dialysis cycler should be taught to use manual systems in case of power outages, or should have a back-up generator to provide temporary power. Home dialysis patients should have a minimum of 2 weeks of PD

supplies and all medications. Waterless hand sanitizers should be kept on hand in case of contaminated water supply. Patients should also be encouraged to have several days of food and bottled water on hand in case of interruption in basic services. Each patient should have a current medication list, a medical alert bracelet, and a plan of how to communicate with the home dialysis unit [230].

A discussion about how long the patient can survive without dialysis may also be necessary along with an emergency diet list and strategy for fluid management. In a prolonged or widespread disaster, the patient may need to seek treatment at a distant dialysis unit or hospital. Each patient should have a list of emergency phone numbers and a list of alternative dialysis units and hospitals. Patients may be referred to the National Kidney Foundation, the regional ESRD Networks, and the Centers for Disease Control and Prevention for additional brochures and dialysis preparedness information [231–233].

Roles of the PD Nurse

The success of individual PD patients, the success of dialysis programs, and the success of PD as a renal replacement modality all depend on contributions of the PD nurse. The combination of roles of the PD nurse is perhaps among the most unique in the profession of nursing. The PD nurse is influential in providing home dialysis care and is often viewed as the team leader for this modality [12, 13]. Balancing nursing autonomy with the multidisciplinary team effort required can provide both professional and personal satisfaction. To achieve this, the PD nurse must integrate a number of varied roles on a daily basis. Each of these roles is important for successful outcomes.

The first role is that of an educator. Providing consistent and creative patient education is the foundation of a successful PD program [8, 142, 234]. Although healthcare professionals do not necessarily receive formal courses in adult education, it is imperative that the PD nurse acquire the knowledge and skills necessary to teach patients and families. This knowledge may come from formal education courses, continuing education, review of the education literature, and information from other colleagues and through anecdotal experiences [138, 139]. Critical content includes principles and theories of education, the characteristics of the adult learner, and teaching methods [112]. The nurse is also responsible for acquiring or developing patient educational materials and establishment of a specific home training plan. These must then be individualized for each patient with chronic kidney disease who chooses PD therapy.

Although educating patients and families is the primary goal of the PD nurse, educating other healthcare providers is also essential. The nurse will often be responsible for educating others regarding specifics of PD. The target audience may include physicians, renal fellows, nephrology and non-nephrology nurses, advanced practice nurses, dialysis technicians, dietitians, social workers, administrators, and allied healthcare personnel (e.g., secretaries, laboratory technicians, insurance representatives) [138, 234–236]. In providing education to other healthcare professionals and support staff, the PD nurse promotes self-care while also promoting PD as a renal replacement therapy.

The PD nurse is also a learner. Acquisition of information about chronic kidney disease, diabetes mellitus, gerontology, peritoneal dialysis, infections, cardiovascular disease, research findings, practice guidelines, and new regulations is a continual process, which is critical both to develop individual expertise and remain clinically competent.

The next role that the PD nurse must fulfill is that of a clinical care coordinator. The patient and PD nurse work together at the central focus of the home care team [1, 12, 13]. The nurse often coordinates the care provided by the nephrologist(s), social worker, dietitian, access surgeon, transplant team, and other caregivers (Table 13.1). Furthermore, the nurse ensures that appropriate communication is established with the primary care physician, nurse practitioner, and specialty consultants. Functioning as a care coordinator requires persistent attention to detail and maintaining consistent channels of communication. The result of this care coordination is the provision of efficient, safe, and competent patient care with smooth transitions between care settings [237].

The PD nurse also has a strong clinical role, starting with the responsibility for developing safe and effective policies and procedures both for the dialysis clinic and self-care at home. The nurse must have clinical assessment skills, clinical expertise, and critical thinking ability [238] to make accurate nursing diagnoses and identify appropriate nursing interventions for complications of chronic kidney disease, PD, cardiovascular disease, diabetes mellitus, and vascular disease. Also, the application of self-care management principles, fostering adherence, and identifying psychosocial needs [239, 240] are part of the clinician role [113, 134]. Finally, the clinical role includes measurement and documentation of short- and long-term outcomes. These data can be compared against regional and national standards and benchmarks to determine the quality of care [35–39, 241]. They can also be used for specific continuous quality improvement projects.

The PD nurse may also participate in clinical research. Most often nurses assist in identifying eligible patients, and with recruitment and data collection. As PD nurses becomes more experienced with and educated in clinical research techniques, they often assume more responsibilities and may participate in clinical trials and multicenter studies [238]. Eventually, some nurses go on to assume lead roles as research investigators. Nurses should also utilize clinical research findings, developing an evidence-based practice whenever possible.

Mentoring is also a role that the PD nurse must fulfill. It is critical to guide new and less experienced nephrology nurses to encourage professional development [242].

Finally, the PD nurse is a leader [242, 243]. To become a respected professional and leader, there must be a balance among the various roles. A leadership job title does not need to be assigned for the nurse to be respected as a leader. The truly professional PD nurse accepts the autonomy the role provides, but at the same time respects the boundaries of the nursing roles and practices accordingly [244–246]. Daily clinical practice requires competency, commitment and integrity. This commitment fosters a sense of trust that patients recognize and respect. And it is this trust contributes to the unique bond between the PD nurse and patient [112]. The patients recognize that the nurse is a leader who provides not only expert clinical care but also compassionate support. Nephrologists recognize the PD nurse as a collaborative partner in providing safe home dialysis care and value the commitment to pursuing standards of excellence [7, 10, 12, 13, 247–249].

Fulfilling these roles depends on the level of competency the PD nurse achieves. It is crucial for the nurse to broaden his/her scope of knowledge. Understanding the literature, networking with expert colleagues, and attending conferences and national meetings are all part of becoming a competent professional. Joining professional organizations and participating in committees and projects enlarges the nurse's professional experience. In turn, this professional enrichment enhances clinical care [249].

Conclusion

In conclusion, to successfully fulfill these roles, the PD nurse requires a broad knowledge base, many skills, and a measure of courage. The nurse must be willing to function autonomously, take risks, balance multiple challenges, and promote and accept change. Above all, the nurse must have the commitment and courage to champion the PD program.

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Chapter 14
Peritoneal Dialysis Access and Exit-Site Care Including Surgical Aspects

P. Kathuria, Z.J. Twardowski, and W.K. Nichols

The key to a successful peritoneal dialysis program is a permanent and safe access to the peritoneal cavity. The catheter should provide optimal and consistent hydraulic function and form a stable interface with the body. A well-healed peritoneal dialysis catheter prevents the periluminal migration of bacteria and leakage of dialysate.

Peritoneal access is an important key point in technique survival. Catheter-related problems and infections cause up to 20% of patients to transfer permanently to hemodialysis; many more require temporary periods on hemodialysis [1]. With the reduction in peritonitis rates, catheter-related complications during peritoneal dialysis have become a major concern.

The history of peritoneal access, different peritoneal dialysis catheters, surgical insertion techniques, infections, and mechanical problems are addressed in this chapter.

Glossary

The terminology pertinent to the currently used peritoneal catheters is reviewed here [2]. After implantation the typical double-cuff catheter has three segments (Fig. 14.1): *intraperitoneal,* located intraperitoneally; *intramural,* contained within the abdominal wall tunnel; and *external,* situated outside of the skin exit. The *peritoneal catheter tunnel* is the passageway through the abdominal wall within which the peritoneal catheter is contained. A properly implanted double-cuff peritoneal catheter creates a tunnel with a short sinus tract, a shallow peritoneal recess, and a 5–7 cm long tunnel proper, which consists of tissue ingrown into the cuffs and a fibrous sheath covering the inter-cuff tunnel segment. A longer tunnel proper (20–50 cm) is typical for the presternal catheter [3]. Figure 14.2 depicts tissue structures in relation to cuff position in healed tunnels. After implantation of a single, deep cuff catheter, the tunnel is composed of three parts: 1) a sinus tract located between the skin exit and the cuff; 2) a peritoneal tunnel recess, which is a peritoneal pocket covered with the mesothelium from the internal tunnel exit to the collagen-mesothelial interface at the cuff; and 3) a tunnel proper, comprising the tissue ingrown into the cuff. Another type of single-cuff catheter is provided only with a superficial cuff, has a short sinus tract, but a long peritoneal recess.

Historical Perspective

Both biologic and technologic evolutions reveal puzzling similarities. A structure of a new species is taken from the existing forms; new technological solutions develop from existing forms as well. In the early years of peritoneal dialysis, there was no specific device for peritoneal dialysis; rather, the devices used in medicine, general surgery, and urology were adapted [4]. A species or technology not adjusted to the environment or requirements is eliminated and is preserved in fossils or museums of technology.

In the older literature three terms were used for the infusion of fluid to and drainage from the peritoneal cavity: peritoneal lavage (from Latin *lavare* = to wash), irrigation, (from Latin *irrigare* = to water), and dialysis (from Greek *dialusis* = to separate). The terms *lavage* and *irrigation*, used frequently in the English literature in the 1930 s, 1940 s, and 1950 s, came from surgical practice of cleaning the peritoneum. *Peritoneal dialysis* indicates removal of toxins from the blood through the peritoneal membrane, and this term was commonly used in German literature in the 1920 s and 1930 s. Since the 1960s, it has been used almost exclusively for the process of toxin removal from the blood through the peritoneal membrane.

P. Kathuria (✉)
University of Oklahoma College of Medicine, Tulsa, Oklahoma
e-mail: Pranay-Kathuria@ouhsc.edu

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Fig. 14.1 Diagram of double-cuff Tenckhoff catheter showing three segments created after implantation

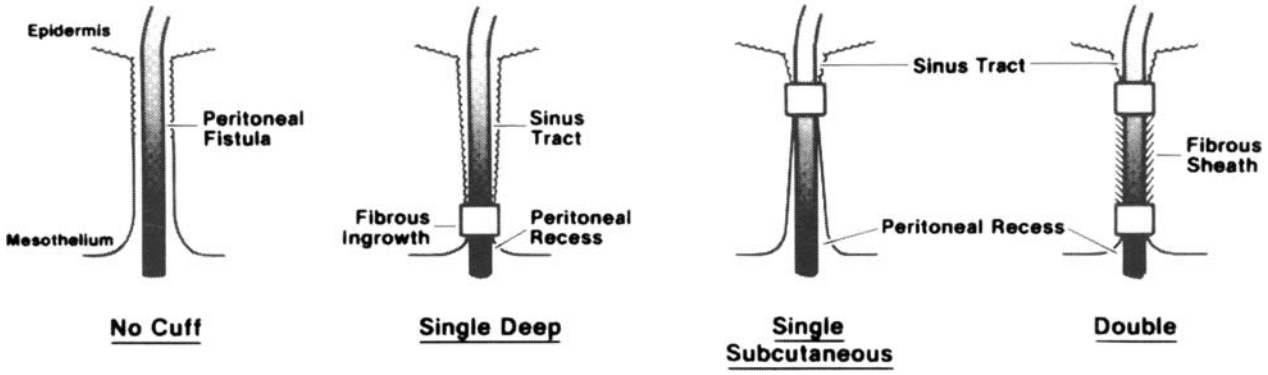

Fig. 14.2 Tissue structures in relation to cuff position in healed tunnels. In catheters without cuffs, a peritoneal fistula is formed. A single deep cuff creates a shallow peritoneal recess and a deep sinus tract predisposing to exit infection. A single subcutaneous cuff generates a shallow sinus tract and a deep peritoneal recess predisposing to pseudohernia. Properly positioned two cuffs limit the depth of both structures

In 1923, Ganter [5] reported his experience in animals and two patients. He used metal needles commonly used at that time for abdominal and pleural punctures. In patients, he did not drain the fluid as he did in guinea pigs, so it was not dialysis as we understand it now; however, there was some dialysis into the saline solution. Two years later at the meeting of the Polish Society of Biology, Landsberg and Gnoinski [6] presented the results of experiments in rabbits. After puncture of the peritoneal cavity with a trocar[1] in the epigastric region the peritoneum was filled with 1 L of Ringer's solution. After 15–30 min of equilibration, the peritoneum was drained through a puncture in the lower region. Because there was some dwell of the dialysis solution, their method should be called intermittent flow peritoneal dialysis in spite of the fact that two trocars were used. Rosenak and Siwon performed several experiments on continuous dialysis in nephrectomized dogs in 1926 [7]. They inserted two glass cannulas through laparotomy. The inflow cannula tip was placed below the liver, the outflow in the Douglas cavity. Simple glass tubes, used in early experiments, were frequently obstructed, so they decided to provide "cannulas with flask shape, multi-perforated, sprinkling can rose-like tips." If the cannula became obstructed despite this modification, they performed omentectomy before inserting new cannulas. One year later, Heusser and Werder carried out experiments on continuous flow peritoneal dialysis similar to those of Rosenak and Siwon. The inflow cannula was similar to theirs, but for outflow they used a rubber drain with multiple side perforations with the tip inserted into the small pelvis. "The omentum was creased with multiple sutures through the lower abdominal wound so that it could not block the openings in the drain tube" [8]. They speculated that the similar technique could be used in patients, and indeed they used it in three cases.

The first continuous flow peritoneal dialyses in humans with acute renal failure caused by poisoning with mercury bichloride were performed in two patients by Balázs and Rosenak in 1934 [9]. For peritoneal access they used glass cannulas distended globularly at the tip and having multiple holes (similar to those used previously by Rosenak and Siwon [7]) or cannulas made of fine wire. The inflow cannula was introduced between the liver and the diaphragm, the outflow cannula was inserted into the Douglas cavity. Both cannulas were introduced by laparotomy under local and light ethyl chlorine anesthesia. In the first patient the continuous dialysis lasted ½ h and 12 L of 4.2% glucose were used, in the second patient 19 L of 0.8% saline were used during 1½ h of continuous dialysis. Both patients died.

The first case of a patient who survived after peritoneal lavage for the treatment was reported by Wear et al. [10]. "A standard gall bladder trochar was introduced in the upper abdomen. The trochar introduced into the lower abdomen was modified by placing numerous small holes in the distal third to avoid occlusion of a single opening by the omentum and intestine. From an insulated reservoir the fluid was introduced into upper cannula. The lower cannula was attached to rubber tubing which hung dependent to a bottle on the floor and acted as syphon." The

[1] From French *trois* (three) + *carre* (side) = three-sided point, a sharp pointed instrument equipped with a cannula, used to puncture the wall of a body cavity and withdraw fluids.

authors used the procedure in five cases, but only one patient survived; it was unclear whether the patient was saved by peritoneal dialysis.

The first intermittent peritoneal dialyses in humans were performed by Rhoads in 1936 and 1937 [11]. In two patients thought to have acute renal failure, peritoneal lavage was performed. The fluid was introduced into the peritoneal cavity through a cannula introduced into the peritoneal cavity under local anesthesia. "Nine liters of fluid were introduced in 6 installments and a total of 6 ½ liters recovered." Temporary improvement in the patients' condition was noted; both patients ultimately died and autopsies revealed chronic glomerulonephritis. The author did not provide a detailed description of the cannula.

No papers on peritoneal lavage, irrigation, or dialysis appeared during the time of Word War II, but the number of renal failure cases after war trauma must have accelerated research on renal replacement therapies and numerous papers on these topics were published in the second half on the 1940s [4].

Abbott and Shea carried out several experiments on dogs to evaluate the methods of peritoneal lavage and desirable solutions. As a result of these experiments, they determined that for removal of dialyzable substances the use of intermittent injection and withdrawal of solution is more efficient than continuous flow lavage, and that the solution should have a chemical composition similar to that of interstitial fluid and should be made slightly hypertonic by the addition of small amounts of dextrose or gelatin or pectin. They performed a limited number of treatments in humans and concluded "that the withdrawal of the fluid could be best accomplished by the use of trochar or insertion of a rubber catheter, since the insertion of a needle does not, as a rule, permit a complete recovery of the injected fluid" [12].

Seligman, Frank, and Fine performed a series of experiments on nephrectomized dogs to determine suitable peritoneal access, optimal flow of continuous flow peritoneal irrigation, and proper irrigation fluid. The access was a mushroom-tip[2] type catheter inserted through an incision or a whistle-tip[3] type inserted using a trocar. Both types had added perforations. Mushroom-type catheters drained more effectively than the whistle-tip type catheters. "To help maintain patency of the irrigating catheters in long term experiments, omentectomy was performed . . . at the time of nephrectomy" [13]. The same group of authors reported the use of this method for treatment of four patients [14]. In all cases, a continuous flow method was used. Initially, the inlet tube was a catheter or a perforated small stainless steel tube. The outlet tube was a whistle-tip type catheter. In later cases, they used two mushroom catheters for inflow and outflow and ultimately they used a mushroom catheter for inflow and a stainless steel surgical drain tube for outflow (Fig. 14.3). The tubes were inserted through surgical incisions and held in place with subcutaneous staysutures. As prophylaxis against peritoneal contamination they incorporated a Mandler (Berkefeld) filter between the solution reservoir and a glass U-tube submerged in a water bath (40–45°C) and connected to the inflow tube. One patient with acute renal failure due to "parenchymatous injury to the kidneys from sulfathiazole administration" was also reported separately in more detail [15]. The mushroom catheter and the sump drain[4] were used in this case. During 7 days of peritoneal irrigation, solution flow ranged from 13 to 35 mL/min and urea peritoneal clearance ranged from 8.4 to 21.0 mL/min. The patient ultimately recovered kidney function. Although in the discussion the authors stated that "[w]e cannot state with finality that the patient would have died without peritoneal irrigation," the severity of the case, 15 days of oliguria/anuria, and improvement during peritoneal lavage seem to justify the assumption that *this was the first patient who survived because of peritoneal dialysis*. Weiss and Mills followed the experience of Frank, Seligman, and Fine using a mushroom catheter for fluid inflow and sump drain for outflow. To improve drainage the sump drain was inserted very low, just above the Poupart's ligament and passed down to the pelvis [16]. Reid, Penfold, and Jones referred to the Frank, Seligman, and Fine paper, but implemented a different technique. They used a Foley[5] catheter for infusion into the peritoneal cavity of twice-normal saline. They drained the fluid through the same catheter after the patient complained of abdominal distension and pain and the appearance of "obvious ascites." The infusion and drainage of fluid continued the following days, but they had difficulty with drainage through the catheter and a considerable amount of fluid leaked around the catheter [17]. Although they used a single catheter and drained the

[2] Mushroom or umbrella catheter, a self-retaining bladder catheter, was invented by de Pezzer in 19th century. It had no terminal opening, only lateral openings.

[3] Whistle-tip catheter = urethral catheter with a terminal opening as well as a lateral one.

[4] Sump drains were double-lumen tubes that allowed air to enter the drained area through the smaller lumen and displace the fluid into the larger lumen. The air sucked back through the larger tube helped to maintain its patency and prevented high negative pressure with consequent suction of adjacent structures into the openings of the large tube. They were used in general surgery and gynecology and in the intraperitoneal space for evacuation of fluid from the peritoneal cavity. The external tubes of sump drains were usually made of a network of stainless steel or brass cords; the internal tubes were solid cannulas.

[5] In 1929, Frederick E.B. Foley (1891–1966) developed a catheter for drainage of urine and retained in the bladder by the distensible balloon.

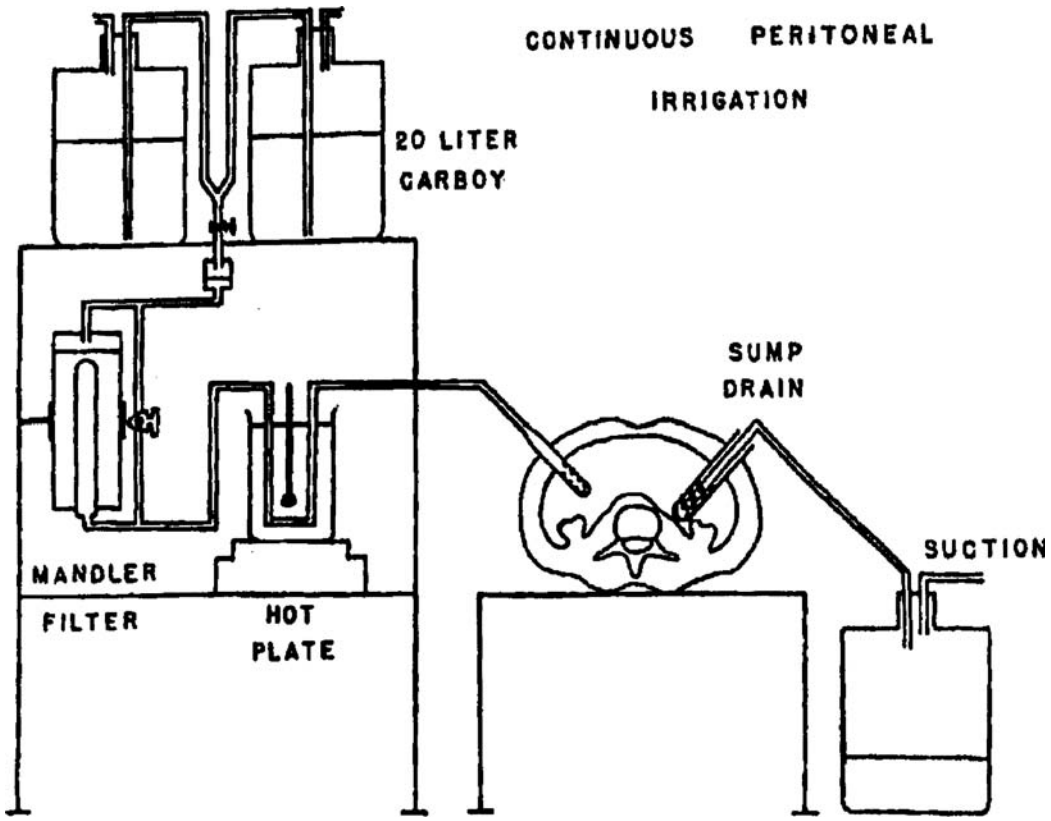

Fig. 14.3 Continuous peritoneal irrigation. A = 20 L carboy, B = Mandler filter, C = hot plate, D = rubber inflow catheter, E = sump drain, F = suction. Modified from [14]

fluid intermittently, the flow method was partly continuous because of constant leakage of fluid around the catheter. Ultimately, the patient recovered.

In 1947 and 1948 numerous papers appeared in the medical literature describing results with peritoneal irrigation [4]. The method of Frank, Seligman, and Fine was generally followed. The major problems encountered by clinicians treating patients with peritoneal irrigation were related to peritoneal access. Rosenak and Oppenheimer [18] listed the five most troublesome complications of peritoneal drains used for fluid outflow: "(1) Rigidity of the tube with resulting pressure on the intestines, (2) Constant suction of contaminated air into the peritoneal cavity, (3) Occasional plugging of the small openings, (4) Leakage of lavage fluid into the dressing, which is a potential source of infection and which make exact determination of nitrogen output difficult, (5) Difficulties of proper fixation of the tube on the abdominal wall." It may be added that fluid leakage made fluid balance very imprecise and resulted in extra nursing work. For the first time they developed a drain specifically for peritoneal dialysis. This was a modified sump drain. Made of stainless steel, the tube provided a rigid extra-abdominal portion, but flexible intraperitoneal portion made of a spiral, stainless steel spring wire with a rounded tip. An adjustable plate was screwed to the outer portion of the steel tube and served for fixation to the abdominal wall by means of adhesive plaster. Compared to the sump drain, the access introduced two important improvements: a flexible tube made of spiral wire instead of rigid pipe and the plate for fixation to the abdominal wall. A second version of the Rosenak-Oppenheimer access was described by Odel et al. [19]. The improved version had two accesses, one for inflow and one for outflow (Fig. 14.4). They were identical, except that the intra-abdominal part of the inflow tube was shorter that that of the outflow tube. The intra-abdominal portion of each tube was made of tightly coiled stainless steel with a rounded tip. Compared to the previous version with a rigid inner tube, in the new version both inflow and outflow accesses had an inner tube made of flexible rubber in the intra-abdominal portion.

In December 1948, Ferris and Odel published their experience with the Rosenak-Oppenheimer access [20]. They used it in only one case, and "found the inflow tube to be entirely satisfactory." However, they experienced considerable difficulty in fluid outflow, because the flexible steel spring appeared to be wound too tightly. They were also concerned with the foreign body reaction to metal and rubber tubes. Accordingly, they improved the Rosenak-Oppenheimer access by changing the intra-abdominal portion of the outer tube (Fig. 14.5). Instead of the spring

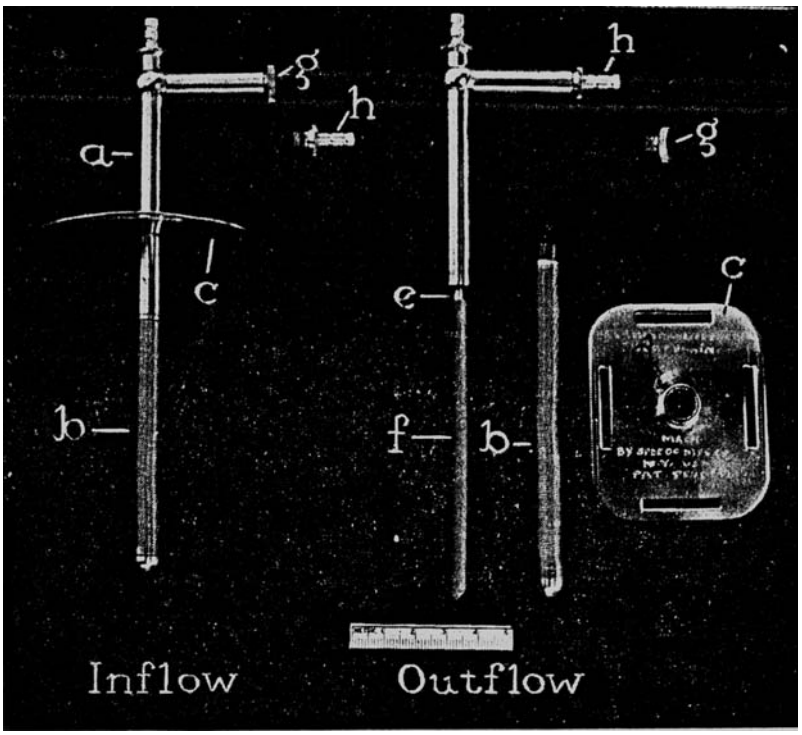

Fig. 14.4 Rosenak-Oppenheimer peritoneal tubes. A = rigid extra-abdominal, b = flexible intra-abdominal, c = malleable metal flange, d = thumbscrew, e = rigid inner portion, f = rubber inner portion, g = metal plug, h = adapter. The inflow tube on the left is assembled; the outflow tube on the right is partly disassembled. Modified from [19]

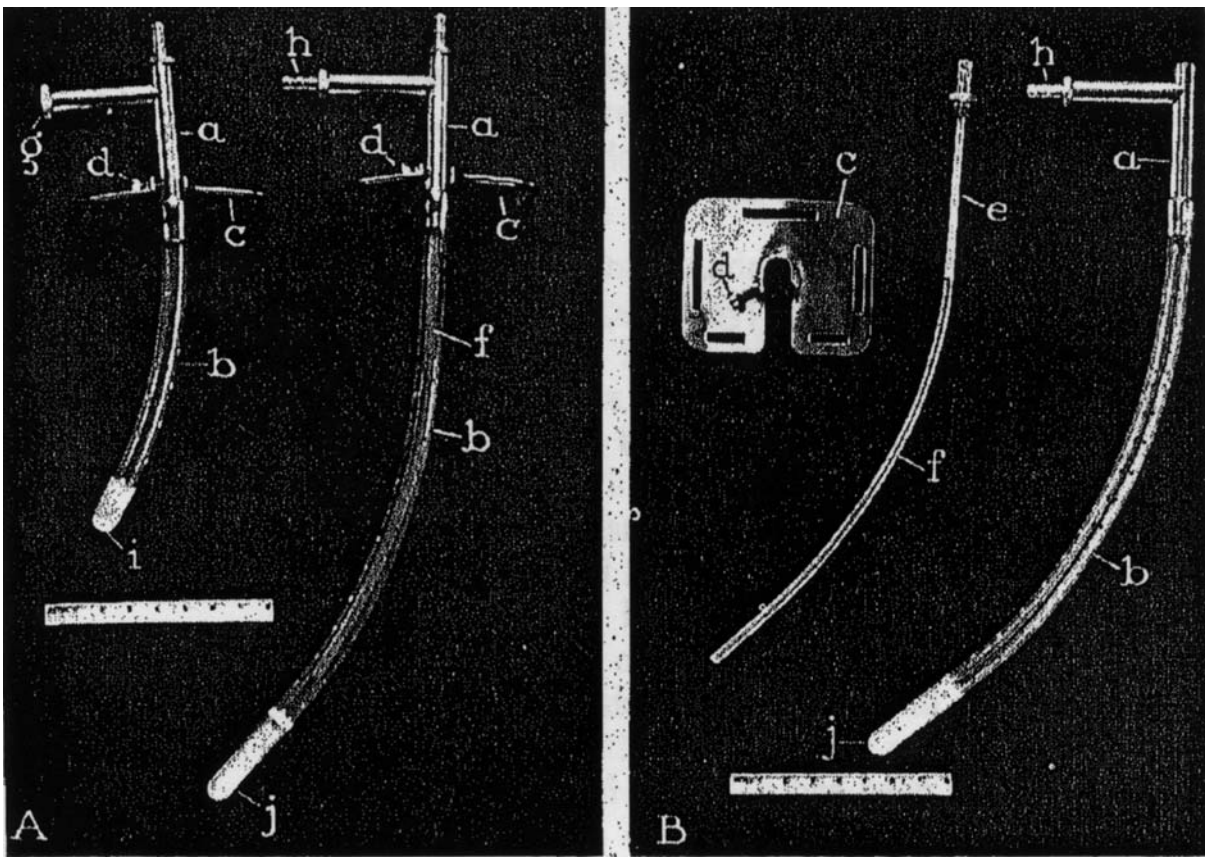

Fig. 14.5 Ferris and Odel tubes for peritoneal lavage. The assembled tubes are on the left. The short tube on the left is the inflow tube. The outflow tube on the right is disassembled to show the component parts. A = rigid extra-abdominal, b = polyvinyl intra-abdominal outer tube, c = malleable metal flange, d = thumbscrew, e = rigid inner portion, f = polyvinyl inner portion, g = metal plug, h = adapter, i = inflow bendaloy, j = outflow bendaloy. Modified from [20]

coil they used a polyvinyl tube with multiple perforations. This tubing was "sweated" into the stainless steel portion of the tube with acetone. The tips of the tubes were provided with plugs consisting of bendaloy[6] completely encased in the polyvinyl. The tubes were weighted with these plugs to insure they would hang dependently in the peritoneal cavity. This was particularly important for the outflow tube to keep the tip in the true pelvis, the place of a fluid reservoir. The intra-abdominal portion of the inner tube was also made of polyvinyl. The extra-abdominal part of the catheters remained essentially unchanged, with the exception of the plate (flange). They cut a slot in the flange so that it could be slipped on the tube after implantation, when proper position of the flange could be determined. Ferris and Odel introduced two important ideas in their access: 1) use of plastic (polyvinyl) for the intra-abdominal segment of the access, and 2) use of weights to keep the tip of the tubing in the true pelvis. Both ideas were emulated later by other inventors.

In 1948, Frank et al. reported further experience with peritoneal irrigation based on 14 additional patients in renal failure [21]. The peritoneal access was markedly modified (Fig. 14.6). Only a sump drain was used for inflow and outflow. The external part of the drain was made of glass closed with a rubber stopper, and contained a side arm for fluid inflow and air inlet. This glass portion was connected through an external flexible rubber tube to a stainless steel tip. An internal flexible rubber tube of a smaller diameter than the external was inserted through the rubber stopper up to the stainless steel tip and connected to the suction line. For the insertion of the sump drain, two incisions were made. The upper incision through the skin to the fascia was made beneath the costal margin; the lower incision entering the peritoneum was made in the lower abdomen on the opposite side. A subcutaneous tunnel connecting these two incisions was made; the metal end of the flexible sump drain was inserted through the upper incision, passed along the tunnel, and inserted into the peritoneal cavity through the lower incision. Thus, for the first time, a long subcutaneous tunnel was created for the peritoneal access. "The patient lies semi-erect so the fluid in the pelvis remains below the upper incision. Thus no contact by possible ebb flow can be made between the fluid and the skin of the abdominal wall." The authors used intermittent or continuous flow technique. For continuous flow technique they used "a small rubber inflow catheter" and a sump drain for outflow. The intermittent flow technique was accomplished with a new catheter by alternating inflow and suction (Fig. 14.7). In intermittent flow peritoneal dialysis, various volumes (500–2,000 mL) were introduced as determined by patients' tolerance, allowed to remain for 15 min to 3 h, after which the fluid was aspirated. Any air entering the system was bubbled through an alkaline solution of parachlorophenol and cresol. Peritonitis episodes were frequent, but edema was not a problem in most patients because hypertonic solutions were used. They cautioned against using too concentrated solutions. In one patient, "a solution of 5% gelatin and 2.5% glucose withdrew fluid so rapidly as to produce shock. Moreover, the hypertonicity may be responsible for the peritoneal irritation and by increasing it still further infection may be even more likely" [21].

A major advance was the introduction of less rigid materials by French physicians in 1949 [22]. They designed polyvinyl tubes, 25–30 cm long, with diameters of 2–3 mm. The terminal 15 cm of the tubes had lateral openings, all 2 or 3 mm. The tubes were introduced into the abdominal wall with the help of trocars. After local anesthesia, the trocar with pointed mandrel was introduced into the peritoneal cavity, then the pointed mandrel was replaced with a blunt rod and the trocar was advanced deeper without the risk of peritoneal trauma. Finally, the rod was removed and the polyvinyl tube was introduced through the trocar sheath. After infusion of 3–4 L of solution, the outflow tube was inserted on the opposite side of the abdomen with the same technique. The authors were very satisfied with the performance of the polyvinyl tubes.

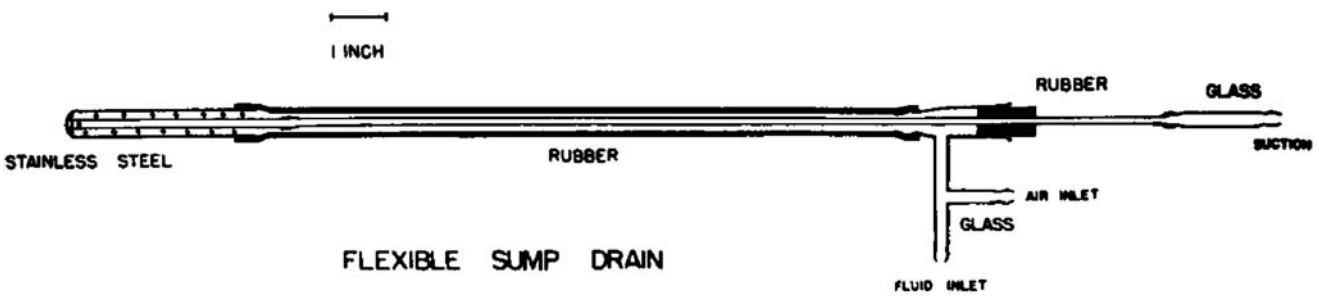

Fig. 14.6 Flexible sump drain of Frank, Seligman, and Fine. Modified from [21]

[6] Titanium-molybdenum alloy

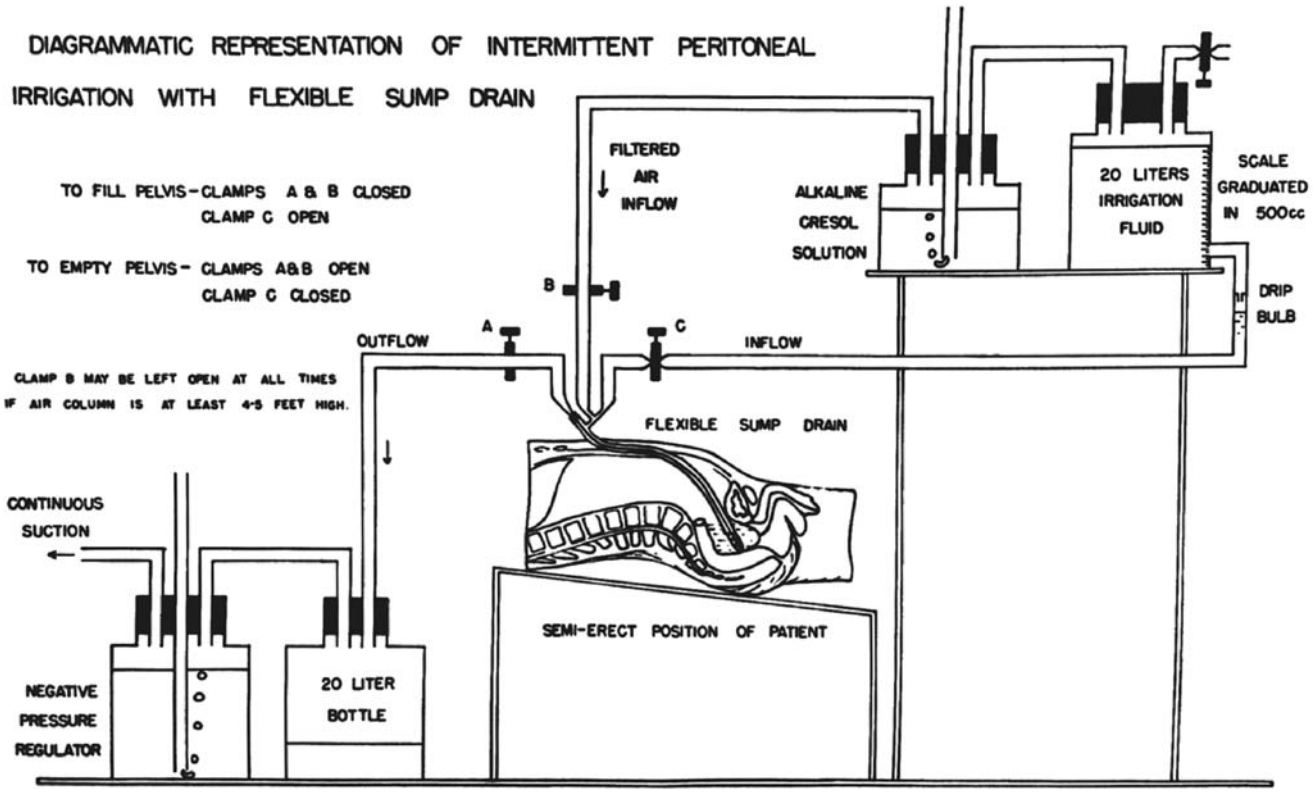

Fig. 14.7 Diagrammatic representation of intermittent peritoneal irrigation with flexible sump drain. Note: to fill pelvis – clamps A & B closed, clamp C open; to empty pelvis – clamps A & B opened, clamp C closed; clamp B might be left open at all times if air column was at least 4–5 feet high. Modified from [21]

Rapid progress in peritoneal dialysis was made in the 1950 s. Grollman et al. [23, 24] reported their experience with intermittent[7] peritoneal lavage in nephrectomized dogs and in five patients. In dog experiments, 1 L of peritoneal fluid was infused into the peritoneal cavity through a needle. After a variable dwell time the fluid was siphoned off through the same size needle, followed by refilling. The exchanges were usually done twice daily in the morning and late afternoon. The technique was modified for patients. The fluid was infused into and drained from the peritoneal cavity through a single polyethylene tube placed through the anterior abdominal wall. "A trocar was inserted as in the routine removal of ascites fluid, the stylet replaced with the polyethylene plastic tube, and the trocar[8] removed." The lavage lasted between 16 and 48 h. According to their experience, "The intermittent procedure just described avoids the complex apparatus, multiple incisions and constant attention necessary when one utilizes a constant perfusion technique. It is, nevertheless, almost equally effective as a means of replacing renal excretory function since ... it requires several hours for equilibrium to be established between fluid in the peritoneum and the blood. A continuous lavage tends, moreover, to result in the channeling of the perfusion fluid and hence may actually prove less efficient..." [23].

The next major progress was made in the late 1950 s when Maxwell et al. reported their experience with 76 peritoneal dialyses [25]. Seemingly minor improvements in the technique provided major improvements in results. The catheter was introduced with a technique similar to that of Grollman et al. [23], but the semirigid catheter was made of nylon[9]

[7] There has been some confusion regarding the terms *intermittent* and *continuous* peritoneal dialysis. Some authors applied the term *continuous* if the lavage was carried on for several days without interruption, and the term *intermittent* if the lavage was interrupted for a night or a day or two [21]. Others applied the term *continuous* if peritoneal fluid flowed continuously between the inflow and outflow accesses. In this terminology, intermittent lavage was carried with only one access and the flow was interrupted [2]. Grollman and his colleagues used the term *intermittent* in the latter meaning, but they performed continuous lavage in the other understanding of this word. To avoid confusion, there was a proposal to use the term *continuous peritoneal dialysis regimen* for dialysis carried out day and night 7 days per week without interruption and *continuous flow peritoneal dialysis technique* for the other meaning of this word.

[8] Here, by trocar, the authors understood the sheath or cannula of the trocar,

[9] Nylon is made of repeating units with amide linkages between them. Hence, it is frequently referred to as a polyamide. Various forms of nylon with various properties are available.

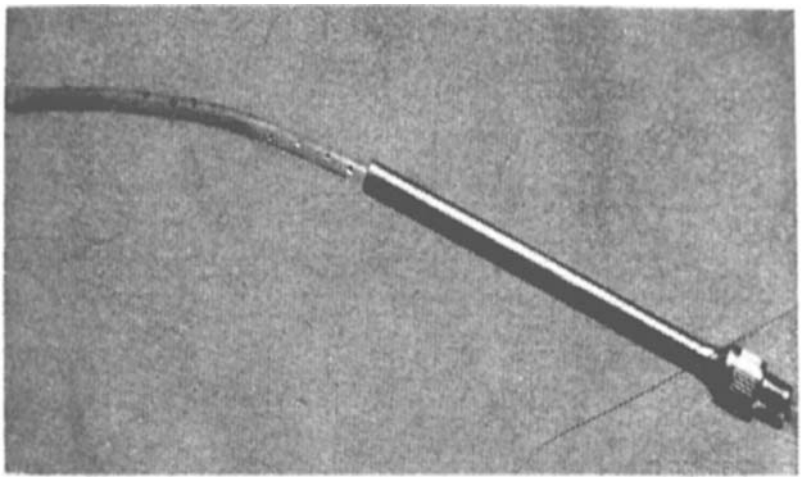

Fig. 14.8 Maxwell's trocar and permanently curved nylon (polyamide) catheter with rounded tip and multiple small perforations at the distal end. Reprinted with permission from [25]. Copyright © 1959, *American Medical Association*. All rights reserved

instead of polyethylene, had rounded tip, and had numerous very tiny perforations (80 holes of 0.02 inch[10] diameter) instead of larger openings at the distal 3 inches (Fig. 14.8). The authors believed that the use of nonirritating plastic prevented omentum and intestines from clinging to the catheter, and that the small diameter of perforations prevented particles of omental fat from plugging the catheter. They used a 17F Duke trocar set for insertion of the catheter.

At the same time, Doolan and co-workers [26] developed a polyvinyl catheter with multiple ridges to prevent omental wrapping. Both catheters were inserted into the peritoneal cavity with the help of a paracentesis trocar. Smooth, plastic materials were much less irritating to the peritoneum than previously used glass, rubber, or steel, thereby omental occlusion became less frequent. The drainage of fluid from the peritoneal cavity was markedly improved, but leakage and pericatheter infections continued to plague the access.

In the early 1960 s, various conduits, buttons, and prostheses were developed to facilitate repeated entrance to the peritoneal cavity. These devices never gained popularity as major complications, particularly peritonitis and adhesion formation leading to technical difficulties, were not eliminated [4]. Disappointed with these poor results, Boen and his collaborators developed the repeated puncture method and published their experience in 1964 [27]. The semirigid catheter was inserted through the 14F trocar described by McDonald [28]. The catheter was removed after each dialysis. Intermittent peritoneal dialysis was carried out once weekly for 14–24 h with 3 L of fluid per hour with the use of cycling machine.

Although McDonald's thin-walled 14F trocar significantly decreased the incidence of pericatheter leaks and bleeding, common with previously used 17F trocars, these were not eliminated. To circumvent these problems, Weston and Roberts invented a stylet catheter, which was inserted without a trocar [29]. A sharp stainless steel stylet ("three-sided trocar point") inserted through the nylon catheter was used to penetrate the abdominal wall (Fig. 14.9). As a result, the abdominal opening fitted snugly around the catheter, thereby preventing leakage. Only local anesthesia was used for catheter insertion. Before catheter insertion the abdomen was filled with dialysis solution via a 14 or 15 gauge needle inserted through the *linea alba* below the umbilicus. Then a small incision was made in the skin, the catheter with the stylet was pierced through the abdominal wall, then the stylet was withdrawn, the catheter advanced to the right or left pelvic gutter, and dialysis was started with 2 L exchanges. After dialysis the catheter was usually removed. This type of catheter is still being used for acute renal failure.

A major step forward in creating a permanent peritoneal access was made in 1964. Gutch [30] noticed lower protein losses with silicon rubber catheters as compared to those with polyvinyl ones, which suggested less irritation of the peritoneum with a new material. About the same time, Palmer, with the help of Wayne Quinton, already successful in manufacturing silicon rubber shunts for hemodialysis, developed a catheter which is a prototype of currently used coiled catheters [31]. The catheter was made of silicon rubber, the intraperitoneal end was coiled and had numerous perforations extending 23 cm from the tip, a long subcutaneous tunnel was supposed to hinder periluminal infection (Fig. 14.10). To impede further infection and leakage, a tri-flanged step was created for securing the catheter in the deep abdominal fascia.

In 1965, Henry Tenckhoff, at the University of Washington, was beginning to treat patients on chronic peritoneal dialysis [32]. After initial few dialysis in the hospital, the patients would be trained for home dialysis. On the weekends,

[10] 0.02 inch = 0.0508 mm

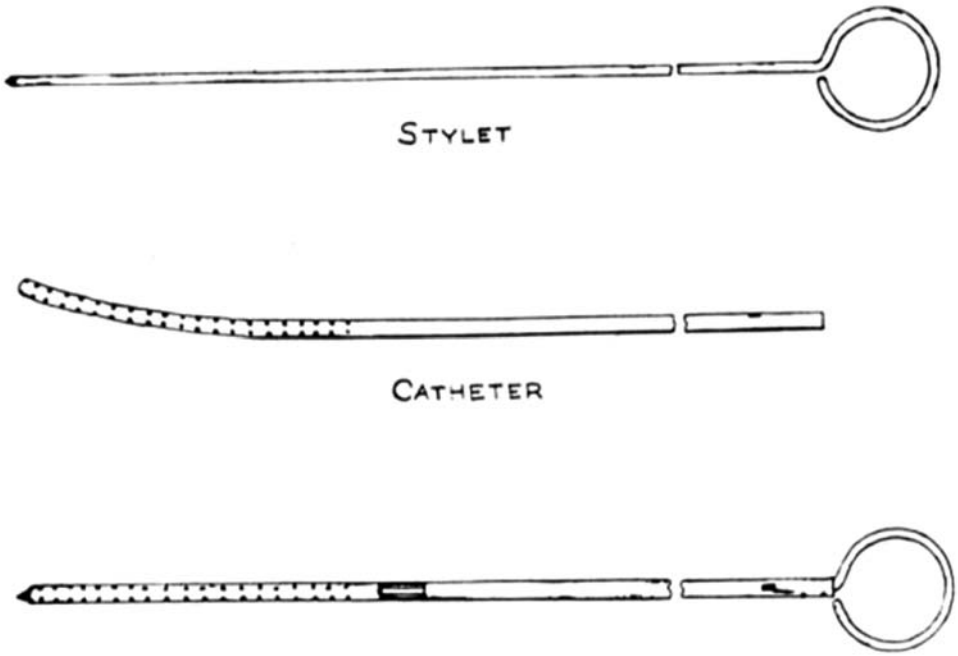

Fig. 14.9 Weston and Roberts' stylet catheter. Modified from [29]

Tenckhoff would go to patient's home, insert the catheter, and begin dialysis. After the appropriate time on dialysis, the patient would remove the catheter and cover the exit wound with a dressing. Although the method was successful in Tenckhoff's hands, the technique was cumbersome, and Tenckhoff recognized its limitations.

In 1968, McDonald and co-workers [33] developed an external seal composed of polyester (Dacron®) sleeve and polytetrafluoroethylene (Teflon®) skirt. Tissue ingrowth into these elements created a firm external seal to prevent leakage and microorganism migration. No subcutaneous tunnel was created; the catheter was inserted straight through the abdominal wall. This catheter never gained popularity, as at the same time Tenckhoff and Schechter published the results of their studies on a new catheter, which provided results superior to any other catheter designed so far [34]. Their catheter (Fig. 14.11) was an improved version of the Palmer catheter. An intra-abdominal flange was replaced by a Dacron® cuff, a subcutaneous tunnel was shortened, and the second, external cuff was used to decrease the length of the catheter sinus tract. Ultimately, the coiled intraperitoneal portion was replaced by a straight segment resembling the Gutch catheter. Intraperitoneal segment was kept open ended and the size of the side holes was optimized to 0.5 mm to prevent tissue suction. A shorter subcutaneous tunnel and straight intraperitoneal segment facilitated catheter implantation at the bedside with the aid of a specially designed trocar (Fig. 14.12). To avoid excessive bleeding the catheter was inserted through the midline. The Tenckhoff catheter has become the gold standard of peritoneal access. Even today, 40 years later, the Tenckhoff catheter in its original form is the most widely used catheter type. Some of the original recommendations for catheter insertion, such as an arcuate subcutaneous tunnel with downward directions of both intraperitoneal and external exits, are still considered very important elements of catheter implantation.

The most common complications of the Tenckhoff catheter included exit/tunnel infection, external cuff extrusion, obstruction (which was usually a sequel of catheter tip migration out of the true pelvis with subsequent omental wrapping or tip entrapment in peritoneal adhesions), dialysate leaks, recurrent peritonitis, and infusion or pressure pain. Numerous devices were tried to improve the results achieved with Tenckhoff catheter – most of them unsuccessfully as this catheter is still preferred by most nephrologists for treatment with peritoneal dialysis.

To prevent exit infection, a subcutaneous catheter was developed by the Stephen et al. [35]. The catheter had two tubes in the peritoneal cavity, and a subcutaneous container. The container was to be punctured for each dialysis. This device was used for continuous flow peritoneal dialysis. To decrease peritonitis episodes, Gotloib et al. [36] developed a prosthesis, which consisted of a Teflon® tube with internal diameter similar to the external diameter of the peritoneal catheter. The head of the tube was funnel shaped to simplify insertion of the catheter. The prosthesis was implanted surgically with the head located in the subcutaneous tissue and the tube penetrating through the parietal peritoneum. After a week, dialysis was started. The skin over the prosthesis head was pierced with a stylet and then the catheter

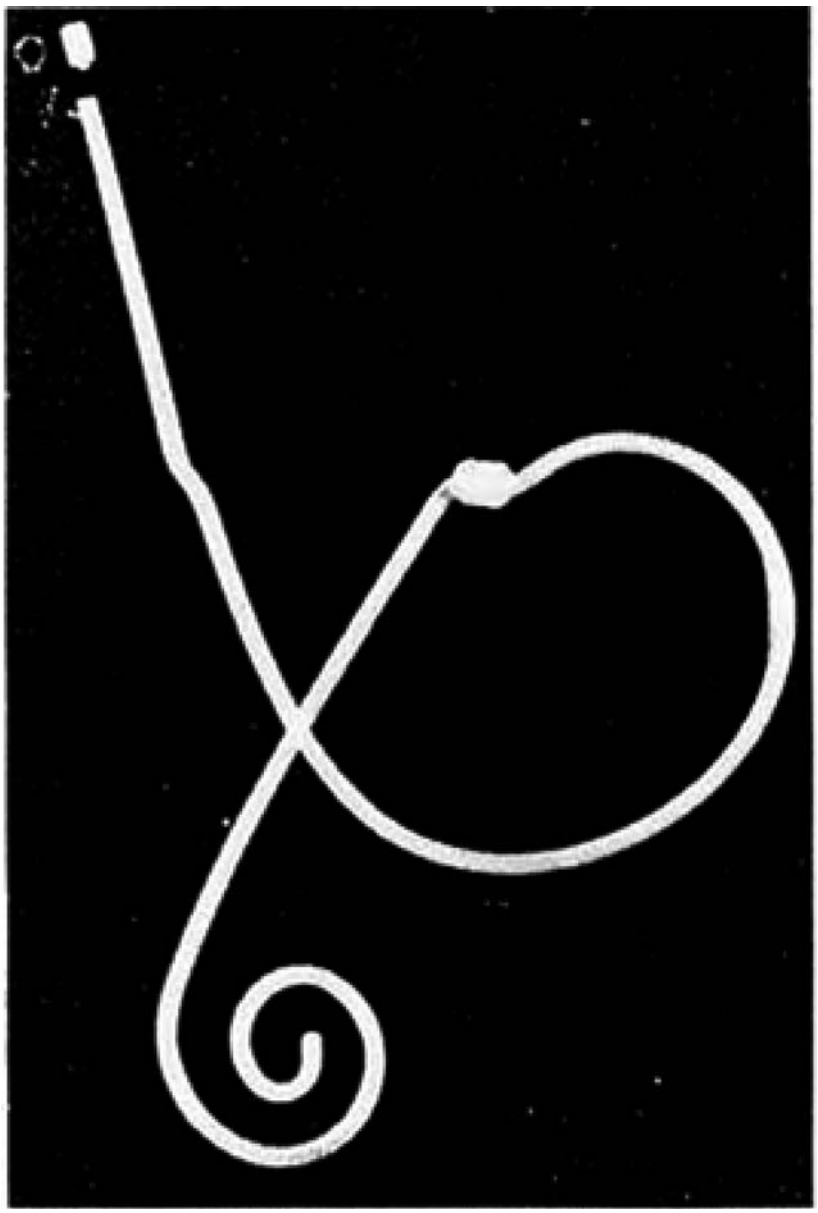

Fig. 14.10 Palmer and Quinton's silicone rubber catheter with triflange step (A) and coiled tip (B). Modified from Palmer, Quinton, and Gray [31]

introduced into the prosthesis, the stylet removed, and the catheter advanced to the pelvic gutter. The catheter was removed after each dialysis. Yet another approach to decrease exit-site infection rates was to position the subcutaneous cuff at the skin level [37]. The catheter tubing was made of Silastic to which was attached a transcutaneous segment with a flange and cuff of expanded polytetrafluoroethylene (PTFE). The flange was located subdermally and the collar protruded through the skin. The cuff was placed perpendicularly through the subcutaneous tissue without a lateral tunnel. Unfortunately, contrary to expectations, such a position tends to increase infection rates [38].

To decrease catheter migration and omental wrapping the intraperitoneal segment of the catheter was provided with a saline inflatable balloon [39] or discs [40]. Valli et al. [41] revived an idea of bulbous distension of glass cannula [7, 9], but, instead of glass, a stiffened silicone rubber with a balloon surrounding the catheter tip was used. In an improved version, the preballoon segment of the intraperitoneal portion of the catheter was eliminated and the balloon was attached to the abdominal wall to avoid migration. The internal segment in the balloon was eliminated; the tube ended at the balloon, which was smaller than in the previous version. Thus, the improved catheter (Valli-2) in its concept was very close to those of mushroom or column disc catheters, but with better material and smaller and more numerous holes [42]. This balloon cannot migrate but still may be obstructed by bowel or omentum. Thornhill et al.

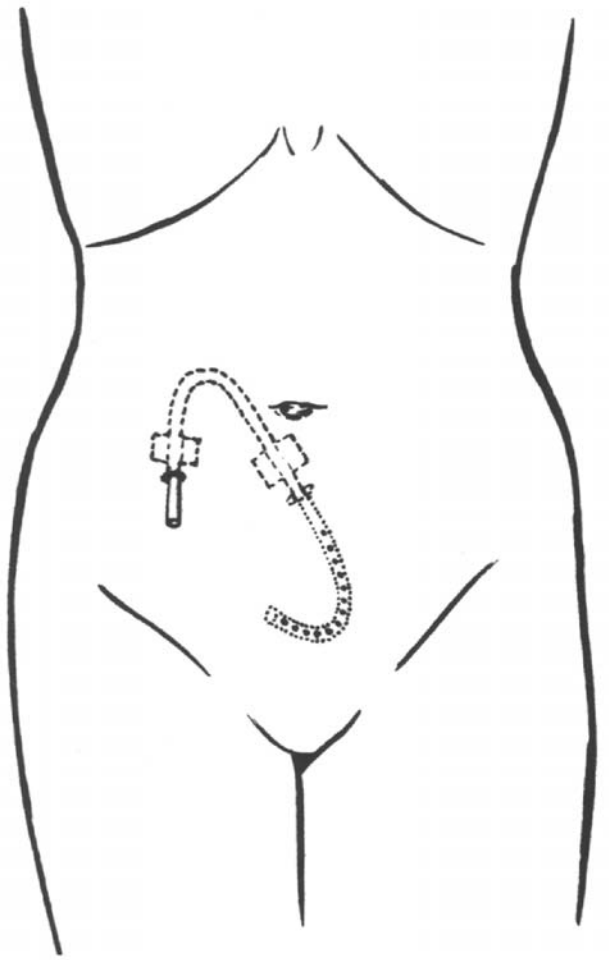

Fig. 14.11 Properly implanted Tenckhoff and Schechter silicone rubber catheter with two cuffs. Modified from [34]

[43] returned to the concept of implanting a mushroom-like structure just below the peritoneum in the left lower abdominal quadrant. However, unlike the de Pezzer rubber catheter, the head of their catheter was made of two parallel discs of silicone elastomer separated by short pillars and anchored to the abdominal wall by a Dacron® felt sleeve. They believed that the column disc catheter would perform better than the mushroom catheter used in the 1940 s and even better than the Tenckhoff catheter. Unfortunately, this was not the case. Compared to the Tenckhoff catheter the rate of catheter obstruction was higher and the catheter survival was markedly lower in the subsequent clinical study [44]. The use of this catheter gradually ceased. In 1993, Ash and Janle [45] changed the intraperitoneal segment of the catheter from the column disc to a longitudinal tube with 1-mm wide "flutes" or grooves on the surface. The intraperitoneal segment lay against the parietal peritoneum and was connected perpendicularly to a transabdominal tube, thus creating a "T"-shaped catheter. The catheter cannot migrate, but still may be obstructed by bowels, adhesions, or omentum. Another approach was undertaken by Chiaramonte et al. [46, 47]. Because the best position of the catheter tip for dialysate outflow is in the true pelvis, they decided to shorten the catheter and implant it very low, just a few centimeters above the symphysis pubis. Such a catheter had a limited capability to migrate outside of the true pelvis and the omental wrapping was less likely as in the majority of people the omentum does not reach below the pelvic brim. This was a return to the old idea of locating an outflow peritoneal access very low, in the Douglas cavity, where conditions for fluid drainage were the best. The insertion point was either on the *linea alba* or McBurney point, 3–4 cm over the pubis. According to the authors, the catheter obstruction rate was very low, other complications were not worse than with the Tenckhoff catheter, with the exception of pericatheter leaks, which were significantly higher. This was related to the low insertion site of the catheter, near the pubis, where intraabdominal pressure in the upright position is higher compared to that of the insertion site of the Tenckhoff catheter near the navel. To keep the catheter tip in the true pelvis, Di Paolo et al. [48] returned to the idea of Ferris and Odel [20] of adding weights into the catheter tips. Instead of bendaloy they incorporated a 12-g tungsten weight at the silicone rubber catheter tip.

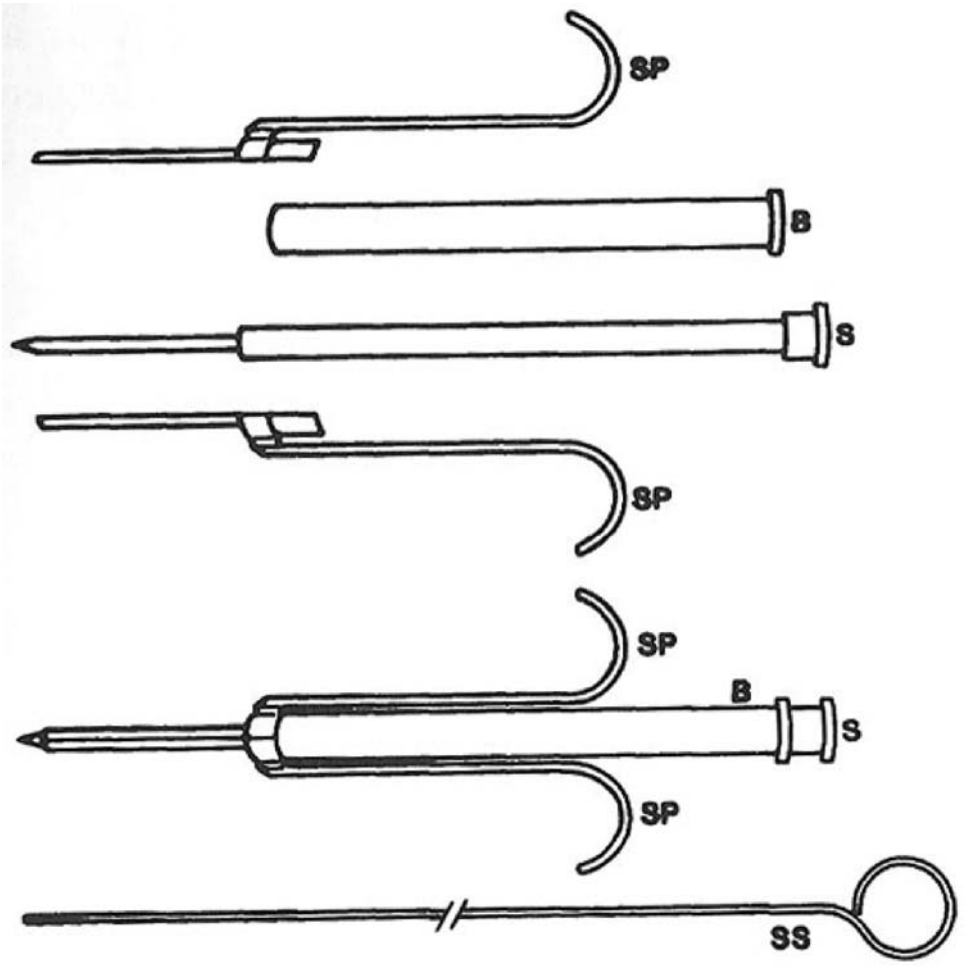

Fig. 14.12 Tenckhoff trocar – assembled (above) and disassembled (below). SP – side pieces; S – pointed stylet; B – barrel; SS – stiffening stilette

Early peritoneal accesses were plagued by pericatheter leaks. The Tenckhoff catheter with Dacron® cuffs drastically decreased this complication in supine peritoneal dialysis. The introduction of ambulatory peritoneal dialysis once again increased the frequency of pericatheter leaks because of increased intraabdominal pressure in the upright position. To prevent this complication, a new catheter was designed. The catheter, dubbed the Toronto Western Hospital Type 2 (TWH-2), was made of silicone rubber tubing and was provided with two cuffs, similar to the Tenckhoff catheter, and two silicone rubber discs to curtail catheter migration; however, it had new features. The catheter was provided with a polyester disc (flange) at the base of the deep cuff and a silicone rubber ring (or bead) situated close to the flange that provided a groove in which a purse string suture could tie the peritoneum tightly [49]. These innovations by themselves did not decrease leakages, so the authors signaled that they started a modified implantation technique. Instead of implantation through the *linea alba*, the catheter was inserted though the rectus muscle.

Several catheters have been developed in recent years aimed at eliminating or decreasing multiple complications of Tenckhoff catheters. Twardowski et al. [50] designed silicone rubber "swan-neck" catheters that are permanently bent between two cuffs. These catheters may be implanted in an arcuate tunnel with their shape undistorted. A similar principle was applied by Cruz to polyurethane catheters (Fig. 14.13) [51]. In 1992, Twardowski et al. [3, 52] described a new catheter that had an exit site on the chest instead of the abdomen (Fig. 14.14). Moncrief et al. [53] described a modified swan-neck catheter with an elongated external cuff. They also substantially changed technique of catheter insertion by keeping the external part under the skin until the ingrowth of the tissue into the cuff is strong. Only after several weeks (three to six or more) is the external part exteriorized.

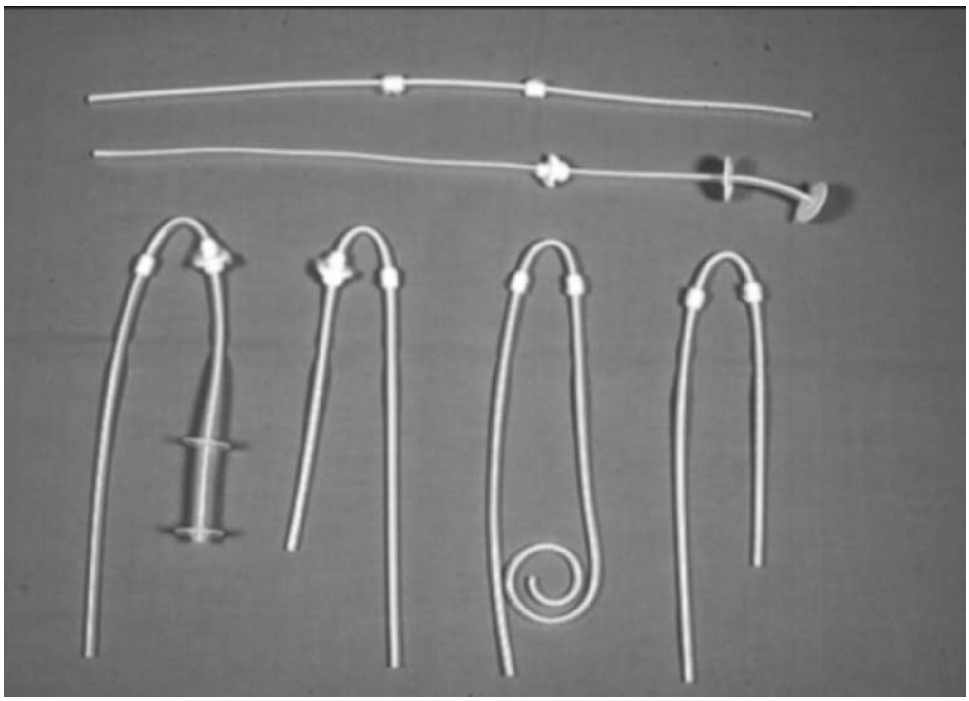

Fig. 14.13 Tenckhoff, Toronto Western Hospital (TWH) catheters and various swan-neck catheters. All swan-neck catheters have two cuffs and bent intramural segment. Swan-neck Missouri catheters have a slanted flange and bead at the deep cuff

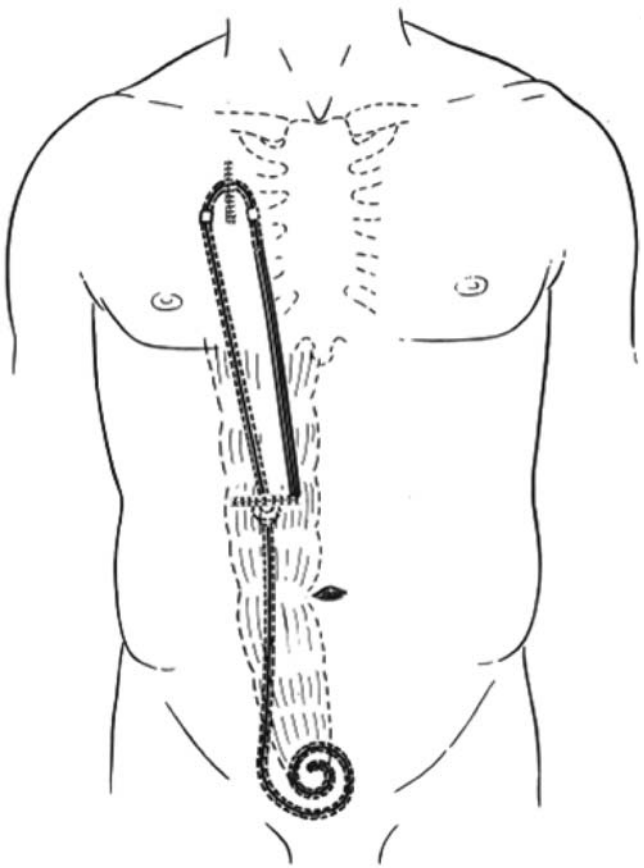

Fig. 14.14 Swan-neck presternal catheter after implantation. The deep cuff with flange and bead is shown in the rectus muscle; the titanium connector is 2–3 inches (5–7.5 cm) above the deep cuff. The middle and superficial cuffs are in the parasternal area, and the exit is 3 cm below the external cuff. Modified from [52]

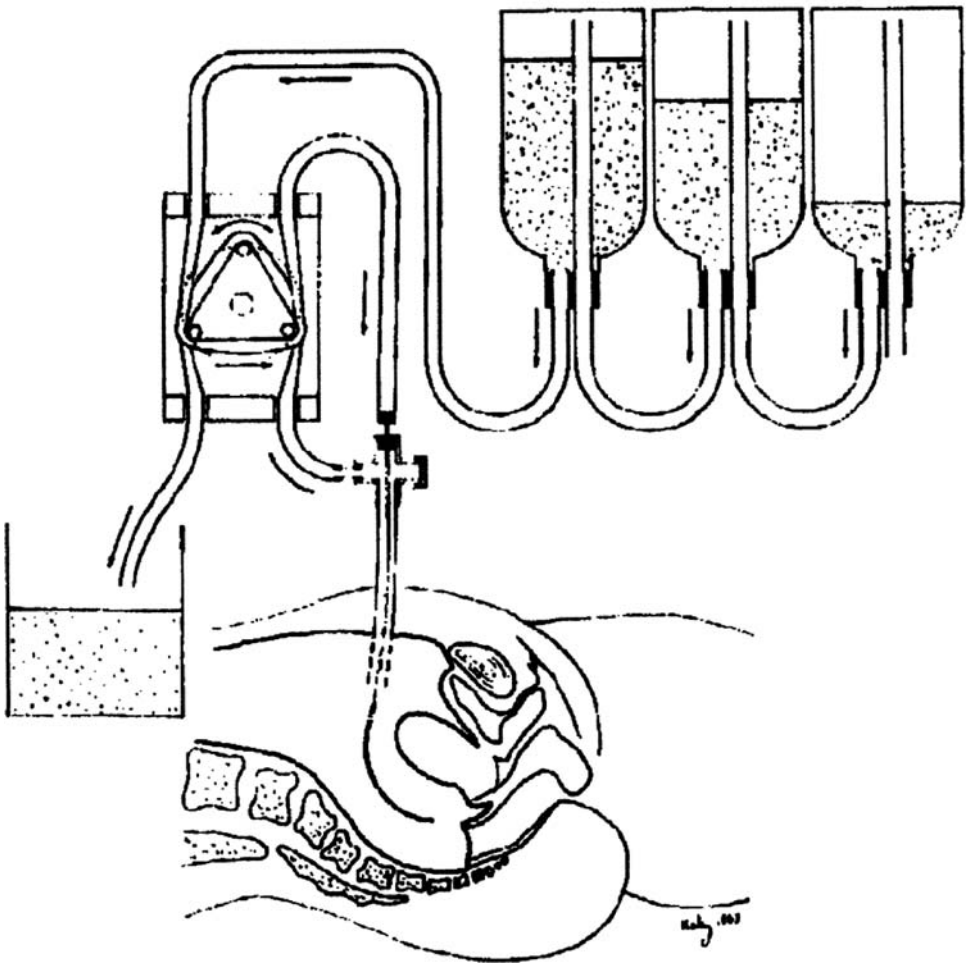

Fig. 14.15 Automatic continuous flow peritoneal dialysis of Lange, Treser, and Mangalat. A = inflow. B = outflow. Modified from [55]

Continuous flow peritoneal dialysis, introduced in animals in 1926 by Rosenak and Siwon [7] and in humans by Balázs and Rosenak in 1934 [9], was used concomitantly with intermittent flow peritoneal dialysis until the late 1960 s (Fig. 14.15). High fluid flows were used with either two catheters [22, 54] or double-lumen catheters. One double-lumen catheter was developed by Lange et al. [55]. The catheter (Fig. 14.16) was composed of a short nylon catheter of 15 cm length with an outer diameter of 4.7 mm and inner diameter of 4 mm and numerous perforations in the distal 3 cm. The catheter was introduced into the peritoneal cavity with a trocar under local anesthesia; the trocar was removed and the catheter was attached to a four-way connector and 2,000 mL of solution was infused to the peritoneal cavity. Immediately thereafter, a stiff nylon catheter, 37 cm long, with an outer diameter of 2.2 mm and inner diameter of 1.4 mm was introduced to the pelvic gutter through the lumen of the large catheter. The internal catheter was tightly sealed in the opening of the cross and connected to the inflow tubing. The fluid inflow was through the inner catheter to the pelvic gutter and drainage was through the large catheter with openings below the parietal peritoneum of the anterior abdominal wall. Stephen et al. [35] used their subcutaneous catheter for recirculating peritoneal dialysis, which was an offshoot of continuous flow peritoneal dialysis.

The technique of continuous flow peritoneal dialysis was abandoned after the advent of continuous ambulatory peritoneal dialysis regimen in the late 1970 s as it was associated with technical difficulties due to catheter obstruction, abdominal pain related to high flow, and less then expected dialysis efficiency because of fluid channeling [56]. There is a renewed interest in continuous flow peritoneal dialysis, as it is believed that new peritoneal accesses may make this modality successful. One of these catheters, a fluted double-lumen catheter, has been recently described by Diaz-Buxo from Fresenius Medical Care North America, Lexington, Maryland, USA [57, 58]. Within the abdominal wall, this catheter consists of two tubes using a novel configuration, where one slightly oval-shaped tube embeds within the other crescent-shaped tube. Externally, the tubes are separate. Intraperitoneally, the tubes are also separated, with each tube terminating with a fluted section. The internal part of this double-lumen catheter is similar to the T-fluted catheter with

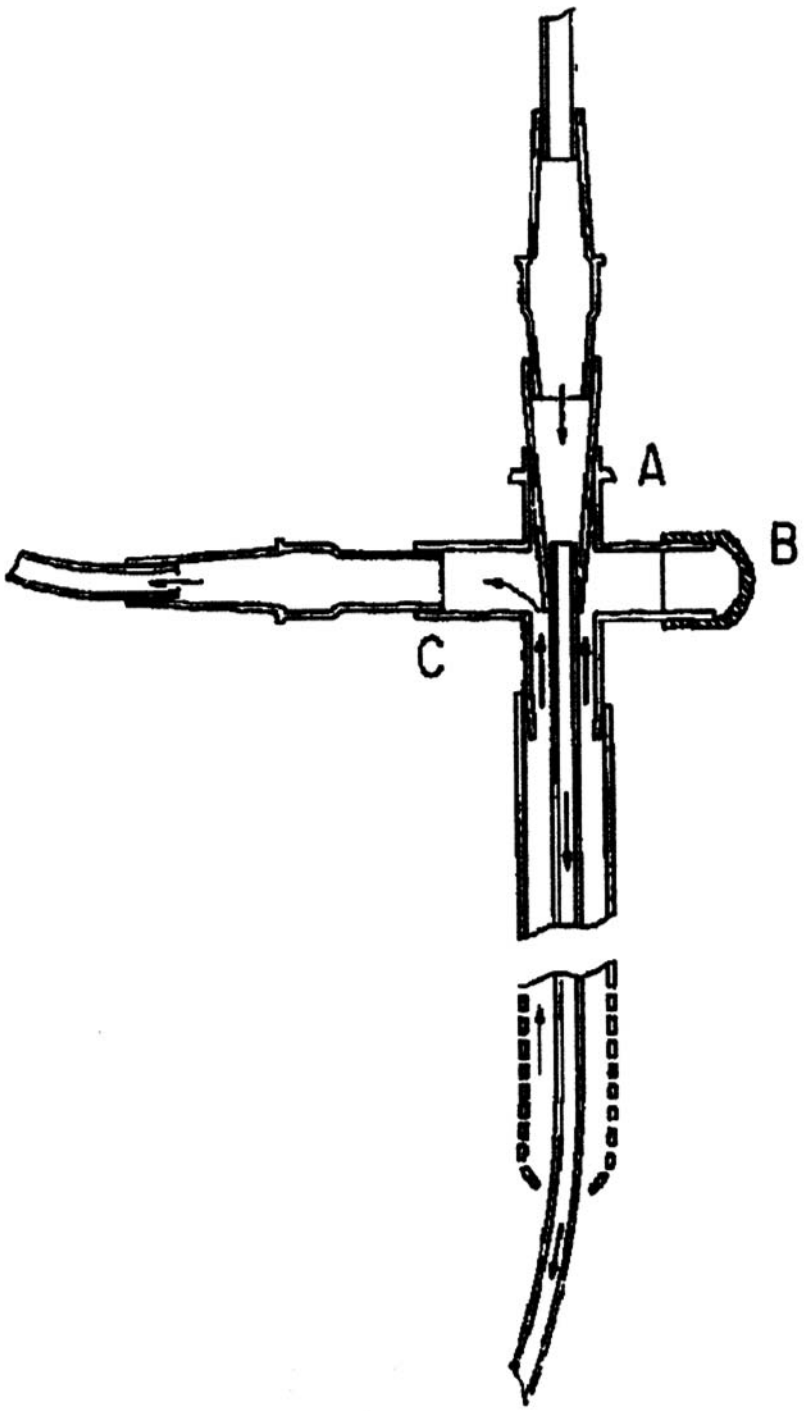

Fig. 14.16 Lange, Treser, and Mangalat's double-lumen catheter for continuous flow peritoneal dialysis. Modified from [55]

the exception that the latter is a single-lumen catheter. Another catheter, a double-lumen catheter with diffuser, has been recently developed by Ronco et al. [59]. The intraperitoneal segment of the outflow tubing has a coiled design. The intraperitoneal segment of the inflow tubing is a short, thin-walled, silicone rubber, round, tapered diffuser with multiple side holes, which allow the inflowing dialysis solution to be dispersed just below the parietal peritoneum, far away from the outflow tubing tip. This design is a reversal of the catheter of Lange et al. [55], where inflow was to the pelvic gutter and drainage through the large catheter with openings below the parietal peritoneum of the anterior abdominal wall.

In agreement with the general pattern of biological and technological evolution, the first peritoneal accesses were devices that had been used in other fields of medicine or surgery. Gradually, the accesses were designed specifically for

peritoneal dialysis. Most of the designs improved the performance of peritoneal accesses, although some led nowhere and were abandoned. The major breakthrough came in the 1960 s with the invention of the Tenckhoff catheter.

Technological evolution never ends. Multiple attempts are being made to eliminate remaining complications of the Tenckhoff catheter, such as exit/tunnel infection, external cuff extrusion, migration leading to obstruction, dialysate leaks, recurrent peritonitis, and infusion or pressure pain. New designs combine the best features of the previous catheters or incorporate a new element. Not all attempts are successful, but many are. The swan-neck catheters with the permanent bend of the silicone rubber in the intratunnel segment have been among the most successful. Consecutive gradual improvement leading to the classic Tenckhoff catheter and subsequent modification of the Tenckhoff catheter are summarized in Table 14.1.

Other innovations have included surface modification of catheters to reduce infections. Silver, because of its antimicrobial activity, has been studied extensively. Surface coating of catheters using ion-beam-assisted deposition

Table 14.1 Development of new features in peritoneal accesses for dialysis in humans

1st Author	Year	Ref.	Fig.	Main new feature(s)	Prior similar concept(s) [ref.]
Balázs	1934	[9]		Bulbous distention of the tip	Sprinkling can rose-like tip of glass cannula (Rosenak and Siwon [7])
Seligman	1946	[13]		Rubber catheter inserted through a trocar	Rubber catheters used in surgery, urology, and gynecology
Rosenak	1948	[18]	2	Sump drain with flexible (spiral spring wire) intra-abdominal part	Sump drain used in surgery
Ferris	1948	[20]	3	Polyvinyl intra-abdominal part; weight to keep the tip in true pelvis	Modification of Rosenak and Oppenheimer [18]
Frank	1948	[21]	4, 5	Flexible rubber tube in a long subcutaneous tunnel	Long tunnel was a new concept for a modified sump drain
Dérot	1949	[22]		Polyvinyl catheter inserted through a trocar	Trocar (Seligman et al. [13]); polyvinyl tube (Ferris and Odel [20])
Grollman	1951	[23]		Polyethylene tube inserted through a trocar	Polyethylene for a catheter is a new concept
Maxwell	1959	[25]	6	Polyamide catheter inserted through a trocar; very tiny lateral perforations, closed tip	Polyamide for a catheter and very tiny perforations were new ideas. Sump drains had a closed tip
Weston	1965	[29]	7	Pointed stylet inside polyamide catheter	Modification of Maxwell et al. [25] catheter
Gutch	1964	[30]		Silicone rubber for catheter tube	Silicone rubber used for hemodialysis shunts and abdominal surgery
Palmer	1964	[31]	8	Silicone rubber, long tunnel, triflange step, coiled tip	Silicone rubber (see above) long tunnel (Frank et al. [21]). Triflange step and coiled tip were new concepts
Tenckhoff	1968	[34]	9, 10	Polyester cuffs attached to silicone rubber catheter	Silicone rubber (Palmer et al. [31], Gutch [30]), cuff was a new concept for peritoneal dialysis catheter
Oreopoulos	1976	[40]	12	Intraperitoneal silicone discs	Protection from omental wrap and tip translocation by distensible balloon (Goldberg and Hill [39])
Ponce	1982	[49]	12	Flange and bead at deep cuff. Insertion through the rectus muscle	These were new concepts
Valli	1983, 1988	[41, 42]	12	Silicone balloon tip with multiple perforations	Bulbous distension of glass cannula (Rosenak and Siwon [7], Balázs and Rosenak [9])
Chiaramonte	1985, 1992	[46, 47]	12	Short intraperitoneal segment, catheter implanted close to the symphysis pubis	Modified Tenckhoff catheter. Implantation of catheter just above the Poupart's ligament (Weiss and Mills [16])
Twardowski	1985	[50]	12	Permanent bend of intercuff segment	Permanent bend was a new idea
Twardowski	1992	[3]	12	Exit on the chest, long tunnel, three cuffs	Exit on the chest and three cuffs were new ideas. Frank et al. [21] and Palmer et al. [31] designed long tunnels
Di Paolo	1996	[48]	12	Tungsten weight at the catheter tip	Bendaloy weight at the tip (Ferris and Odel [20])

of silver was shown to be effective in reducing infections in our initial animal studies [60, 61], but such catheters have not been studied in human subjects. Another technology to treat catheters is by silver ion beam implantation therapy, wherein the silver ions penetrate the catheter to a depth of 200–300 nm. In a study of 67 such silver-treated catheters and 72 controls, no differences in exit-site infections or peritonitis were noted [62]. The failure to reduce infections may be secondary to the low surface availability of silver. Further, the lack of effect on peritonitis may be secondary to the lack of silver in the internal lumina by this technology. An alternative is to impregnate the catheter matrix with silver. The distribution of submicron silver evenly through the matrix creates a larger antimicrobially active surface than can be created by surface coating [63]. The silver ions are released from the matrix into the unstirred water layer of the surface and are available to interact with the free sulfhydryl groups of bacterial enzyme systems [63]. In vitro studies have demonstrated the antimicrobial activity of these silver-impregnated catheters against coagulase-negative staphylococci (CNS), *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa,* and *Candida albicans* [64]. While no studies have been done with silver-impregnated peritoneal dialysis catheters, clinical tests with silver-impregnated vascular catheters have not consistently shown favorable results [65, 66].

A preliminary evaluation of a silver ring device mounted on a catheter showed significant reductions in exit-site infections in a population with a very high exit-site infection rate [67]. A subsequent randomized study showed this device to be ineffective in reducing catheter-related infections. The rate of catheter explantation was similar in the study and control group. Displacement of the silver ring into the tunnel track contributed to infections and catheter loss in almost 6% of the patients [68]. The authors postulated that the piston movement of the catheter may have prevented the ring from being in constant contact with the skin.

Early exit site colonization is associated with higher catheter loss [69]. This has led to studies with antibiotic coated catheters. In-vitro studies show that antimicrobial impregnated catheters loose their efficacy with time [70] but at least theoretically, these catheters would be effective at the most crucial time post-implantation. Clinical studies have shown that intravenous catheters impregnated with chlorhexidine and silver sulfadiazine or minocycline and rifampin are effective in reducing bacterial colonization of catheters with the data being somewhat controversial on reduction of catheter related blood stream infections [71, 72]. Antimicrobial impregnated peritoneal catheters have been studied in rats [73, 74]. In one study, after implantation, the exit sites of both control and impregnated catheters were inoculated with S. *aureus*. All of the control catheters developed colonization at the exit-site and intra-peritoneally seven days post-implantation. In the impregnated catheters, none had intra-peritoneal colonization while12.5% had colonization of the exit-site [73]. In another animal study, Trooskin and colleagues [74], peritoneal dialysis catheters with anionic antibiotic bonded to cationic surfactants, were found to be more resistant to colonization after exit site and intraluminal bacterial challenges. In a prospective randomized study of 86 patients, catheters which were bonded with cefoxitin were unable to show decrease in exit-site infections and peritonitis when compared with the control group [75]. Further refinement of this technique may make this approach effective in the future.

Favorable experience gained with alumina ceramic in orthopedic surgery, otorhinolaryngology, and dentistry inspired Amano et al. [76] to use alumina ceramic for a peritoneal catheter. In this catheter the part of the tubing designated to be contained within the sinus tract is replaced by a rigid alumina ceramic connector. Dog experiments with this material revealed only minimal skin down growth. Preliminary human experience was encouraging [76], but no long-term results have yet been published.

This chapter will describe in detail some of those catheters that are in current use, their insertion technique, postimplantation care, and long-term results. New, emerging techniques will be briefly reviewed.

Currently Used Chronic Peritoneal Catheters

The chronic peritoneal catheter is composed of an intraperitoneal and extraperitoneal portion. The latter comprises a tunnel within the body wall (intramural) and an external (outside the exit site) portion. The intraperitoneal and extraperitoneal portions differ in various catheters and there are many combinations of those. Figure 14.17 shows combinations of intraperitoneal and extraperitoneal designs of currently available chronic peritoneal catheters.

A survey conducted at the Annual Dialysis Conference in 2005 looked at the choice of peritoneal dialysis catheters and implantation techniques over the preceding year [77]. Worldwide, the Tenckhoff catheter was the most popular, used in 65% of patients, followed by the swan-neck catheter in 26% patients. The swan-neck catheter was used in 36% of patients in the United States and 49% in Europe. In this survey, no usage of the swan-neck catheter was reported from Canada, where almost three quarters of the catheters were Tenckhoff and the rest Toronto Western Hospital catheters. Mexico and Central America exclusively used Tenckhoff catheters. Over 90% of the catheters had two cuffs and 68% had coiled intraperitoneal sections. Surgical implantation was used for 72% of patients and 16% were peritoneoscopically placed [77].

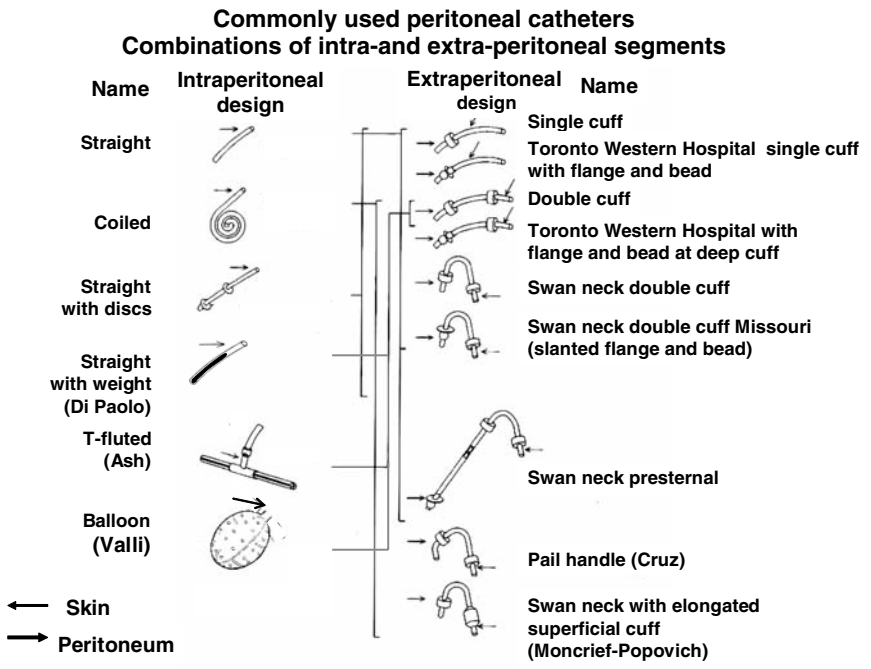

Fig. 14.17 Currently available chronic peritoneal catheters showing combinations of intraperitoneal and extraperitoneal designs. Modified and updated from [129]

Among the pediatric population in this survey, the Tenckhoff catheter was predominant (59%), with swan-neck catheters being used in 41% of patients. In Mexico and Asia the Tenckhoff catheter was used exclusively in children. The majority of the catheters were implanted surgically in this population as well [77]. A survey in 1994 had shown an increase in utilization of swan-neck catheters in the Unites States [78] and it now appears that Europe is following the trend. The swan-neck catheters are associated with fewer episodes of early outflow track obstruction and catheter migration but have not been shown to decrease peritonitis [1, 79]. The use of swan-neck catheters is recommended preferentially by the International Society of Peritoneal Dialysis [1]. The most commonly used catheters are described in detail below.

Straight and Coiled Tenckhoff Catheters

The catheter consists of silicone rubber tubing with a 2.6 mm internal diameter and a 5 mm external diameter (Figs 14.1 and 14.13). The catheter is provided with one or two polyester (Dacron®), 1-cm-long cuffs. The overall length of the adult straight double-cuff catheter is about 40 cm. The lengths of segments are as follows: intraperitoneal, about 15 cm; intercuff, 5–7 cm (intramural); external, 16 cm. The intraperitoneal segment has an open end and multiple 0.5-mm perforations at a distance of 11 cm from the tip. The coiled Tenckhoff catheter differs from the straight in having a coiled, 18.5-cm-long perforated intraperitoneal end. As mentioned above, the coiled catheter reduces inflow infusion "jet effect" and pressure discomfort. All Tenckhoff catheters are provided with a barium-impregnated radiopaque stripe to assist in radiological visualization of the catheter.

Swan-Neck Catheters

The swan-neck catheter is the second most commonly used catheter at present. Its design is based on a retrospective analysis of complication rates with Tenckhoff and Toronto Western Hospital catheters. This analysis showed that the lowest complication rates were with double-cuff catheters implanted through the belly of the rectus muscle and with both internal and skin exits of the tunnel directed downwards; however, the resulting arcuate tunnel led to frequent

Table 14.2 Swan-neck catheter features preventing complications

Exit/tunnel infection	Downward exit, double cuff, short sinus
External cuff extrusion	Permanent bend between cuffs
Intraperitoneal tip migration	Downward intraperitoneal entrance
Pericatheter leak	Insertion through the rectus muscle
Peritonitis	Decreased tunnel infections
Infusion/pressure pain	Coiled intraperitoneal tip

external cuff extrusion [50]. Swan-neck catheters feature a *permanent bend* between cuffs (Table 14.2) [80]. The catheter was dubbed "swan-neck" because of its shape. As a result of this design, catheters can be placed in an arcuate tunnel in an unstressed condition with both external and internal segments of the tunnel directed downwards. A downward-directed exit, two intramural cuffs, and an optimal sinus length reduce exit/tunnel infection rates. A *permanent bend* between cuffs eliminates the silastic resilience force or the "shape memory," which tends to extrude the external cuff. A downward-directed peritoneal entrance tends to keep the tip in the true pelvis, reducing its migration. Insertion through the rectus muscle decreases pericatheter leaks by promoting fibrous ingrowth into the Dacron® cuff. Lower exit/tunnel infection rates curtail peritonitis episodes. Finally, swan-neck catheters with a coiled intraperitoneal segment minimize infusion and pressure pain.

Swan-neck prototypes (Fig. 14.18) were designed in 1985 and were used briefly between August 1985 and April 1986. These catheters were made with 80° of arc angle and were inserted in a reversed U-shape tunnel with the incision at the top of the tunnel [81]. Only 27 of these catheters were inserted because we noted a tendency to cuff extrusions, which we considered a risk for exit infections [82]. Further observations confirmed our predictions. Cuff extrusion occurred in nine catheters and led to exit infections and finally to catheter removal. Initial excellent results with these catheters because of elimination of leaks and malfunctions were obviated later by high infection rates. Cuff extrusions resulted from resilience forces pushing on the external cuff due to an insufficient bend of the catheter and too long a distance between cuffs. We considered these catheters as suboptimal and discontinued their use in April 1986 [82, 83]. Based on this unfavorable observation the catheters were modified; the new catheters, swan-neck 2 and 3 catheters, had straight intraperitoneal segments. A major improvement was in the inter-cuff shape; the distance between cuffs was shortened from 8.5 to 5 cm in swan-neck 2 and to 3 cm in swan-neck 3 catheters and the bend was increased from 80° to 170–180° arc angle. The catheters were provided with short or long intraperitoneal segments, selected according to patient size and insertion site, to secure the catheter-tip position in the true pelvis [82, 84]. Because in several patients infusion pain occurred due to a "jet effect" and/or tip pressure on the peritoneum, we modified the intraperitoneal segment of the catheters, replacing a straight segment with a coiled one (swan-neck coiled). These catheters were introduced in January 1990 and within a month swan-neck straight catheters were phased out [83].

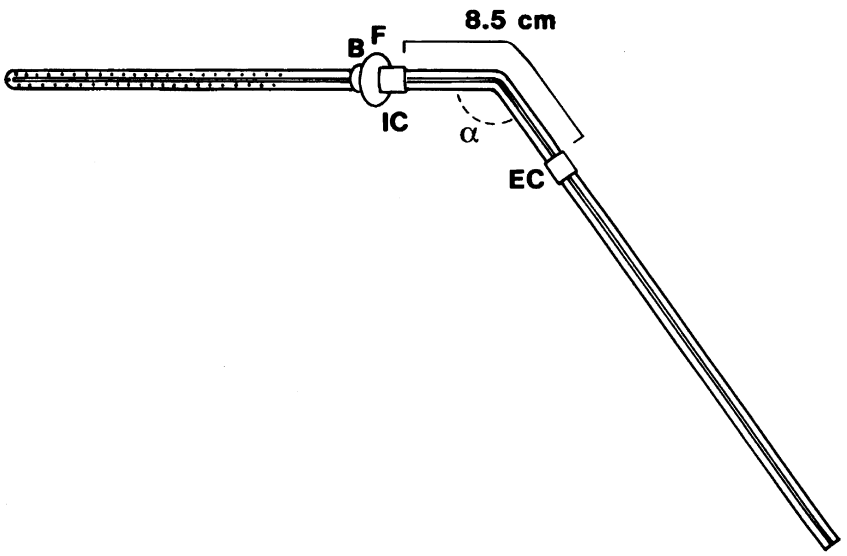

Fig. 14.18 Swan-neck Missouri prototype catheter. Arc angle = 180° – α = 80°. Cuff extrusions were common with these catheters because of insufficient bend and too long a distance between cuffs. We consider these catheters as suboptimal and we have not used them since April 1986

Swan-Neck Tenckhoff Straight and Coiled Catheters

The Tenckhoff type of the swan-neck peritoneal dialysis catheter is provided with two Dacron® cuffs. It differs from the double-cuff Tenckhoff catheter only by being permanently bent between cuffs. This type of catheter may be inserted at the bedside and does not require surgical insertion; however, a subcutaneous pocket and tunnel has to be created in the same way as for other swan-neck catheters. The intraperitoneal segment of the swan-neck coiled catheter is identical to that of the Tenckhoff coiled catheter [84]. All swan-neck catheters are manufactured by Covidien (Mansfield, MA 02048, USA).

Swan-Neck Missouri Straight Catheter

The swan-neck Missouri abdominal catheter has a flange and bead circumferentially surrounding the catheter just below the internal cuff; the flange and bead are slanted approximately 45° relative to the axis of the catheter. The catheters for left and right abdominal tunnels are mirror-images of each other. A swan-neck abdominal Missouri 2 abdominal catheter with a 5-cm inter-cuff distance is used in average to obese people (Fig. 14.19). A swan-neck abdominal Missouri 3 abdominal catheter with a 3-cm inter-cuff distance is used in lean to average persons [84].

Swan-Neck Missouri Coiled Catheter

The intraperitoneal segment in all swan-neck coiled catheters is 34 cm from the bead to the tip of the coil. Swan-neck abdominal Missouri 2 coiled abdominal catheters with the 5-cm inter-cuff distance (Fig. 14.19) are used in average to obese people. Swan-neck abdominal Missouri 3 coiled catheters with 3-cm inter-cuff distance are used in lean to average persons. The catheters for left and right tunnels are mirror-images of each other [84]. The overall survival values of straight and coiled swan-neck Missouri abdominal catheters are not significantly different, but none of the

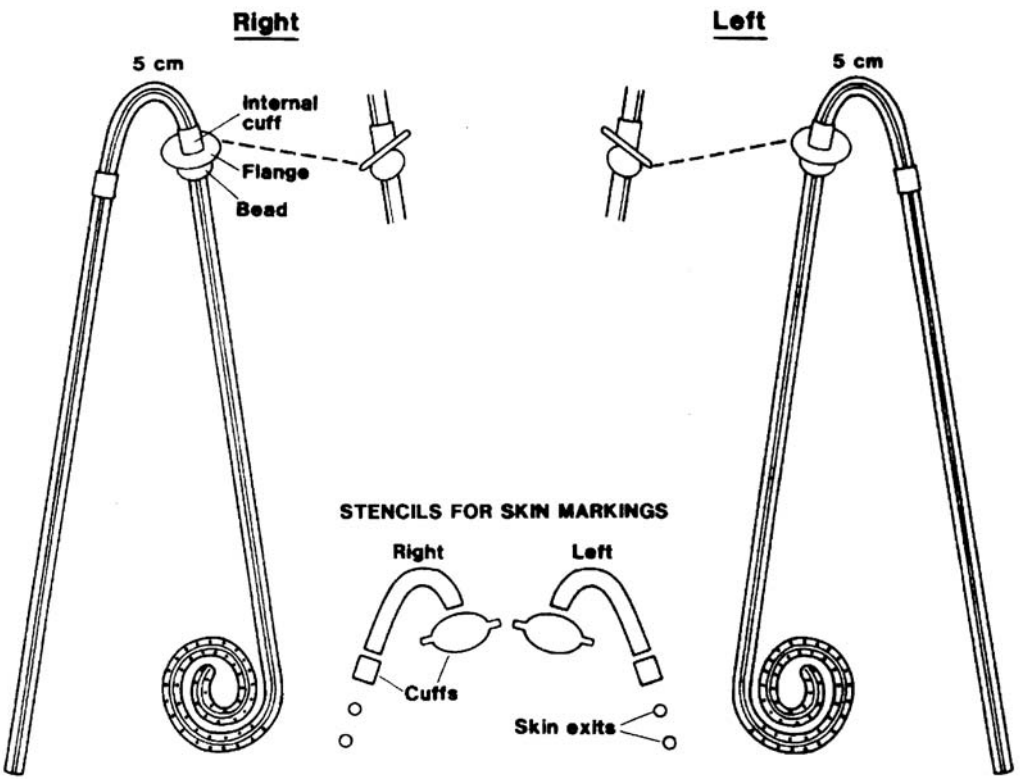

Fig. 14.19 Swan-neck Missouri 2 coiled (curled) catheters and stencils. Swan-neck Missouri 2 catheters have 5-cm intercuff distance and intraperitoneal length of 32 cm from the bead to the tip. The flange and bead are slanted approximately 45° relative to the tubing axis. The catheters for left and right tunnels are mirror-images of each other. The stencil follows exactly the shape of the intramural segment. The stencil can be flipped to be used for right or left catheter. The holes for exit-site markings are located 2 and 3 cm from the cuff. A 3-cm mark is used for average or obese persons, a 2-cm mark is suitable for lean or average persons

patients experienced infusion or pressure pain with coiled catheters, whereas this complication occurred in several patients who had catheters with straight intraperitoneal segments [83]. Swan-neck catheters are also available in smaller sizes for children and infants.

Swan-Neck Presternal Catheter

Potential advantages of exit location in the chest instead of in the abdomen are shown in Table 14.3. The chest is a sturdy structure with minimal wall motion; the catheter exit located on the chest wall is subjected to minimal movements, decreasing chances of trauma and contamination. Also, in patients with abdominal ostomies and in children with diapers, a chest exit location reduces the chances of contamination. Moreover, a loose garment is usually worn on the chest and there is thus less pressure on the exit. Surgical experience indicates that wounds heal better after thoracic surgery than after abdominal surgery; this may, in part, be related to less chest mobility. Obese patients have higher exit-site infection rates and a tendency to poor wound healing, particularly after abdominal surgery. The subcutaneous fat layer is much thinner on the chest than on the abdomen. If fat thickness *per se* is responsible for quality of healing and susceptibility to infection then chest location may be preferred for obese patients. All these favorable factors, together with easy exit-site care using a magnifying mirror, significantly reduce exit-site infections. The location of the exit site on the chest is particularly advantageous in small children because of the greater distance from diapers and is subjected to fewer traumas during crawling/creeping. The catheter is also advantageous for psychosocial reasons. A chest exit location allows a tub bath without the risk of exit contamination. Although the exit site can be located in the presternal or parasternal area we will usually refer to this catheter as presternal for simplicity. However, implantation directly over the sternum should be avoided to prevent catheter damage during median sternotomies used for cardiac surgery. A long catheter tunnel, combined with three cuffs, may curtail pericatheter bacterial penetration into the peritoneal cavity, thus reducing the incidence of peritonitis [3, 84, 85].

To accommodate these principles we modified the swan-neck peritoneal catheter to have an exit on the chest but preserving all advantages of the swan-neck abdominal Missouri coiled catheters, minimizing catheter obstruction, cuff extrusion, pericatheter dialysate leak, and infusion pain. A major difference from the swan-neck abdominal Missouri catheter is in the length of the subcutaneous tunnel. The catheter (Fig. 14.20) is composed of two silicone rubber tubes, which are cut to an appropriate length and connected end to end at the time of implantation [84, 85]. Figure 14.14 shows the catheter in relation to the torso after implantation. The implanted lower (abdominal) tube constitutes the intraperitoneal catheter segment and a part of the intramural segment. The upper or chest portion of the tube constitutes the remaining part of the intramural segment and the external catheter segment. The lower tube is identical to the swan-neck abdominal Missouri catheter, with the exception that it is not bent and does not have a second cuff. The proximal end of the lower tube is straight and with a redundant length to be trimmed to the patient's size at the time of implantation. A titanium connector, provided in a package, is to be used to connect the two components at the time of implantation.

Table 14.3 Potential advantages of the swan-neck presternal catheter compared to the swan-neck Missouri catheter

Attribute	Advantage	Explanation
Exit on the chest	Decreased risk of exit infection	Good immobilization
		Good wound healing
		Loose garment/less pressure
		Easy exit-site care
		Less fat thickness
		Far from ostomies*
		Far from wet diapers**
		Less trauma with creeping**
	Psychosocial	Better body image for some patients
		Easy exit-site care
		May take tub bath without risk of exit contamination
Three cuffs	Decreased risk of peritonitis	Strong (triple) barrier
		Long tunnel, long distance for bacterial penetration

*In patients with ostomies.
**In small children

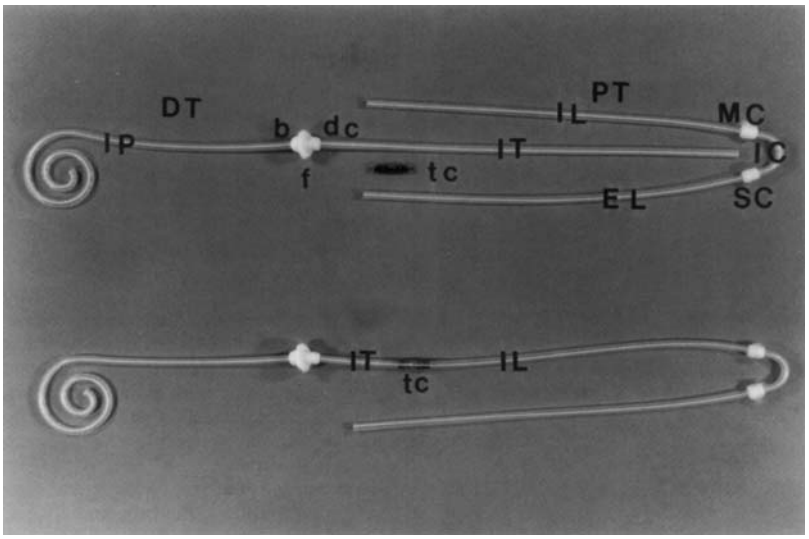

Fig. 14.20 Swan-neck presternal catheter: two tubes of the swan-neck presternal peritoneal catheter before (top) and after (bottom) connection. Both tubes and bead are made of silicone rubber moulded in the shapes as shown. A flange and all cuffs are made of woven polyester fibers. Proximal (upper, chest) tube (PT) consists of an intra-tunnel limb (IL), medial (center) cuff (MC), inter-cuff segment (IC), superficial cuff (SC), and external limb (EL); 1–2 cm of the external limb adjacent to the superficial cuff is intended to be in the sinus tract of the tunnel (from the cuff to the exit). Distal (abdominal, lower) tube (DT) consists of an intra-tunnel segment (IT), deep (distal, preperitoneal) cuff (dc), flange (f), bead (b), and intraperitoneal segment (IP). After implantation (bottom), the intra-tunnel limb (IL) of the chest tube and the intra-tunnel segment (IT) of the abdominal tube are trimmed to the size of the tunnel and coupled with titanium connector (tc)

The upper tube carries two porous Dacron® cuffs, a superficial and middle or central cuff, spaced 5 cm apart. The tube between the cuffs has a permanently bent section defining an arc angle of 180°. The distal lumen of the upper tube communicates with the proximal lumen of the lower tube through the titanium connector. The tubing grip of the titanium connector is so strong that the two parts of the catheter, especially after connection reinforcement with monofilament or braided suture, in practice cannot separate spontaneously in the tunnel [86]. The swan-neck presternal catheter is available for children and infants [87]. Tubing diameter is smaller for pediatric patients.

Moncrief–Popovich Catheter

This catheter is a modified swan-neck Tenckhoff coiled catheter (Fig. 14.17) with a longer subcutaneous cuff (2.5 cm instead of 1 cm). This catheter is most commonly used in conjunction with the Moncrief–Popovich implantation technique (see below).

Radiopaque Stripe

The slanted flange and bead, and bent tunnel segment, require that the swan-neck abdominal Missouri abdominal and Toronto catheters for right and left tunnels be mirror-images of each other. To facilitate recognition of right and left Toronto and Missouri catheters, each catheter has a radiopaque stripe in front of the catheter (Fig. 14.19). In a swan-neck presternal catheter the stripe also facilitates proper alignment of the lower and upper tubes. The stripe is also useful during insertion and postimplantation care, facilitating recognition of catheter twisting. Because of this last feature Tenckhoff-type catheters are also provided with the stripe. Right and left swan-neck Tenckhoff catheters differ only with respect to the position of the stripe. Unlike swan-neck Toronto and Missouri catheters, with the slanted flange, the swan-neck Tenckhoff catheter may be implanted on either side. In this case the stripe may be positioned in the back of the catheter. Nevertheless, to retain uniformity of the stripe position anterior it is recommended that swan-neck Tenckhoff catheters be inserted with the corresponding tunnel direction (right tunnel with right catheter, left tunnel with left catheter).

Other Catheters

Catheters used in small numbers, such as recently designed catheters with one-center experience (T-fluted [45], self-locating [48]) and those used in smaller numbers (Cruz [51, 88], Toronto Western Hospital [40], Life-cath or Column disc [43], Valli [41, 42] and Gore-Tex [38] catheters), will not be described in detail. Readers are referred to the original publications.

Accessories for Implantation of Catheters

Stencils

Stencils have been developed for skin markings to facilitate creation of proper tunnels for swan-neck catheters [84]. Stencils are for swan-neck abdominal Missouri 2 (Fig. 14.19), swan-neck abdominal Missouri 3, and swan-neck abdominal Tenckhoff catheters. The stencils follow exactly the shape of the intramural segments of the catheters and the catheter tunnels must follow the shape of the catheters exactly as designed to maximize the advantages of this design. The stencils can be flipped to be used for right or left catheters. The holes for exit-site markings are located 2 and 3 cm from the superficial cuff. A 3-cm mark is used for average or obese persons; a 2-cm mark is suitable for lean or average persons. Stencils for swan-neck Tenckhoff catheters also reflect precisely the shape of their intramural segments.

Stiffening Stylet

A 62-cm-long stiffening catheter guide is used to facilitate catheter insertion into the true pelvis. During insertion, approximately 1 cm of catheter is left beyond the tip of the catheter guide to protect the intestine. The catheter resumes its natural coiled shape after the stylet is removed [84].

Tunneling Devices

Tenckhoff Trochar

Tenckhoff developed a special trochar for bedside insertion of cuffed catheters into the peritoneal cavity (Fig. 14.12). The trochar (available from Covidien, Mansfield, MA 02048, USA) consists of a sharp, stainless-steel stylet; a solid, wide, open-ended barrel; and two side-pieces with handles [89].

Scanlan Tunneler/Bard Tunneler

A Scanlan (Scanlan International, St. Paul, Minnesota, USA) or Bard tunneler (Bard Peripheral Vascular Division, Inc., Tempe, Arizona, USA) is used during swan-neck presternal catheter implantation to create a tunnel extending from the abdominal wall incision to the presternal or parasternal area. A tunneler that will accommodate vascular grafts up to 8 mm is suitable for presternal catheter implantation. The tunneler, developed for tunneling vascular grafts, consists of an outer sheath with a blunt tip, and a stiff rod with handle. The stiff metal rod serves to stiffen the tunneler as it is pushed through the subcutaneous tissue and a spring clamp or suture hole at the tip is used to grasp or attach the upper tubing and pull it through the sheath [90].

Exit Trochar

The catheter tunnel extending from the superficial cuff to the skin exit should have a diameter close to that of catheter tubing. Thus, the last portion of the tunnel (from external cuff to the exit) should be made with a piercing trochar, e.g., the Faller trochar (Covidien, Mansfield, MA 02048, USA) or a 3/16 inch (4.76 mm, F15) trochar designed for the Hemovac system (Zimmer Mfg. Co., St. Louis, Missouri, USA) or the trochar from a 19 Blake drain (Ethicon Inc. a Johnson & Johnson Company, Somerville, New Jersey, USA) of external diameter similar to that of the catheter tubing [84, 90].

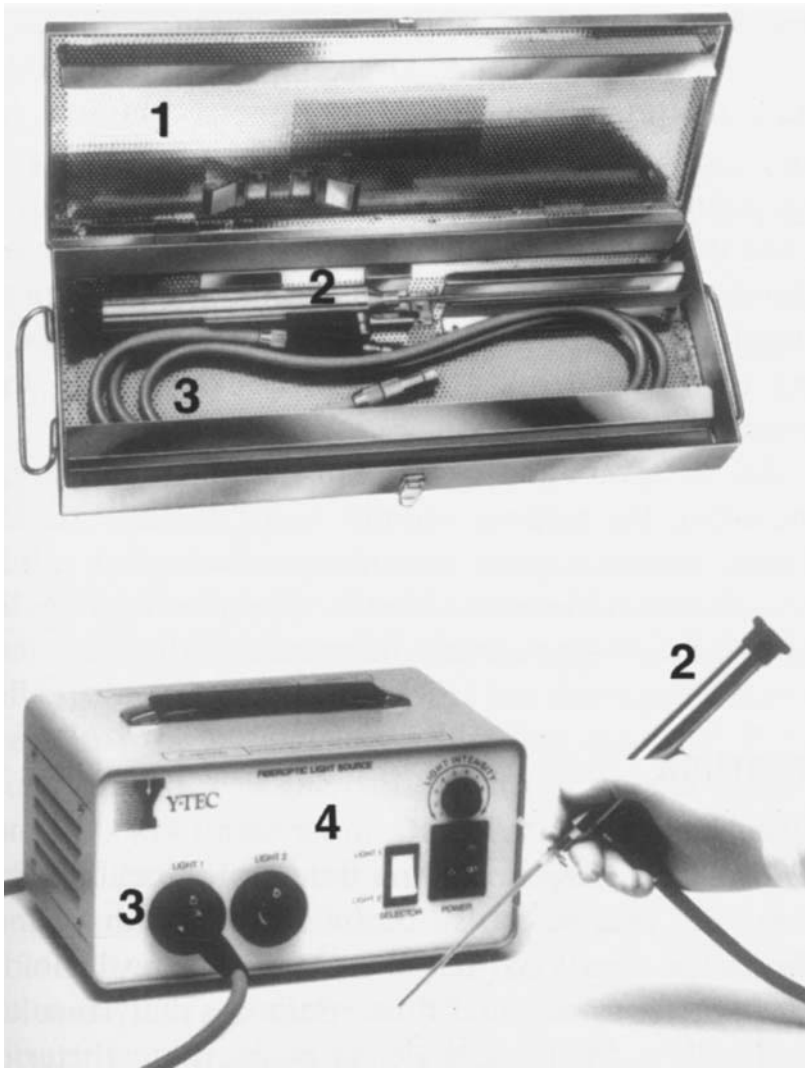

Fig. 14.21 Components for the peritoneoscopic catheter insertion. Above: the sterilization tray (1); the Y-TEC® scope (2); and the light guide (3). Below is the Y-TEC® light source (4), with the scope (2), and light guide (3)

Peritoneoscopic Equipment

The basic equipment (Fig. 14.21) required for peritoneoscopic insertion (manufactured and distributed by Medigroup, North Aurora, Illinois, USA) includes a 2.2-mm diameter, 15-cm long Y-TEC peritoneoscope with a 2.5-mm steel cannula with internal trochar and a spiral-wound Quill catheter guide surrounding the cannula [91, 92].

Seldinger (Guidewire) with Peel-Away Sheath Equipment

The essential instruments (Fig. 14.22) for this technique include a guide needle, attached to a syringe, a Seldinger guidewire, and a tapered dilator with surrounding scored peel-away sheath [93–96]. The necessary equipment and videos can be obtained through Cook Critical Care, Division of Cook Inc., Bloomington, Indiana, USA.

Titanium Connectors, Tyton Ties, and a Tension Tool

After implantation, the catheter must be connected to the peritoneal dialysis set. A titanium connector serves this purpose. A single-piece connector shown in Fig. 14.23 is simply inserted into the end of the external catheter tubing.

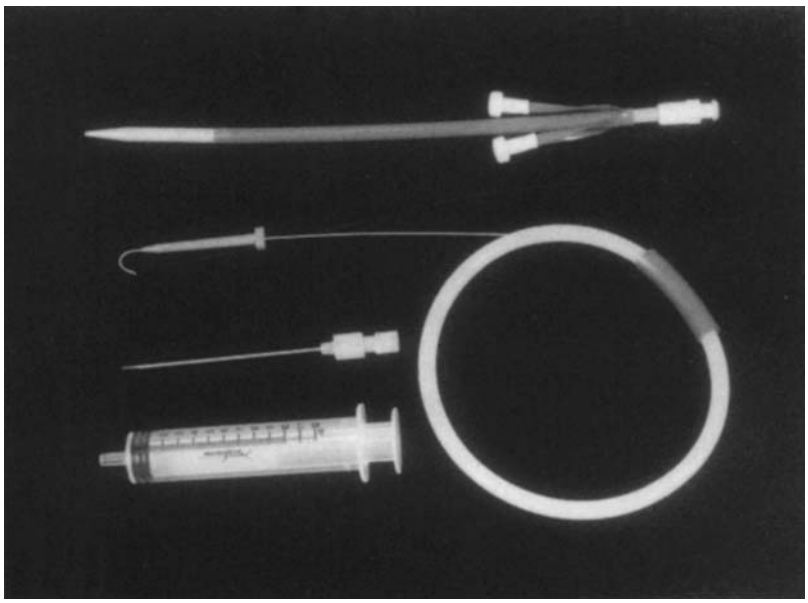

Fig. 14.22 Equipment for guidewire insertion method. From the top: peel-away sheath with dilator, guidewire, needle, and syringe

The external part is equipped with a female Luer lock adapter and sealing cap. The intracatheter adaptor is barbed and its external diameter is slightly larger than the internal diameter of the tubing to avoid accidental disconnection; however, this titanium connector has been associated with numerous instances of spontaneous separations. Tyton ties and a tension tool (Tyton Corporation, Milwaukee, Wisconsin, USA) routinely used to secure bundles of electrical wirings, and available in department stores, may be used to prevent disconnection of the titanium adaptor from the tubing. A 4-inch (100-mm) tie is placed around the distal end of the catheter over the adapter. Care is taken to place the tie in the groove between adapter ridges and not over a ridge. Then the tie is tightened with the tension tool that also trims the excess length. The locking segment is located at the stripe, which will be positioned at the front of the patient (Fig. 14.23). This keeps the added bulk away from the patient [84, 97, 98].

A recently introduced two-piece adapter (Baxter Healthcare Corporation, Deerfield, Illinois, USA), shown in Fig. 14.24, is very safe and no instances of accidental connector disengagements have been reported. The only disadvantage of this design is the substantially higher price.

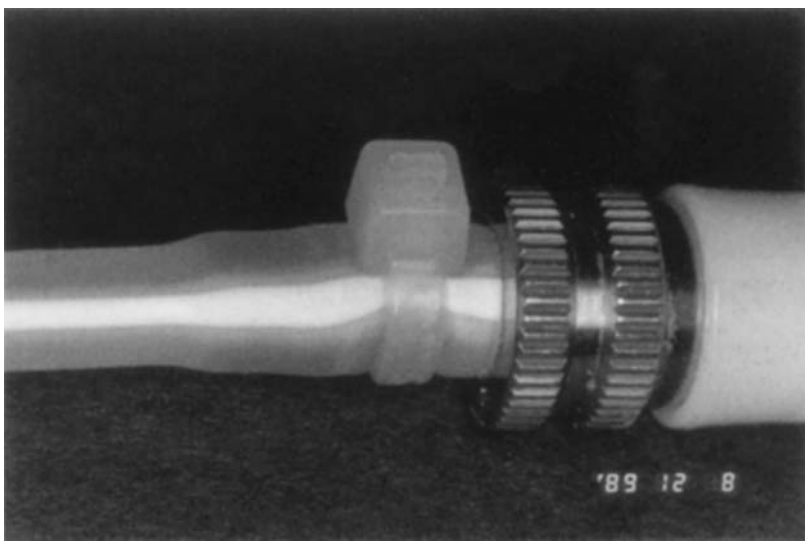

Fig. 14.23 A single-piece titanium adaptor with a barbed connector in the catheter tubing and a male Luer lock connector attached to the female connector of the extension tube. The nylon tie is in place over the catheter/barbed connector junction. The locking segment is over the stripe and will be away from the patient's skin

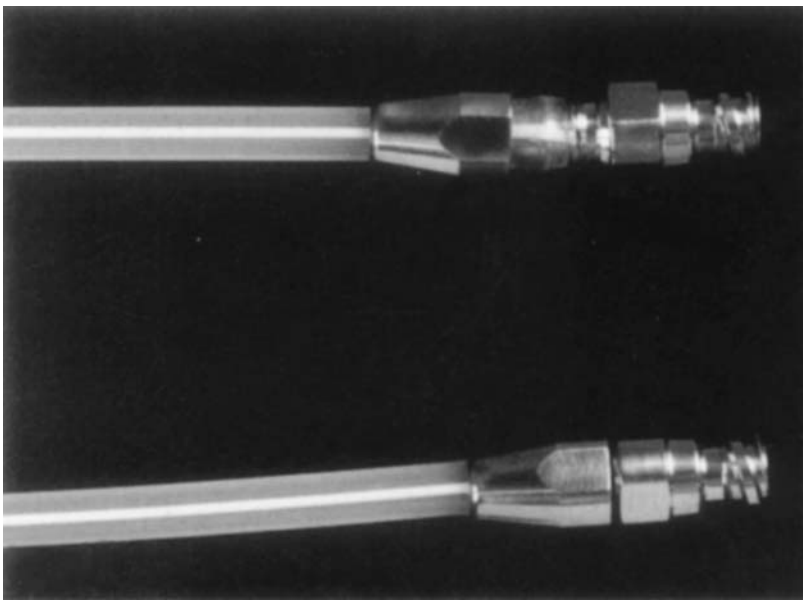

Fig. 14.24 A two-piece adapter (locking titanium adapter – Baxter) with two parts disengaged (upper), with adaptor inserted into the external end of the catheter and after the two pieces are screwed together and tightened (lower)

Insertion of Rigid Catheters

Rigid Catheters for Acute Dialysis

The two most widely used rigid catheters in North America are the Stylocath (Abbott Laboratories, North Chicago, Illinois, USA) and the Trocath (Baxter Healthcare Corporation, Deerfield, Illinois, USA).

Preinsertion Patient Assessment and Preparation

When the need to start peritoneal dialysis is urgent, one may elect to access the peritoneal cavity through a rigid catheter. This catheter can be inserted at the bedside, with minimal preparation. Equipment required for paracentesis is all that is needed.

Bedside insertion *should not* be offered to patients who are extremely obese, or have had previous abdominal surgery, since abdominal adhesions increase the risk of unintentional viscus perforation. In addition, this approach should only be done in children by an experienced pediatric nephrologist or a nephrologist with a pediatrician in attendance. If a nephrologist places the catheter a surgeon should be on stand-by, in case of complications. The patient should receive preoperative sedation and have nothing to eat or drink at least 12 h prior to the procedure.

All observers and persons in the immediate area, including the patient, should wear surgical masks. Those patients who experience discomfort while completely supine should raise their heads slightly. In conscious patients it may be useful to familiarize them with the Valsalva maneuver. The operator and assistant(s) should "scrub, gown and glove." A "circulating" nurse should be present to assist.

Insertion Technique

Using sterile precautions, a small stab wound (2–3 mm) is made in the midline under local anesthesia, 2–3 cm below the umbilicus. The stab wound should be small so that the abdominal wall holds the catheter firmly and thus minimizes dialysis solution leak. With the stylet in place, the catheter is introduced through the abdominal wall by a short thrust, or preferably with a rotary motion. The operator will recognize the loss of resistance as a "pop" as soon as the peritoneal cavity is entered. While the catheter is being thrust through the abdominal wall its tip is directed towards the coccyx. Because successful perforation of the abdominal wall for introduction of the catheter requires a sensitive "feel" for the pressure applied, prior infusion of 2–3 L of dialysate will distend the abdomen, which in turn will facilitate this maneuver. Some infuse 2 L of dialysis fluid via a small-gauge needle prior to stylet puncture. A cooperative patient can also assist successful perforation by voluntarily tightening the abdominal musculature.

Once the peritoneal cavity has been entered the stylet is withdrawn a few centimeters and the catheter is advanced deep into the pelvis. If the operator encounters resistance while the catheter is being advanced, or if the patient

complains of pain, the advance in this direction should be stopped and another direction tried. If this is still not possible, the operator may infuse 2–3 L of dialysis solution into the peritoneal cavity if this has not been done. This can be via the catheter if the holes in the distal end are within the abdominal cavity. This infusion accomplishes two important objectives: first, it facilitates recognition of the "true" intraperitoneal space; second, dialysis solution in the peritoneal cavity reduces the likelihood of viscus perforation by moving the intra-abdominal contents away from the advancing catheter.

After one or two good in-and-out exchanges, the catheter is firmly secured to the skin with the aid of a metal disc.

Complications

Table 14.4 shows complications of rigid catheter insertion. After catheter implantation, bloody effluent appears after the first exchange in approximately 30% of cases [99, 100]. This bleeding (usually minor) comes from the small vessels in the abdominal wall. After three or four exchanges, bleeding usually stops, unless the procedure has damaged a major vessel or the patient has a bleeding disorder. Pressure applied over the catheter insertion site usually controls minor bleeding. If the bleeding is copious it may obstruct the catheter; in this event it, is a common practice to add 1,000 units of heparin to each liter of dialysate to minimize the risk of obstruction. Intraperitoneal heparin is not absorbed in sufficient quantities to influence systemic coagulation.

Dialysis solution leak is encountered in 14–36% of patients after rigid catheter insertion [99–101]. Frequent manipulation of the catheter to improve drainage increases the risk of dialysis solution leak from the catheter-exit site. Such leaks may also occur when the catheter is not properly secured to the skin. The risk of external leak is higher in elderly or debilitated patients who have lax abdominal walls. The presence of a large intra-abdominal mass, such as a polycystic kidney, may raise the intra-abdominal pressure to high levels and promote dialysis solution leak around the catheter after the standard 2-L volume has been instilled.

Fluid may extravasate into the abdominal wall, particularly in patients who have had a previous abdominal operation or multiple catheter insertions. This complication usually results from tears in the peritoneum or represents an infusion of dialysate into the "potential" space between the layers of abdominal wall. Uncommonly, dialysis fluid may enter the pleural cavity [101–109]. In such cases, peritoneal dialysis is usually discontinued and the patients are switched to hemodialysis. Acute hydrothorax results from either a traumatic or a congenital defect in the diaphragm.

Inadequate drainage is frequent during initial dialysis, and may be due to one or more of the following factors: loss of siphon effect, one-way obstruction, and/or incorrect placement of the catheter. One-way (outflow) catheter obstruction may have multiple causes. Fibrin or blood clots may be trapped in the catheter and block the terminal holes, especially when dialysis is complicated by major hemorrhage or peritonitis. Poor outflow may also reflect extrinsic pressure on the catheter from adjacent organs such as a sigmoid colon full of feces or a distended bladder. Omental wrapping is likely if the catheter is misplaced into the upper abdomen.

Occasionally, accidental penetration of the extraperitoneal space by the catheter may cause poor drainage. In such a situation, continued infusion produces further dissection, and the fluid may become trapped and is no longer available for drainage. Loculation of fluid, another cause of poor drainage, is encountered in patients who have had previous intra-abdominal operations or peritonitis. Such loculation, caused by adhesions, not only diminishes the surface area available for dialysis but may seriously reduce ultrafiltration capacity. The incidence of this complication is low, varying between 0.5 and 1.3% [110–118]. Abdominal distension and even respiratory compromise may develop in some patients with inadequate drainage.

Poor ultrafiltration may leave the patient hypervolemic and on occasions rapid hypertonic exchanges can cause excessive fluid removal leading to hypovolemia and hypotension. Rapid exchanges may also be complicated by sodium sieving leading to hypernatremia [100, 115, 119]. Acute peritoneal dialysis may be complicated by significant protein losses in dialysate ranging from 10 to 20 g/day [118–120].

Table 14.4 Complications of rigid catheter insertion

Bleeding
Dialysis solution leak
Poor drainage
Extraperitoneal space penetration
Viscus perforation
Peritonitis
Abdominal pain
Loss of rigid catheter in the peritoneum

Perforation or laceration of internal organs during bedside insertion of a catheter has been frequently reported. Lacerated or perforated organs include the bowel, bladder, liver, a polycystic kidney, aorta, mesenteric artery, and hernia sac [100, 112, 114, 121–123]. Abdominal distension due to paralytic ileus or bowel obstruction may predispose the patient to bowel perforation. Those who are unconscious, cachectic, or heavily sedated are also at high risk. Clinical evidence of bowel perforation includes sudden, sharp, or severe abdominal pain followed by watery diarrhea, and poor drainage of dialysis solution, which may be cloudy, foul smelling, or mixed with fecal material. Such a situation requires prompt removal of the catheter, and allowing the perforation to seal off completely in about 12–24 h. An exploratory laparotomy may be necessary and surgical consultation should be obtained.

Abdominal pain may be encountered in as many as 56–75% of patients with the first use of the catheter [100, 110, 118]. There are many causes of abdominal pain, but catheter-related pain occurs when it impinges on any of the viscera. Pain may occur during inflow and outflow of dialysis solution and also when the solution is dwelling. Inflow pain is often related to the acidity of the solution, its temperature, the jet effect from a straight catheter, or distension of tissues around the catheter. These complications can be dealt by adding sodium bicarbonate (5-25 mEq/L), warming the solution or adjusting the infusion rate [119]. Outflow pain is due to entrapment of omentum in the catheter during the siphoning action of fluid drainage. Constant pain during dialysis indicates pressure effects on intra-abdominal organs and often produces continuous rectal or low-back pain. This complaint calls for an adjustment in catheter position.

The incidence of peritonitis, when the stylet catheter is used, increase with time the catheter is left in the abdomen [124]. Phu et al [125] studied veno-venous hemofiltration and acute peritoneal dialysis with a rigid catheter for infection-associated acute renal failure. He reported an incidence of 42% of cloudy dialysate with only one patient having confirmed peritonitis. Chitalia et al [120] reported 5 episodes of peritonitis among 87 patients treated for hypercatabolic acute renal failure with either continuous equilibrating peritoneal dialysis or tidal peritoneal dialysis with the abdomen accessed with a stylet catheter.

Loss of a part or the entire rigid catheter has been reported following its manipulation with the trochar in place [113, 114, 126–128]. The distal end of the catheter may be amputated after intra-abdominal kinking of the catheter, followed by manipulation. However, the presence of broken catheters within the abdominal cavity may not cause symptoms or ill-effects. During laparoscopy, broken catheters have been found lying freely in the peritoneal cavity without causing a peritoneal reaction, or have been found walled off by mesentery without an inflammatory reaction. On routine postmortem examination, Stein [128] discovered such a catheter in a patient who had previous peritoneal dialysis. Exploration to retrieve the catheter maybe unnecessary because laparotomy may be more hazardous than leaving the catheter in a severely ill patient. Laparoscopic retrieval may be considered and likely will be tolerated in almost all patients. The incidence of catheter loss into the peritoneal cavity has been greatly reduced since the introduction of a design which incorporates a metal disc with a central hole; this not only allows the catheter to pass through the abdominal wall but also holds the catheter snugly to the skin of the abdominal wall.

Insertion of Soft Catheters

Because of the high frequency of dialysis solution leak, and poor drainage necessitating frequent catheter manipulation and resultant peritonitis with the use of rigid catheters, some centers prefer to insert a single- or double-cuff Tenckhoff catheter for treatment of acute renal failure. Tenckhoff recommended use of a single-cuff catheter for acute cases [1]. For treatment of chronic kidney disease, only soft catheters are used.

Patient Preparation

Acute Dialysis

Patient assessment and preparation before soft catheter implantation for treatment of acute renal failure is the same as that before rigid catheter insertion.

Chronic Dialysis

Patient preparation before catheter implantation for treatment of chronic kidney disease is more elaborate [1, 84, 97, 129, 130]. Immediately prior to surgery, chest and/or abdominal hair should be removed with an electric clipper. Prophylactic antibiotics prior to implantation are recommended.

Abdominal Exit

The belt line of a patient is identified, preferably in the sitting or standing position, with slacks or pants as usually worn [1, 129]. Depending on the size and shape of the abdomen, presence of previous scars, right- or left-handedness, and patient's preference, the tunnel is marked using the stencil (available with swan-neck catheters) in such a way that the exit hole would be created at least 2 cm from the belt line. Skin markings may be made with any good surgical marker.

Women usually wear a belt above the umbilicus; hence stencils are often marked below the belt line in female patients. The catheter should not be subjected to excessive motion with patient activities, and there should not be pressure on the tunnel when the patient bends forward. In obese people, with pendulous abdomens, it is mandatory to insert the catheter above the skin-fold so they can see the exit for its care. Men usually prefer a belt line below the umbilicus and there may not be enough space below the belt line; therefore a stencil is generally marked above the belt line in male patients. The label of the chosen catheter type is written on the belly of the patient. A band with the catheter label is also attached to the patient's left wrist.

Enemas are no longer recommended. Instead, the patient should take a shower if able. Skin markings may require remarking if they become faint after a shower. Antibiotic prophylaxis prior to catheter insertion is recommended and is discussed in a subsequent section of this chapter.

Presternal Exit

Depending on the size of the patient, the abdominal cuff and flange location is marked over the rectus muscle [90]. To secure the catheter-tip position in the true pelvis, but without an excessive pressure on the pelvic peritoneum, the position of the cuff should be above or at the level of the umbilicus in all persons. To determine a preferred position of the deep cuff, a coiled catheter tip is placed on the pubic bone and the cuff position is marked. On the chest, a superficial cuff is marked at the second or third intercostal spaces and the exit 3 cm from the cuff in the presternal or parasternal area. It is preferable not to cross the midline in patients likely to have heart surgery. Care is taken to avoid an exit site too close to bra lines in females. Prophylactic antibiotics, shower, and bowel prep are used in the same way as for abdominal exit.

Catheter Preparation

Immediately before implantation, the catheter is removed from the sterile peel pack and immersed in sterile saline. The porous Dacron® cuffs and Dacron® flange are gently squeezed under saline to remove air [84, 90, 131]. Thoroughly wetted cuffs provide markedly better tissue ingrowth compared to unwetted, air-containing cuffs [84, 90].

Implantation Method

Blind (Tenckhoff Trochar)

At the bedside, a sterile procedure must be strictly followed while inserting the catheter. A 2–3 cm incision is made in the skin at the insertion site (e.g., the midline 2 cm inferior to the umbilicus). This places the site of entry at the linea alba, a point of minimal vascularity and tissue resistance [92]. The lateral margins of either rectus muscle are alternative sites because they are also relatively avascular. It should be remembered that the placement through the belly of the rectus muscle using blind insertion may cause injury to the inferior or superior epigastric artery.

Through the skin incision the wound is deepened to the linea alba with blunt dissection using a curved hemostat. At this time, an "anchoring" suture is inserted in the fascia. The peritoneal cavity is entered with a "priming needle" (a "catheter over a needle," venicath-type needle, or a stylet peritoneal catheter) into the superior aspect of the wound and through the linea alba. One must take care to ensure "intraperitoneal" placement of all hole outlets of the priming device. If the parietal peritoneal membrane is separated from the preperitoneal tissue this will result in "preperitoneal" infusion of dialysis fluid and make impossible any further intraperitoneal infusion of dialysis fluid by this method. Furthermore, the expansion of the preperitoneal "pocket" is extremely painful. When dialysis solution infusion produces pain, the operator should suspect preperitoneal instillation; however, the heavily sedated or anesthetized patient may not be able to voice an objection. At this time poor dialysis solution inflow may also indicate that hole outlets are lodged in a preperitoneal position, although one might also anticipate a moderate restriction of flow in any case, given the relatively small lumen of the access catheter.

Following sterile connection of the administration tubing to the priming device, 2–3 L of dialysis solution are infused into the peritoneal cavity, until the patient feels distended. While dialysate is being instilled to the desired volume, the Tenckhoff catheter should be "prepared" by wetting it with a small volume of normal saline. Air from the cuffs is removed by squeezing. A wetted stiffening stylet is inserted into the catheter, thus straightening and "stiffening" it to permit introduction of the catheter into the Tenckhoff trochar, and beyond it into its correct intra-abdominal position.

It is useful to predilate the linea alba with a smaller trochar or dilator rather than a needle, thereby facilitating introduction of the larger Tenckhoff trochar. With firm but gentle pressure, and a twisting action, the trochar with its pointed stylet in place (Fig. 14.12) is pushed into the peritoneal cavity via the small perforation. Immediately after the resistance ceases (indicating entrance into the peritoneal cavity), the obturator is removed. The true intraperitoneal placement should be recognized by the "welling-up" of dialysis solution into the barrel of the trochar. If the operator has instilled enough dialysis solution during the priming procedure, he/she should insert the trochar until its wider portion comes to rest on the linea alba. This portion should not enter the peritoneal cavity, thus keeping the perforation at the desired diameter. This larger barrel is designed not only to accept the Tenckhoff catheter, but it also allows for the passage of the Dacron® cuffs.

The catheter is threaded on a stiffening stylet. About 1 cm of catheter is left beyond the tip of the stylet to protect the intestine. Proper placement of the catheter in the pelvis will greatly facilitate siphon drainage. During this phase of insertion, certain details, although they may seem trivial, if not attended to with care may produce unfavorable results. For example, as the catheter is introduced into the trochar on its way to the abdominal cavity, the tip should be passed smoothly beyond the trochar. Careful, gentle, and angular movement of the trochar and stiffened catheter (adjusting its intra-abdominal position and relationship to abdominal contents) may be needed to achieve easy passage of the catheter deep into pelvis.

Once the catheter has completed its "internal" course, the detachable trochar barrel should be removed, leaving the split side-pieces *in situ* for easier manipulation until the final positioning is satisfactory. At this point the stiffening stylet should be removed while the operator holds the catheter firmly in place. Once the desired depth of placement is achieved, the remaining catheter is "fed" into the peritoneal cavity while slowly withdrawing the stiffening stylet until the preperitoneal (inner or deep) Dacron® cuff comes to rest on the linea alba. Then the trochar is separated into its two longitudinal sections and withdrawn, leaving the catheter cuff in proper position. The ideal location for the internal cuff is at the preperitoneal level. However, if the catheter is intended for a short-term use until the patient recovers from an acute renal failure event, the location of deep cuff at the preperitoneal level is not as critical as in the case of long-term use. The Dacron® cuff must not be left positioned in the peritoneal cavity.

Catheter patency is tested in the same manner described in the surgical procedure. When the function is deemed satisfactory the catheter is secured in place to the linea alba with an anchoring suture before preparing for the creation of the subcutaneous tunnel towards the proposed exit site.

After choosing the catheter exit site, a stab wound (not an incision) is made using a blade, taking care to penetrate only the skin. The opening should be just the size of the catheter. Choose a site that will permit the creation of a tunnel of an appropriate length and shape of the catheter. A subcutaneous tunnel is created using a malleable uterine sound or the Faller trochar, being careful to manipulate the catheter gently. For the swan-neck Tenckhoff catheter, the tunnel must follow the skin marking made prior to the insertion. The outer cuff should be positioned approximately 2 cm from the skin exit. The recommended method for tunnel creation for the swan-neck Tenckhoff catheter is to make a superior subcutaneous pocket as described for surgical insertion (see below) and penetrate the exit with the piercing trochar. No sutures are used at the exit site. The titanium connector is then inserted into the end of the catheter. The skin of the insertion wound is sutured, and appropriate surgical dressings applied. Dressings are applied for at least 1 week while leaving an accessible length of catheter to permit the catheter to be handled without disturbing the dressings.

Peritoneoscopic

The use of peritoneoscopy for peritoneal catheter placement was developed by Ash at Lafayette, Indiana [92, 132, 133]. Tenckhoff and swan-neck Tenckhoff (straight and coiled) catheters may be implanted with this technique. Like blind insertion, it is performed through a single abdominal puncture. No fluid is instilled before insertion of the cannula and the trochar into the abdomen (through the medial or lateral border of the rectus). The trochar is removed, and the scope is inserted through the cannula. After assuring the intraperitoneal location by observing motion of glistening surfaces, the scope is removed and 600 cm^3 of air placed in the peritoneal cavity with the patient in the Trendelenburg position. The scope is reinserted and, during continuous observation, scope, Quill, and cannula are advanced into the clearest space and most open direction between the parietal and visceral peritoneum. Following this, the scope and

cannula are removed and the Quill catheter guide is left in place. The next step in the procedure involves the dilation of the Quill and musculature to approximately 0.5 cm. This is large enough to allow the catheter to be easily inserted through the rectus muscle and for the cuff to be advanced into the muscle. The catheter follows the path previously viewed by the peritoneoscope as directed by the Quill guide. As long as the Quill guide stays in position the catheter will advance into the desired place. The catheter is advanced on a stylet and is actually "dilating" its way until the cuff arrives and stops at the muscular layer. Placing the cuff in the musculature can be accomplished using a pair of hemostats advancing the cuff within the Quill guide. Thereafter, the Quill guide is removed, hydraulic function of the catheter checked, the tunnel made subcutaneously using a trochar, and the catheter brought out through the exit site – similar to the surgical insertion technique.

Excellent results with this technique were reported by its originator. Copley et al. [133] have reported their 1,183 patient-months experience with 135 double-cuff swan-neck coiled catheters inserted peritoneoscopically over a 40-month period. Complications were few and the overall 40-month survival probability was 62%. Nine catheters were removed because of obstruction and 16 for catheter-related infections.

Seldinger (Guidewire) and Peel-Away Sheath

This technique may be used for insertion of straight and coiled Tenckhoff catheters as well as of swan-neck Tenckhoff straight and coiled catheters. The preinsertion patient preparation is similar to the preparation described for rigid catheter insertion. The procedure may be done with [96] or without [93, 94, 134] prefilling the abdomen with dialysis solution. Prefilling of the abdomen is accomplished through a temporary peritoneal catheter.

In the "dry" method a 2-cm incision is made and the "dry" abdomen is entered with an 18-gauge needle (e.g., the Verres needle as used for laparoscopy). A guidewire is passed through the needle and the needle is withdrawn. The introducer (dilator) with sheath is passed over the guidewire. After the dilator-sheath is inserted, the dilator is removed, leaving the sheath in place. The Tenckhoff or swan-neck Tenckhoff catheter, stiffened by a partially inserted blunt stiffening stylet, is then directed down into the sheath [96]. The catheter may also be introduced without the stiff stylet [78, 134]. As the cuff advances, the sheath is split by pulling tabs on its opposing sides. Splitting the sheath allows the cuff to advance to a position within the abdominal wall. By further splitting and retraction, the sheath is removed from its position around the catheter. A subcutaneous tunnel is then created as in surgical placement. With this technique, the incidence of early leak is very low. However, the risk of viscus perforation and improper placement of catheter are the drawbacks of this technique.

Surgical (by Dissection)

Surgeons perform majority of catheter implantations; and 72% of catheter implantations are performed by surgical dissection [77]. Dissective placement is mandatory for catheters with stabilizing devices (e.g., flanges) at the parietal surfaces (Toronto Western Hospital, swan-neck Missouri abdominal, and swan-neck presternal). The paramedian approach through the rectus muscle, currently used in our center, will be described [84].

The surgical placement can be done either using a general anesthetic or using conscious sedation and local anesthesia. The decision depends on both surgeon and patient preference and somewhat on accepted local practice. Because of the long tunnel for the presternal catheter, our practice has been to use a general anesthetic to ensure patient comfort.

The surgical preparation of the abdominal wall consists of a scrub with Betadine soap, pat-drying, and painting with Betadine paint solution. Alternatively, DuraPrep, an iodine containing preparation, can also be used. It aids in adhering the sterile transparent surgical drape. In patients with iodine sensitivity, an alternative prep should be used. Skin markings are often very faint after surgical preparation and require remarking with a sterile surgical pen. Finally, the abdomen is covered with a sterile, iodine impregnated transparent surgical drape. The skin and surrounding tissues of the incision sites and tunnel are anesthetized with 1% lidocaine or 0.25% Marcaine (bupivicaine).

A 3–4 cm transverse incision is made through the skin and the subcutaneous tissue. Perfect hemostasis, preferably using electrocautery, is mandatory. The anterior rectus sheath is exposed and may be infiltrated with 1% lidocaine. A transverse incision is made in the anterior rectus sheath (Fig. 14.25). The rectus muscle fibers are separated bluntly in the direction of the fibers down to the posterior rectus sheath. Self-retaining retractors are helpful to hold muscle fibers away from the operative field. The sheath posterior rectus peritoneum may be infiltrated with 1% lidocaine. A 5-mm incision, reaching the peritoneal cavity, is made with a scalpel and stretched slightly (Fig. 14.26). The edges are grasped and elevated creating a pneumoperitoneum. A purse-string nonabsorbable suture of 2-O monofilament is then placed through in the posterior rectus sheath, transversalis fascia, and the peritoneum under direct vision.

The catheter is threaded on a long, blunt stiffening catheter guide. About 1 cm of catheter is left beyond the tip of the stylet to protect the intestine. The edges of the opening are lifted. The catheter is inserted through the opening and

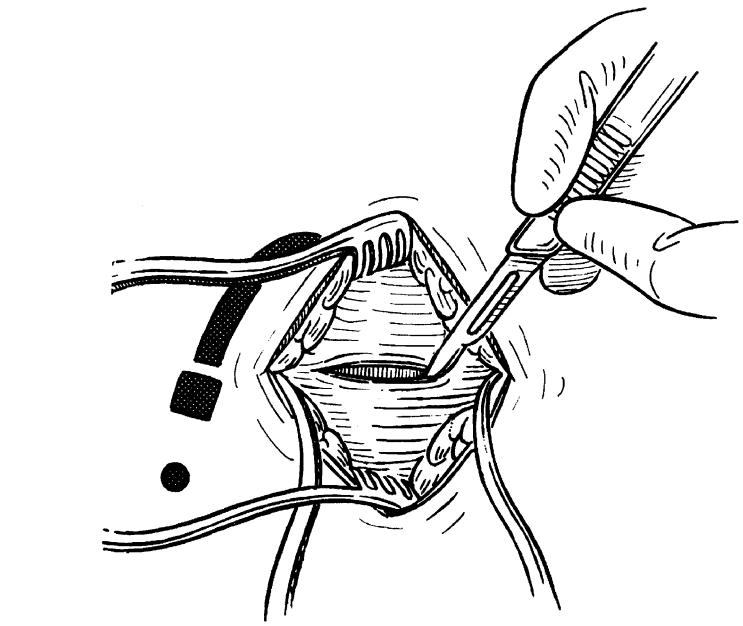

Fig. 14.25 An incision through the anterior rectus sheath

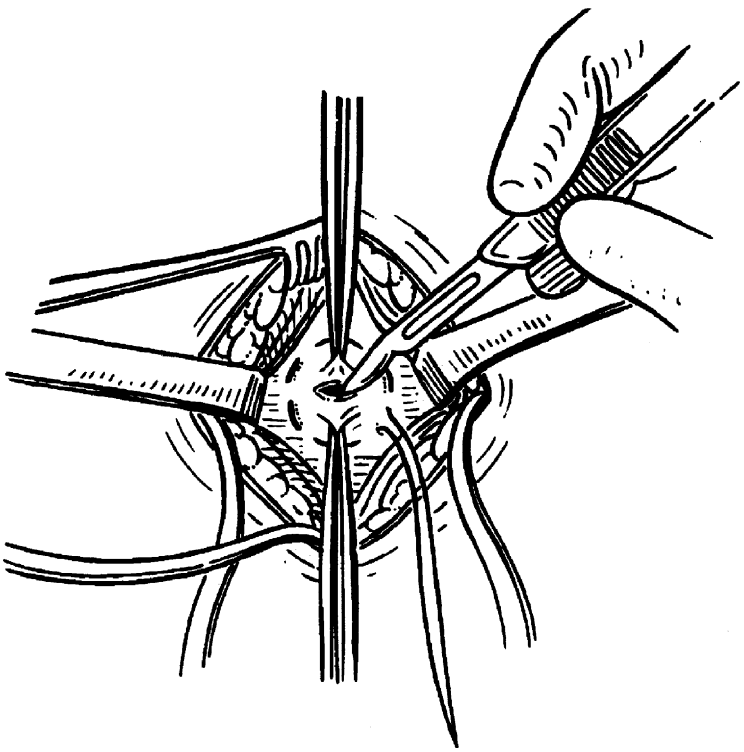

Fig. 14.26 The posterior rectus sheath has been exposed, a purse-string suture has been made, and a 5-mm incision reaching the peritoneal cavity is being created with a scalpel

introduced into the opposite deep pelvis if there is no resistance. If awake, the patient may feel some pressure on the bladder or rectum. When the catheter with catheter guide is about half to three-quarters inserted, the catheter guide is removed and the catheter continues to be directed into the pelvis.

Using a combination of retraction on the peritoneal edge and pushing, the bead is introduced into the peritoneal cavity. The flange is placed flat on the posterior rectus sheath and the purse-string suture is tied securely between the bead and the flange (Fig. 14.27). The stripe must be positioned anteriorly and the flange is anchored with at least two 2-O monofilament, nonabsorbable sutures into the posterior rectus sheath at the 6 and 12 o'clock positions (Fig. 14.28). The self-retaining retractors are removed and the deep or internal cuff is buried among the muscle fibers. A small stab wound is made in the anterior rectus sheath above the transverse incision. The catheter is grasped with a right-angled hemostat and pulled through the stab incision (Fig. 14.29). The stripe is positioned anteriorly. The

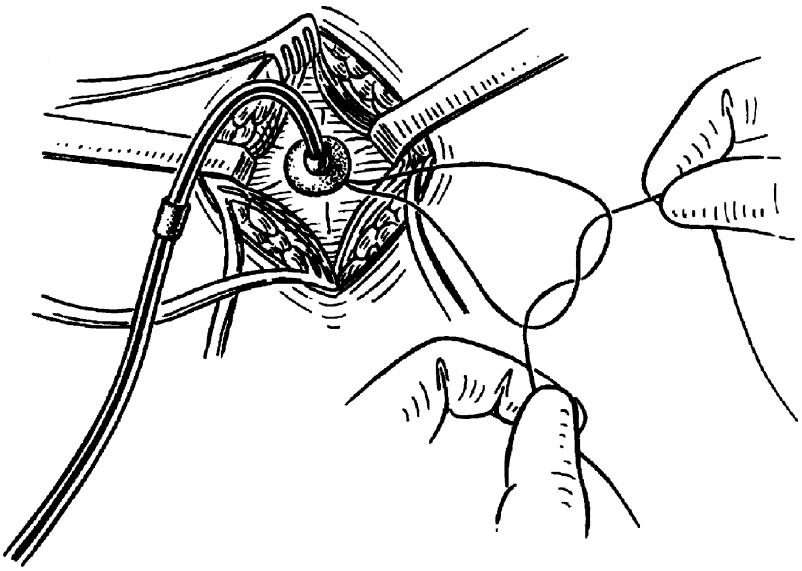

Fig. 14.27 A purse-string suture of peritoneum and rectus fascia is tied securely between the bead and the flange

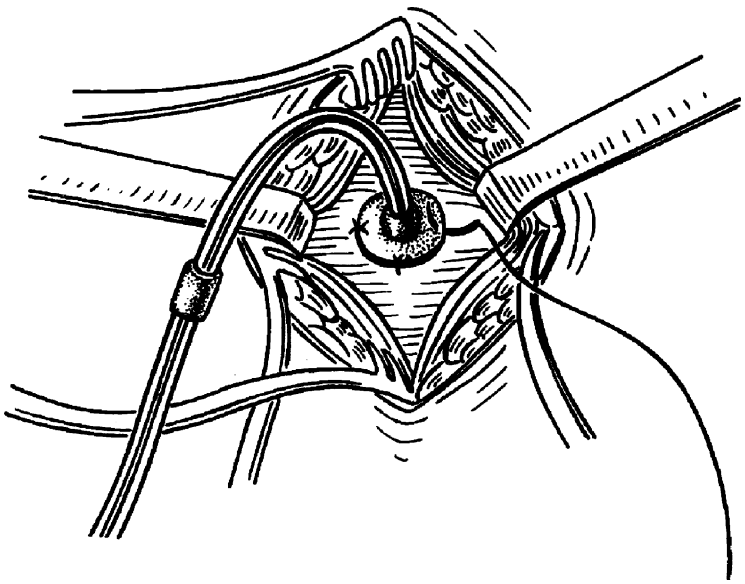

Fig. 14.28 The flange is anchored with four 2-O monofilament, nonabsorbable sutures into the posterior rectus sheath at the 6, 9, 12, and 3 o'clock positions

remaining procedure differs for the swan-neck abdominal Missouri and the swan-neck presternal catheter. The relationship of the catheter to the tissue structures of the abdominal wall is shown in Fig. 14.30.

Swan-Neck Abdominal Missouri

A superior subcutaneous pocket is made to the level of skin marking to accommodate the bent portion of the catheter and the external cuff (Fig. 14.31). The catheter tunnel extending from the cuff to the skin exit should have a diameter close to that of catheter tubing. Thus, the last portion of the tunnel (from external cuff to the exit) should be made with a piercing trochar, e.g., the Faller trochar (Covidien, Mansfield, MA 02048, USA) or a 3/16-inch (4.76 mm, F15) trochar for Hemovac system (Zimmer Mfg. Co., St. Louis, Missouri, USA) or the trochar for a 19 Blake drain (Ethicon, A Johnson & Johnson Company, Somerville, New Jersey) with an external diameter similar to that of the catheter tubing [84, 90, 97, 135]. A trochar is attached and carefully passed through the pocket and the external exit indicated by the stencil mark (Fig. 14.32). The bent portion of the catheter is positioned carefully in the subcutaneous pocket. Care is taken to keep the stripe facing frontward. The external cuff is positioned 2–3 cm from the skin exit. *No sutures are placed at the exit site to secure the catheter*. A titanium adapter is attached to the catheter and an extension tube is connected to the adapter [84]. A 1-L bag of sterile saline or dialysis solution containing 1,000 units of heparin is spiked via the extension tubing and the solution is infused. The fluid should all run in 5 min. The wound is checked for

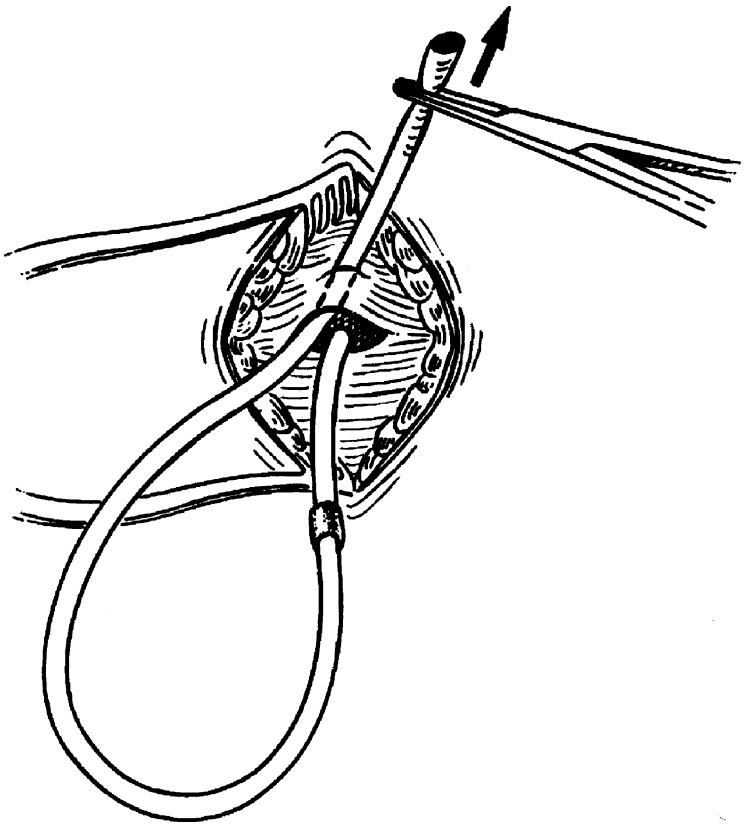

Fig. 14.29 The catheter is passed through the incision centered above the transverse incision

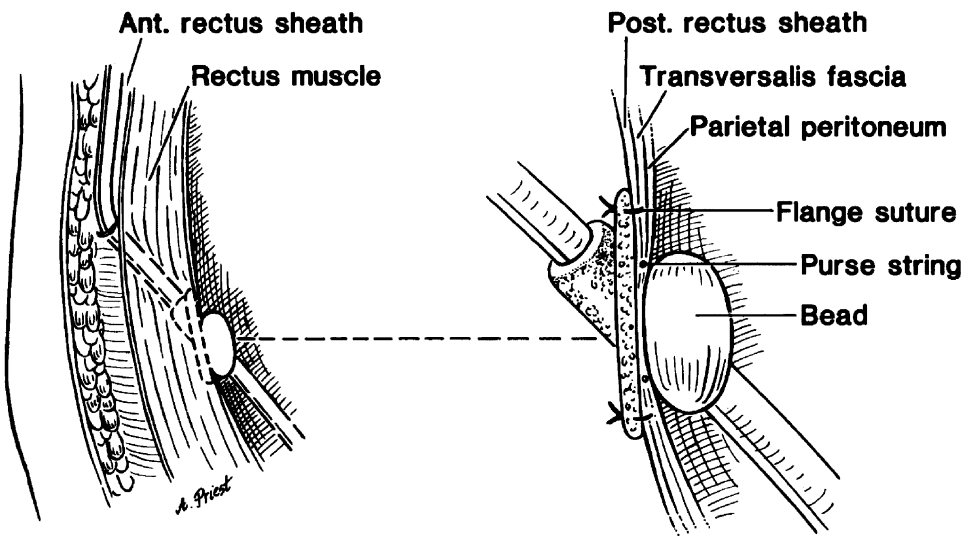

Fig. 14.30 The relationship of the catheter to the tissue structures of the abdominal wall. The bead is in the peritoneal cavity, the flange is flat on the posterior rectus sheath, the purse-string is between the bead and the flange, the deep cuff is in the rectus muscle

leaks and inspected for hemostasis. The transverse incision in the anterior rectus sheath is closed with a 2-O monofilament nonabsorbable suture. After infusing the dialysis fluid, the bag should be lowered to the floor and at least 200 mL of solution should drain within 1 min. If good flow is obtained the wound is irrigated and the skin incision is closed with absorbable subcutaneous and subcuticular sutures. The catheter is never sutured at the exit site. The position of the catheter is confirmed while still in the operating room on an abdominal X-ray. The incision is covered with Steri-strips, several layers of high-absorbency gauze dressings, and secured with Tegaderm®, which also immobilizes the catheter. The dressing is to be left in place for a week. In cases with bleeding, fever, or large drainage from the incision or exit the dressing should be changed earlier.

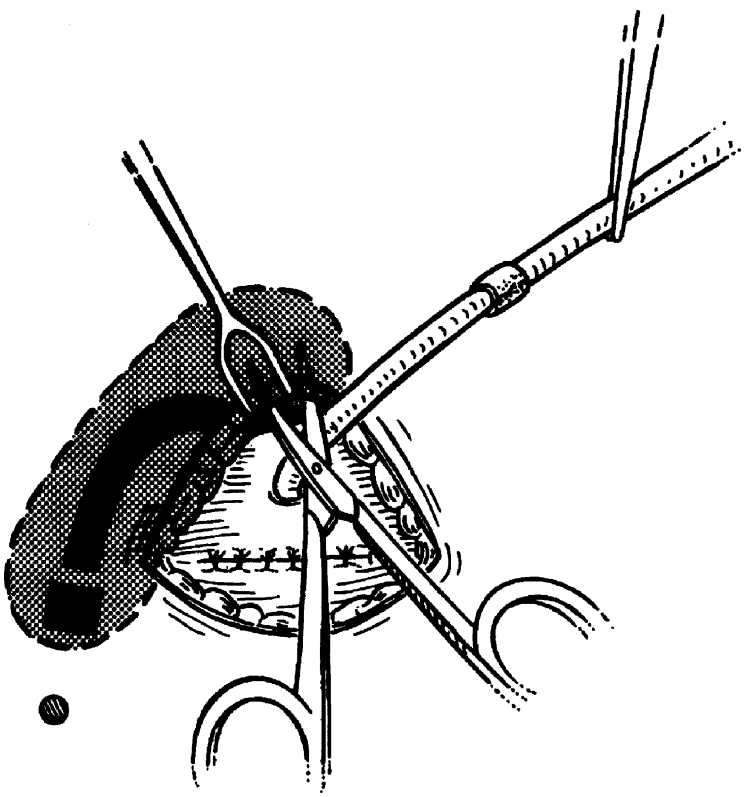

Fig. 14.31 A subcutaneous pocket is made to the level of skin marking to accommodate the bent portion of the catheter and the external cuff

Swan-Neck Presternal

A vertical 3–4 cm incision is made in the parasternal area (Fig. 14.33) at the level of the second and third rib at the stencil site [90]. Using a combination of sharp and blunt dissection, a superior subcutaneous pocket is made on both sides of the incision to accommodate the bent section of the upper (chest) tube of the catheter. The pocket is dissected enough to accommodate the middle and superficial cuffs (Fig. 14.34). Careful hemostasis is essential.

A Scanlan or Bard tunneler is used to create a tunnel extending from the abdominal incision to the presternal or parasternal area to permit joining the upper and lower tube. The tunneler, developed for tunneling vascular grafts, consists of an outside disposable or reusable sheath, blunt tip, and an inner rod with a handle at one end and a spring clamp or suture hole at the other. The metal rod serves to stiffen the tunneler as it is pushed through the subcutaneous tissue and the spring clamp or suture hole is used to secure the catheter and pull it through the sheath. Keeping the stripe in front as a guide, the abdominal end of the presternal portion of the catheter is pulled caudally through the sheath, and the sheath is removed by pulling in the caudal direction (Fig. 14.35).

The middle cuff of the upper catheter is carefully placed on the stencil mark. When the catheter is appropriately positioned the lengths of the two parts of the catheter are measured and the catheters are trimmed to an appropriate length. Sufficient length on each portion should be left to facilitate connection. A titanium connector is inserted into the presternal end and then the connector is inserted into the abdominal end of the catheter. The stripes on both tubes are positioned facing up. A 1-O Ethibond® tie is now placed and tied on both tubes over the appropriate groove of the titanium connector. The two sutures are tied together (Fig. 14.36) and the titanium connector is positioned in the subcutaneous tissue approximately 5–8 cm superior to the abdominal incision.

A trochar of the same size as the catheter tubing is attached and carefully passed through the pocket and the external exit site indicated by the stencil mark (Fig. 14.37). The stripe should be facing front. The trochar is disconnected. The bent portion of the catheter is carefully positioned in the subcutaneous pocket. The titanium Luer lock connector is attached. No sutures are placed at the exit site to secure the catheter. One liter of normal saline is infused through the infusion set and drained immediately. Outflow should be approximately 200 mL in 1 min. The wounds are checked for leaks, irrigated, and inspected for hemostasis. The transverse incision in the anterior rectus sheath is closed with a 2-O monofilament nonabsorbable suture. Skin incisions are again inspected for hemostasis. Any bleeding vessels are controlled with electrocautery and the incisions are closed with absorbable subcutaneous and subcuticular sutures. The operative site is covered with several layers of high-absorbency gauze dressings and secured with Tegaderm®, which also immobilizes the catheter. The dressing is to be left in place for a week.

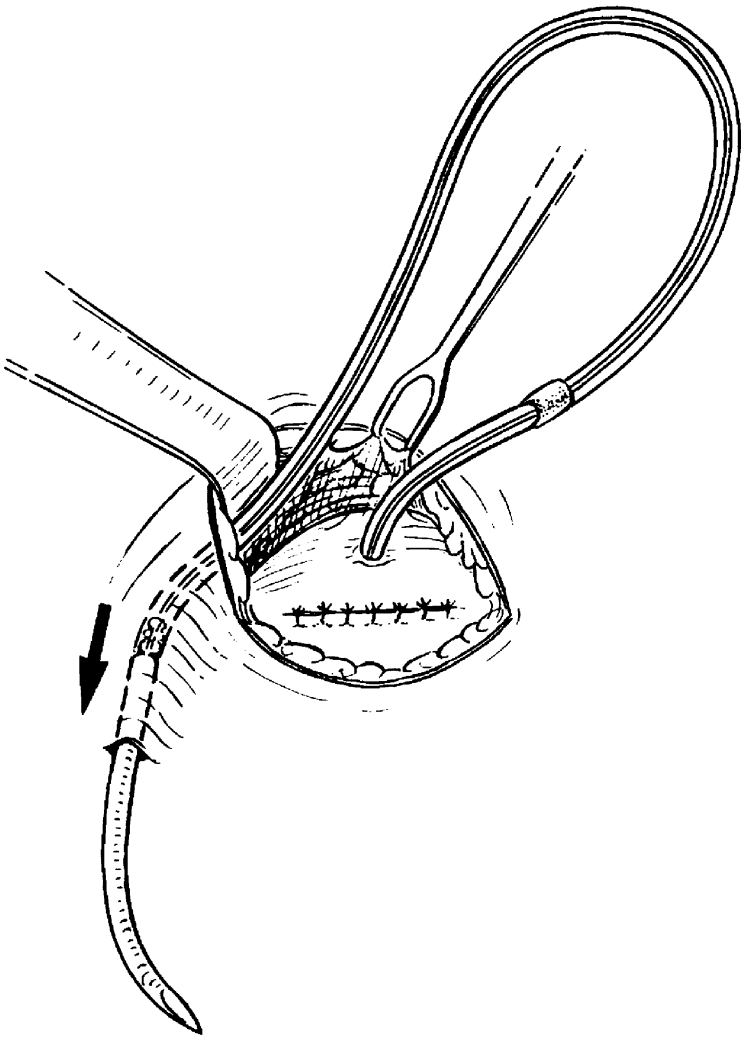

Fig. 14.32 A trochar is attached and passed through the pocket and the external exit indicated by the stencil mark. The piercing trochar is the same diameter as the tubing

Tenckhoff

This technique is similar to that of the swan-neck Missouri abdominal catheter; however, because there is no inter-cuff bend, the anterior stripe position is not essential and the subcutaneous pocket is not needed. Instead a straight upward or laterally curved tunnel is made with the help of a piercing trochar. The subcutaneous cuff is positioned 2–3 cm from the exit. As there is no flange, the deep cuff is positioned longitudinally, parallel to the rectus muscle fibers, on the posterior rectus fascia.

Swan-Neck Tenckhoff

A combination of techniques for the Tenckhoff and swan-neck Missouri abdominal catheters is used. The deep (inner cuff) is positioned longitudinally on the posterior rectus sheath with the stripe facing front. As explained earlier, in an earlier section entitled "Radiopaque Stripe," if the left catheter is used for the right tunnel and vice-versa, the stripe must be positioned posteriorly. The subcutaneous pocket is made in the same way as with swan-neck Missouri catheter.

Moncrief–Popovich Technique

This is an operative technique characterized by subcutaneous embedding of the external limb of the dialysis catheter at the time of implantation. The buried catheter is exteriorized after 3–5 weeks or when indicated to initiate dialysis [53]. This technique has been characterized as the "AV fistula of peritoneal dialysis" [136]. The advance placement of the catheter and the subcutaneous placement allow it to heal in a sterile environment. When exteriorized, patency is easily

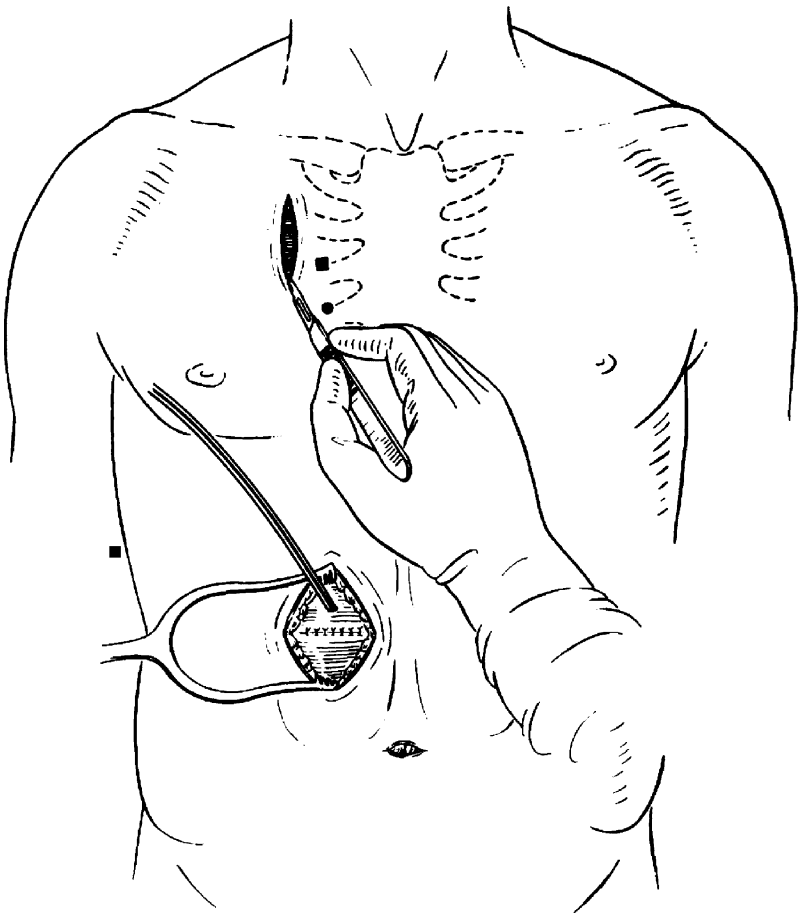

Fig. 14.33 Vertical incision in the parasternal area

established by irrigation or occasional use of a thrombolytic and only an occasional catheter needs surgical intervention [137]. Using swan-neck catheters with this technique, Moncrief and co-workers [53, 138] reported a significant reduction in pericatheter infections, exit-site infections and peritonitis but others have found no difference in peritonitis rate [139]. Some authors have noted an increase in perioperative complications such as seromas and subcutaneous hematomas [140]. A video [141] demonstrating the technique is available from the Austin Biomedical Research Institute, Austin, Texas, USA.

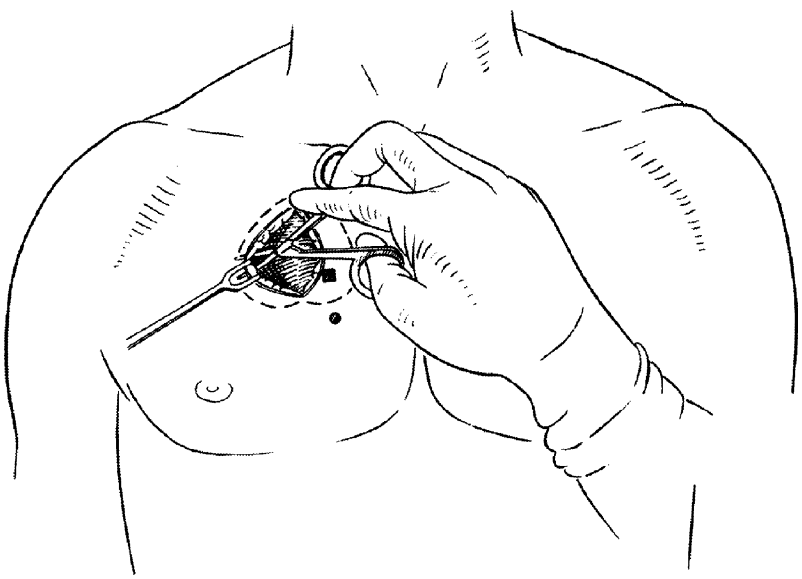

Fig. 14.34 Two small subcutaneous pockets are made on both sides of the chest incision to accommodate the bent section of the upper tube of the catheter

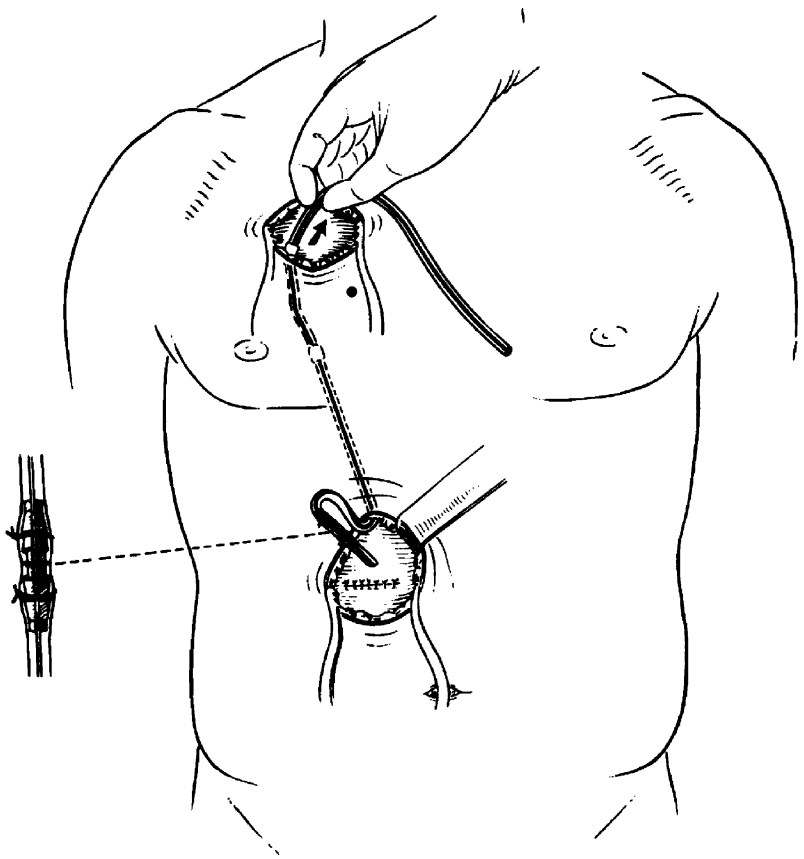

Fig. 14.35 A tunnel between the abdominal and chest incisions is made with a Scanlan tunneler, the upper tube is pulled caudally through the sheath

Laparoscopic Technique

Since the early 1990 s, there has been a significant change in the surgical approach to the abdomen. Starting in the early 1990 s laparoscopic approaches for all varieties of abdominal conditions began to replace traditional techniques. Naturally, these minimally invasive techniques were applied to placement of abdominal catheters. For almost two decades there has been a significant and increasing number of publications showing the efficacy and utility of using minimally invasive techniques for placing continuous ambulatory peritoneal dialysis catheters and managing their complications [142–153].

Nijhuis et al. [153] and Crabtree [154] have described a laparoscopic technique using a two-puncture technique for the placement of a continuous ambulatory peritoneal dialysis catheter. A pneumoperitoneum is created using a combination 4.5 mm trochar/Veress needle introduced into the contralateral upper abdominal quadrant. Crabtree and Fishman [154] use nitrous oxide to create a pneumoperitoneum allowing the procedure to be done under local anesthetic. A 3.5-mm zero-degree laparoscope is inserted through this trochar and an abdominal exploration is carried out. A 1.5–2 cm long incision is made in a perimedian site on the ipsilateral side of the abdomen. The subcutaneous tissues are dissected and the anterior rectus sheath is transversely incised. Using blunt dissection a pathway is created between and beneath the muscle. A 10-mm trochar is passed under visual control above the transversalis fascia and peritoneum. The trochar is then introduced into the abdominal cavity under direct vision and the peritoneal catheter is positioned in the pouch of Douglas. The cannula is removed and the catheter withdrawn so that the deep cuff is situated within the rectus muscle. The incisions are closed in standard fashion. This technique allows visual control and correct placement of the catheter in the pelvis. By placing the catheter in this fashion the authors have reduced their catheter-related problems and established a functioning catheter in about three-quarters of the cases.

The laparoscope can also be used for other purposes in patients on chronic peritoneal dialysis [155–159]. Specifically, catheter malposition and intra-abdominal adhesions are two conditions in which the laparoscope may be of considerable help. Entry to the abdominal cavity is established by direct cut down or Veress needle puncture in one of the upper abdominal quadrants. If an open technique is used, a purse-string suture is placed in the peritoneum and posterior fascia so that a snug fit around the trochar will be obtained. The trochar is inserted under direct vision with both techniques and a pneumoperitoneum is created by connecting to a CO_2 source. If the Veress needle approach is

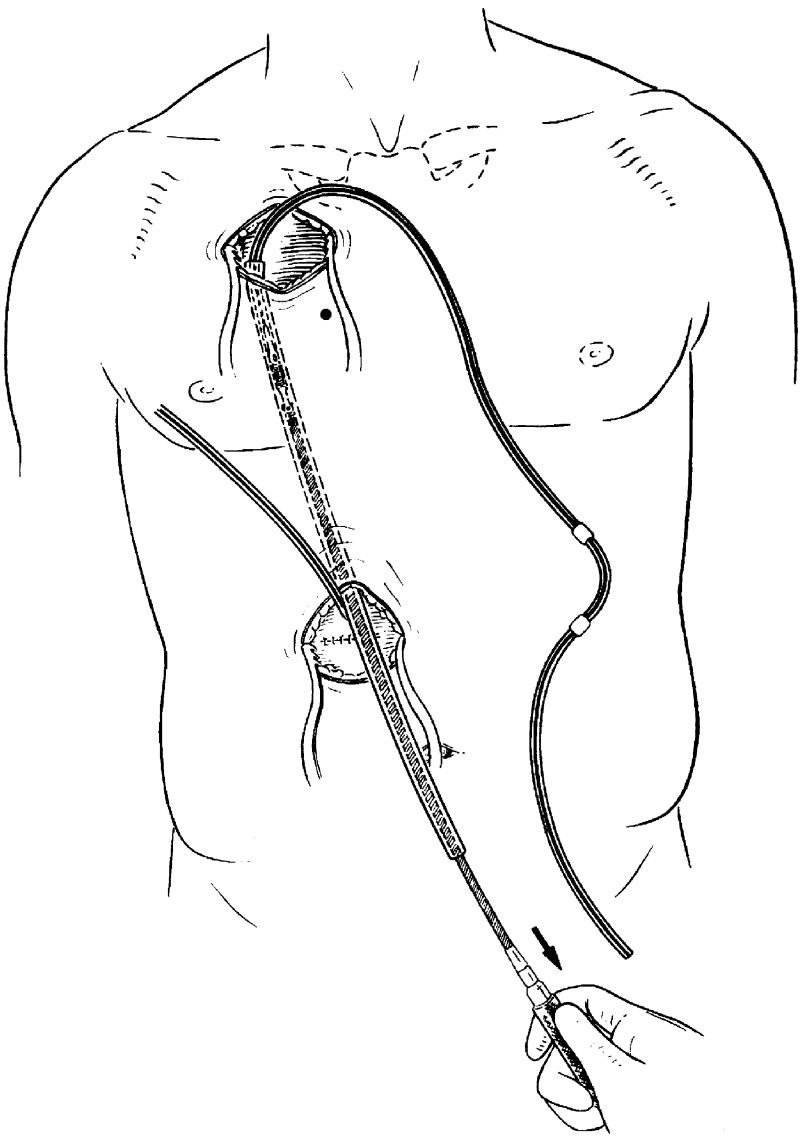

Fig. 14.36 Both parts of the catheter are tied over the titanium connector and the catheter is pulled cephalad

chosen, a pneumoperitoneum is first created then entry to the abdomen is made under direct vision using a Visiport Plus (Tyco Healthcare Norwalk, Connecticut, USA). Visual inspection will then demonstrate the problem of either adhesions and/or catheter malposition. Clinical judgment is used to place a second port, which is done under direct vision. Using grasping forceps or an electrocautery hook or scissors, the catheter can be repositioned, or the adhesions may be taken down. These techniques are of great help in salvaging an otherwise unworkable catheter.

Immediate and Early Postoperative Care

In the operating room, the position of the catheter is checked by a plain X-ray of the abdomen. Absence of catheter kink in the tunnel and the catheter-tip location in the true pelvis usually predict excellent catheter function. A liter of saline should be instilled in the peritoneal cavity and drained to confirm function prior to closing the incisions. Appropriate dressing of the exit site is placed in the operating room.

Postoperatively, we recommend performing exchanges until the dialysate return is clear. These may be done manually or using a cycler. One thousand units of heparin are added to each liter of dialysis solution. One-half or 1-L volumes of dialysis solutions are used for these exchanges. In spite of clear dialysate in the first postimplantation washout, the dialysate is usually blood-tinged in these exchanges. Once the dialysate returned is clear, the catheter is capped until peritoneal dialysis is initiated. There is no consensus whether a peritoneal washing should be performed

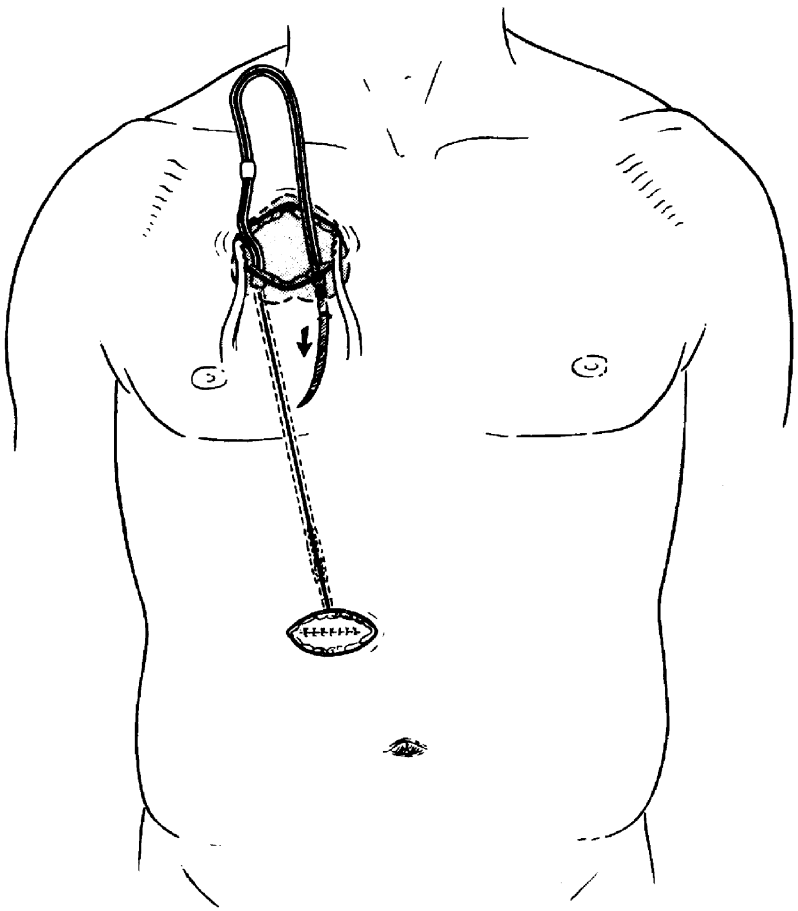

Fig. 14.37 A trochar of the same size as the catheter tubing is attached and carefully passed through the pocket, and the external exit is indicated by the stencil mark

once a week during the break-in period. The Moncrief technique of catheter implantation, leaving the external catheter buried until later exteriorization has not shown an increased rate of catheter obstruction.

Peritoneal dialysis should preferably be delayed for 2 weeks after implantation to allow for good healing and to prevent leaks [160]. If dialysis is required immediately, the options are to perform hemodialysis in the interim or to use low volume exchanges on peritoneal dialysis in the supine position. We do not commence peritoneal dialysis in the vertical position sooner than 14 days post implantation; thus, continuous ambulatory peritoneal dialysis (CAPD) or a last bag continuous cycling peritoneal dialysis (CCPD) are not used for 14 days.

Factors Influencing Catheter Complications

The common complications of peritoneal dialysis catheters include exit/tunnel infection; external cuff extrusion; obstruction, which is usually a sequel of catheter-tip migration out of the true pelvis with subsequent omental wrapping or tip entrapment in peritoneal adhesions; dialysate leaks; peritonitis; and infusion or pressure pain (Table 14.5). This section of the chapter will describe factors that influence these complications. A video illustrating these factors is available [97].

Table 14.5 Catheter-related common complications

Exit/tunnel infection	Pericatheter leak
External cuff extrusion	Peritonitis
Catheter obstruction	Infusion or pressure pain

Tissue Reaction to a Foreign Body Penetrating Skin

The tissue reaction begins immediately after a break in the integument occurs. Bleeding from capillaries and body fluids forms a coagulum of a hydrophilic fibrin–fibronectin gel and cellular debris. Various cytokines coordinate the subsequent entry of inflammatory cells and fibroblasts and the formation of new blood vessels [161]. Polymorphonuclear leukocytes phagocytose local bacteria and, together with the coagulum, form a scab. The polyester cuff also fills with clotted blood. Gradually, neutrophils, macrophages, fibroblasts, and new capillaries penetrate between the polyester fibers. Macrophages coalesce into giant cells and completely or partially surround the polyester fibers. Fibroblasts produce collagen fibers, which intertwine with the polyester fibers. The formation of the strong fibrous tissue is completed after approximately 6 weeks. Healing of the sinus starts beneath the scab with the production of granulation tissue composed of new vessels and fibroblasts. A mature granulation tissue is formed when neutrophils are replaced with mononuclear leukocytes, and fibroblasts lay down collagen fibers. Upon this tissue, there is a peripheral ingrowth of new epidermal cells.

Epidermal cells spread over the granulation tissue beneath the scab. Based on animal experiments it has been widely accepted that epithelial cells spread over granulation tissue until they meet epithelial cells from the opposite "shore" or until they encounter dense collagen fibers [162–171]. Winter [165] postulated that, in naturally occurring percutaneous organs such as teeth, the inhibition of epithelial migration is achieved by a periodontal membrane, which consists of bundles of collagen fibers embedded in the cementum of the tooth. In his view, other situations in which epidermal cell migration is inhibited include macroporous implants and skin autographs. Finally, he theorized that the basement membrane, a collagenous structure, also inhibits basal cell invasion of the dermis. The hypothesis that collagen fibers play a paramount role in inhibiting epithelial cell spreading led to the development of several devices of porous material to encourage dermal ingrowth and to prevent epithelialization of the tunnel ("marsupialization") [131, 167, 171, 172]. It has been suggested that the epithelium adjacent to a silicone catheter tends to migrate towards and beyond the subcutaneous cuff, creating a sinus between the tubing and the skin that is prone to bacterial colonization with subsequent infection [163].

The development of an epithelialized tract is well supported in animal models [60, 167, 170, 172] and in our previous reviews we cited these data as relevant in human peritoneal catheter sinus tracts [135, 173, 174]. However; our observations of catheter tunnels removed from patients showed that in almost all human peritoneal catheter tunnels the epithelium does not reach to the cuff, but stops a few millimeters from the exit in the sinus tract [175]. These observations lead us to believe that granulation tissue *per se* can also inhibit epidermal cell spreading. This observation also has an important influence on catheter design and implantation, particularly the material for the superficial cuff and its distance from the exit.

In humans, unlike experimental animals, the spreading of epidermis is slow. This discrepancy should not be surprising because the epidermal turnover rate in such animals is about six to seven times faster than in humans [176]. We found that in fast-healing catheter exits in humans the epidermis starts entering into the sinus after 2–3 weeks; in slow-healing exits the epidermis starts entering into the sinus after 4–6 weeks [69]. The healing process is complete after about 4–8 weeks, when the epidermis covers approximately half of a visible sinus tract with the remaining half covered with granulation tissue [69].

Tunnel Morphology after Healing Process Is Completed

A detailed description of peritoneal catheter tunnel morphology has been published elsewhere [175]. A well-healed tunnel of a double-cuff swan-neck Missouri catheter removed electively (Fig. 14.38) showed four segments: tissue ingrown to the flange and internal cuff, tissue surrounding the inter-cuff segment, tissue ingrown into the external cuff and the sinus tract. The most external part (0.5–1 cm) of the sinus tract and the skin surrounding the skin exit of the tunnel constitute the exit site. In the majority of humans the epidermal cells penetrate only a few millimeters from the skin exit and may reach the cuff located less than 15 mm from the exit [175, 177]. Although unusual, a single instance of keratinized epithelium penetration all the way to a cuff located 45 mm from the exit has been reported [178]. Close to the exit, the surface of the sinus tract is covered with wrinkled epidermis, containing all layers of epidermis including a horny layer. Deeper in the sinus, the epidermis loses the horny layer and becomes similar to the mucosal epithelium; hence the surface becomes glistening and white. The rest of the sinus tract is covered with the granulation tissue that is yellowish in appearance. A thick layer of collagen fibers surrounds the sinus. The granulation tissue contains numerous multinucleated giant cells, capillaries, cellular infiltrate composed mostly of mononuclear cells, and scant collagen fibers. The collagen fibers do not attach to the smooth surface of the silicone rubber, the material from which most peritoneal dialysis catheters are made.

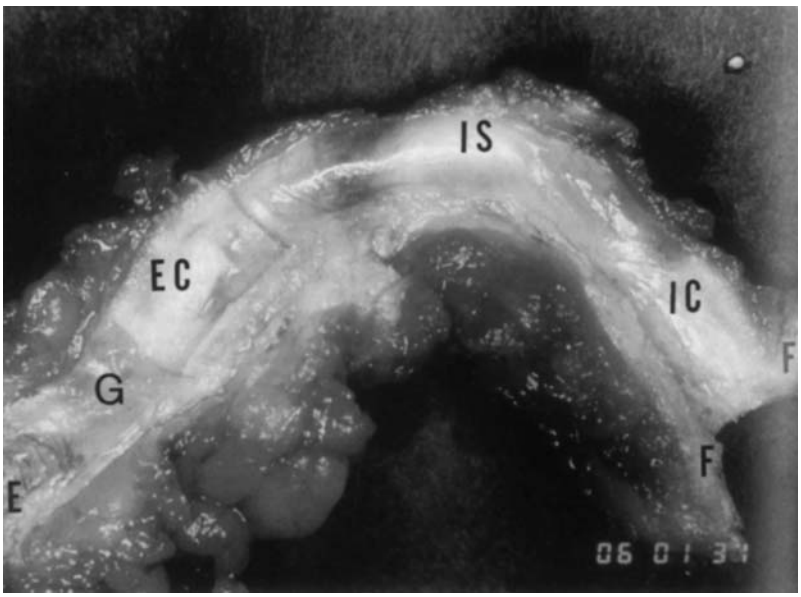

Fig. 14.38 A well-healed tunnel of a double-cuff swan neck Missouri catheter removed electively. From the left: E, epithelium; G, Granulation tissue; EC, external cuff; IS, intercuff segment; IC, internal cuff; F, flange

The junction between the granulation tissue in the sinus and the cuff is well defined. The cuff is surrounded by a dense fibrous capsule that contains numerous capillaries. About 80% of the polyester fibers are surrounded completely or partially by multinucleated giant cells. Spaces between the polyester fibers are filled with mature collagen and fibroblasts. No neutrophils are seen in an uninfected cuff.

The junction between the cuff and the inter-cuff segment shows a smooth surface without granulation tissue. The glistening, shiny inter-cuff tunnel segment resembles a tendon sheath and contains numerous micropits. The absence of any cellular reaction indicates that bacteria do not reach to this part of the tunnel. The surface is covered with an amorphous, mucinous substance on top of a modified layer of fibroblasts forming pseudo-synovium. There are no giant cells in this segment because silicone rubber *per se* does not induce giant cell formation.

The transition between the inter-cuff segment and the deep cuff is abrupt due to change from an avascular, acellular, fibrous sheath to a highly vascular and cellular tissue ingrown into the cuff. If the deep cuff is implanted into the muscle, the fibrous capsule surrounding the cuff and the cuff tissue itself are highly vascularized, otherwise the tissue ingrown into the cuff is similar to that of the external cuff.

Factors Influencing Healing and Early Infection

The most important factors influencing healing process and early infections are (Table 14.6) tissue perfusion, mechanical factors, sinus bacterial colonization, epithelialization, local cleansing agents, exit direction, and systemic factors.

Tissue Perfusion

The coagulum and necrotic tissue are gradually removed from the tunnel. Part of the necrotic tissue is absorbed and part is drained out of the tunnel. The tunnel should not be too tight with reference to the catheter circumference, so as to allow free drainage of necrotic tissue and to prevent tissue edema; both these factors decrease local perfusion and oxygen tension [179], which are critical for the wound-healing process. On the other hand, too large an incision prolongs healing by the shear volume of repair needed and the movement of loose tubing in the tunnel [180].

Table 14.6 Factors influencing healing process and infection

Tissue perfusion	Cleansing agents
Mechanical factors	Exit direction
Microorganisms	Systemic factors
Epithelialization	

Mechanical Factors

Mechanical stress slows the healing process [163]; thus the catheter should be relatively tightly anchored in the tunnel and also well immobilized outside the tunnel, especially during the break-in period [137]. Frequent dressing changes involve catheter manipulation, and hence should be avoided during the healing period. Constricting sutures at the exit site may cause pressure necrosis with skin sloughing, and facilitate bacterial penetration into the tissue; they must not be used [137].

Microorganisms

The presence of microorganisms in the wound is the major cause of impaired healing [181]. Bacterial counts exceeding 10^5 organisms per gram of tissue are associated with poor wound healing. Beta-hemolytic streptococci may affect healing regardless of the bacterial count in the wound [182]. Bacteria prolong inflammation and interfere with epithelialization, collagen deposition, and wound contraction [181]. Endotoxins produced by the bacteria stimulate release of collagenase, which contributes to collagen degradation and destruction of surrounding tissues [181]. Wound contamination by bacteria in association with hypoxia potentially suppresses macrophage-regulated fibroblast proliferation [183].

Maintaining sterility of the exit and sinus in the initial healing period is of utmost importance. Antibiotic penetration into the coagulum is poor; therefore, antibiotics should be present in sufficient concentration in blood and tissue fluids before the coagulum is formed. This may be achieved if antibiotics are given prior to implantation and is evidenced by several studies and a meta-analysis documenting preoperative intravenous prophylaxis reduce early peritonitis but not exit-site/tunnel infection [184].

Epithelialization

Epidermal cells grow over the granulation tissue beneath the scab. If the scab is forcibly removed during cleansing, the epidermal layer is broken, thus prolonging the process of epidermization. Sinus epithelialization is supported by sterile and undisturbed conditions at the exit. Again, frequent dressing changes facilitate exit contamination; on the other hand, liquid serous or sanguineous exudate at the exit promotes bacterial growth. Therefore, the exit should be kept dry, but dressing changes should not be too frequent.

Cleansing Agents

The objective of wound cleansing is to remove the organic and inorganic debris and to create conditions optimal for wound healing. Cleansing agents should not only decrease the number of bacteria, but also be harmless to the body defenses. Strong oxidants such as povidone-iodine and hydrogen peroxide are cytotoxic to mammalian cells [185, 186] and may impair angiogenesis [187]. It is prudent to apply such antiseptics only to the intact skin surrounding the wound or granulation tissue and avoid the sinus track [188]. Nonionic, amphophilic, nontoxic surfactants, widely used in burn wound care, facilitate necrotic tissue removal without jeopardizing body defense mechanisms [185, 189]. These include agents such as 20% Poloxamer 188 (Shur-Clens®; Calgon Vestal Laboratories, St. Louis, Missouri, USA) and Puriclens® (Care-Tech Laboratories, Inc, St. Louis, Missouri, USA), which are innocuous, yet excellent in cleansing the exit from contaminants.

Exit Direction

Exit direction is also important. Immediate postimplantation drainage of necrotic tissue is facilitated by gravity when the exit is directed downwards.

Systemic Factors

During the healing process, part of the granulation tissue is gradually resorbed and replaced by fibrous tissue. The fibrous tissue and part of the granulation tissue is covered with the epidermis [175]. Impaired nutrition, diabetes mellitus, uremia, hypothyroidism, obesity, chemotherapy, and corticosteroids are factors known to decrease wound healing by impeding the process of fibrosis [181]. It is prudent to avoid permanent catheter implantation while the patient is severely uremic, malnourished, or taking glucocorticoids.

Factors Influencing Infection of Healed Catheter Tunnel

Design of the catheter and its location in the created tunnel influences exit and/or tunnel infection. Other factors that may influence infection rate include bacterial colonization of the sinus, *S. aureus* nasal carriage status, catheter skin exit direction, sinus tract length, number off cuffs, and materials for the external cuff and the tubing in the sinus (Table 14.7).

Table 14.7 Factors influencing infection of healed catheter tunnel

Bacterial colonization of the sinus
Staphylococcus aureus nasal carriage
Catheter skin-exit direction
Sinus tract length
Number of cuffs
External cuff material and tubing in the sinus

Bacterial Colonization of the Sinus

Almost all healed catheter sinuses are colonized by bacteria [190]. It has been well documented in the surgical literature that wound infection is the result of imbalance between the host defense and bacteria [182]. The number of bacteria as a critical factor in wound infection was already recognized in World War I [191]. Elek [192] demonstrated that it requires 7.5×10^6 staphylococcal organisms to produce a pustule in normal human skin but the number of bacteria necessary to cause infection was reduced 10,000-fold in the presence of a single suture. Bacterial virulence is also important; *S. aureus* or *P. aeruginosa* are more likely to induce an inflammatory response than is *Staphylococcus epidermidis*.

It appears that there is a constant interaction between the colonizing bacteria and the body defense mechanisms at the sinus tract. The part of the sinus tract covered with epidermis seems to respond to bacteria in the same way as the rest of the body integument but the part covered with granulation tissue appears to respond by constant exudation of serum with white blood cells to suppress bacterial proliferation and curb their penetration deeper into the sinus. If the number of bacteria increase, then the amount of exudate increases and granulation tissue proliferates and becomes more vascularized. The number of bacteria entering deeper into the sinus depends on the number and species of bacteria at the exit site, exit direction, as well as sinus tract length, the latter an important contributing factor in the amplitude of catheter movement in the sinus. Optimum defense mechanisms, after the sinus is healed, are observed best in undamaged epidermis and granulation tissue; trauma to these structures may tilt the balance in favor of microorganisms and allow their rapid multiplication.

Nasal Carriage of S. *aureus*

The nose of patients on peritoneal dialysis is colonized by a variety of microorganisms including *S. aureus*, coagulase-negative *Staphylococcus*, and Gram-negative organisms [193]. While no association has been found between nasal colonization by coagulase-negative *Staphylococcus* and Gram-negative bacteria and peritoneal dialysis infections [193, 194], there is a strong association between *S. aureus* nasal carriage and catheter infections.

S. aureus principally resides in the anterior nares (vestibulum nasi or "nose picking area") [195]. There is strong correlation between the nasal and hand carriage of *S. aureus*. In the study by Boelaert et al. [196], 15 of 20 hemodialysis patients who carried *S. aureus* in their nares also carried the organism on their hands, but only two of 20 patients who did not carry *S. aureus* in their nares carried *S. aureus* on their hands ($p < 0.001$). Eighty-seven percent of patients who carried *S. aureus* in their nares and on their hands carried the same strain at both sites. Thus, it is likely that bacteria are carried from the nares to the vicinity of the catheter exit on hands.

Cross-sectional studies have established that approximately 50% of dialysis patients are nasal carriers of *S. aureus* [197, 198]. Nasal carriers are categorized into three groups based on longitudinal studies: persistent, intermittent, and noncarriage. Persistent carriers are usually colonized by a single strain of *S. aureus* over long durations of time, while intermittent carriers may carry different strains over time [195]. The load of *S. aureus* in the anterior nares of persistent carriers is higher resulting in increased dispersal and risk for infections [199]. In a study with median follow-up of 33 months, persistent nasal carriers had three times the number of peritoneal dialysis related infections than intermittent carriers and noncarriers, with majority of the isolated *S. aureus* being identical to the nasal isolates [200]. Luzar et al. [197] in a multicenter study reported on the increased incidence of exit-site infections in nasal carriers of *S. aureus*; in 85% of these infections the strain from the nares and the strain causing the infection were similar in phage type and antibiotic profile. The risks of staphylococcal catheter-related infections are higher in nasal carriers with diabetes mellitus or those who are immunosuppressed [201].

A few studies have failed to find an association between *Staphylococcus* carriage and *Staphylococcus* catheter-related infections [202, 203]; however, the overwhelming evidence does support this association. Furthermore, several studies have documented the benefits of treating the nasal colonization of *S. aureus* [204–208] and are discussed in a subsequent section of this chapter.

Catheter Skin-Exit Direction

The original recommendation of a downward-pointing exit came from Tenckhoff and Schechter [34]. A retrospective analysis from the University of Missouri found that compared to upward-directed exits, the exits directed downwards tended to be infected less frequently and, once infected, were significantly less resistant to treatment [50]. Several other authors have demonstrated superiority of downward directed exit sites in both pediatric and adult populations [209–211]. This should not be surprising since upward-directed tunnels facilitate exit contamination by gravity-aided flow of sweat, water, and dirt (Fig. 14.39). Once the exit is infected, it is resistant to treatment because of poor external drainage; rather, the pus tends to penetrate deeper into the tunnel. In addition, downward drainage of necrotic tissue immediately postimplantation is easier than drainage against gravity.

The advantage of caudal exit direction in preventing and treating infections has support in several other clinical conditions. Periodontitis, which may be considered as a naturally occurring "foreign" body exit-site infection, most frequently effects the lower incisors ("exits" directed upwards) [212]. The influence of exit position on the frequency and tenacity of paranasal sinus infections was postulated by Zuckerkandl in the nineteenth century. The relatively frequent infections of the maxillary sinus are believed to be due to unfavorable positions for discharge because the *ostium maxillare* (in the upright position of the body) is located at the highest point of the cavity; the cavity must be completely filled with secretions before the discharge may escape [213]. All of the other cavities are more favorably constructed for drainage and less likely to be infected [213]. The use of downward directed tunnels have been demonstrated to be effective in reducing exit-site infections in chemotherapy catheters and pediatric hemodialysis tunnels [214, 215].

Lateral pointing exit sites may be necessary in some individuals due to body habitus. In a retrospective study, downward and lateral catheter tunnel-track and exit site produced equivalent outcomes for infectious and mechanical complications [216].

Swan-Neck Catheters

Based on the observations that downward-exiting catheters are less likely do develop infections, Twardowski et al. developed the permanently bent swan-neck catheter with an inverted U-shaped arc between the deep and superficial cuffs. The U-shaped, arcuate bend allows the catheter to exit the skin pointing downward and the intraperitoneal segment is also directed downward to the pelvis [50]. The preformed shape promotes pelvic orientation by eliminating

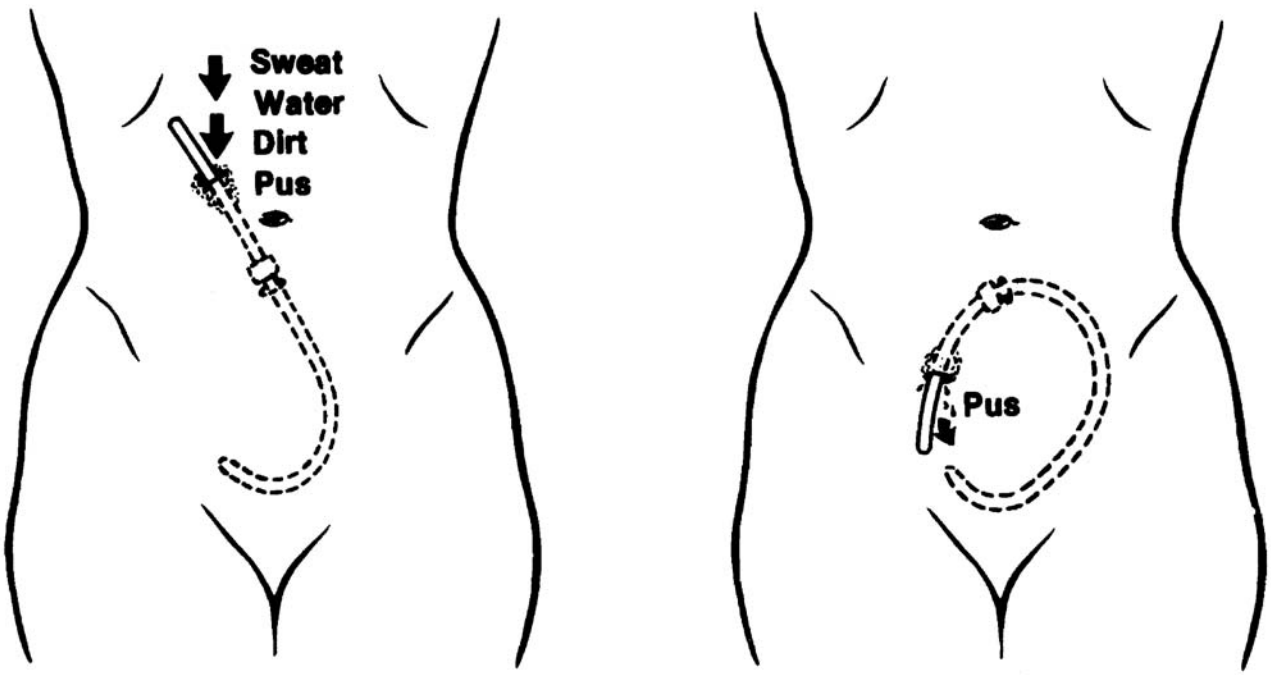

Fig. 14.39 *Left*: exit easily contaminated with down-flowing sweat, water, and dirt; difficult pus drainage prolongs treatment. *Right*: good pus drainage facilitates recovery. Reproduced from [50] with permission

shape memory effects. The surgical insertion of swan-neck catheters requires greater planning and technical skill for creating an appropriate tunnel than a straight catheter [1]. The data from Twardowski et al. [83], Lye et al. [217], and others has shown reduced exit-site infections with swan-neck catheters while others such as Hwang and Huang [218] and Eklund et al. [219, 220] demonstrated no benefit in the incidence of exit-site infections. These swan-neck catheters offer benefits in a lower incidence of cuff migration [79] and less frequent drainage related issues [79, 217, 220, 221].

Sinus Tract Length

The epidermis covering the sinus tract undergoes a turnover probably similar to the normal epidermis with cell maturation and desquamation; granulation tissue produces exudate. All these contents, if not expelled, create a favorable milieu for bacterial growth. With a long sinus tract the chances of infection are higher [162–164]; therefore, the sinus tract should be as short as possible. Tenckhoff recommended that "the subcutaneous Dacron®; felt cuff should be located immediately beneath the skin exit" [89]. Such a localization of the cuff, however, predisposes to its extrusion. Indeed, in some centers the rate of extrusion reached 100% [222]. In other centers the rate, although lower, was high enough to question the wisdom of using the superficial cuff at all. The most recent recommendation is to place the subcutaneous cuff at least 2–3 cm from the exit site [223].

Number and Location of Cuffs

There are three basic shapes and designs for the Dacron® cuffs: a single cuff around the catheter, usually placed in the rectus muscle but sometimes on the outer surface of the rectus; dual cuffs around the catheter, one in the rectus sheath and the other in the subcutaneous tissue; and a disc-and-ball deep cuff, with the parietal peritoneum sewn between the Dacron® disc and the silicone ball (Toronto-Western and Missouri catheters) [224]. The presternal catheters have three Dacron® cuffs: The upper tube carries two cuffs, a superficial and a middle or central spaced 5 cm apart, and a single deep cuff incorporated on the abdominal tube.

Single external-cuff catheters were used by Tenckhoff for treatment of acute renal failure. This type of catheter used in patients undergoing chronic intermittent peritoneal dialysis yielded similar results to those of the double-cuff catheter; however, with continuous ambulatory peritoneal dialysis, double-cuff catheter survival was better than of these catheters [225]. The complications of catheters with a solitary external cuff include the development of pseudohernias due to high intra-abdominal pressure from the constant presence of fluid in the peritoneal cavity. The use of such catheters has been abandoned.

Another type of single-cuff catheter has only a deep cuff. This type of catheter has been used because of problems with external-cuff extrusion and the questionable value of the external cuff. Earlier studies found such single-cuff catheters to be associated with a shorter time to first peritonitis episode and shorter survival times than the double-cuff catheters [211, 226–229]. However, the matter is not settled as a randomized controlled trial of 60 patients compared single- versus double-cuff catheters and found no differences in peritonitis, exit-site infections, and catheter survival [230].

Material for the External Cuff and Tubing in the Sinus

Peritoneal dialysis catheters are manufactured using highly biocompatible polymers, which minimize the foreign body reaction and enhancing device longevity. A thin fibrous capsule usually develops around the catheter but does not adhere to the catheter. Consequently, a potential space exists between the catheter and the fibrous layer that allows movement of the catheter and permits infection to spread from the exit site to the peritoneal cavity. Fabric cuffs are used to provide anchorage to the catheter [231]. The external cuff, if used, may play a role in preventing the spread of epidermal cells into the sinus track. As an example of perfect arrangement the anatomy of the tooth/gingival interface is cited [171]. The periodontal ligament attaches to the cementum, creating an extremely strong bond. The cementum is composed of hydroxyapatite crystals, collagen fibers, proteoglycans, and mucopolysaccharides [232]. Such a living material is unlikely to be used for the external cuff.

The traditional cuffs are made of polyester fiber (Dacron®). Soon after implantation, there is an acute inflammatory reaction characterized by the accumulation of polymorphonuclear cells and activated macrophages and eventually develop into foreign body giant cells. Later, fibroblasts and blood vessels grow into the cuff. In mature uninfected cuffs, histopathology reveals giant multinucleated cells, sparse mononuclear cells, and collagen fibers intertwined with the polyester fibers. A fibrous capsule surrounds the cuff. The tissue ingrown into the cuff *per se*

does not seem to constitute a critical barrier for infection spreading [175]. It seems that the basic beneficial role of the external cuff in infection prevention is by anchoring of the catheter resulting in restriction of its piston-like movements, thus decreasing transport of bacteria into the sinus. Favorable results with a "wing" instead of cuff appear to give clinical support to this hypothesis [233]. This "wing," however, does not seem to anchor the catheter as well as the cuff. Cuffs made of titanium fiber mesh have been evaluated in animal models and appear more biocompatible and integrate more favorably in the surrounding tissue [234].

Bioactive coating of catheters may be an alternative to cuffs. In animal studies, a bioactive glass-ceramic coating of silicone catheters was successful in inducing tissue adhesion of silicon catheters by promoting adhesion and cell proliferation [231]. In another animal study, a biocompatible silicone material with micropores was used as a cuff. The micropores facilitated ingrowth of blood vessels and loose collagen and cellular matrix, improving biointegration and decreasing exit-site infections. However, further studies and human data are needed to accept a substitute for polyester fabric (Dacron® velour) as a material for the external cuff.

In animal studies, it has been demonstrated that polyurethane intravenous catheters are less prone to infections than silastic intravenous catheters [235]. This may be related to differences in surface irregularities effecting microbial adherence. No studies have addressed differences in exit-site infection between polyurethane and silicon rubber peritoneal dialysis catheters in a direct comparative study. The incidence of exit-site infections with the Cruz dialysis catheter, which is made from polyurethane, are no different than reported in literature for silicone catheters [236, 237]. However polyurethane catheters are less biostable and the Dacron® cuff is more likely to separate from the catheter [238].

Exit Sites: Classification and Care

Exit-Site Appearance Post Implantation

Unless a large hematoma in the wound is present, all exits look the same a week after implantation [69]. The exit is painless or minimally tender with light pink color of less than 13 mm in diameter from border to border (including the width of the catheter). Blood clot or serosanguineous drainage is visible in the sinus. No epidermis is visible in the sinus and the sinus lining is white and plain. Signs of good healing include a decrease in color saturation and diameter around the exit, change of drainage to serous, decreased drainage amount, decreased tenderness, and progression of epidermis into the sinus. An increase in color, diameter, or saturation around the exit; change of drainage to yellow; change of granulation tissue color to mottled, pink or red; or change of granulation tissue texture into slightly exuberant or exuberant are signs of poor healing.

Our exit-site study [69, 239] revealed four types of healing exits: 1) Fast-healing exits had no drainage or minimal moisture deep inside by the third week; epidermis started to enter into the sinus within 2–3 weeks, progressed steadily, and covered at least half the visible sinus tract 4–6 weeks after implantation. 2) In slow-healing exits without infection, epidermis started to enter into the sinus after 3 weeks or progressed slowly and did not cover half the visible sinus by 5 weeks; the sinus might have had serous or serosanguineous, but never purulent, drainage persistent up to 4 weeks. 3) Healing interrupted by infection initially looked identical to the fast-healing exit, but within 6 weeks the epidermis had not progressed, or had regressed, granulation tissue became soft or frankly fleshy; drainage increased and/or became purulent. 4) In slow-healing exits due to early infection, granulation tissue became soft or fleshy and/or drainage became purulent by 2–3 weeks; sinus epidermization was delayed or progressed slowly, only after infection was appropriately treated.

Classification of Exit-Site Appearance

Attempts to classify exit appearance into two categories (infected and not infected) are difficult, if not impossible, because infected and uninfected exit appearances overlap. This overlap is due to the peculiarity of tissue reaction to the foreign body penetrating the skin, and stems from the delicate balance between bacteria in the sinus and host defenses as described above. The presence of a small amount of exudate causing crust formation does not indicate infection, but if the bacterial attack is more severe, or the host defenses are weakened, then the amount of exudate increases; granulation tissue proliferates, becomes more vascularized, epithelium regresses, and signs of infection become obvious. Low-grade exit infection may abate without systemic antibiotics.

We have performed extensive evaluation of exit-site characteristics [69, 190]. From the 565 evaluations of 61 healed exit-sites in 56 patients evolved a new classification [240]. The classification is based on the cardinal signs of inflammation as proposed by Aulus Cornelius Celsus in his treatise, *De Medicina*, written in the first century AD. These are well known: *calor* (heat), *rubor* (redness), *turgor* (swelling), and *dolor* (pain). Additional features, specific for an exit of any skin-penetrating foreign body, are drainage, regression of epidermis, and exuberance (profuse overgrowth) of granulation tissue ("proud flesh"). Granulation tissue is defined as exuberant if it is significantly elevated above the epidermis level. Scabs and crust do not indicate infection. Culture results did not influence exit classification. Positive cultures in exits not inflamed indicate colonization, not infection. Cultures were commonly negative from infected exits on antibiotic therapy. However, inflammation in almost all cases is caused by infection, regardless of culture results. Inflammatory responses to tubing itself or local irritants are rare.

Improvement or deterioration of inflammation is associated with respective decreases or increases of pain, induration, drainage, and/or exuberant granulation tissue, and/or regression or progression of epithelium in the sinus. Increased lightness (pink, pale pink) or darkness (deep black, brown) and decrease in color diameter indicate improvement, increase in red color saturation and diameter indicate deterioration. Ultimately, a new classification with five distinct categories of exit appearances has been established: acute infection, chronic infection, equivocal, good, and perfect. Two special categories are included: external cuff infection and traumatized exit. Trauma may result in various appearances. Cuff infection may not be associated with exit infection. Detailed descriptions of the various exit appearances illustrated by over 200 color photographs have already been published [69, 190, 239–241]. The characteristics for each category of catheter exit site are summarized in Table 14.8.

Acute Catheter Exit-Site Infection

This involves purulent and/or bloody drainage from the exit-site, spontaneous or after pressure on the sinus, and/or swelling; and/or erythema with diameter 13 mm or more from border to border; and regression of epithelium in the sinus. Acute catheter inflammation lasts less than 4 weeks and may be accompanied by pain, exuberant granulation tissue around the exit or in the sinus, and the presence of a scab or crust.

The common pathogens are *S. aureus* and *P. aeruginosa* [242–245]. Other organisms causing exit-site infection are coagulase-negative *Staphylococcus*, diphtheroids, anaerobes, streptococci, legionella, and fungi. Exit-site culture may be negative in patients receiving antibiotics.

Chronic Catheter Exit-Site Infection

These are characterized by purulent and/or bloody drainage from the exit-site, spontaneous or after pressure on the sinus; and/or exuberant granulation tissue around the exit and/or in the sinus; and regression of epithelium in the sinus. Chronic infection persists for more than 4 weeks and crust or scab is frequently present. Swelling, erythema, and/or pain indicate exacerbation. Exit culture may be negative in patients receiving antibiotics.

Equivocally Infected Catheter Exit Site

There is purulent and/or bloody drainage, which cannot be expressed outside the sinus, accompanied by the regression of epithelium, and occurrence of slightly exuberant granulation tissue around the exit and/or in the sinus. Erythema with a diameter less than 13 mm from border to border may be present, but pain, swelling, and external drainage are absent. Exit culture may be negative in patients receiving antibiotics.

Good Catheter Exit

Exit color is natural, pale pink, purplish, or dark and there is no purulent or bloody drainage. Clear or thick exudate may be visible in the sinus. Mature epithelium covers only part of the sinus; the rest is covered by fragile epithelium or plain granulation tissue. Pain, swelling, and erythema are absent. Positive peri-exit smear culture, if present, indicates colonization not infection.

Perfect Catheter Exit

This is at least 6 months old with its entire visible length of sinus tract covered with the keratinized (mature) epithelium. Exit color is natural or dark and there is no drainage. A small, easily detachable crust may be present in the sinus or around the exit. Positive peri-exit smear culture, if present, indicates colonization not infection.

Table 14.8 Characteristics of each category of exit-site appearance

	Perfect	Good	Equivocal	Acute infection <4 weeks	Chronic infection >4 weeks	Cuff infection without exit infection
Exit						
Pain/ tenderness	None	None	None	May be present	Only if exacerbation	May be present over cuff
Colour	Natural, pale pink or dark	Natural, pale pink, purplish or dark, bright pink <13 mm	Bright pink or red <13 mm	Bright pink or red >13 mm	Bright pink or red >13 mm only if exacerbation	Natural, pale pink, purplish or dark, bright pink <13 mm
Crust	None or small, easily detached or specks of crust on dressing	None or small, easily detached or specks of crust on dressing	Present, may be large and difficult to detach	Present	Present, may be difficult to detach	Typically absent
Scab	None	None	None	May be present	May be present	Absent
Drainage	None	None	None even with pressure on sinus; dried exudate on dressing	Purulent or bloody, spontaneous or after pressure on sinus; wet exudate on dressing	Purulent or bloody, wet exudate on dressing	Chronic or intermittent; purulent, bloody, tenacious or "gluey"
Swelling	None	None	None	May be present	Occurs only if exacerbation	Cuff induration may be felt on palpation; negative ultrasound does not rule out the diagnosis
Granulation tissue	None	None	Plain or slightly exuberant	Slightly exuberant or "proud flesh" may be present	"Proud flesh" or slightly exuberant typically visible	None
Sinus						
Epithelium	Strong, mature; covers visible sinus	Strong, mature at rim; fragile or mucosal deeper	Absent or covers part of sinus	Absent or covers part of sinus	Absent or covers only part of sinus	Covers most or all of sinus; may be macerated
Granulation tissue	None	Plain beyond epithelium	Slightly exuberant	Slightly exuberant or "proud flesh"	"Proud flesh" or slightly exuberant	None or exuberant deep in sinus
Drainage	None or barely visible; clear or thick	None or barely visible clear or thick	Purulent or bloody, sometimes clear	Purulent or bloody	Purulent or bloody	Purulent, bloody, gluey; may be seen only after pressure on cuff; clot or dried blood in sinus

Trauma may result in pain, bleeding, scab, and deterioration of exit appearance. Exit appearance depends on intensity of trauma and time of evaluation. Reprinted from [241] with permission

External Cuff Infection Without Exit Infection

There is intermittent or chronic, purulent, bloody, or gooey drainage, spontaneous or after pressure on the cuff, and induration of the tissue around the cuff. Exuberant granulation tissue may be seen deep in the sinus; sinus epithelium may be macerated. Exit site may look normal on external examination. Ultrasound may show fluid collection around the cuff, but negative ultrasound does not rule out cuff infection. Exit culture may be negative in patients receiving antibiotics.

Traumatized Exit

Features of traumatized exit depend on the intensity of trauma and the time interval until examination. Common features of trauma are pain, bleeding, scab, and deterioration of exit appearance (e.g., perfect exit transforms to good or equivocal or acutely infected).

Alternative Exit-Site Classification Systems

Several alternative classification of exit sites have been proposed [246–248]. The scoring system by Schaefer et al. [246] is based on an Exit-Site Score (ESS, 0–10). The parameters include the presence of an erythema (0, none; 1, <0.5 cm; 2, >0.5 cm), a crust (0, none; 1, <0.5 cm; 2, >0.5 cm), tenderness (0, none; 1, moderate; 2, severe), swelling (0, none; 1, moderate; 2, severe), and discharge (0, none; 1, clear; 2, purulent). The exit site is considered infected if the total score exceeds 4 or greater. Purulent drainage alone is sufficient to indicate infection [246] . This system has been validated only in children.

Exit-Site Care

Early Care

Early colonization of the exit was the most significant factor in determining the healing pattern; the later the colonization, the better healing [69]. Positive culture from either sinus washout or peri-exit smear 1 week after implantation was associated with early exit infection, a higher peritonitis rate, and a high probability of catheter loss due to an exit/tunnel infection, and higher peritonitis rate; however, the time to the first peritonitis episode was not shorter than in the groups with later exit colonization [69].

The goal of early care is to delay bacterial colonization and to minimize trauma to the exit site. After implantation, the exit site should be covered with sterile gauze and occlusive dressings must be avoided. Gauze dressings can wick away drainage from the exit and keep the exit site dry. It is generally agreed that postoperative dressing changes should be restricted to specially trained staff [249]. Dressings should not be changed frequently unless there is evidence of bleeding or significant drainage [250]. Our usual practice is to change dressings every week for the first 2 weeks. Once the exit is colonized, by week 3 in the majority of cases [69], more frequent dressing changes are indicated, because the major rationale for infrequent dressing changes, avoidance of exit colonization, no longer exists. Moreover, more frequent cleansing of the exit will decrease the number of bacteria at the exit. Aseptic technique, including both masking and wearing sterile gloves, should be used for postoperative dressing changes. Nonionic surfactant such as 20% poloxamer 188 (Shur-Clens®) is used to help gauze removal if it is attached to the scab. If the scab is forcibly removed, the epidermal layer is broken, a new scab has to be made, and the epidermization is prolonged. Care is taken to avoid catheter pulling or twisting. The exit sites may be cleaned with normal saline, nonionic surfactant, hydrogen peroxide, or povidone-iodine. Povidone-iodine and hydrogen peroxide are cytotoxic and should be kept out of the exit-site sinus. After cleansing, the exit site should be patted dry with sterile gauze, covered with several layers of gauze dressings, and secured with air-permeable tape.

The exit and visible sinus should be evaluated for quality of healing at each dressing change throughout the 6-week healing period. If healing does not progress, if there are signs of deterioration or infection, the exit is probably already colonized [69]. A clinical culture of the exudate should be taken, and an appropriate systemic antibiotic should be given.

It is recommended that patients do not shower or take tub baths post-catheter implantation, to avoid colonization with waterborne organisms, and to prevent skin maceration. Once more frequent dressing changes are started (after approximately 2 weeks), the patient may take a shower, but only before the dressing change, otherwise he/she must take sponge baths and avoid exit wetting.

Protecting the catheter from mechanical stress is extremely important, especially during break-in. Catheters should be anchored in such a way that the patient's movements are only minimally transmitted to the exit. Although a variety of devices are available to immobilize the dialysis catheter, these devices have not been shown to be any more effective than tape and dressings in preventing infections [251]. The method of catheter immobilization should be individualized, depending on exit location and shape of the abdomen.

Chronic Exit-Site Care

Local Care

The components of chronic exit-site care include assessment and cleansing of the exit-site, immobilization of the catheter and protection of the exit site from trauma. Chronic exit-site care is the responsibility of the patient or the caregiver along with close attention by the physician and nurses on office visits.

Frequent, preferably daily, exit site care is optimal. Cleansing of the exit site is essential to reduce resident bacteria. The exit site is first washed with antibacterial soap and water or with a nonionic surfactant such as 20% poloxamer 188 (Shur-Clens®). Povidone-iodine, chlorhexidine, and Amuchina may be used as disinfectants in routine exit-site care. These agents should not be allowed into the exit-site sinus. After cleansing, the exit has to be patted dry with sterile gauze.

The results of a prospective study by our group indicate that cleaning with soap and water is the least expensive and tends to prevent infections better than povidone-iodine painting and hydrogen peroxide cleaning [252]. Others have found povidone-iodine to be superior to nondisinfectant soap [253].

Amuchina is an electrolytic chloroxidizing solution containing sodium hypochlorite. Amuchina exerts bactericidal, viricidal, and fungicidal effects on a variety of pathogens through generation of hypochlorous acid. Amuchina 10% (ExSept plus) and Amuchina 5% (ExSept) have been found to be as effective as povidone-iodine 10% in preventing exit-site infections [254]. In an open-label, single-center prospective pediatric study, Amuchina 50% was compared to amuchina 3%. The rates of exit-site infections were similar in both groups. Amuchina 3% is the most cost effective option compared to Amuchina 50%, povidone iodine 10% or chlorhexidine 4% [255]. Amuchina may occasionally cause scab formation and exit-site irritation [254].

A dressing cover for 6–12 months after implantation is recommended. Continued use of dressings is indicated for infected exit sites or likely to be contaminated. Patients should avoid submersion in water, particularly in a Jacuzzi, hot tub, or public pool, unless watertight exit protection can be implemented. The surrounding skin is coated with a skin protector and secured with Tegaderm®. Prolonged submersion in water containing high concentrations of bacteria frequently leads to severe infection with consequent loss of catheter. Swimming in the ocean, and well-sterilized private pools, is less dangerous. Exit care must be performed immediately after a shower or water submersion, with particular attention to obtaining a well-dried exit. Patients with the swan-neck presternal catheter may take a hot tub bath without exit-site submersion. Because of this feature this catheter was dubbed the "bath-tub" catheter [3].

Antibiotic Prophylaxis

Exit-site infections are commonly caused by *S. aureus* and *P. aeruginosa* [242–245]. Mupirocin is a carboxylic acid that inhibits bacterial protein synthesis by binding isoleucine t-RNA synthetase and is active against staphylococci and streptococci but not enterococci or Gram negatives [256]. Data supports the use of mupirocin at the exit site to decrease exit-site infections and peritonitis by *S. aureus* [207, 257–260]. The usual recommendation is to apply mupirocin daily after cleansing. Once-weekly application of mupirocin to the exit site has also been shown to be effective in decreasing exit-site infections and peritonitis episodes comparable to those obtained with daily application [261, 262].

Alternative to mupirocin, gentamicin cream [263] and ciprofloxacin otologic solution [237] are effective in reducing the incidence of *S. aureus* as well as Gram-negative exit-site infections. Bernardini et al. randomized 133 individuals to exit-site mupirocin or gentamicin cream [263]. Catheter infection rates were 0.23/yr with gentamicin cream versus 0.54/yr with mupirocin ($p = 0.005$). *S. aureus* exit-site infections were infrequent in both groups (0.06 and 0.08/yr; $p = 0.44$). While there were no pseudomonal exit-site infections in the gentamicin group, there were 0.11 episodes per patient year in the mupirocin arm. Peritonitis rates were 35% lower in the gentamicin arm, with a striking decrease in Gram-negative peritonitis. Montenegro et al. randomized 164 individuals to exit-site care with soap and water only versus exit-site care with soap and water plus application of 1 mg ciprofloxacin (0.5 mL otologic solution) [237]. Ciprofloxacin reduced exit-site infections to 0.06 episodes per patient-year of exposure in contrast to 0.41 episodes in the control group ($p = 0.001$). *S. aureus* infections were significantly reduced and none of the treated patients developed pseudomonal exit-site infections.

Table 14.9 Antibiotic protocol options for preventing exit-site infections

1. Exit-site mupirocin:
a. Daily after cleansing in all patients
b. Daily after cleansing in carriers only
c. In response to a positive exit-site culture for *Staphylococcus aureus* denoting carriage
2. Intranasal mupirocin twice per day for 5–7 days:
a. Every month, once patient identified as a nasal carrier
b. Only in response to positive nose culture
3. Exit-site gentamicin cream daily in all patients after cleansing

Source: Reproduced with permission from [223]

The nasal carriage of *S. aureus* is also a risk factor in peritoneal dialysis–related infections [197, 200, 204, 205]. The treatment of *S. aureus* nasal carriage with intranasal mupirocin twice a day for 5–7 days has been shown to decrease the incidence of *S. aureus* exit-site infections [204–206], and in some studies peritonitis and catheter loss [205, 206]. On meta-analysis, intranasal mupirocin was found to have no benefit on decreasing peritonitis rates and catheter loss [264]. Periodic retreatment is frequently necessary because of a high recolonization rate [204–206]. This may be done routinely at monthly intervals or based on periodic screening. Since the strains of *Staphylococcus* colonizing the exit site may be different from the nose [265], exit-site prophylaxis may be the preferred option and is more convenient. An alternative to intranasal mupirocin is the use of oral rifampin in a dose of 600 mg/day for 5 days every 3 months to reduce *S. aureus* exit-site infections [207, 208]. In a randomized study, mupirocin and rifampin were equally effective in reducing *S. aureus* peritonitis and catheter loss, however, rifampin was often poorly tolerated [207]. In a meta-analysis of studies on prophylaxis against *S. aureus*-related infections in patients on dialysis, resistance to rifampin ranged from 0 to 18.2% and the drug had to be discontinued in 6.6% of patients due to toxicities [266]. The overall benefit of mupirocin prophylaxis (nasal and exit-site) were evaluated in another meta-analysis; there was a highly significant relative risk reduction of 37% for all *S. aureus* infections, 34% for peritonitis, and 38% for exit-site infections [267].

There are few side-effects associated with the mupirocin, mainly nasal irritation and discharge for the nasal route [204]. Exit-site mupirocin ointment can structurally damage polyurethane and should be avoided with these catheters [268]. An increasing prevalence of mupirocin resistance is being reported [269, 270]. Perez-Fontan has reported that high-level resistance to mupirocin (defined as an MIC $\geq$512 μg/mL) increased from nonexistent in the period 1990–1996 to 12.4% in 1999–2000. He also noted that the accumulated incidence of *S. aureus* exit-site infection in the period 1997–2000 was 32.3% in patients colonized by mupirocin-resistant *S. aureus* as compared with 14.5% in those colonized by mupirocin-sensitive *S. aureus* ($p = 0.03$), suggesting a substantial impact of the development of resistance [269]. In these reports, none of the isolates were methicillin-resistant [269, 270] nor are there reports of development of cross-resistance [271]. Prolonged usage and multiple intermittent courses of mupirocin appear to be the factors most frequently associated with the development of mupirocin resistance [271]. However, one study that examined mupirocin resistance over a 7-year period reported no increased prevalence in mupirocin resistance over this time period [272]. Programs should perform periodic surveillance to detect the emergence of resistant strains.

The International Society of Peritoneal Dialysis recommendations on antibiotic protocols for preventing exit-site infections are reproduced in Table 14.9 [223].

Early Complications Related to Peritoneal Access

Early complications post-soft catheter insertion are similar to those after implantation of the rigid catheter, but their frequency is lower, particularly with surgical, peritoneoscopic, or laparoscopic insertion. Blood-tinged dialysate is common postimplantation but severe bleeding occurs very rarely with surgical insertion. Dialysate leaks are unlikely if ambulatory peritoneal dialysis is postponed for at least 10 days after implantation [273]. This complication is particularly rare with the Toronto Western Hospital, swan-neck Missouri abdominal, swan-neck presternal, and Lifecath® column disc catheters. Early leak is usually external and may be confused with serous drainage from the exit. A diagnosis of a leak is supported by a higher glucose concentration in the drainage compared to the simultaneously measured blood glucose concentration.

Poor dialysate return is usually due to catheter obstruction if loss of siphon or tubing occlusion is ruled out. The most common reason of catheter obstruction is occlusion of the tip by bowel and/or bladder or intraluminal formation

Table 14.10 Early catheter obstruction

Cause	Prevention/treatment
Occlusion by bowel	Laxatives
Occlusion by bladder	Empty bladder
Clot	Rinse out blood, heparin, urokinase, dislodge
Omental wrap	Partial omentectomy
Multiple adhesions	Adhesiolysis
Kink in the tunnel	Surgical correction

of clot (Table 14.10). Emptying the bladder and using laxatives may restore catheter function if there is obstruction by bladder or bowel. Clot may be prevented by rinsing out blood from the peritoneal cavity and using heparin or can be dislodged by forceful injection through the tubing into the peritoneal cavity or pulling by suction using a syringe filled with heparinized saline. If these maneuvers are unsuccessful the catheter may be filled with urokinase (Abbokinase) 5,000 IU, diluted in normal saline. Thrombolytics like tissue plasminogen activator and urokinase may open the obstruction in 10–15% of cases [274–277]. Using high pressure during fluid infusion, Hashimoto et al. [278] were able to open six catheters occluded by clots. Catheter kinking in the tunnel is usually associated with two-way obstruction, is recognizable on abdominal X-ray in two views, and requires surgical correction as soon as diagnosis is made. If the catheter is not kinked, but does not function for 2 weeks, omental wrapping or multiple adhesions are most likely and omentectomy or adhesiolysis using laparoscopy may be required.

A reversed one-way peritoneal catheter obstruction, in which the fluid can be drained but the next infusion cannot be performed, is extremely rare. In one such case, the catheter tip was obstructed with a clot which caused inflow obstruction. The catheter tip was obstructed with a clot, which caused inflow obstruction. This clot was removed by suction with a syringe. We speculated that the clot was firmly anchored in the catheter tip, and that only a few proximal side-holes were open. The outflow was not obstructed because the catheter tip must have been located in a large pocket of free peritoneal space. The clot behaved like an accordion. During drainage the clot became stretched and narrowed (like an accordion bellow in extension) and fluid was able to flow through some of the side-holes. During infusion the clot buckled up and widened (like a compressed accordion bellow), completely occluding the central lumen and side-holes [279].

Another reason for obstruction may be catheter adherence to the peritoneum. This complication was found in children who have undergone partial omentectomy at the time of insertion of a single-cuff, straight Tenckhoff catheter. Relocation of such catheters may be attempted with a so-called "whiplash" technique [280]. After localization of the catheter adherence site, using a strict sterile technique, a blunted steel trochar is inserted into the catheter and gently advanced until the trochar tip is 5–7 cm proximal to the tip of the catheter. Using a deep cuff as a fulcrum, and using short and rapid whiplash motions, the catheter is then freed from the adherence point. The catheter tip is then, under fluoroscopy, relocated to a new site. A modification of this method using a pliable copper thread was successfully used in adults [281]. A catheter that has migrated to the upper abdomen may be relocated using a guidewire [282–284]. Although these methods may obviate the need for surgery, they are not without risk. The guidewire may break during manipulations, may perforate the catheter, and may lead to recurrent peritonitis.

Catheter migration out of the true pelvis is seen frequently on abdominal X-rays done for various reasons in patients with functioning catheters. While about 20% of X-rays showed the catheter tip translocated to the upper abdomen, only 20% of these translocated catheters (4% of the total) were obstructed or malfunctioning. The remaining functioning malpositioned catheters were either permanently translocated or repositioned spontaneously to the true pelvis. About 3% of catheters in our series were obstructed with the tip in the true pelvis [285].

While the great majority of malpositioned catheters are not obstructed, a catheter with its tip in the upper abdomen is still about six times more likely to be obstructed than a normally positioned catheter. The migration of the catheter tip may, however, be the result of the obstruction rather than its cause; omentum entangling the catheter tip may be responsible for its translocation.

Repositioning of the internal catheter segment is best done surgically using a laparoscopic method (see above). In our experience, if this method fails to restore catheter function because the peritoneum is not usable for peritoneal dialysis because of massive adhesions, catheter relocation or replacement in such a situation is worthless. The patient must be transferred to hemodialysis.

Viscus perforation is unlikely with surgical catheter insertion. Early peritonitis with a soft catheter is half of that reported with a rigid catheter, even in treatment of acute renal failure [126]. Abdominal pain is more likely with straight catheters due to "jet effect" and tip pressure, as discussed in the section on infusion/pressure pain.

Late Complications Related to Peritoneal Access

Factors influencing catheter complications have been discussed earlier. Complications are not randomly distributed throughout the life of the catheter. Whereas leaks and catheter malfunction occur shortly after catheter implantation, infectious complications lead to catheter failure later.

Exit-Site Infections

The use of a classification system facilitates early diagnosis of exit problems, and treatment can be more specific. Exit-site care and treatment for each appearance category are summarized in Table 14.11.

Table 14.11 Exit-site treatment and care for each category of exit-site appearance

	Equivocal infection	Acute infection	Chronic infection	Cuff infection
Evaluation	Culture and sensitivities on peri-exit smear; Gram stain	Culture and sensitivities on exudate; Gram stain	Culture and sensitivities on exudate; Gram stain	Palpation of cuff and tunnel; culture and sensitivities and Gram stain of exudate (spontaneous or after pressure on cuff); ultrasound of cuff/tunnel
Initial therapy	Cauterize slightly exuberant granulation tissue. Topical mupirocin. Exit care daily; clean with mild disinfectant soap; do not use strong oxidants on granulation tissue; use a sterile absorbent dressing.	Cauterize slightly exuberant and exuberant granulation tissue. First-generation cephalosporin for Gram-positive organisms; quinolone for Gram-negative organisms; vancomycin for methicillin-resistant *S. aureus*. Exit care daily or b.i.d.; clean with mild disinfectant liquid soap or nonionic surfactant agent; do not use strong oxidants on granulation tissue; use a sterile, absorbent dressing.	Cauterize slightly exuberant and exuberant granulation tissue. First-generation cephalosporin for Gram-positive organisms; quinolone for Gram-negative organisms; vancomycin for methicillin-resistant *S. aureus*. Exit care daily or b.i.d.; clean with mild disinfectant liquid soap or nonionic surfactant agent; do not use strong oxidants on granulation tissue; use a sterile, absorbent dressing.	Cauterize proud flesh. Initial antibiotic therapy based on Gram stain results.
48 h	Change to Neosporin, gentamicin, or chloramphenicol ointment if Gram-negative organisms on culture.	Adjust therapy according to culture and sensitivities.	Adjust therapy according to culture and sensitivities.	Adjust antibiotic according to culture and sensitivities.
Follow-up	If no improvement in 2 weeks, change to systemic antibiotic based on initial culture and sensitivities. Continue therapy 7 days past achieving a good appearance.	Evaluate weekly; reculture if no improvement. Continue to treat for 7 days after achieving a good appearance.	Evaluate every 2 weeks; reculture every 2 weeks if no improvement on appropriate therapy. Add synergistic drug or change antibiotic according to culture and sensitivities. If infection recurs repeatedly after achieving a good appearance: (a) consider chronic antibiotic suppression; (b) if no improvement after a month of treatment, suspect cuff infection and treat as such. If accompanying peritonitis, remove catheter.	Re-evaluate every 2 weeks; reculture monthly. If no remission: (a) consider cuff shaving; (b) consider catheter replacement. If accompanying peritonitis, remove catheter.

Modified from [241] with permission

Acute Exit-Site Infection

A culture of exit-site exudate or, if there is swelling/erythema without expressible exudate, a smear culture of the skin surrounding the exit should be taken as soon as a clinical diagnosis of an acute exit-site infection is made. Recommendations for the care of infected exit-sites are based on sound surgical practices and anecdotal experiences. Increasing the frequency of dressing changes to once or twice a day helps the healing process, especially in those with copious drainage. Nonirritating solutions (e.g., nonionic surfactant) are preferred cleansers to remove drainage and reduce the number of microorganisms. An infected exit should be covered with a sterile nonocclusive dressing to absorb drainage, protect against trauma, and shield against superinfection.

An attempt may be made to treat early infections with erythema and no drainage with topical treatments. These treatments include application of soaks to the exit twice to four times daily, as well as the application of dry heat. Soaking solutions include normal saline, hypertonic saline, sodium hypochlorite, dilute hydrogen peroxide, povidone-iodine, and 70% alcohol [223, 249, 286, 287]. Local applications of povidone-iodine ointment, mupirocin, and Neosporin® cream, ointment, or ophthalmic solutions have been recommended [223]. Topical antibiotics are of limited value in treating acute or chronic infection with copious drainage because of the inability to achieve sufficiently high local concentrations [288]; however, topical antibiotics are helpful once drainage diminishes.

Depending on the clinical appearance, empiric antibiotic therapy may be initiated immediately or delayed until the results of the culture are available. Prior cultures or the Gram stain may guide initial therapy. Gram-positive organisms are treated with an oral penicillinase-resistant penicillin, cephalexin, or sulfamethoxazole trimethoprim. In slowly resolving or particularly severe-appearing *S. aureus* exit-site infection, rifampin 600 mg daily is added. Oral antibiotics are equally effective as intraperitoneal antibiotics for most ESI with the exception of methicillin-resistant *S. aureus* [223]. Vancomycin should be avoided in the routine treatment of Gram-positive exit-site infection and tunnel infections to prevent emergence of resistance. Gram-negative organisms may be treated with oral quinolones such as ciprofloxacin. The presence of *P. aeruginosa* should prompt the use of two antibiotics with different mechanisms of action such as ciprofloxacin and ceftazidime or an aminoglycoside. These infections are often refractory to treatment and have frequent relapses [223, 289]. Very often *Pseudomonas* exit-site infections resolve only after catheter removal. Antibiotic therapy should be continued until the exit site appears entirely normal, with a minimum of 2 weeks of therapy.

Exuberant granulation tissue (proud flesh) is cauterized with a silver nitrate stick, a procedure widely used in surgical practice, veterinary and human [288, 290]. No more than one or two applications are necessary in most patients with acute infection. This procedure speeds up the healing process and facilitates epithelialization. Cauterization should be restricted to granulation tissue only, and accidental touching of the adjacent epithelium should be avoided. Use of a magnifying glass aids in precise cauterization. This can be done safely by a physician or nurse [291].

Catheter immobilization is a sound practice providing protection against accidental trauma. Trauma leads to bleeding, and blood is a good medium for facilitating growth of microorganisms. Catheter immobilization should be continued or implemented during the acute infection stage.

An ultrasound of the exit site is indicated to evaluate for presence of tunnel and cuff involvement if the infection fails to respond to 2 weeks of appropriate antibiotics. Since patients with *S. aureus* and *Pseudomonas* sp. exit-site infections have a high incidence of cuff and tunnel involvement, an ultrasound examination when the cultures are reported should be a consideration. Another indication for ultrasound is the presence of simultaneous exit-site infection and peritonitis [292].

Most acute infections respond favorably to therapy. An exit-site with an acute infection in association with proud flesh and bleeding requires prolonged antibiotic therapy. Association with a positive nasal culture had no influence on the outcome. Conditions that delay healing or make therapy ineffective are cuff and/or tunnel infection, infection due to a resistant organism or a virulent pathogen, and patient noncompliance [223, 293]. Recurrent infections that progress to chronic infection and/or cuff infection are associated with a poor prognosis. Catheter removal is indicated when acute exit-site infection leads to tunnel infection and peritonitis. Management of cuff infection is discussed later in this section.

Chronically Infected Exit Site

The work-up leading to the proper diagnosis of a chronically infected exit site is similar to that performed to diagnose acute infection. These infections are hard to treat. Once the culture and antibiotic sensitivity results are available, an appropriate antibiotic should be started. A combination of synergistic antibiotics is preferred to a single agent, to avoid emergence of resistant organisms, since the therapy is given over a prolonged period. In chronic infection, the bacterial flora or the antibiotic sensitivity may change during the course of treatment. Therefore, an unresponsive exit site may

have to be cultured repeatedly for timely diagnosis. The response to treatment is usually slow. An ultrasound of the catheter tunnel may be indicated to evaluate for cuff infection. The features of the chronic infection change very slowly to those of an equivocal exit and then eventually to those of a good exit site.

The antibiotic therapy and local care of the exit site are continued until the desired features of a good exit are achieved. In some cases, exit features change to equivocal and remain as such for a long time. In such instances, the systemic antibiotic is discontinued and replaced with a topical antibiotic. Chronic infection requires repeated cauterization of exuberant granulation tissue. Typically, weekly cauterization for several weeks is necessary. The cauterization is continued as long as the proud flesh persists. The cauterization will discolor the proud flesh from red to gray. Some cases of chronic infection may require long-term (many months) suppressive doses of a systemic antibiotic. Typically, these cases show reinfection on discontinuing the systemic antibiotic. It is likely that such cases represent undiagnosed cuff infection. Chronic exit-site infections may require catheter removal.

Local care is similar to that used in treating acute infection. After achieving the features of an equivocal exit, the frequency of local care may be reduced to once a day.

Equivocal Exit

The equivocal exit site is a subclinical form of infection. If left untreated, most equivocal exits will progress to acute infection. Therefore, aggressive management of equivocal exits assumes great importance. Aggressive local care with a topical antibiotic may cure most equivocal exit sites. Exits with external, slightly exuberant granulation tissue, which usually progress to acute infection, require systemic antibiotics. Cauterization of the slightly exuberant granulation tissue in the sinus may be necessary.

An acute infection may acquire equivocal features during the recovery phase. Such an exit site warrants less aggressive therapy compared to one with acute infection; the key to therapy being daily local care while systemic antibiotics may be discontinued.

Local therapy with topical antibiotics is the mainstay of treatment for an equivocal exit site. A topical antibiotic is chosen based on the exit swab culture results. The topical antibiotics that we have successfully used include mupirocin, Neosporin®, gentamicin, chloramphenicol, and tobramycin. This effectiveness is due to the absence of copious drainage from the sinus tract. Systemic antibiotic may be used in cases unresponsive to topical therapy. Response to therapy is usually excellent, with cure occurring in almost all instances.

Good and Perfect Exit

The care of these exit sites has been discussed earlier in this section. Catheter immobilization, protection from trauma, use of liquid soap and water for daily care, and use of Shur-Clens® to remove large, irritating crust are appropriate measures to prevent infection. In our experience, a perfect exit is unlikely to become infected unless severely traumatized or grossly contaminated after submersion in water loaded with bacteria.

Traumatized Exit

Bleeding is a common squeal of trauma. Extravasated blood is a good medium for bacterial growth. Bacteria that have colonized the exit multiply rapidly in the presence of decomposing blood and infect the disrupted tissue. Infection may occur as early as 24–48 h after trauma. The prompt administration of an antibiotic, chosen based on the history of skin colonization, may prevent acute infection. In the absence of the information about previous skin colonies, an antimicrobial agent sensitive to Gram-positive organisms, such as a cephalosporin or a quinolone, may be chosen. Therapy may have to be continued for about 7 days after achieving a good appearance. Aggressive treatment is necessary in every instance of trauma reported by the patient. Local care requires gentle cleansing of all blood from the exit site.

External Cuff Infection with or Without Exit Infection

Ultrasound examination of the tunnel is a valuable tool in the diagnosis of cuff infection. While positive findings with ultrasound examination help to establish a diagnosis of tunnel infection, a negative examination does not rule out the existence of an infection [294]. Cuff infection responds to therapy slowly, if at all, and a complete cure is unlikely. A sonolucent zone around the external cuff 1-mm thick following a course of antibiotic treatment and involvement of the proximal cuff are associated with poor outcomes [295]. Vychytil has suggested that in *S. aureus* tunnel infections, if sequential ultrasounds done every 2 weeks do not show a 30% decrease in the hypoechoic area around the cuff, the catheter should be removed [292].

Local care has to be given aggressively. Among the surgical options is catheter removal with simultaneous or delayed catheter replacement [296, 297]. Deroofing of the sinus tract and external cuff shaving [298–301] and replacement of the external tubing segment by catheter splicing [302–304] are other surgical options. The latter two options allow for the continuation of peritoneal dialysis without the need to switch to hemodialysis. In our experience cuff shaving prolonged catheter life for approximately 6–12 months [291]. These temporary measures may be suitable for patients who are expected to stay on therapy for a short period, e.g., patients awaiting transplant; however, cuff infection is a strong indicator for catheter removal in long-term peritoneal dialysis patients. Anecdotal reports suggest that cuff shaving may provide better results in presternal catheters [305]. This may be related to the presence of three cuffs and a long tunnel in the presternal catheter. Shaving of the subcutaneous cuff leaves two cuffs as a double barrier against peri-luminal bacterial penetration.

Peritonitis

Peritonitis on peritoneal dialysis usually develops because of touch contamination or pericatheter spread of bacteria. Touch contamination causes peritonitis by skin commensals such as coagulase-negative *Staphylococcus*, Corynebacterium, diptheroids, and occasionally Gram-negative organisms [193, 306, 307]. Exit-site and tunnel infections are associated with a pericatheter spread of infection [308]. In a trial examining the risk factors for peritonitis, the development of an exit-site infection doubled the risk of subsequent peritonitis [309]. The organisms commonly associated with such infections are *S. aureus* and *P. aeruginosa* [242–245]. Occasional patients develop peritonitis due to hematogenous seeding, bowel perforations or gynecological spread of organisms. Bowel trauma is a known catheter complication [310].

Tunnel infections often require removal of the catheter without which the patient may suffer from recurrent or relapsing peritonitis from the same organism. Even with exit-site infections, occult tunnel infections may be present may cause a high failure rate to therapy. Another cause of recurrent or relapsing peritonitis is the development of bacterial biofilm layers on the catheter. Bacterial biofilms are microbial colonies enclosed in a self-produced polymeric matrix and adherent to the catheter. *S. aureus* and coagulase-negative *Staphylococcus* are the most common organisms forming biofilms. Bacteria in the biofilm are in a sessile form and are intermittently shed in a planktonic form, which can be pathogenic. Biofilm infections are often slow to produce symptoms. Mature biofilms develop resistance to antibiotics, phagocytes, and biocides [311]. The poor penetration of antibiotics into the biofilm may explain antibiotic resistance. Alternatively, the bacteria may enter into a nongrowing state or a spore-like state in which they are protected from killing [312, 313]. Relapsing peritonitis has also been reported due to colonization of presternal catheter at the site of titanium connector. In this case, a removal of the chest segment of the catheter resulted in resolution of relapsing peritonitis [314].

Infusion or Pressure Pain

Some patients may experience pain with infusion of dialysate. This pain may be due to the acidic pH (pH 5.2–5.5), hyperosmolality, or temperature of conventional dialysate [315]. Localized pain may result from irritation from the catheter tip as it rests against the pelvic wall or intra-abdominal organs [316]. The jet effect of rapidly flowing dialysis solutions may also cause abdominal pain. In some rare instances, compartmentalization from adhesion formation around the catheter may cause severe abdominal pain [317].

Coiled catheters are less likely to induce abdominal pain than straight catheters because more of the solution flows shower-like through side-holes, with only part of it through the main lumen that is not in direct contact with the peritoneal membrane. Moreover, the poking force of the coiled catheter is smaller than that of the straight one because the coiled intraperitoneal segment is more flexible. Finally, the larger contact area of the coiled catheter with the parietal peritoneum further reduces the pressure compared to the straight catheter tip.

In the majority of cases, the pain is transient and disappears within a few weeks. Assessment of the catheter by routine radiographs, contrast catheterograms, or CT-peritoneography may be indicated. Table 14.12 shows the maneuvers, which may be used to alleviate the pain. Decreased infusion rate is frequently helpful. If pain occurs only at the beginning of inflow and the end of outflow, incomplete drainage and/or tidal mode for nightly peritoneal dialysis may be successful. Alkalization of conventional dialysate with sodium bicarbonate or use of local anesthetics is sometimes effective, but at the potential cost of increased peritonitis and therapy burden. The use of bicarbonate and bicarbonate/lactate solutions having a physiological pH has been shown to reduce infusion pain [315]. If all these maneuvers are ineffective, the catheter has to be replaced. The replacement catheter should be a coiled one and the catheter should be implanted in such a way that no undue pressure is exerted at the tip.

Table 14.12 Maneuvers to alleviate infusion pain

Slower infusion rate
Incomplete drainage
Tidal mode for nightly peritoneal dialysis
Solution alkalization (sodium bicarbonate: 2–5 mEq/L)
Bicarbonate or bicarbonate/lactate peritoneal dialysis solutions
1% lidocaine – 2.5 mL/L (50 mg/exchange)
Catheter replacement

External Cuff Extrusion

A cuff positioned close to the exit site predisposes it to extrusion. There are at least two forces favoring cuff extrusion (Table 14.13): 1) the pushing force of catheter resilience and 2) pulling and tugging on the catheter. The tendency of a straight catheter implanted in an arcuate tunnel to straighten, due to resilience, plays the most important role in cuff extrusion (Fig. 14.40). Manipulation of the catheter with frequent CAPD exchanges also contributes to this complication. There is also a possibility that high hydrostatic pressure in the abdomen with the constant presence of fluid in the peritoneal cavity, while the patient is ambulatory, also tends to extrude the external cuff.

The external cuff should be implanted approximately 2–3 cm beneath the skin as a compromise between the need of a short sinus tract to prevent infections but not so short as to favor cuff extrusions [1, 223]. Also, resilience forces should be eliminated by creating the tunnel in a shape similar to the shape of the catheter. Tugging on the catheter should be avoided. It is extremely important to avoid resilience forces pushing on the cuff if implanting it

Table 14.13 Causes of cuff extrusion

Catheter resilience
Pulling and tugging
Intra-abdominal pressure?

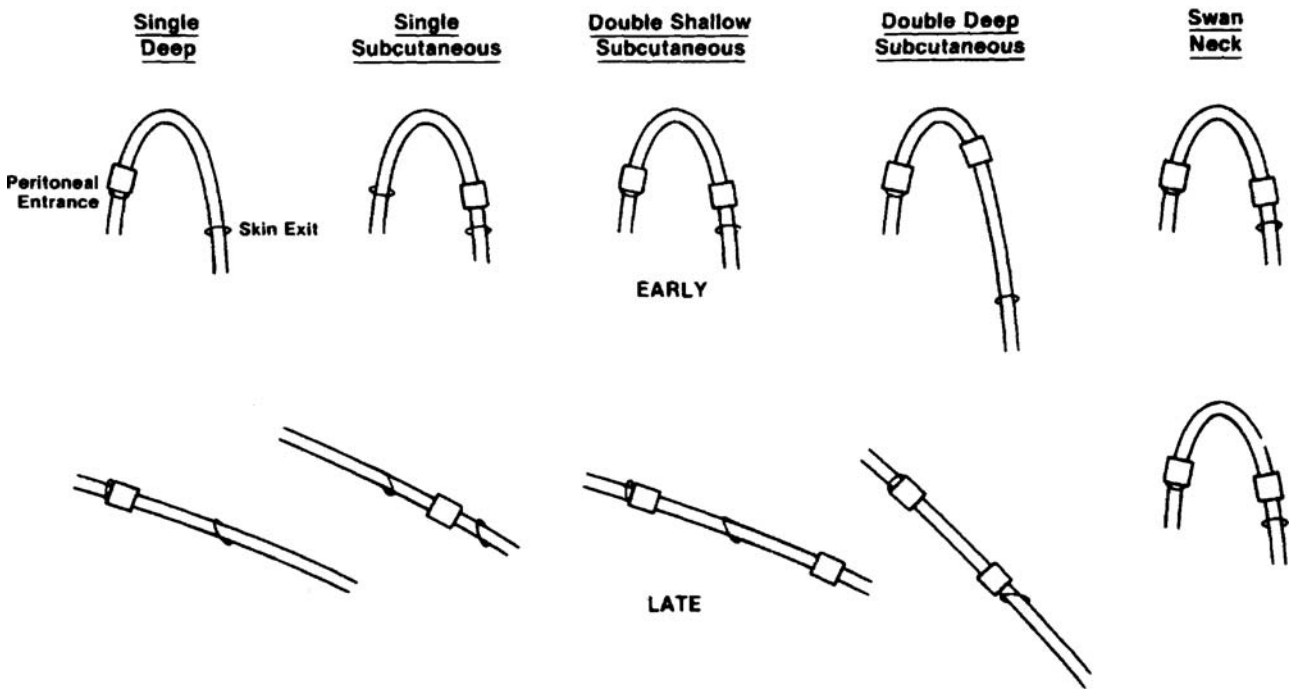

Fig. 14.40 Straight and swan-neck catheters in arcuate tunnels. Upper panel shows catheter configuration immediately after implantation, lower panel portrays catheter shape several months later. Straight catheters forced into arcuate tunnels gradually assume natural, straight configuration. Single-cuff catheters do not extrude cuffs. With long distance between cuffs and shallow subcutaneous tunnel, the external cuff extrusion is inevitable (center), whereas short distance between cuffs and deep position of the subcutaneous cuff precludes its extrusion. Swan-neck catheter maintains its shape

relatively close to the skin exit. The catheter should not be implanted in a site with subcutaneous edema, to avoid cuff extrusion once the edema is resolved. We also recommend a 2-week period of wound healing occur before beginning dialysis training. This helps to seal and anchor the Dacron® cuffs by tissue ingrowth.

If the cuff is not infected it is left alone; however, the cuff usually becomes infected during this process and requires systemic antibiotics or even surgical intervention. If there is no peritonitis and no deep cuff infection then the catheter may be saved, at least for some time, by shaving off the infected superficial cuff [298, 301]. Infection is another cause of cuff extrusion. In this instance the cuff becomes infected while still in the sinus, and is extruded by tissue retraction around the cuff. Two such extrusions were observed with swan-neck Missouri abdominal catheters [83]. We also observed a patient who traumatized her presternal catheter and developed a superficial and mid-cuff infection leading to a tunnel infection. The tunnel was opened and drained and the catheter was shortened to a "one cuff" (deep) catheter which continued to function years after the drainage procedure.

Catheter Obstruction

"Capture" of the catheter by active omentum may cause outflow obstruction. Obstruction from this cause, in the absence of peritonitis, when it occurs is usually a postoperative event (related to a new catheter). We have never seen an obstruction (in the absence of peritonitis) due to omental "capture" as a late event. We believe that Silastic® is more prone to attract omentum very early. In due course of time, with or without use, a proteinaceous (not bacterial) biofilm catheter coating may make the Silastic® less "foreign" to omental tissue. Slow drainage due to catheter translocation, obstruction by bowel, or fibrin clot formation occurs from time to time in some patients. Laxatives and/or addition of heparin 500 U/L of dialysis solution are usually successful in restoring good catheter function. Some patients have permanently translocated catheter out of the true pelvis. If the catheter functions (even with slower drainage), we do not attempt to reposition the catheter. If catheter does not function after implementing simple maneuvers, more aggressive measures, similar to those described in the section on early soft catheter complications should be tried (see above).

An unusual cause of Cruz catheter blockage, which occurred 4 weeks after initiation of dialysis as a result of the tip wrapping by a fallopian tube, has been reported [318]. The fimbriae of the oviduct penetrated through the side-holes of the catheter and occluded the central lumen. Catheter function was restored surgically. A high dialysate flow and bigger side-holes of the polyurethane device (the Cruz® catheter) as compared to silicone rubber catheters might have contributed to this complication.

Catheter-Tip Migration

One- or two-way catheter obstruction is usually the result of catheter wrapping by the omentum. The best condition for dialysate drainage is created with the catheter tip in the true pelvis because, in the majority of people, the omentum does not reach to the true pelvis. Tenckhoff recommended a caudal direction of the intraperitoneal catheter segment to prevent catheter tip migration out of the true pelvis [89]. If the exit site is directed caudally and a straight tunnel points cephalad the catheter *must* have an intraperitoneal bend to place the tip near the true pelvis, and the tip can easily translocate out of the true pelvis due to the silastic "shape memory." The internal cuff operates like a fulcrum on which resilience forces flip the catheter tip into the upper abdomen (Fig. 14.41). If the tip translocates to the left upper abdomen the peristalsis of the descending colon may restore proper position of the tip; however, a tip translocated to the right upper abdomen usually does not return to the proper position because the forces of both catheter resilience and ascending colon peristalsis push the tip upwards. In support of this hypothesis are observations that, when a catheter is implanted with a straight subcutaneous tunnel, with the external exit directed downwards and the intraperitoneal entrance directed upwards, even if the catheter tip is placed into the true pelvis during insertion, it migrates out to the upper abdomen significantly more frequently compared to the opposite tunnel direction [80, 319]. Our experience indicates that the dominant factor in catheter-tip position is the resilience force of the catheter. To avoid the unfavorable influence of resilience forces on the intra-abdominal catheter segment, the catheter needs to be molded in the shape in which it is to be implanted in the tunnel.

The problem of tip migration was approached differently by Oreopoulos et al. [40], who provided the intraperitoneal segment of the catheter with two silicone discs. Once the catheter is in the true pelvis, these discs hinder translocation of the catheter tip. Recently, Di Paolo et al. [48] provided the catheter tip with a small, tungsten weight incorporated into the silicone rubber to prevent catheter migration out of the true pelvis. The migration rate of these

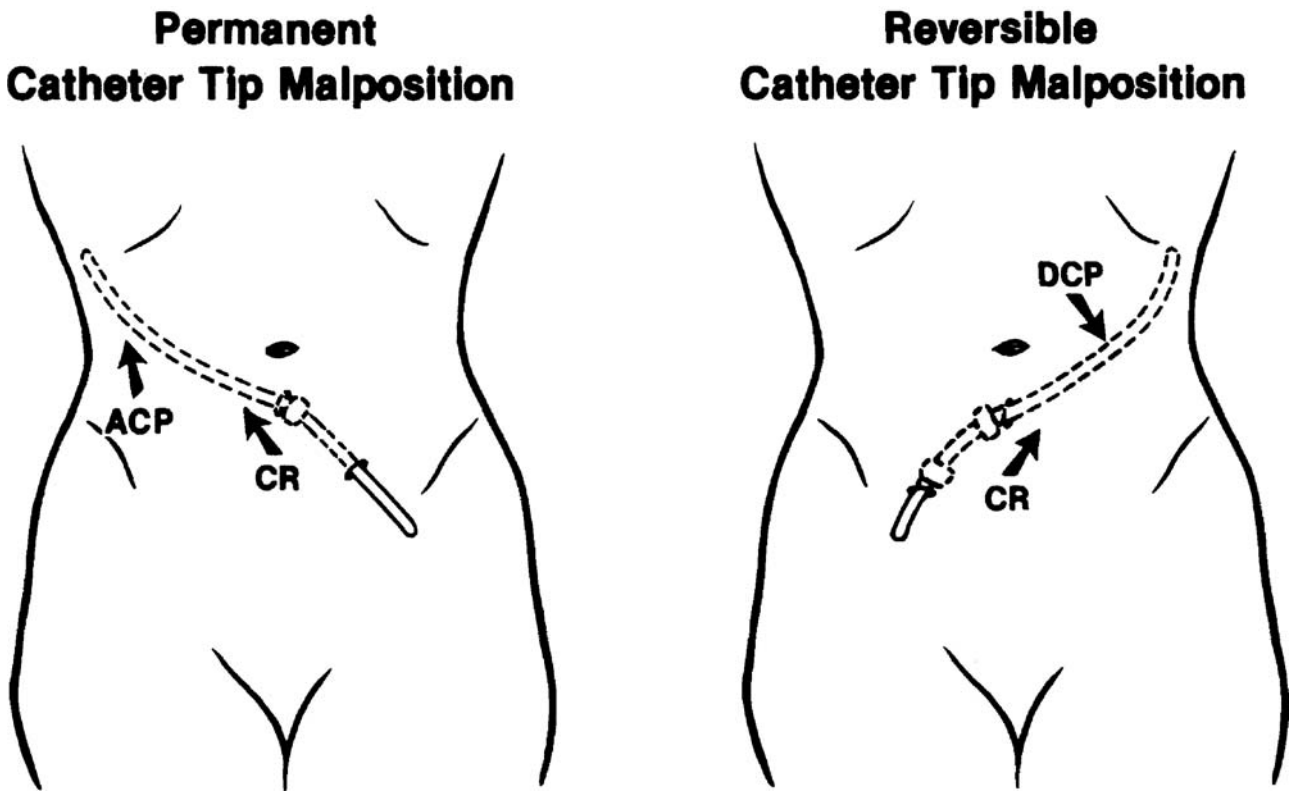

Fig. 14.41 Straight catheter insertion: catheter tip migration out of true pelvis with external exit directed downwards and intraperitoneal entrance directed upwards pointing either to liver or spleen. Note the tendency of catheter to assume its original shape. ACP = ascending colon peristalsis; DCP = descending colon peristalsis; CR = catheter resilience

catheters (no dislocation in 32 catheters over 468 patient-months) was significantly lower than Tenckhoff catheters (nine dislocations in 26 catheters over 415 patient-months). No detrimental effects of these weights were reported. The migration rate of Tenckhoff catheters was unusually high in this study. Catheters with a coiled intraperitoneal segment have more intraperitoneal mass and like the weighted tip catheters appear less likely to migrate out of the pelvis.

Pericatheter Leak

To avoid excessive bleeding, the catheters have frequently been inserted through the midline. In patients treated by intermittent peritoneal dialysis, dialysate leaks are rare because the intra-abdominal pressure is low in the supine position. In CAPD patients, pericatheter leaks are more frequent due to the continuous presence of dialysate in the upright position where the intra-abdominal pressure is higher. Insertion of the deep cuff into the belly of the rectus muscle, as recommended by Helfrich et al. [320], markedly reduces chances of pericatheter leak because of tissue ingrowth from the rectus muscle.

Dialysis solution leaks may occur months or even years after starting CAPD. Management of late leak is similar to that described for early leak. However, most cases of late leak are refractory to conservative therapy and require surgical repair. As discussed earlier, pericatheter leaks are more likely with the midline catheter insertion than with the insertion through the rectus muscle [80, 320]. Similar to the acute leak, this complication is rarely seen with the catheters provided with a bead and polyester flange at the deep cuff (Toronto Western Hospital, swan-neck Missouri abdominal, swan-neck presternal).

Contrary to the early leaks, which are usually external, the late leaks infiltrate the abdominal wall (Table 14.14). The acute leak causes a sudden drop of ultrafiltration and usually occurs after a sudden increase in intra-abdominal pressure (heavy lifting, coughing, or straining). The leak may be mild and intermittent. Such a leak may be difficult to localize. Immediately after leak occurrence the patient may be in good fluid balance without edema of lower

Table 14.14 Late dialysate leak

Acute	Chronic
After heavy lifting, coughing, or straining	Usually a sequela of acute leak
Sudden drop of ultrafiltration	Poor ultrafiltration
May be mild and intermittent	Fluid overload
Abdominal wall edema	Localized abdominal edema
Peau d'orange	Usually without thigh edema
Spongy feeling	

extremities. Abdominal wall edema reveals a dimpling of the skin that gives it the appearance of the skin of an orange *(peau d'orange)* and spongy feeling on palpation. Chronic leak is usually a sequel of an acute leak but may occur gradually. The patient is usually fluid overloaded due to poor ultrafiltration. A repeated peritoneal equilibration test shows unchanged solute transport characteristics but drain volume is lower [321]. Various radiologic procedures to diagnose leaks are discussed below.

Unusual Complications

Organ Erosion

Peritoneal dialysis catheters may cause hemoperitoneum by causing minor tears of the omental vessels [322]. Occasionally, a peritoneal catheter has been reported to have eroded into the mesenteric vessels leading to hemoperitoneum [323]. Peritoneal catheters may cause damage of the internal organs leading to intra-abdominal bleeding [324, 325]. Peritoneal lacerations from a catheter may lead to genital edema or other internal leaks [326]. Erosion into the small intestine, colon, and rectum are also reported on occasion [310, 327–332]. There are reports of transvaginal leak of peritoneal fluid caused by erosion of the vaginal vault by the peritoneal catheter [333, 334].

These complications are mostly described with the straight Tenckhoff catheter and the Toronto Western Hospital catheter [310, 327–331]. Though less common, such complications are also reported with coiled catheters [332]. It is thought that pressure exerted by "soft" but resilient tubing with a pointed tubing end of the straight Tenckhoff catheter or the relatively sharp silastic discs of the Toronto Western Hospital catheter leads to organ or bowel erosion. In most instances, the catheters had not been used for 1–12 weeks before the complication was diagnosed [327, 329–331]. In a dry abdomen, the peritoneum and the bowel are free to rub against the catheter leading to organ erosion.

Mechanical Accidents

Scissors or sharp objects may accidentally cut the external segment of the peritoneal dialysis catheter. Natural wear of catheters after prolonged use, repeated use of clamps, and exposure to certain disinfectants may also cause the catheter to be damaged [335]. Catheters will not self-seal if punctured and such instances may occur during implantation procedure and shaving of the cuff.

To avoid system contamination the patients are instructed to clamp the catheter immediately and cover the area with sterile gauze. If the damage is close to the adaptor, sectioning the damaged segment and inserting another adaptor is a simple procedure. If the damage leaves the catheter too short and there is at least 15 mm of tubing from the exit site, then the catheter may be saved by using the using the peritoneal catheter Peri-Patch® repair kit (Covidien, Mansfield, MA 02048 USA).

The Peri-Patch® repair kit contains a silicone rubber catheter extension with a double-barbed connector inserted in one end and a beta-cap adapter. While repairing the catheter, a sterile procedure must be strictly followed. The operator should "scrub, mask, and glove." A "circulating" nurse should be present to assist. The operating field has to be well protected with sterile towels; the catheter should be wrapped with Betadine®-soaked gauze for 5 min. The catheter is transversely cut with a sterile blade proximal to the damaged site. The catheter clamp is released and the catheter is squeezed with fingers. The patient is asked to strain, to allow dialysate flow from the peritoneal cavity. The flowing dialysate will flush any contaminant. While the fluid is still flowing, the barbed Teflon® tubing of the repair kit is inserted into the catheter as far as possible. Then the silicone rubber tubing of the repair kit is clamped to stop dialysate flow. The connection is dried with gauze. A mould is positioned over the connection and filled with sterile silicone glue. The extension tubing is connected to the catheter in the usual way. The glue cures for 72 h.

Antibiotic prophylaxis for reducing risk of peritonitis should be administered. Using this method we have been able to extend the life of seven peritoneal catheters by a mean of 26 months (range 1–87 months) [335].

Material Breakdown and Catheter Fracture

Functional integrity of the peritoneal catheter is paramount for a successful long-term peritoneal dialysis program. The age of the catheter, the material of the catheter, physical trauma, exposure to chemicals, and oxidants are crucial factors.

Dialysis catheters are made with either silicon rubber or polyurethane. While both these materials are biocompatible, each offers unique characteristics. Silicon rubber catheters cause minimal trauma to surrounding tissues and minimal leeching of plasticizers. Polyurethane has a greater strength and allows catheters to be made with thinner walls and larger lumina [336].

The polyurethane catheters are susceptible to organic solvents and plasticizers [336]. Organic solvents such as alcohol, acetone, isopropyl alcohol, dipropylene glycol methyl ether, deobase (kerosene), and benzene are found in adhesives, adhesive removers, and disinfectants. Plasticizers such as polyethylene glycol are found in ointment bases such as that of mupirocin and naturally in cholesterol and skin oils. The organic solvents can solubilize the polyurethane or cause reversible swelling of the catheter which eventually leads to surface cracking and splitting. Plasticizing agents get absorbed onto the catheters and cause softening or plasticization of the catheters [336]. These changes cause a decrease in tensile strength and lower the yield point. Caution must be exerted to avoid exposure of polyurethane catheters to these solvents and plasticizers. Mupirocin cream instead of ointment should be used in prophylaxis of exit-site infections [268, 337]. Silicon catheters are more resistant to hydrolysis due to their highly cross-linked polymer structure. However, silicone rubber catheters are more likely to be damaged by Betadine® and develop cracks or become brittle [338].

There are reports that inclusion of barium sulfate throughout the entire catheter to render it radiopaque could make the catheter brittle [338]. Currently, the catheters contain only a stripe of barium sulfate and seem to be less prone to this mode of failure.

Implanted peritoneal dialysis catheters are also subjected to mechanical trauma and biodegradation. Silicon catheters usually develop surface erosions with time, largely as a consequence of dynamic mechanical stress. In contrast, polyurethane catheters develop deep fissures and cracks that are likely caused by a combination of macrophage and leukocyte oxidation, environmental stress cracking, and mineralization [339–342].

Allergic Reactions

Among the differential diagnosis of cloudy bags is peritoneal fluid eosinophilia. This condition is diagnosed when eosinophils constitute greater than 10% of the total peritoneal fluid white blood cell count and the eosinophil count exceeds 100 cells per cubic milliliter of peritoneal effluent.

In many cases the peritoneal fluid eosinophilia occurs early after the initiation of PD and is felt to represent a reaction to the plasticizers in the PD catheter or plastic dialysate bags [343, 344]. Other causes include introduction of air or blood into the peritoneum [345], bacterial peritonitis [346], and reactions to icodextrin [347, 348] and dialysate additives. Prior reports put the incidence between 5–61%, but the incidence has significantly receded in recent years due to improvement in the quality of peritoneal dialysis materials. In most cases the eosinophilia resolves without treatment [343, 349, 350]. Coating of the catheter with proteinaceous biofilm may decrease its ability to cause an allergic reaction. Persistent cases may respond to steroids or a mast-cell-stabilizing antihistamine [351–354].

Allergic eosinophilic dermatitis due to silicone rubber is also reported [355]. Topical therapy with steroids or antihistamines may help in some patients.

Radiologic Imaging in Diagnosis of Complications

Peritoneal dialysis catheters contain radiopaque materials that allow the catheter position to be determined by simple abdominal radiographs. The catheter tip should lie deep in the Pouch of Douglas. Plain radiographs also provide information on constipation and ileus, which may impact catheter performance. Contrast catheterograms performed by injecting iodinated contrast material through the PD catheter may be useful in identifying catheter obstructions, kinks, and adhesions around the catheter.

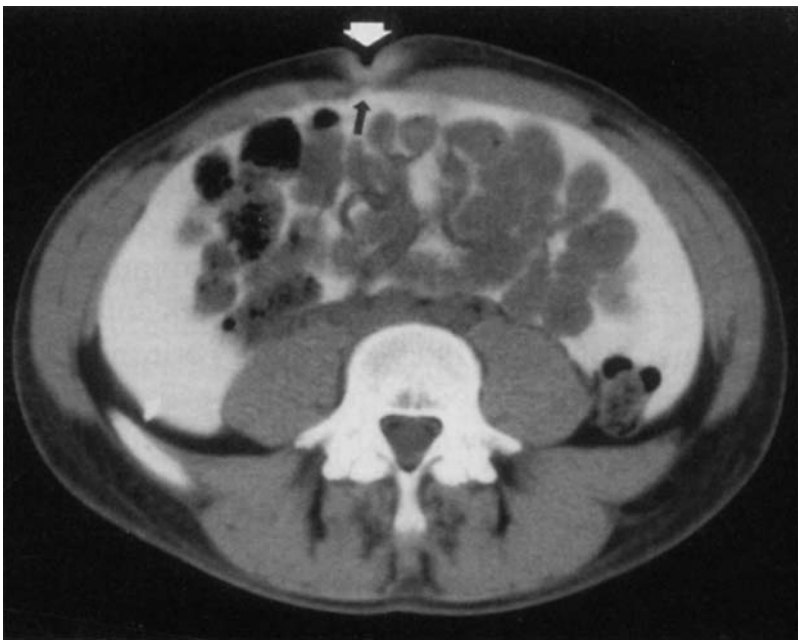

Fig. 14.42 In a CAPD patient a small area of swelling around the umbilicus occurred after lifting a 100 lb weight. CT scan of the abdomen after infusion of 2 L of contrasted dialysate shows a small amount of extravasated contrast containing dialysate in the umbilical area (white arrow)

While plain computerized tomography scans of the abdomen are useful in diagnosis of some complications, these have been replaced by CT-peritoneography. One hundred to 300 mL of iodinated contrast is added to 1,000–2,000 mL of peritoneal dialysate and instilled into the abdomen [356–358]. After instillation of this solution, the patient is encouraged to roll on his or her sides or to walk or perform other activities that may increase the intra-abdominal pressure. An option to increase intra-abdominal pressure is to increase the instilled volume of dialysate by 500 mL over the usual fill volume. A CT scan is performed approximately 2 h later. This procedure allows for the diagnosis of leaks, hernias, adhesions, and chronic peritoneal sclerosis and may identify etiologies of recurrent or relapsing peritonitis. An example of a leak in the periumbilical area without relation to the catheter is shown in Figs 14.42 and 14.43. A leak around the Tenckhoff catheter implanted through the midline is shown in Fig. 14.44.

An alternative to CT-peritoneography is MRI-peritoneography [359–361]. While the MR scans are usually performed using gadolinium-based dye added to dialysate, saline or the dialysate itself can provide a hyper intense

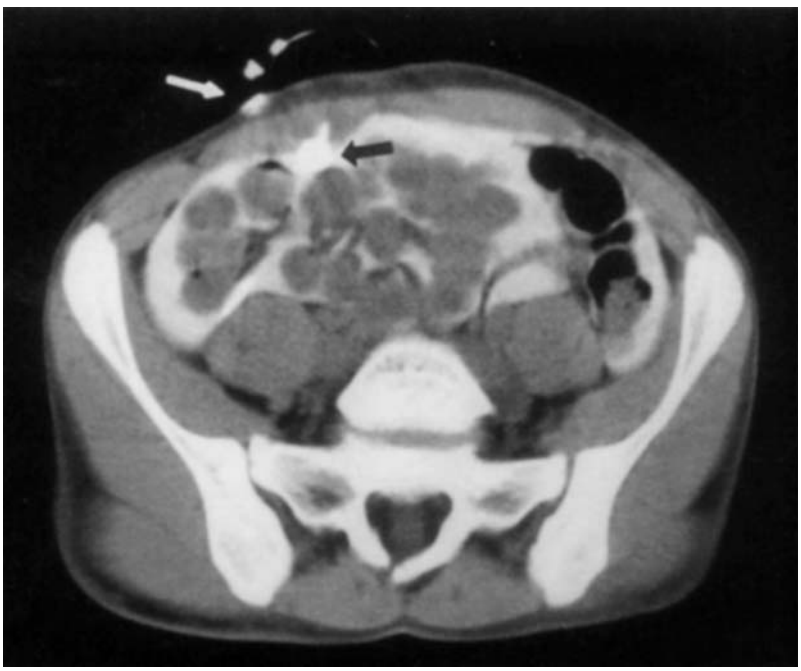

Fig. 14.43 Swan-neck Missouri catheter entering the peritoneal cavity in the vicinity of the extravasated fluid. The intraperitoneal bead (black arrow) and intramural segment leaving the subcutaneous tunnel (white arrow) are clearly recognizable. No extravasated fluid is seen around the catheter entrance into the peritoneum. Pericatheter leak is ruled out

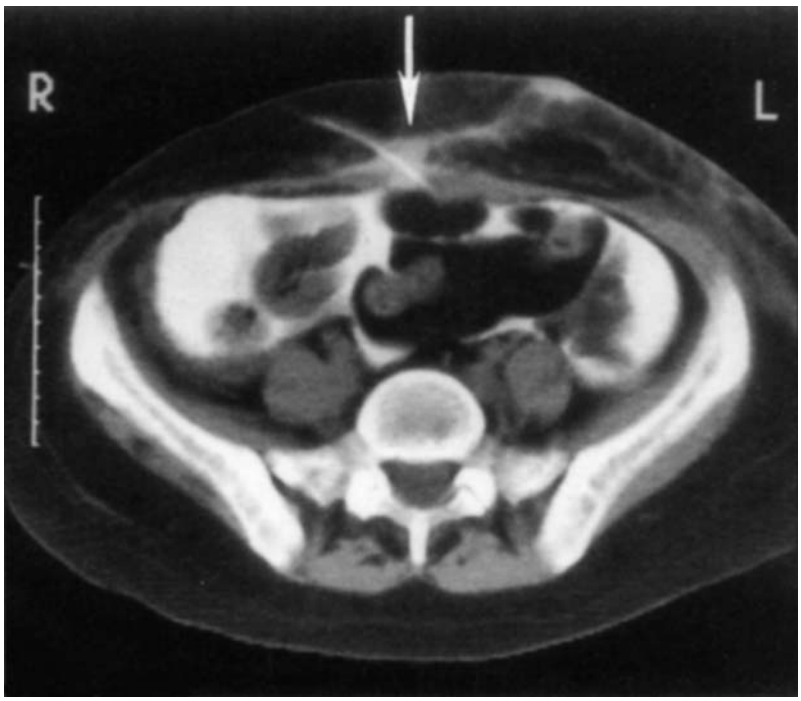

Fig. 14.44 Contrast-enhanced dialysate extravasating around the Tenckhoff catheter (arrow) implanted through the midline

image on T2 imaging due to the electrolyte content of the solution [360]. A potential risk of nephrogenic systemic fibrosis has been described with the intravenous administration of gadolinium in patients with kidney disease [362] but not with intraperitoneal administration so far. A retroperitoneal leak is demonstrated in Fig. 14.45.

Peritoneal scintigraphy is performed by adding 2–5 millicuries of technetium 99 m isotope to a bag of peritoneal dialysis solution [363, 365]. Multiple views in anterior-posterior, lateral, and oblique projections are taken to diagnose leaks and hernias. After completion of the procedure, the dialysate along with the instilled isotope is drained limiting the dose of radiation exposure [365]. Delayed scans are recommended in initially negative studies to diagnose small leaks [364].

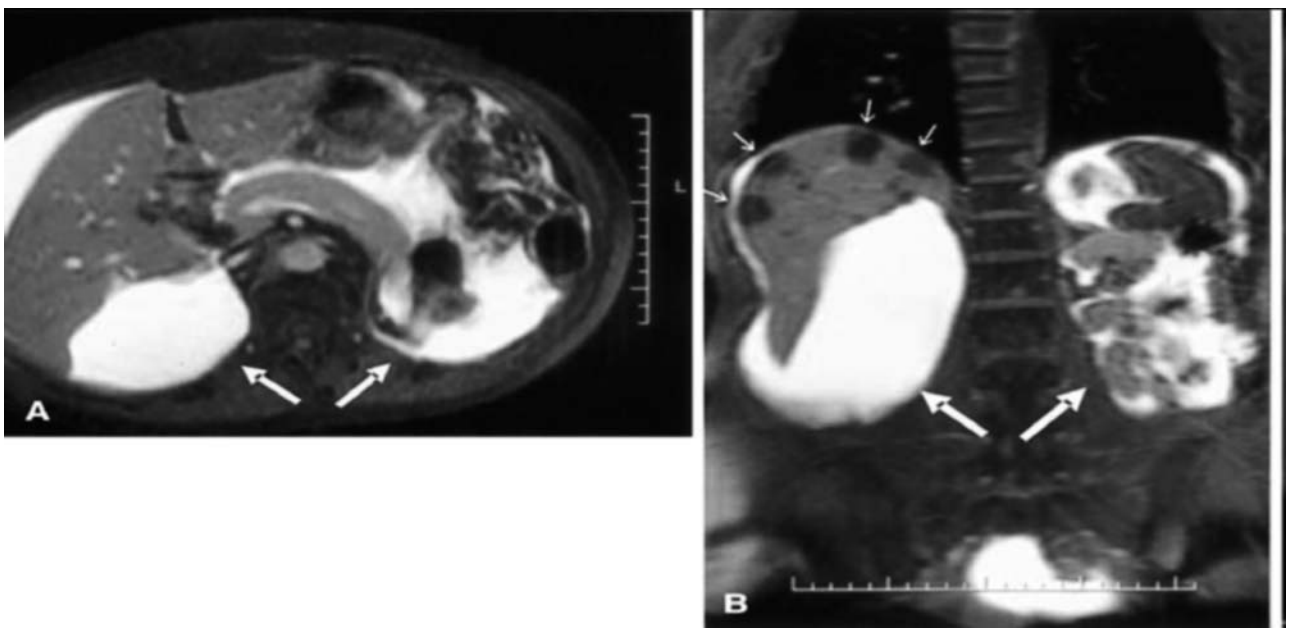

Fig. 14.45 Retroperitoneal fluid leak. (a) axial and (b) coronal T1-weighted images demonstrate retroperitoneal fluid leak (large arrows) in a patient who had bilateral nephrectomy secondary to polycystic kidney disease. Note multiple liver cysts (small arrows). With permission from Springer Science and Business Media [361]

An ultrasound is a good modality to assess the catheter tunnel. High resolution images can be obtained with a high frequency transducer. The intraperitoneal catheter is hard to visualize with ultrasound but Doppler interrogation while injecting saline may reveal the tip [292, 366, 367]. Due to the echogenicity of the catheter wall, acoustic shadows may hide fluid collections unless the tunnel is carefully examined from different angles. The ultrasound is an excellent modality to diagnose catheter tunnel and cuff infections [292, 367]. The normal catheter tunnel has a low-echo circumferential rim around the catheter and the cuff is seen as a cotton-like isoechoic area [366]. Tunnel infections cause a widening and loss of clarity of the circumferential area around the catheter. Abscesses may also be diagnosed on ultrasound and appear larger areas of decreased echotexture. Abscesses may be compressible and Doppler interrogation may show increased blood flow in the wall with no signal from the center of the pus collection [368]. Ultrasounds may also be used to follow response to therapy. This has been discussed in the section on exit-site infections.

Catheter Removal

Indications

The need for catheter removal occurs under various conditions. These may be broadly categorized under two headings: catheter malfunction and complicating medical conditions with a functioning catheter. Finally, the catheter may be removed electively because it is not needed.

Catheter Malfunction

The decision to remove the catheter is usually made only when conservative measures (described in the sections on early soft catheter complications and catheter obstruction, and in Table 14.10) to restore function have failed. Catheter malfunction requiring catheter removal may be seen in the following conditions: 1) intraluminal obstruction with blood or fibrin clot or omental tissue incarceration, 2) catheter tip migration out of the pelvis with poor drainage, 3) a catheter kink along its course, 4) catheter tip caught in adhesions, and 5) accidental break in the continuity of the catheter.

Functioning Catheter with a Complication

Under the following conditions catheters may have to removed: 1) recurrent peritonitis with no identifiable cause; 2) peritonitis due to exit-site and/or tunnel infection; 3) catheter with persistent exit-site infection; 4) tunnel infection and abscess; 5) late recurrent dialysate leak through the exit site or into the layers of the abdominal wall; 6) mycobacterial or fungal peritonitis; 7) bowel perforation with multiple organism peritonitis; 8) refractory peritonitis of other causes; 9) severe abdominal pain either due to catheter impinging on internal organs or during solution inflow; and 10) catheter cuff extrusion with infection.

Functioning Catheter That Is No Longer Needed

This situation is encountered after a successful renal transplantation or peritoneal dialysis is discontinued because dialysis is no longer needed, or the patient transfers to another form of dialysis.

Removal Methods

Uncuffed Catheter

Removal of the uncuffed catheter is a simple procedure. After cutting the anchoring suture the catheter is simply pulled out and the opening is covered with a sterile dressing.

Cuffed Catheters

A Tenckhoff catheter inserted through the midline may be removed at the bedside. After preparation of the operating field, local anesthesia is applied around the cuffs, the incisions are reopened, the cuffs are excised, and the catheter is pulled. The incisions of catheters removed for cuff/tunnel infection should be packed open and allowed to heal by

second intention. In our experience, calcium–sodium alginate fibers (Kaltostat Wound Dressing) are excellent for wound packing. The fibers absorb exudate very efficiently, control minor bleeding, and protect the wound from contamination. Once-daily dressing change is usually sufficient for wound packing with the fibers.

The catheters inserted through the belly of the rectus muscle require surgical dissection in the operating room to remove. Although the catheter can be removed using a local anesthetic, patient comfort usually dictates a general anesthetic, particularly for the Toronto Western Hospital, swan-neck abdominal Missouri, and presternal catheters. After an appropriate surgical scrub and routine draping the incision is reopened. The anterior rectus fascia is reopened along the site of the previous incision and the catheter/cuff/flange are sharply dissected free of the ingrown rectus muscle. The previously placed fixation sutures in the flange and the purse-string sutures are cut and, with traction and continued sharp dissection, the abdominal portion of the catheter is removed. Care must be taken to protect the underlying viscera. The remaining small opening into the abdomen is closed with O or OO Prolene® sutures. The anterior fascia is reapproximated in a similar fashion. Depending on the clinical indication for removal, the incision may either be closed or packed open and allowed to heal by second intention.

Swan-Neck Presternal Catheter

Removal of a swan-neck presternal peritoneal dialysis catheter is a surgical procedure performed in the operating room, preferably with general anesthesia. After an appropriate surgical scrub and routine draping of both the chest and abdomen, both the chest and abdominal incisions are reopened. Bleeding is controlled with electrocautery. Using blunt and sharp dissection, the two cuffs at the bent portion of the catheter are freed from the adjacent subcutaneous tissue. Working from the abdominal incision, the catheter is divided between sutures *above* the titanium connector. The chest portion of the catheter is pulled out in a cephalad direction through the chest (parasternal) incision. The abdominal part of the catheter is then removed in an identical way as described for the swan-neck Missouri abdominal and Toronto Western Hospital catheters. Depending on the clinical indication for removal the two incisions may either be closed or packed open and allowed to heal by second intention.

Operations in Peritoneal Dialysis Patients

Extra-Abdominal

A number of operative procedures may be carried out in the dialysis patient. The patients may undergo a variety of extra-abdominal operations such as coronary artery bypass, lower extremity revascularization, carotid endarterectomy, and, on occasion, the creation of a hemodialysis access. Prior to the operative procedure the dialysis fluid should be drained. Since the abdominal cavity has not been violated, dialysis may be started immediately following the patient's return to the surgical floor. Special caution is required in patients who have presternal catheters. Patients undergoing coronary artery bypass surgery or thoracotomy require particular attention to the location of the presternal catheter to avoid damage to the catheter. Peritoneal dialysis may be restarted on the day of surgery in the supine position in these patients.

Abdominal

A whole series of abdominal operations may be contemplated and carried out in patients on chronic ambulatory peritoneal dialysis. The operations range from cholecystectomy to colectomy to hernia repairs. Operations on the abdominal wall carry less risk to the patient from the standpoint of developing peritonitis or catheter loss. These operations include all abdominal wall hernias and they can be carried out with some ease and a high degree of safety.

Intra-abdominal procedures on the intestine or the gallbladder for acute or chronic disease may predispose to a risk of infection or loss of the catheter secondary to infectious complications. Procedures such as laparoscopic cholecystectomy can be carried out with minimal risk of spillage of bile or contaminated contents, and after rinsing the abdominal cavity the catheter can be rested and dialysis begun in a few weeks time. In the case of a perforated viscus such as a perforated sigmoid diverticulum or a perforated peptic ulcer with peritoneal soilage the catheter will undoubtedly be lost at that setting. It is safer to remove the peritoneal catheter with massive abdominal soilage because the presence of a foreign body will often prolong or potentiate the risk of persisting infection. Once the patient

is recovered from the acute intra-abdominal process consideration can be given to restarting peritoneal dialysis. Depending upon the extent of peritonitis and intra-abdominal adhesion formation, peritoneal dialysis may or may not be possible.

In general, prior to abdominal procedures the abdomen should be drained prior to operation. In our institution we use a first-generation cephalosporin as a prophylactic antibiotic for elective operations and therapeutic antibiotics based on culture for operations associated with significant intra-abdominal soilage. As mentioned, those patients having significant intra-abdominal peritonitis are better served by removal of their catheter at the time of their initial operation with a re-establishment of peritoneal dialysis at a future date. After an elective operation such as cholecystectomy, in-and-out exchanges in the supine position are started immediately after the patient reaches the floor. We limit the volume of exchanges to 1 L and heparin 1,000 units per liter are added to the fluid. These exchanges continue until the dialysate is clear. Ceftazidime 500 mg is added to the last exchange and that exchange is not drained. Metronidazole 500 mg *per os*/intravenous/rectal is used for 5 days following elective procedures. The day following the operation, in-and-out exchanges are repeated until the dialysate is clear and again 500 mg of ceftazidime is added to the last exchange, which is not drained for 12 h.

To prevent incisional hernia/leak ambulatory peritoneal dialysis is delayed for 2–6 weeks depending upon the type of operation and the general condition of the patient. Collagen maturation is slower in diabetic, immunosuppressed, and undernourished patients. Restart of peritoneal dialysis should be delayed in such patients.

Concluding Remarks

Peritoneal catheters are lifelines for peritoneal dialysis patients. While advances in catheter placement and subsequent care have made it possible to obtain and maintain access to the peritoneal cavity safely over an extended period of time, catheter-related complications remain responsible for over 20% transfers out of peritoneal dialysis. Meticulous care starting prior to catheter insertion with choosing the site of insertion, appropriate surgical techniques, and subsequent care are essential to the success of peritoneal access. Complications must be addressed early to save the catheter and the peritoneum complimented by the use of appropriate imaging techniques. Further research and innovation will form the basis of future improvements in outcomes.

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Chapter 15
Monitoring the Functional Status of the Peritoneum

D.G. Struijk and R. Khanna

The integrity of the peritoneal membrane is essential for long-term treatment of peritoneal dialysis (PD) patients. Unlike an artificial kidney used for hemodialysis, the peritoneal membrane consists of living tissue. This implies that the properties of this membrane are not constant, but may change under the influence of endogenous or exogenous factors. Thus, it is important to monitor the peritoneal membrane in time. Data obtained during follow-up are crucial in the development of more biocompatible solutions. For the individual patient these data could be used to tailor the dialysis adequacy or to predict clinical problems such as ultrafiltration failure or peritoneal sclerosis.

Direct evaluation of the peritoneal membrane is not feasible, as until now no simple, effective, and safe procedure exists to obtain peritoneal tissue during the dialysis period. Peritoneal tissue can be obtained during surgical procedures for various indications, which usually also mark the end of the peritoneal dialysis treatment. Fortunately, each dialysis exchange can provide valuable information about peritoneal structure and function. In this chapter the various methods to indirectly analyze the peritoneal membrane will be described. First, attention will be given to measurement of markers in peritoneal effluent. Secondly, monitoring the peritoneal membrane by using its properties to transport solutes and water will be discussed.

Mesothelial Cell Markers

The Mesothelium

The main function of the mesothelium is prevention of friction between abdominal organs when they move, and thereby prevention of the formation of adhesions. During PD, mesothelial cells are also likely to be involved in local host defense [1]. The currently used PD solutions are toxic to cultured mesothelial cells [2]. They reduce cell viability [3], inhibit the synthesis of interleukin (IL)-6 and prostaglandins [4], and induce apoptosis [5]. Data obtained from incidental peritoneal biopsies indicate that PD leads to signs of mesothelial degeneration and regeneration [6–12], as well as replacement of the mesothelial cell layer by a thick fibrous band in long-term PD patients [13] and patients who develop peritoneal sclerosis [12, 14]. Acute infectious peritonitis is associated with discontinuity or denudation of the mesothelial layer [8, 12–15]. Remesothelialization usually occurs after the infection has been cured but it might be incomplete [8, 13, 16]. Mesothelial-cell cultures from effluents during peritoneal dialysis show markedly varied morphologic features, ranging from a cobblestone-like appearance similar to that of mesothelium derived from omentum to fibroblast-like cells or mixed cell populations [17].

Cancer Antigen 125 (CA125) as a Marker of Mesothelial Cell Mass

In vivo study of the mesothelium has become possible by the discovery of CA125 as a marker of mesothelial cell mass or cell turnover in stable continuous ambulatory peritoneal dialysis (CAPD) patients [18, 19]. CA125 is a glycoprotein with a molecular weight exceeding 200,000 Dalton in gel filtration experiments [20]. However, size heterogeneity is present. The murine monoclonal antibody OC125 detects two subunits, 237,000 Da and 186,000 Da. Higher and lower molecular weight subspecies, present in the cytoplasm and extracellular matrix of CA125-producing cells, were found

D.G. Struijk (✉)
Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
e-mail: d.g.struijk@amc.uva.nl

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using other monoclonal antibodies [21]. CA125 is expressed in coelomic epithelium during embryonic development [22]. In adult tissues, CA125 has also been demonstrated on the epithelium of the female genital tract and on mesothelial cells in the pleura, pericardium, and peritoneum, particularly in areas of inflammation and adhesions [22]. The function of CA125 is unknown.

CA125 in Serum During Various Conditions and Renal Replacement Therapy

The development of a radioimmunoassay for CA125 concentrations in serum [23] enabled its use as a tumor marker for ovarian neoplasm's [24–29]. It has also been detected in cells of some benign ovarian tumors and in other carcinomas, especially in those of the uterus, cervix, and breast [30, 31]. Besides increased serum CA125 levels in ovarian cancer, increased concentrations in various other conditions have also been found, such as endometriosis [32], pelvic inflammatory disease [33], and malignant peritoneal mesothelioma [34], and in patients with various liver diseases [35].

During renal replacement therapy most studies on this subject showed that serum concentrations in hemodialysis patients [36–38] and PD patients [18, 39, 40] were similar to those obtained in individuals with normal renal function. One study reported higher concentrations in hemodialysis and PD patients than in normal controls and patients with a functioning kidney graft [41]. Another study in hemodialysis patients only showed increased serum concentrations when fluid in the serosal cavities (peritoneum, pleura, or pericardium) was present [42]. In contrast, low values have also been described in PD [43]. One study reported an increase in serum CA125 after implantation of a PD catheter and during peritonitis [44], but the latter finding could not be confirmed in another investigation [45]. The difference between the two studies is that peritonitis, catheter implantation, and other abdominal surgery were taken together in the former [44], but abdominal surgery and catheter removal were not included in the latter [45]. It can be concluded from the above studies that serum CA125 is not influenced by renal function or by the type of renal replacement therapy.

CA125 in Ascites

High peritoneal fluid concentrations of CA125 can be found in ascites of patients with liver disease [35], in fluid obtained during gynecologic surgery [46, 47], and in healthy women undergoing laparoscopy [47]. The cutoff value in the latter study was 8,450 U/mL, a value that exceeds normal serum concentration by about 2,000-fold. This suggests local intraperitoneal production or release. The decrease in serum CA125 that was found after paracentesis in patients with liver disease also suggests that CA125 in the ascitic fluid was the cause of the elevation [35]. The presence of CA125 in mesothelial cells [22], the high values in mesothelioma [34], as well as the increase after mechanic [48] and infectious [35] trauma to the mesothelium, make it likely that peritoneal mesothelial cells are the source of CA125 in peritoneal fluid.

Release of CA125 by Cultured Human Peritoneal Mesothelial Cells

Mesothelial cells can be obtained by enzymatic digestion of pieces of omentum [49] and cultured until confluence and for 10 days thereafter [50]. In two studies the CA125 concentration in the supernatant increased with the duration of culture and was proportional to the amount of cells brought into culture [18, 19]. The increase in supernatant CA125 was exponential before confluence and linear after that time point [19]. This is consistent with a constant production in time per cell. Most of the secretion was constitutive and from the apical side [19, 51]. On the contrary, in a recent study no relation was found between the number of mesothelial cells after lysis with trypsin and CA125 in the supernatant [52]. One study reported a limited increase in CA125 release after stimulation with cytokines such as IL-Iβ and tumor necrosis factor (TNF)-α at day 5 of the culture [51], but this could not be confirmed in two other studies using the same cytokines at day 8 of the culture [19] or after reaching confluence [52]. This suggests that stimulation with cytokines has some effect on CA125 production when the confluence of the monolayer is not perfect, but that a confluent mesothelial monolayer releases CA125 only constitutively. Finally, chronic exposure of mesothelial cells for 4 weeks to glucose (45 mM) decreased the CA125 content of their cytosol and the release of this antigen into the culture medium while cytokine production increased [52]. This confirmed earlier experiments from the same group and, as not all cell functions were reduced, the authors explained their results by changes in the phenotype of the mesothelial cells [53]. Whether the in vitro experiments can be extrapolated to the human situation remains questionable, as studies with more biocompatible dialysate solutions but still containing glucose almost universally demonstrated an increase of CA125 concentration in time (see below). Lysis of freshly isolated omental cells showed the presence of intracellular CA125, the amount ranging from 0.16 to 0.31 U/10^3 cells [19], indicating a marked intraindividual variability. CA125 is almost undetectable in lymphocytes, monocytes, granulocytes, and fibroblasts [45], making peritoneal mesothelial cells the most likely source for local CA125 release during PD. From the above in vitro studies with cultured

mesothelial cells showing a constitutive release after confluence, it can be concluded that CA125 released from mesothelial cells probably can be used for follow-up of mesothelial cell mass in individuals, as long as no lysis of cells occurs. It most likely cannot be used for interindividual comparison of mesothelial cell mass.

CA125 in Peritoneal Dialysate in Stable Peritoneal Dialysis Patients

Mesothelial cells in peritoneal effluent are CA125-positive when investigated with immunohistochemistry [18, 54]. The median percentage of CA125-positive cells was 92%, but ranged between 0 and 100%. Values between 75 and 100% were found in 80% of patients [54]. In most studies a relationship was found between the number of mesothelial cells in peritoneal effluent of PD patients and effluent CA125 concentration [18, 19, 54]. In one paper where the authors used flow cytometry analysis to count mesothelial cells in effluent and a radioimmunoassay to measure CA125 [55], no relationship was found. This might be caused by differences in methodology as the flow cytometry counting method for mesothelial cells has a poor correlation with results obtained by microscopy [54] due to the presence of clusters of mesothelial cells. Also, radioimmunoassay for the measurement of CA125 was not validated in peritoneal effluent and has been reported to be unreliable for low concentrations [56].

A first cross-sectional analysis with a commercial microparticle enzyme immunoassay to measure CA125 concentrations in the effluent of the long night dwell in 24 patients on continuous ambulatory PD yielded values ranging between 5.2 and 76 U/mL, median 18 U/mL [18] (the measurements of CA125 are done on the effluent of the patient itself; centrifugation or concentration procedures are not necessary). Subsequently, it was shown that CA125 dialysate concentrations increased linearly during a 4-h dwell [57, 58] as well as dwell exceeding 4-h [59]. Because of the effect of time on concentrations, low values have been found when measured after a 4-h standardized dialysis dwell [60], which implies that either the method should be accurate in the low range, or longer dwells should be used. Although the glucose concentration of the dialysate has no significant effect on CA125 release [57], a high glucose concentration will cause more ultrafiltration and therefore decrease effluent CA125 concentration. To compare CA125 in samples with various dwell times it was advised to calculate appearance rates of CA125 [59]. One group advocates correction of CA125 appearance rate for body surface area, but the evidence is not convincing [61].

Dialysate CA125 is not influenced by gender [39]. The majority of cross-sectional studies found no relationship between CA125 appearance rate and patient age in adults [39, 61] and children [62, 63]. One study suggested a relation between CA125 and persistent inflammatory state, indicated by elevated serum IL-15 levels, and leading to a negative influence on nutritional status [64]. Due to the limited number of patients included in the cross-sectional studies, and the various methodologies used, normal baseline values for dialysate CA125 have not yet been established.

CA125 and Peritoneal Transport

Mesothelium is unlikely to be directly involved in the transport of solutes from the circulation to the dialysate [65]. Transport is dependent mainly on vascular surface area, that is, the number of perfused peritoneal capillaries [66, 67]; but an indirect effect of mesothelial cells cannot be excluded. Cultured mesothelial cells are able to produce various cytokines, chemokines, and prostaglandins, some of which are vasoactive [68] and involved in the changes in peritoneal permeability that occur during peritonitis [69–71]. Some studies reported a positive correlation between dialysate-to-plasma ratios of creatinine and dialysate CA125 [55, 72, 74], while this was not found in other studies [39, 58, 60–62]. This positive relation was found especially in the early phase of the dialysis treatment and might be explained by cytokines and vasoactive substances produced by mesothelial cells [73, 74]. The increase in peritoneal transport in time has been explained by neovascularization in the peritoneal membrane [75]. This could explain the disappearance of the initial relation between CA125 and peritoneal solute transport in long-term peritoneal dialysis.

Dialysate CA125 and Duration of Peritoneal Dialysis

A first cross-sectional analysis in stable PD patients showed a large interindividual variability of dialysate CA125 during the first 2 years of PD in some patients [60]. All patients treated for more than 4 years, however, had values below 12 U/mL. A similar effect of duration of PD was confirmed in some later studies [39, 54, 62, 72] but not in others [55, 58, 61, 62]. Differences in duration of follow-up or methodology of the CA125 determinations may have caused these variable results. However, a decrease in CA125 appearance rate has been found during longitudinal analysis [57, 76, 77]. Low values have been found in peritoneal sclerosis patients [78–79]. It can be concluded that a single low CA125 appearance rate is difficult to interpret. Serial longitudinal observations showing a decrease suggest loss of mesothelial cell mass.

Temporary discontinuation (peritoneal resting) has been advocated in PD patients with peritoneal hyperpermeability and ultrafiltration failure [80, 81]. Patients treated with peritoneal resting for clinical signs of peritoneal membrane failure later on during their treatment had lower dialysate CA125 levels than those not needing temporary discontinuation [58]. Although experience is limited, peritoneal resting might lead to an increase in effluent CA125 [79]. In one study it was suggested that, when CA125 concentration did not increase after withdrawal of peritoneal dialysis, this was predictive for peritoneal sclerosis development [79].

Dialysate CA125 and Peritonitis

Acute peritonitis causes an early increase in CA125 appearance rate to more than twice the control value obtained after recovery from infection [45]. The maximum value is reached on the second day and is followed by an initial decrease, and then followed by a second increase on days 4–6. Patients with a large increase in CA125 had more severe peritonitis, as judged by higher effluent cell counts and higher hyaluronan appearance rates. The time-course during peritonitis suggests an initial increase due to massive release from necrotic mesothelial cells, followed by remesothelialization. However, this explanation needs further confirmation.

Dialysate CA125 concentrations after recovery from peritonitis were not different from those in stable PD patients [45]. Together with the absence of a relationship with the incidence of peritonitis [39, 55, 58, 60–62, 72], this finding suggests that remesothelialization occurs after a majority of peritonitis episodes. However, a sudden irreversible drop in dialysate CA125 has been described in one patient after an episode of peritonitis caused by *Pseudomonas aeruginosa* [57]. A further analysis comparing pre- and postperitonitis CA125 appearance rates showed that a decrease of more than 10% was present in half of the episodes [82]. This occurred especially in peritonitis caused by *Staphylococcus aureus*.

It can be concluded that the interpretation of the CA125 appearance rate during peritonitis is different from that in stable PD patients. High concentrations during peritonitis are therefore not indicative of a large mesothelial cell mass, but of massive necrosis.

Dialysate CA125 as Marker of Biocompatibility of Dialysis Solutions

Long-term PD causes alterations to the peritoneal membrane, most probably due to continuous exposure to currently used bioincompatible dialysis solutions (Chapter 27). Loss of mesothelial cells is one feature of these alterations. Studies with dialysis solutions that are more biocompatible from a theoretical point of view have been done mainly in vitro [2]. By virtue of their nature, exposure time is short in these studies. Follow-up of dialysate CA125 in patients during treatment with more biocompatible dialysis solutions could provide information on their biocompatibility in vivo, at least with respect to the mesothelium. Increasing CA125 concentrations in the absence of inflammation during follow-up suggests an increase in mesothelial cell mass.

In the vast majority of all clinical studies using more biocompatible dialysate solutions CA125 in the dialysate increased, whereas it decreased after switching to the standard solutions [78, 83–93]. It appears from these studies that dialysate CA125 is a useful marker for in vivo biocompatibility assessment of dialysis solutions, at least with respect to their effect on mesothelium.

Conclusions

Changes in dialysate CA125 over time probably indicate changes in peritoneal mesothelial cell mass in noninfected PD patients. For proper assessment, the duration of the dwell should be standardized or CA125 production expressed as appearance rate. Due to the large interindividual variability, probably caused by differences in the number of cells expressing CA125 and in the amount of CA125 per cell, a single measurement is often not informative, especially when a low value is found. The main importance of dialysate CA125 is in the follow-up of individual patients, where a decline indicates loss of mesothelial cell mass and failure to increase after peritoneal resting might predict the development of peritoneal sclerosis. The CA125 concentration can also be used as an in vivo marker of biocompatibility in the evaluation of new dialysis solutions. However, more research is necessary, especially on the field of morphological functional relationships.

Other Mesothelial Cell Markers

Cultured mesothelial cells are capable of secreting a large number of substances other than CA125, such as phosphatidylcholine, hyaluronan, cytokines, chemokines, and factors for coagulation and fibrinolysis. All these substances are also present in the peritoneal effluent of CAPD patients.

Phospholipids

The phospholipids in drained dialysate consist of phosphatidylcholine for 55–85% [94–96]. The phospholipids synthesized by cultured mesothelial cells have a similar fatty acid composition [96]. Their composition is markedly different from that of the phospholipids present in cell membranes [96]. The phospholipids are stored in the lamellar bodies within the mesothelial cells and secreted by exocytosis of these bodies from the apical part of the cells [98, 99]. The role of phosphatidylcholine in serous cavities is probably to decrease friction between the various organs that they contain [96]. Probably the phosphatidylcholine concentration in peritoneal effluent can be regarded as an indicator of the metabolic activity of the mesothelium during peritoneal dialysis.

Glycosaminoglycans

Serum levels of hyaluronan are higher in patients with renal failure and hemodialysis and in CAPD patients than in subjects with normal renal function [100–103]. Glycosaminoglycans are also present in CAPD effluent as proteoglycans and hyaluronan [104, 105]. Increased hyaluronan levels in serum as well as dialysate are found to be accurate predictors of death and morbidity in CAPD [100, 106]. The hyaluronan concentration in the dialysate exceeds its serum concentration by two- to threefold [100, 101]. Using gel permeation chromatography on peritoneal effluents and supernatants of cultured mesothelial cells, no size differences in hyaluronan were found, pointing to the mesothelium as the most likely source of this glycosaminoglycan [101]. The proteoglycans, mainly chondroitin and dermatan sulphate, are also produced by mesothelial cells [107].

Cytokines, Prostanoids, Chemokines, and Growth Factors

Elevated serum levels of TNF-α and IL-6 are often found, probably related to the presence of renal failure [108–111]. Cultured mesothelial cells can synthesize the proinflammatory cytokine IL-1 [112], the anti-inflammatory cytokine IL-6 [113], and the chemokines IL-8 [114, 115], HuGRO-α, RANTES, monocyte chemoattractant protein (MCP)-1, and IP-10 [116]. The synthesis of the first two cytokines is markedly augmented after stimulation with IL-1β and TNF-α [112–117]. Besides these cytokines, prostanoids also are synthesized in vitro by mesothelial cells [117]. Measurable levels of these cytokines are found in spent dialysate [71, 118, 125]. The concentrations are mainly higher than in serum, confirming the possibility of local production by peritoneal mesothelial cells. TNF-α is also present in peritoneal effluent [126]. In stable uninfected CAPD patients there was no evidence for local production, but only for diffusion from the circulation [126]. This would be in accordance with the observation that cultured mesothelial cells do not synthesize significant amounts of this cytokine. The observation that spent dialysate is a powerful stimulus for IL-6 and IL-8 production by cultured mesothelial cells [127] probably reflects an in vivo mechanism whereby TNF-α diffuses from the circulation into the dialysate and triggers the mesothelial cells to release IL-6 and IL-8. Although the exact origin of vascular endothelial growth factor (VEGF) is not known, mesothelial cells are also capable of producing VEGF [128].

Coagulation and Fibrinolytic Factors

The peritoneal effluent of CAPD patients contains various coagulation and fibrinolytic factors, such as the prothrombin fragments 1 and 2, antithrombin III, thrombin-antithrombin III (TAT) complexes, fibrin monomers, fibrinopeptide A, D-dimer, fibrin degradation products, tissue plasminogen activator (t-PA), and plasminogen activator inhibitor type 1 (PAI-1) [129, 130]. Evidence for local synthesis was found for fibrinopeptide A, TAT complexes, D-dimer, and to a lesser extent for t-PA and PAI-1 [129]. The latter may, however, be an underestimation

because both proteins bind to fibrin [130]. Cultured mesothelial cells produce both t-PA and PAI-1 [130, 131]. Stimulation with TNF-α led to a reduction in the synthesis of t-PA and an increase in that of PAI-1 [130, 131], thus promoting coagulation and decreasing fibrinolysis. The chronic instillation of dialysate in rats, however, enhanced the activity of peritoneal plasminogen activator in mesothelial cells, suggesting an adaptation process [132].

Markers of Other Peritoneal Structures

Peritoneal structures that are involved in the process of peritoneal dialysis include not only the mesothelium, but also the submesothelial interstitial tissues that contain capillaries and lymphatics. The stromal tissue is composed of collagen fibers and retiform elastic laminae in a relatively acellular ground substance, in which fibroblasts and occasional mast cells and macrophages are present [9, 11, 133]. This matrix is made up of mucopolysaccharides such as hyaluronan and chondroitin sulphate [134]. Morphological alterations occur in all parts of this "membrane" during peritoneal dialysis.

Markers of the Interstitial Tissue

Like mesothelial cells, cultured human peritoneal fibroblasts are capable of secreting IL-6 and IL-8 after stimulation with IL-1β or TNF-α [135]. Cultured human synovial fibroblasts have been found to secrete hyaluronic acid, especially after exposure to histamine [136]. Also, stimulation with IL-1, IL-6, and TNF-α increased hyaluronan production [137]. These findings imply that a contribution of submesothelial fibroblasts to the effluent concentrations of IL-6, IL-8, and hyaluronan cannot be excluded. Transforming growth factor (TGF)-β is present in peritoneal effluent in concentrations that indicate local production [138–140]. However, it is present in an inactive form.

The procollagen peptides procollagen I C-terminal peptide (PICP) and procollagen III N-terminal peptide (PIIINP) are split off procollagen I and III [141]. Serum concentrations of these peptides have been used as markers of collagen synthesis in patients with liver diseases [142, 143] and in bone [144]. Their serum concentrations are increased in renal failure, hemodialysis, and CAPD patients [102, 145, 146]. The concentrations of these procollagen peptides in spent peritoneal effluent exceed their serum concentrations on most occasions [145–148]. This suggests that the dialysate concentrations can be used as markers of collagen synthesis in the peritoneum.

No data are available on the presence of specific endothelial cell markers in drained peritoneal dialysate.

Markers During Peritonitis

Hyaluronan is the tissue marker in peritoneal effluent that showed the largest increase during the acute phase of peritonitis [45, 101]. The average increment was about tenfold compared to the uninfected situation. No changes were found in the serum concentrations of hyaluronan. Twofold increases were found for the peritoneal appearance rates of phospholipids, CA125, PICP, and PIIINP [45]. The peak of CA125 and phospholipids was on the first days of the infection; the peak concentration of the procollagen peptides occurred significantly later, with a median value on day 4. A second peak of CA125 was observed on days 5–7. These findings could imply mesothelial cell loss during the acute phase of inflammation, followed by wound healing, as reflected in the later peaks of PICP and PIIINP (collagen synthesis) and CA125 (remesothelialization). Peritonitis caused no change in the serum concentrations of these markers [45]. The absence of relationships between tissue markers and cytokine levels (see below) during infectious peritonitis is not in favor of a direct relationship between the magnitude of the inflammatory response and the degree of tissue damage and repair. This is supported by data on metalloproteinases (MMP). MMP-9 is produced by a variety of cells, including mesothelial cells, macrophages, and neutrophils, while MMP-2 is constitutively secreted by mesothelial cells. Peritonitis leads to increased effluent levels of MMP-9, but has no influence on MMP-2 [149]. All these data make it likely that other factors than the inflammatory ones, such as pre-existing peritoneal abnormalities, contribute to the development of peritoneal damage.

Markers of coagulation and fibrinolysis are both elevated in spent dialysate during peritonitis [130, 150]. The increase was more pronounced for the coagulation parameters than for the fibrin degradation products. This might explain the fibrin formation that is sometimes found during peritonitis. Also, a reduced fibrinolytic capacity is present as judged from decreased concentrations of D-dimers and PAP (the irreversible complexes of α2-antiplasmin to free plasmin) in combination with increased concentrations of PAI-1, the main inhibitor of tissue plasminogen activator. It is speculative whether this shift in the balance between procoagulant and fibrinolytic factors is important in the formation of adhesions. PAI-1 promotor polymorphism did not predict peritoneal failure after a severe peritonitis [151].

The dialysate concentrations of cytokines are also very markedly elevated during the acute phase of peritonitis [69, 122]. A relationship has been found between dialysate cell number and the effluent concentration of IL-8 [122], and also between the dialysate neutrophil number and the effluent concentration of the chemokine HuGRO [152]. The increase of IL-6 was 854-fold, that of IL-8 was 327-fold, and that of TNF-α was 35-fold. Only in the initial phase of the inflammation was evidence obtained for local production of TNF-α [126]. TNF-α and IL-6 were increased in the dialysate 1 day before overt peritonitis [153]. No significant changes occurred in the serum concentrations of these cytokines [69, 122], which is in accordance with clinical observations that CAPD-related peritonitis is a localized inflammation on most occasions. The effluent concentrations of prostaglandins are also increased during peritonitis [69, 70, 124, 125]. This rise was more pronounced for the vasodilating prostaglandin E2 (PGE2) and 6-keto-placental growth factor (PGF)1α(12-fold) than for the vasoconstricting thromboxane B2 (TXB2) (5-fold) [69]. It appeared that the functional changes during inflammation were related to changes in inflammatory mediators: the time course of the effective peritoneal surface area was related to alterations in IL-6 and TNF-α. The changes in the intrinsic permeability of the peritoneum to macromolecules were mainly related to those in PGE2, and, to a lesser extent, to TNF-α [69]. This was confirmed by intervention studies with indomethacin [70, 125]. Intraperitoneal administration of this cyclo-oxygenase inhibitor lowered the effluent levels of the prostanoids [70, 125]. It also influenced the intrinsic permeability, but had no effect on the time course of the effective surface area [70]. In one study, soluble intercellular adhesive molecule (sICAM-1) and hyaluronan were lower at the end of the treatment in patients who later had a relapse/reinfection [154].

Markers During Long-Term Peritoneal Dialysis

Four cross-sectional studies have been published on the effect of duration of CAPD treatment on the phospholipid concentrations in the effluent [76, 96, 155, 156]. In the first two studies, lower concentrations were reported the longer the duration of CAPD, but this could not be confirmed in the last two. The maximal durations of CAPD were 46 [15], 74 [77], and 87 months [156]. A significant fall in phosphatidylcholine levels was found when patients were followed during the first half-year of CAPD treatment [156]. In one study a relationship was found between loss of ultrafiltration and low dialysate phosphatidylcholine levels [96], but this could not be confirmed in the other ones [156, 157].

No trend in time is present for hyaluronan in most studies [76, 103, 158]. Only in one study was a relation found between the length of time on dialysis and the amount of hyaluronan excretion in the dialysate [159]. Dialysate concentrations of PICP have been reported to increase during a 1-year interval [160]. However, in another study no relation was found between mass appearance rates of PICP, PIIINP, and ICTP and the duration of dialysis treatment [148, 158]. Also no effect of the duration of PD was found on dialysate levels of MMP-2 [161]. Transforming growth factor (TGF)-β is present in peritoneal effluent in concentrations that indicate local production [138–140]. Dialysate TGF-β has been described related to peritoneal transport parameters [138], marginally related [140], or unrelated [139]. These conflicting data might be caused by the fact that it is present in an inactive form and bound to α2-macroglobulin in the circulation. Effluent TGF-β is not related to the duration of PD. In contrast to TGF-β, the dialysate concentration of VEGF is closely related to peritoneal transport parameters [139, 162, 163]. Due to the high interindividual variability, no relationship with time on PD was found in a cross-sectional analysis [139], but longitudinal follow-up of individual patients showed an evident increase in time [164]. Especially the AA genotype of VEGF was associated with progressive increase in peritoneal transport [165]. Effluent connective tissue growth factor (CTGF) showed relationships with peritoneal transport parameters in a cross-sectional analysis, but not with the duration of PD or the dialysate concentrations of VEGF or TGF-β [166]. Also PAI-1 promotor polymorphism was not associated with long-term changes in peritoneal transport [151].

Markers During Peritoneal Sclerosis

High dialysate levels of type 1 and III procollagen peptides have been reported in 1 patient with peritoneal sclerosis [167]. This was not confirmed when studying more patients during longitudinal follow-up [78]. In a large multicenter study the MMP-2 levels in patients with mild peritoneal injury, moderate peritoneal injury, severe peritoneal injury (EPS), and infectious peritonitis were significantly higher than those in control patients [161]. However, almost all patients had decreased dialysate CA125 and hyaluronan concentrations. On the contrary, another study found an abrupt increase of hyaluronan excretion in four patients who discontinued CAPD within 6 months due to ultrafiltration failure [159]. Two of these four patients were diagnosed with sclerosing encapsulating peritonitis at autopsy. Dialysate hyaluronan concentration tended to be lower in patients from Hong Kong who developed peritoneal adhesions than in those who did not, but the difference was not statistically significant [106]. As effluent hyaluronan is mainly produced by mesothelial cells in noninfected patients, the low effluent concentrations may reflect loss of mesothelial cell mass.

Dialysate Markers of Biocompatibility of Dialysis Solutions

Apart from CA125, hyaluronan, procollagen peptides, and cytokines are used to evaluate potentially more biocompatible solutions. As already mentioned, dialysate CA125 levels almost universally increase with the new solutions. Hyaluronan decreased in most studies [87, 89, 168] but remained stable in others [92] during the use of the more biocompatible solution. PICP either increased [89] or did not change [87] after the use of the newer fluids. Cytokines also either increased or remained stable during the study fluids compared with the less biocompatible control fluids [87, 89, 92, 168]. It can be hypothesized that the decrease in hyaluronan is caused by less remodeling of the interstitium. The increase in CA125 as well as various cytokines can be explained by better preservation or function of the mesothelial cells.

Monitoring the Peritoneal Membrane Using Solute and Water Transport

Interpretation of Solute Transport in Relation to the Structures of the Peritoneal Membrane

The capacity of the peritoneal membrane for the transport of solutes is determined by its effective surface area as well as its intrinsic permeability. The effective surface area is probably determined by the number of capillaries perfused, as well as the flow within these capillaries [169, 170]. Alternatively, splanchnic volume and not flow rate could be of importance for solute transport [66]. It is not known which part of the peritoneum is most responsible for its intrinsic permeability. Changes in mesothelium or interstitium, as can be seen after CAPD treatment, could be of importance [10, 171, 172]. However, the mesothelium is not a significant barrier to small solute transport [173]. Although the interstitium cannot act as a membrane due to its large gaps [174], it might be a diffusive barrier to solutes [175–178]. It seems that hyaluronan, highly negatively charged, is primarily involved in the restriction of proteins, which are restricted to 50% of interstitial space [179]. No data are available on the possible impact of long-term changes in the interstitium on peritoneal transport. As it has been assumed that the peritoneal capillary represents the major barrier in blood to peritoneal transport [180, 181], changes in solute transport might reflect ultrastructural changes of these vessels.

It has been found that the transport of low- and middle-molecular-weight solutes is size-dependent [182, 183] and not hindered by the intrinsic permeability of the peritoneum [184–186]. Therefore, the transport of these solutes must be mainly dependent on the effective peritoneal surface area. Especially for low-molecular-weight solutes, it has been suggested that stagnant fluid films in the capillaries of the peritoneum and in the peritoneal cavity could be important [187, 188]. Evidence for this theory is given by in vitro and in vivo experiments, which studied solute clearance after mixing by shaking or externally applied vibration [189–191]. However, for the interpretation of changes in solute transport in time, stagnant fluid layers are not considered to be important, first because it is not very likely that these stagnant fluid films will change in time, and second because the permeability tests are performed under standardized conditions.

The transport of macromolecules, is size-selectively restricted, either by restricted diffusion [192] or by convection through large pores [193], which makes it likely that clearances of serum proteins are dependent both on effective surface area and permeability. A negative electric charge has been demonstrated in rats at the level of the peritoneal microvessels and the subserosal interstitium [194], as well as within mesothelial cell structures and at the level of the submesothelial basal lamina [195]. Neutralizing the anionic sites by intraperitoneal administration of protamin improved solute clearance of macromolecules in the rabbits by 100% [196]. However, in humans the transport of negatively charged proteins from blood to dialysate occurred in an equal rate as the transport of neutral dextrans with the same Einstein-Stokes radii [192]. Also no differences were found in the transport of four IgG subclasses with different mean isoelectric points ranging from 7 to 9.5 [197, 198]. The intrinsic permeability of the peritoneal membrane to the transport of macromolecules from the circulation to the dialysate can be characterized by the peritoneal restriction coefficient [199, 200].

In conclusion, changes in low-molecular-weight solute transport are explained by changes in vascularization of the peritoneal membrane. Changes in the transport of macromolecules can either be attributed to changes in the capillary wall or to changes in the interstitial tissue.

Interpretation of Fluid Transport in Relation to the Structures of the Peritoneal Membrane

The driving force for water transport through the peritoneal membrane is the difference between osmotic and hydrostatic pressures between the peritoneal capillaries and the dialysate. This pressure is exerted over small pores and through the water channels in the endothelium of peritoneal capillaries and vessels resulting in transcapillary

ultrafiltration (TCUF). The anatomic equivalents of the small pores are probably the interendothelial clefts [201]. Through these pores, low-molecular-weight solutes are also transported. The transendothelial water channels have been identified morphologically as aquaporin-1 by aquaporin-CHIP antiserum–specific staining of peritoneal endothelial cells [202–204]. Aquaporin-1 is impermeable to solutes. Therefore, crystalloid osmotic-induced free water transport occurs through them. The contribution of free water transport to the TCUF is especially important when a hyperosmolar solution is used, because the small pores are influenced by tonicity only to a limited extent. This is due to their very low reflection coefficient to glucose. In contrast, solutions with low osmolarity will induce little free water transport [205]. Fluid within the peritoneal cavity can disappear either by transport through the peritoneal membrane or by transport through the peritoneal lymphatics. The magnitude of this transport during a short dialysis dwell with a hypertonic solution is still a matter of debate [206, 207].

The difference between TCUF and fluid loss from the peritoneal cavity is the net ultrafiltration (NUF). The definition of impaired NUF varies in the literature. Looking at NUF it can be defined as NUF of less than 400 mL/4 h on 3.86%/4.25% glucose dialysate, less than 100 mL/4 h for 2.27%/2.5% glucose and a value of less than –400 to –500 mL/4 h for 1.36%/1.5% solutions [208]. The International Society of Peritoneal Dialysis committee on ultrafiltration failure has advised to standardize the definition of ultrafiltration failure to less than 400 mL after a 4-h dwell test with 3.86%/4.25% glucose [209].

In conclusion, apart from mechanical causes, changes in ultrafiltration volume can be caused by various mechanisms. Most frequently, it can be the result of changes in the vascular surface area leading to either slower or faster dissipation in the osmotic gradient [210]. Secondly, it can be the result of changes in aquaporin-mediated water transport either by loss of aquaporins or functional impairment [211, 212]. Thirdly, it could be caused by fluctuations in fluid resorption from the peritoneal cavity [213].

Tests for the Measurement of Solute and Fluid Transport

Many parameters of peritoneal membrane transport can be measured (Table 15.1). Various tests have been developed to measure these parameters in order to monitor the peritoneal membrane. These tests vary from simple but practical tests that generate only part of these parameters to more complex tests that are laborious and use specific laboratory tests.

The Peritoneal Equilibrium Test (PET)

The principle of such a test was proposed by several authors [214–217]. Since its introduction by Twardowski et al. in 1987 [218], it is the most widely used test to assess peritoneal transport in CAPD patients. This is probably due to the simplicity of the test. Numerous papers have been published using this test in pediatric [219] and adult patients [220].

Test Procedure

After a dwell of 8–12 h, the PET is performed during a 4-h dwell using glucose 2.27%/2.5% dialysate. Dialysate is sampled from the drained effluent before the test, from the test bag at 0, 10, 30, 60, 120, and 180 min, after drainage, and from the following bag before inflow and immediately after inflow. Serum is sampled at the end of the test. In those samples low-molecular-weight solutes (sodium, potassium, urea, creatinine, glucose) and total protein are measured.

Table 15.1 Parameters of peritoneal transport function

Solute transport
Low-molecular-weight solutes (MTAC, D/P ratio)
Macromolecules (clearances)
Peritoneal restriction coefficient
Fluid transport
Net ultrafiltration
Transcapillary ultrafiltration
Free water transport
Small pore water transport
Large pore water transport
Fluid reabsorption/lymphatic absorption

Calculated Parameters

Peritoneal solute transport is calculated by the dialysate over plasma ratio (D/P ratio) of sodium, potassium, urea, creatinine and total protein, and the dialysate$_{240}$/initial dialysate ratio of glucose (D/D_o). Residual volume can be calculated using the dilution of solutes present in the effluent. NUF is calculated as the difference between the drained and the instilled volume. NUF can be corrected for the calculated residual volume before and after the test.

Interpretation of the Test

Patients are categorized into four groups of low, low-average, high-average, and high transporters according to the values of solute transport. A high transporter is defined as a patient with either a D/P_{Cr} exceeding the mean + 1 SD, or a D/D_o of less than the mean D/D_o –1 SD. High average transporters have a D/P_{Cr} between the mean and mean + 1 SD, or a D/D_o between the mean and mean –1 SD. Analogously, the other two groups are defined. This classification into transport categories based on D/P ratios may be confusing as it suggests that the patients are grouped according to their total solute transport. As peritoneal mass transfer and peritoneal clearance of a small solute during dwells of 4 h or more are dependent mainly on drained volume, patients with a high D/P ratio of creatinine may in fact have a low mass transfer and clearance of this solute [221]. The D/P ratio of low-molecular-weight solutes is dependent mainly on the surface area of the peritoneal membrane (see above), so renaming of the four "transport" categories should be considered. They could be renamed either to high, high-average, low-average, and low D/P ratio, to very large, large, medium, and small surface area [209] or according to the speed of transport into very fast, fast, slow, and very slow transport. Recommendations have been made on the mode and quantity of peritoneal dialysis according to the transport status of the patients [218, 219]. The dip in the D/P of sodium gives an impression of free water transport [211].

Drawbacks

Especially when hypertonic dialysis fluids are used, D/P_{Cr} is also influenced by convective transport from the circulation to the peritoneal cavity [222, 223]. Likewise D/D_o is not only dependent on diffusion, but also on uptake into the lymphatic system. However, no differences were found for the D/P ratios of urea and creatinine between a PET using 1.36%/1.5% and 3.86%/4.25% [224] or a PET with 2.27%/2.5% and 3.86%/4.25% [225, 226]. Although the PET should be performed after a long dwell, D/P ratios of low-molecular-weight solutes are not influenced by a short preceding dwell [227–229]. However, a dry day [227] or the use of polyglucose [230] for the long dwell did result in higher D/P ratios of small solutes and protein. Only NUF, but not TCUF and fluid reabsorption are measured. Failure to correct for overfill volume will result in overestimation of NUF [231, 232]. The residual volume at the beginning and end of the dwell may vary [233]. If they are not calculated this may also result in overestimation or underestimation of NUF.

The PET can be enhanced by either correcting the sodium dip for sodium diffusion [234] or by measurement of intraperitoneal volume after 1 h followed by reinfusion. The latter allows calculation of free water transport by the method of La Milia without influencing the results of solute transport and NUF [235].

Fast PET

In order to reduce the costs and the time commitment for the test a simplification of his PET test was proposed by Twardowski [236]. As expected, a good correlation between the PET and the Fast PET is found [237].

Test Procedure

The fast PET is performed during a 4-h dwell using glucose 2.27%/2.5% dialysate. Dialysate is sampled after drainage. Serum is sampled at the end of the test. In those samples low-molecular-weight solutes (urea, creatinine) are measured.

Calculated Parameters

Peritoneal solute transport is calculated by the dialysate over plasma ratio (D/P ratio) of urea and creatinine. NUF is calculated as the difference between the drained and the instilled volume.

Interpretation of the Test

Like the original PET test, patients are categorized into four groups of low, low-average, high-average, and high transporters according to the values of solute transport.

Drawbacks

These are similar to the PET.

Mini-PET

This test has been proposed by La Milia et al. to assess small solute as well as free (transcellular) water transport [238]. It is based on the assumption that during the first hour of a 3.86%/4.25% exchange the free water transport is maximal, as glucose in the dialysate is at its highest concentration, and that diffusive sodium transport is very low, because of a low plasma to dialysate sodium gradient, the total sodium transport is mainly due to convective transport through small pores. Water transport through small pores is calculated as the sodium removal divided by the plasma water sodium concentration. Free water transport is calculated by subtracting small pore water transport from the total ultrafiltration volume.

Test Procedure

It is similar to the standard PET. However, the test is performed using 3.86%/4.25% glucose during a 1-h dwell.

Calculated Parameters

The same parameters are calculated as the standard PET, although after 1 h instead of 4 h. In addition, net ultrafiltration can be separated into small pore and free water transport.

Interpretation of the Test

Like the PET test, patients are categorized into four groups of low, low-average, high-average, and high transporters according to the values of solute transport. Changes in NUF can be attributed to changes in small pore and free water transport.

Drawbacks

The test shares many of the same possible errors with the PET (like the effect of the preceding dwell, overfill volume, and residual volume). Ultrafiltration is measured after 1 h, so the internationally accepted definition of ultrafiltration failure can not be used. As peritoneal transport during the first hour of the dwell is higher [239], the agreement between transport categories using a 1- or 4-h dwell is only around 80%. This also makes comparison of this test with the standard PET more difficult.

Accelerated Peritoneal Examination (APEX)

The APEX test is, according to the authors, more convenient than the PET [240]. It summarizes in a single number the peritoneal permeability both to glucose and urea. This is using the time at which glucose and urea equilibration curves (using percentages as units) cross. This point is also referred to as the optimal ultrafiltration dwell time. The shorter the APEX time, the larger is the peritoneal vascular surface area and, conversely, the longer this time, the lower is the peritoneal vascular surface area. Only data for pediatric patients are published [241, 242]; in adults, details are only published in the French literature. No comparative studies with other peritoneal equilibrium tests are published.

Standard Peritoneal Permeability Analysis (SPA)

This test is also based on the original PET. The most important modification is the use of dextran 70 as a volume marker. The SPA can be applied in pediatric [243] and adult patients [244, 245]. This makes it possible to analyze various fluid kinetics. The SPA can be used to analyze the transport properties of the peritoneal membrane [246] as well as for its long-term follow-up [247].

Test Procedure

Prior to instillation of the test solution the peritoneal cavity is rinsed and immediately drained by gravity after inflow is completed. The test is performed during a 4-h dwell with 3.86%/4.25% glucose [244, 245]. To the test bag dextran 70 is added to calculate peritoneal fluid kinetics [248]. Dialysate samples from the test bag of 10 mL each are collected before inflow and at 10, 20, 30, 60, 120, 180, and 240 min after instillation of the test solution. Also, a dialysate sample is taken from the following bag immediately after inflow. Blood samples are taken at the start and at the end of the test.

Calculated Parameters

Peritoneal solute transport of low-molecular-weight solutes (urea, creatinine, urate) is calculated as mass transfer area coefficient (MTAC) and glucose absorption. Macromolecular solute transport (β2-microglobulin, albumin, IgG, α2-macroglubulin) is calculated as a clearance. The intrinsic permeability to macromolecules is functionally characterized by the peritoneal restriction coefficient [198, 249]. The peritoneal restriction barrier, i.e. the intrinsic permeability of the membrane, can be characterized mathematically by the relationship between peritoneal clearance of various molecules and a size-dependent physical property of these macromolecules. Transcapillary ultrafiltration, fluid loss from the peritoneal cavity (effective lymphatic absorption), intraperitoneal volume, and net ultrafiltration are calculated during the dwell using the dilution and disappearance of the volume marker [248]. The residual volume before and after the test is also calculated using the dextran 70 dilution. By the method proposed by La Milia using sodium measurements in dialysate and plasma [238], transcapillary ultrafiltration can be separated in transcellular water transport and transport through small pores [249]. The accuracy of this method can be enhanced by correction for sodium diffusion during the dwell [250].

Interpretation of the Test

MTAC of low-molecular-weight solutes represents the peritoneal vascular surface area. Clearances of proteins represent peritoneal vascular surface area as well as intrinsic peritoneal permeability. This intrinsic permeability is also represented by the peritoneal restriction coefficient. Detailed data are generated on NUF, TCUF, fluid reabsorption, and aquaporin-mediated water transport.

Like with the PET, patients can be categorized into four transport categories. As the MTAC instead of the D/P ratio corrects for convective solute transport, some patients were placed in different transport categories, based on whether the SPA or the PET was used for the calculations. This phenomenon was most evident for creatinine (59 out of 138 tests would have led to misplacement), but it was also present, although to a lesser extent, for glucose (31 out of 138 tests) [244].

Drawbacks

The test is laborious and uses nonstandard laboratory determinations such as high-performance liquid chromatography (HPLC) for dextran 70.

Dialysis Adequacy and Transport Test (DATT)

Test Procedure

The test procedure is 24-h dialysate collection in CAPD patients using their usual dialysate prescription. The total volume is measured and dialysate and serum creatinine are determined.

Calculated parameters

D/P ratio of creatinine and fluid removal in 24 h are calculated.

Interpretation of the Test

Basically the interpretation is similar to the fast PET but confined to solute transport.

Drawbacks

The test is only suited for CAPD patients [251, 252]. The correlation with the PET is fair but far from good for a test measuring the same parameter ($r = 0.81$). Bland and Altman analyses of the data are not given. To interpret changes in time, the patient should not change the prescription in time.

Computer Software Available for Measuring the Properties of the Peritoneal Membrane

Three major software programs are currently available for evaluating peritoneal solute and fluid transport. These programs are PD Adequest® (Baxter Healthcare Corporation, Deerfield, Illinois, USA), the Personal Dialysis Capacity test (PDC®) (Gambro, Lund, Sweden), and Patient On Line (POL®) (Fresenius Medical Care, Bad Homburg, Germany). These programs use different mathematical models and different data collecting procedures. Although data can be obtained for monitoring the peritoneal membrane they are developed for individualized kinetic modelling of dialysis adequacy.

PD Adequest 2.0

PD Adequest 2.0 uses the Pyle-Popovich model, which is based on a two-compartmental model assuming a homoporous membrane model [253]. Key aspects of the three-pore model [254] are also incorporated. The program is validated in pediatric [255] and adult patients [256] and also for a polyglucose solution [257].

Test Procedure

The test procedure and required data are similar to the PET. Although the glucose concentration of the test bag can be chosen, it is advisable to use the same glucose concentration for the preceding dwell for more accurate prediction of fluid reabsorption. Three dialysate samples can be entered for the test. Unlike the PET, no sample is taken from the dwell following the test bag. Urea, creatinine, and glucose are measured in the dialysate and these solutes together with albumin in serum during the test.

Calculated Parameters

MTACs and D/P D/D_o ratios of urea, creatinine and glucose are given. Also, NUF, fluid reabsorption, and LPA (hydraulic permeability) are given.

Interpretation of the Test

Basically, the interpretation of the data calculated by PD Adequest 2.0 is similar to the PET results, including separation into different transport groups.

Drawbacks

As the setup of the test is identical to the PET, many of its drawbacks also apply to this test.

Peritoneal Dialysis Capacity Test (PDC)

The program uses the three-pore model of Rippe [258]. The program has been evaluated in a number of studies in pediatric as well as adult patients [258–262].

Test Procedure

The test starts with a short dwell (2–3 h), followed by two intermediate dwells (4–6 h), and another short exchange (2–3 h), and finally a long overnight dwell. The glucose concentrations are also varied so that one of the short dwells is performed with another glucose concentration than the others. Patients take samples from all drained bags. They also record the weight of the bag before and after instillation of the fluid as well as the time of instillation and drainage. The dialysate samples are analyzed for urea, creatinine, glucose, and albumin (protein). Blood samples are taken at the beginning and the end of the test for determination of sodium, urea, creatinine, glucose, and albumin (or protein).

Calculated Parameters

A peritoneal surface area parameter $A_0/\Delta X$, the final reabsorption rate of fluid from the abdominal cavity to blood when the glucose gradient has dissipated (Jv_{AR}), and the large pore fluid flux (J_{VL}) are calculated.

Interpretation of the Test

The area parameter is determined by the diffusion of small solutes and represents the peritoneal vascular surface area. Changes in Jv_{AR} represent changes in fluid absorption rate. Using the $A_0/\Delta X$ and J_{VL} it is possible to differentiate between changes in surface area and membrane permeability.

Drawbacks

The parameters given by this test can only be obtained using its program. This makes comparison of the results from the literature with other more popular tests impossible. Ultrafiltration is given in fluid removal during 24 h, so the internationally accepted definition of ultrafiltration failure cannot be used. Like most other tests, TCUF is not subdivided in free and small-pore water transport. Also, residual volume after a dwell is not given.

Patient On Line (POL)

The data are analyzed using a variable volume kinetic model and a phenomenological description of ultrafiltration [263, 264].

Test Procedure

During 24 h for each exchange fill volume, drain volume, dwell time, and glucose concentration are recorded. Dialysate is sampled for urea, creatinine, and glucose.

Calculated Parameters

PT50 (time required to reach 50% solute equilibrium) and also the D/P ratios of the collected various dwells are given.

Interpretation of the Test

The PT50 represents peritoneal vascular surface area. Patients can be categorized in the various transports using graphical output.

Drawbacks

The primary parameter (PT50) given by this test can only be obtained using its program. This makes comparison of the results from the literature with other more popular tests impossible. Ultrafiltration depends solely on the prescription the patient is using, so the internationally accepted definition of ultrafiltration failure can not be used. Although a model is used that calculates the fluid profile, TCUF is not subdivided in free and small-pore water transport. Also, residual volume after a dwell is not given. Finally, no data exist about its use for monitoring the peritoneal membrane.

Conclusions

Many aspects of peritoneal transport can be measured. Depending on the question a simple or a complex test can be chosen. These tests are important in solving unanswered questions of peritoneal physiology and pathology, and studying the effects of dialysis solutions and drugs on the membrane. However, they are also essential in monitoring of the membrane characteristics of the individual patient.

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Chapter 16
Adequacy of Peritoneal Dialysis, Including Fluid Balance

J.M. Burkart and J.M. Bargman

As a renal replacement therapy, dialysis, at best, can approximate only a portion of normal renal function (Table 16.1). Despite these deficiencies, however, dialysis has remarkably extended the lives of chronic kidney disease patients, some for decades. Although many patients do very well on dialysis, the survival of patients is markedly reduced compared to age- and race-matched people in the general population [1]. The extent to which ongoing uremia in the form of underdialysis contributes to this overall mortality rate in the dialysis population is unknown. Some have suggested that inadequacy in the prescribed dose of dialysis contributes to these high mortality rates [2, 3]. As a result, more attention has been paid to patient outcome and to optimizing total solute clearance.

Although "adequate" dialysis is crucial for the wellbeing of any dialysis patient, adequacy of peritoneal dialysis or any renal replacement therapy is difficult to define. The word "adequacy" comes from the Latin word "*adequare,*" which means "to equalize." Ideally, this would imply that adequate dialysis would return the patients' lifestyle and life-expectancy to what it would have been if the patient never had renal disease. "Optimal" dialysis prescriptions are said to be those in which there is no further incremental improvement in patient outcome as the dose is increased further, while also imparting minimal negative effects on the patient's quality of life.

One powerful reason for the lower life-expectancy in dialysis patients is that they have at least one serious chronic medical condition (kidney disease) and therefore are "patients" and not healthy individuals. In addition, these patients tend to have multiple co-morbid diseases, particularly of the cardiovascular system, at initiation of dialysis that can also adversely influence outcome [4]. However, in providing dialysis we have some influence on the patient's total solute clearance and ultrafiltration. Nephrologists must do their best to provide enough renal replacement therapy to be sure that the amount of dialysis delivered is not the rate-limiting step that determines whether the patient lives or dies. This chapter discusses adequacy issues for peritoneal dialysis (PD) in terms of total solute clearance and ultrafiltration. We will try to emphasize that adequacy of dialysis is much more than total small solute clearance.

Which Yardstick for Adequacy of Dialysis Should We Use?

Many of the known clinical manifestations of uremia, such as decreased appetite, metallic taste, nausea, vomiting, pericarditis, pleuritis, and encephalopathy, are obvious. There is evidence to suggest that underdialysis may be associated with hypertension [5] and lipid abnormalities [6], both of which may increase the risk of atherogenesis, cardiovascular disease and mortality. Uremic neuropathy may not be diagnosed until it is far advanced, at which time it may be irreversible [7]. Because of the insidious onset and potentially fatal or irreversible nature of some manifestations of uremia, nephrologists needed a laboratory parameter that measures the delivered amount of solute clearance while predicting patient outcome. There is no documented single substance that has been shown to be the "uremic toxin." Undoubtedly, the clinical manifestations of the uremic syndrome are the result of the synergistic effect of an entire family of uremic toxins of both small and middle molecular weights. Therefore, because there is no single uremic toxin, we have to rely on *surrogate markers* for uremia. Currently, solutes such as urea nitrogen, creatinine, and β_2-microglobulin are commonly used.

J.M. Burkart (✉)
Wake Forest University Health Sciences Center, Bowman Gray School of Medicine, Winston Salem, North Carolina
e-mail: jburkart@wfubmc.edu

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Table 16.1 Solute removal by dialysis and by the human kidney

	Human kidney	HD–standard flux	HD–Hi flux	CAPD
Urea (L/week)	750	130	130	70
Vitamin B_{12} (L/week)	1,200	30	60	40
Inulin (L/week)	1,200	10	40	20
β_2-microglobulin (mg/wk)	1,000	0	300	250

The Case for Small Solute Clearance

It is a common clinical experience that, if PD patients manifest uremic symptoms, they usually improve after increasing the volume or number of exchanges per day [8]. Fig. 16.1 demonstrates the theoretical influence of the number of PD exchanges on the weekly solute clearance for a wide range of molecular weights. Since increasing the number of exchanges per day results in a marked increase in small solute (MW $<$ 500 Da) clearance, but only a minimal or negligible increase in large or middle molecule clearance, it seems that overall small solute clearance, not middle or large molecular weight clearance, may be at least partly responsible for uremic toxicity.

Total solute clearance ($K_{\text{renal}} + K_{\text{peritoneal}} = K_{\text{rp}}$) for PD is commonly estimated in terms of urea clearance as weekly Kt/V_{urea} or, if using creatinine as weekly creatinine clearance (CCr), normalized to 1.73 m^2. These calculations assume that residual renal and peritoneal clearances are equal, although this is not the case. Residual renal GFR is typically determined as the sum of urea and creatinine clearances divided by 2, and is felt to be an estimate of glomerular filtration [10]. The equations for calculating total solute clearance can be found in the Appendix.

The Case for Larger Solutes and "Middle Molecules"

In the early days of dialysis, it was recognized that patients receiving peritoneal dialysis had the same, or even improved, correction of the uremic state compared to patients receiving intermittent hemodialysis (HD). This improvement occurred even though the PD patients had higher levels of serum creatinine and urea compared to those on HD. It was postulated that the PD patients likely had better removal of larger molecular weight uremic toxins, the so-called "middle molecules," through the more porous peritoneal membrane compared to the cellulosic HD membranes. Furthermore, because removal of middle molecules is time-dependent, peritoneal dialysis done 24 h a day, 7 days a week, would have a major advantage over intermittent therapies. Therefore, PD was recognized by many as working in a way different from HD, and the reduced small solute clearance was compensated by better removal of these middle molecules. Indeed, many working in the HD field thought that outcome in HD might be improved by optimizing middle molecule removal, and the "square meter-hour" hypothesis in HD suggested that this should be done by using larger kidneys and longer duration of HD. In other words, HD tried to recapitulate PD with longer time on dialysis and better middle molecule removal.

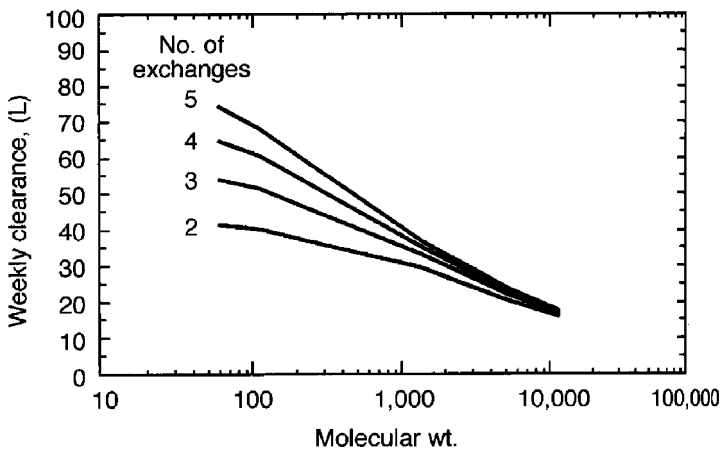

Fig. 16.1 The influence of the number of CAPD exchanges on the weekly solute clearance for a range of solute molecular weights derived from a computerized model of peritoneal transport [9]

However, the environment changed with the publication of the National Cooperative Dialysis Study (NCDS) in [11]. This study of dose of hemodialysis compared longer and shorter times on HD and a higher and lower time-averaged concentration (TAC) of urea in a 2 × 2 factorial design. There were approximately 40 patients in each of the four groups, and the primary outcome was hospitalization for non-access-related reasons. This important study demonstrated that good outcome (remaining unhospitalized) was associated with a lower TAC urea. What also is important to recognize is that the number of hours the patient was on HD just missed statistical significance at $p = 0.06$, and was stated to be not significant in the abstract. This study renewed emphasis on urea removal as an important factor in the outcome of hemodialysis patients. The data from this study was reworked from the ungainly TAC urea to the new term Kt/V urea in the so-called "mechanistic analysis" of Gotch and Sargent [12]. This very important study suggested that, in patients with an adequate protein intake, the results of the NCDS could be explained by a "step function" where attainment of a per-session Kt/V urea of 0.9 was associated with good outcome, whereas values less than this were associated with "failure," i.e., hospitalization. (Subsequent re-analyses by others suggested that the Kt/V urea and outcome could be modeled as a continuous, rather than step function [13].) The publication of the NCDS in a high-impact journal, and the development of the easier-to-use Kt/V urea refocused adequacy of dialysis toward small solute removal. The middle molecule removal, and its surrogate, time on dialysis, received much less attention. It is interesting to speculate how concepts of adequacy might have evolved if the p value for time on HD in the NCDS had been 0.05 instead of 0.06.

Small Solute Kinetics and Peritoneal Dialysis After the NCDS and Kt/V

Since urea kinetics appeared to be a good prognosticator of adequacy and outcome in patients on HD, many working in PD assumed that these indices could apply equally well to their patients. It appears that the appreciation that PD worked in a way not well-captured by small solute kinetics fell by the wayside for many as part of the new enthusiasm for urea kinetics.

Many studies, therefore, looked at patient outcomes in terms of relative risk of death or morbidity and its relationship to total small solute clearance. Their significance and relevance to predicting patient outcome have been reviewed elsewhere [14]. The multiple-outcome studies published during the 1990s differed in methodology and number of patients enrolled. All tended to conclude that outcome (relative risk of death) was, in some way, related to total small solute clearance. These studies are briefly reviewed below.

Kt/V Data: Small Solute Clearance and Outcome

Theoretical Constructs

In the original description of CAPD, Popovich and Moncrief predicted that an anephric 70 kg patient (total body water or $V = 42$ L) would remain in positive nitrogen balance when prescribed five 2-L exchanges/day [15]. Based on theoretical data, others felt a patient would need the equivalent of a weekly Kt/V of 2.0–2.25 [16, 17].

Based on theoretical constructs, if maintenance of positive nitrogen balance were the desired outcome, a target weekly Kt/V of 2.0–2.25 would be necessary.

Univariate Analysis

A series of cohort studies attempted to provide clinical validation of the theoretical data described above. Blake et al. [18], using urea kinetics and an anthropometric method to calculate V, found limited value in predicting patient outcome by total Kt/V (patients with a total Kt/V of < 1.5 had a higher relative risk of death). Lameire et al. [19, 20] reported that the mean weekly total Kt/V in a group of 16 patients who had been on PD at least 5 years was > 1.89 (most of whom were anuric), while DeAlvaro et al. [21] found that patients with a weekly Kt/V of >2.0 were more likely to survive. Taken together, these studies, using univariate analysis, which did not examine the role of other important variables (such as diabetes, cardiovascular disease, and age), suggested that a total Kt/V of < 1.9 was associated with an increased risk of death.

Multivariate Analysis

Using multivariate analysis of data, Teehan et al. [22] suggested that increased patient age, time on dialysis, lower serum albumin levels, and lower weekly total Kt/V were predictive of decreased patient survival. The 5-year survival for patients with a total Kt/V of > 1.89 was >90%. Maiorca et al. [23] evaluated a group of *prevalent* PD patients who had been on dialysis for a mean of 35 ± 26 months and followed them for up to 3 years. Patients with a mean weekly total Kt/V during the study period of at least 1.96 had a better overall survival. They did not find an increased survival rate for patients with a mean weekly total Kt/V of >2.03 versus those with a total Kt/V of 1.96–2.03. It is important to note that these prevalent patients had a mean residual renal glomerular filtration rate (GFR) of 1.73 mL/min at enrolment into the study. Indeed, this was one of the first studies to suggest that residual renal clearance had an independent effect on patient survival. Genestier et al. [24] retrospectively evaluated 201 CAPD patients followed for 23.95 ± 21.37 months using baseline values only. They found that baseline weekly total Kt/V must be higher than 1.7 for optimal survival, and their data did not support a decrease in the relative risk with any further increase in Kt/V. None of these studies evaluated the effect of the decline in overall solute clearance over time, and it was uncertain as to what benefit, if any, patients would achieve if the weekly Kt/V was higher than the recommended cutoffs.

A prospective multicenter cohort study of *incident* patients in several participating centers in Canada and the United States (CANUSA) evaluated the association of total solute clearance (Kt/V, creatinine clearance) and nutrition as time-dependent covariates with patient mortality, technique failure, and hospitalization [25]. Baseline residual renal GFR in this cohort was approximately 3.8 mL/min at enrolment into the study (39 L/week). These data suggested that total solute clearance (K_{pr}) predicted outcome. Every 0.1 unit increase in total weekly Kt/V was associated with a 6% decrease in the relative risk of death; similarly, every 5 L/1.73 m^2/week increase in total creatinine clearance (CCr) was associated with a 7% decrease in the relative risk of death. Over the range of the clearances studied there was no evidence of a plateau effect. The predicted 2-year survival associated with a constant Kt/V of 2.1 was 78%. The weekly total CCr that was associated with a 78% 2-year survival was 70 L/1.73 m^2.

Results of the CANUSA study, therefore, in its first iteration [25] showed a significant correlation between total Kt/V urea or creatinine clearance and outcome, defined as mortality. This finding suggested that PD patients were not really different from HD patients, and that this study was the PD version of the NCDS, showing once again the importance of small solute kinetics on outcome.

Although the CANUSA study gave the most cogent evidence that survival on PD is related to total solute clearance, it is important to note that the results were based on theoretical constructs and two very important assumptions: 1) total solute clearance remained stable over time, and 2) one unit or mL/min of clearance due to residual renal function is equal to one unit or mL/min of clearance due to PD. In fact, total solute clearance decreased over time as residual renal function decreased with no corresponding increase in the peritoneal component (Fig. 16.2).

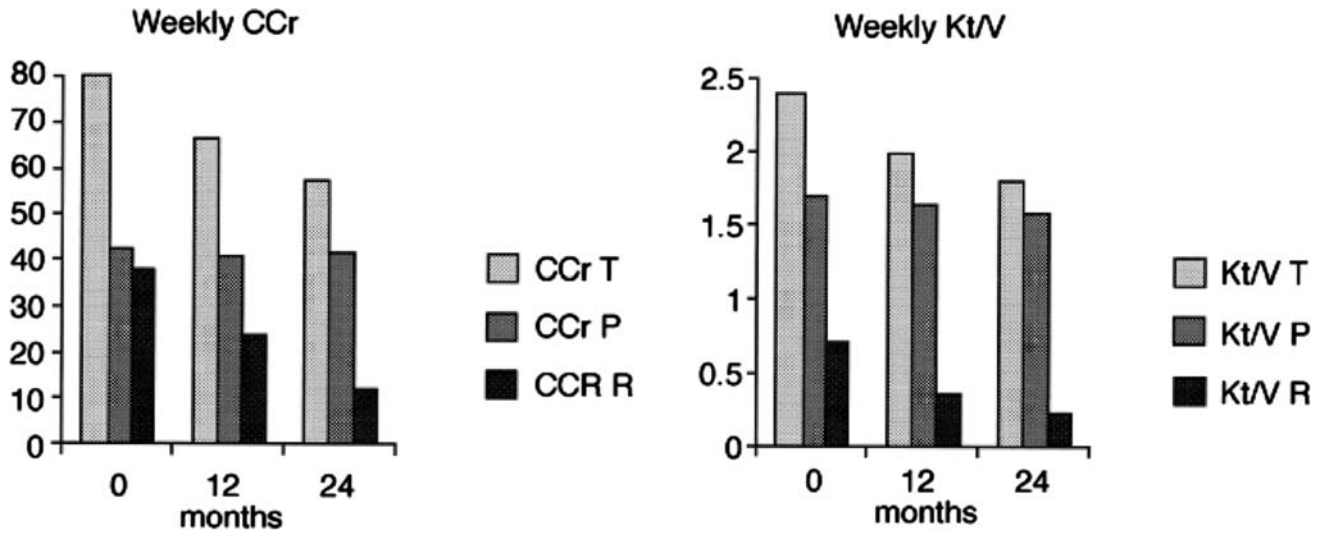

Fig. 16.2 Total solute clearance over time for residual renal function (RRF) and peritoneal clearance (K_p) for both Kt/V and creatinine clearance (CCr) in the CANUSA study [25]

Around the time of the publication of the CANUSA study, however, some attention was beginning to focus on the role of residual renal function (RRF). As mentioned above, Maiorca demonstrated that patients with more residual renal function were more likely to survive, compared to those who had less renal function or were anuric [23]. An important study by Diaz-Buxo, using a large PD patient database, demonstrated that, statistically at least, the dose of PD had no impact on patient survival, whereas the amount of RRF did predict this endpoint [26].

Re-analysis of the CANUSA study, which had been seminal in refocusing adequacy of PD on small solute parameters, demonstrated that the survival benefit of higher Kt/V urea and creatinine clearance lay solely in that contributed by the RRF. The dose of PD, similar to the analysis of Diaz-Buxo, had no effect on survival (RR 1.00 for each increment in peritoneal Kt/V urea). However, for each 5 L/week of residual renal GFR, there was a 12% reduction in mortality (RR 0.88) [27]. (It is important to recognize that a weekly GFR of 5 L corresponds to a GFR of just 0.5 mL/min.) Around the same time, similar analyses of other databases came to the same conclusion: when there is RRF, the dose of PD is not associated with improved survival [20]. Within the span of a few years, studies from the Netherlands [28], Hong Kong [29], and the United States [20] all suggested that residual renal function bore a closer relationship to survival than the dose of peritoneal dialysis as measured by small solute kinetics.

These findings raise two important questions: why is residual kidney function so important, and why isn't the dose of PD important?

The Importance of RRF

Firstly, it is important to address the possibility that the association between RRF and survival represents an epiphenomenon. It may be that intrinsically healthier patients keep their RRF longer, and they have better survival because they are healthier, and not because of anything that the kidneys are contributing. Another possibility is that, on the other hand, those who lose their RRF are selectively transferred to HD, a form of "informative censoring" [30]. However, since the association between preserved RRF and survival is also noted in those patients on HD [31], the issue of "informative censoring" may not be so important.

While ongoing GFR contributes to small solute clearance, it is likely that the renal contribution of excretion of the larger molecular weight uremic toxins is proportionately more important [32] In other words, it vastly underestimates the renal excretory function to measure it only by Kt/V urea or even creatinine clearance. For example, it has been appreciated for years that RRF is important in reducing levels of β-2-microglobulin in dialysis patients [33–35]. So while the RRF may add to the calculation of Kt/V urea or creatinine clearance, it does not capture the more powerful effect that this function has on survival.

Another important aspect of RRF is salt and water excretion by the kidneys and the contribution this makes toward maintenance of the euvolemic state. Several studies have presented indirect evidence that this may be the case. For example, ongoing RRF is closely associated with PD patients remaining normotensive. Put another way, loss of RRF appears to predict the patient on PD becoming hypertensive [36, 37]. Another study that examined risk for the development of left ventricular hypertrophy (LVH) in PD patients found that those with the most preserved RRF had the lowest incidence of LVH, and, conversely, patients who had lost RRF had the highest left ventricular mass index [38]. In the reanalysis of the CANUSA study, urine volume was a stronger predictor of survival than GFR [27]. Whether diuretic-induced increases in urine salt and water excretion have the same protective effect is unknown [39].

Finally, it may be that the intrinsic "anti-inflammatory" effect of functioning renal parenchyma that has been described in the general, nondialysis population, also applies to RRF in those on dialysis. Studies in the general population have shown that loss of renal function is associated with cardiovascular death in a way that cannot be fully explained by "conventional" risk factors [40]. This effect is so powerful that a patient has a much greater chance of dying than reaching dialysis-dependence. Whatever this effect is that leads to greater cardiovascular death at a GFR of 30 mL/min compared to a GFR of 60 mL/min may also be operative at a GFR of 1 mL/min compared to a GFR of 10 mL/min

Why Isn't the Dose of PD Important?

This is the corollary question that follows from the observation that, in the presence of RRF, the dose of PD does not predict survival. There are a number of different explanations that may not be mutually exclusive.

Dose of PD Is Important but Is Statistically Eclipsed by the Overwhelming Effect of RRF

This indeed has face validity, and is supported by studies in anuric patients that suggest that, in the absence of renal function, dose of PD as measured by small solutes [41] or ultrafiltration [42] does contribute to survival. (See section on anuric patients, below.)

Increased Dose of PD Is Important but Will Not Statistically Affect Survival in a Study with Relatively Small Numbers of Patients and Short Follow-up

Compared to studies in other subspecialties, such as cardiology, studies in dialysis have relatively small numbers of patients. Further, power calculations often tend to predict a mortality rate higher than what eventuates, leading to an inability to find statistical significance. The ADEMEX study was a randomized, controlled study of dose of dialysis in incident and prevalent patients in Mexico [43]. Close to 1,000 patients in total were assigned to either the control group (2 L four times a day) ($n = 484$) or the "intervention" group ($n = 481$), where the dose of PD was increased to the Dialysis Outcomes Quality Initiative (DOQI) target at the time of the study of a weekly peritoneal creatinine clearance of 60 L. The two cohorts were well matched in all aspects, and approximately 55% of patients in both groups were functionally anephric. During this study, the control group continued on the 2 L four times a day regimen. In the intervention group, 64% of the patients received four exchanges of 2.5 L, and the rest four exchanges of 3 L. Subsequently, 22% of the intervention group was assigned a fifth daily exchange via a night exchange device to try to get the peritoneal clearance to target. Despite all these machinations, only 59% of the patients reached the target peritoneal creatinine clearance of > 60 L/week. The use of the larger fill volumes and the night exchange device also resulted in greater daily ultrafiltration in the intervention group.

There were 157 deaths in the control group and 159 in the intervention group. The primary analysis demonstrated that the relative risk (RR) of death in the intervention group was 1.00 compared to the control group. In other words, there was no difference in the two groups, despite adequate difference achieved in small solute removal. When patients were stratified according to a number of other predefined characteristics, including age, body size, anuria, serum albumin, diabetes, and nPNA, there was still no difference in outcome between the two dosing groups. Cox multivariate analysis revealed that age, the presence of diabetes, serum albumin, and residual renal function (but not dose of PD) were all predictors of survival.

One question about the negative results of this study is whether a difference could have been seen using more patients or longer follow-up. Certainly the survival curves do not show evidence of divergence that might have become important with longer follow-up. The intervention group did have fewer deaths attributed to congestive heart failure (5.7% versus 13.4% in the control group), but the intervention group also had greater daily ultrafiltration, so this may be a volume effect, not a result of more small solute clearance. Also, the deaths were more often attributed to "uremia/hyperkalemia/acidosis" in the control group (12.2%) compared to the deaths in the intervention group (5.1%). However, it is important to remember that the physicians were not blinded to the dose of dialysis their patients received, and may have been more inclined to assign the cause of death associated with underdialysis to the patients they knew to be in the control group.

A second randomized, controlled trial of dose of dialysis and outcome was performed in Hong Kong [44]. Patients were randomized into three different dose groups of PD. There were just over 100 patients in each group. Despite randomization, there were some differences in baseline characteristics that bordered on statistical significance. The three assigned total Kt/V ranges were 1.5–1.7; 1.7–2.0; and >2.0. As with the ADEMEX study, there was a statistical difference in dose of dialysis received over the course of the study. The 2-year survival was 87.3, 86.1, and 81.5% (the highest-dose group), not statistically different from each other. Indeed, the only secondary outcome difference was that the group receiving the lowest peritoneal dose were more likely to receive erythropoietin treatment after 1 year of treatment. Having said that, however, this group also had the highest serum hemoglobin at last follow-up of 31 months (10.0 versus 8.8 versus 8.9) [44].

Greater Dose of PD May Improve Well-Being or Quality of Life but Not Affect Survival

It may be difficult to prove a difference in survival by modification of dose of dialysis over a 2-year period. Patients with serious co-morbidity will be prone to succumb to their illness regardless of the dose of dialysis, and those with little co-morbidity may tolerate underdialysis without dying, or be censored to follow-up because of supervening renal

transplantation. Interestingly, in the HEMO study, which also examined the effect of dose of hemodialysis on mortality [45], the effect of low versus high flux was seen only in the subgroup of patients who were on dialysis longer than the median time of 3.7 years. One explanation may be that in the group remaining on HD for 3.7 years or longer, those with serious co-morbidity have died, and those with little co-morbidity may have been transplanted. In other words, it is possible that the dose of dialysis (in this case high versus low flux) is important only in the subset of patients with "moderate" co-morbidity. This remains conjectural.

We have witnessed poorly adherent patients with little co-morbidity who are obviously clinically underdialyzed and may have complications related to that (erythropoietin resistance, hypertension, hyperparathyroidism) and may look and function poorly, but who do not necessarily die within 2 years. Therefore, 2-year mortality may not be the best measure when examining for the effect of solute clearance on outcome. Also, an increase in the dose of dialysis may have beneficial effects other than prolonging survival. One small study showed that increased dose of PD in patients with complaints construed as uremic resulted in resolution of many of the symptoms. The benefit may have been the result of a placebo effect, as the study wasn't blinded, but it does suggest the possibility that more dialysis can make the patient feel better, despite not affecting the "hard" outcome of survival [8]. Neither a prospective multicenter study in the Netherlands [28] nor data from the ADEMEX study [46] were able to show an association between dose of peritoneal dialysis and benefit in quality of life. In these studies, however, there was a correlation between the amount of residual renal function and quality of life.

Dose of PD and Outcome in Patients without RRF

It is clear from the review of the studies cited above that the presence of RRF has an overwhelming influence on mortality, and this may be part of the reason why the dose of PD is not significant. In patients without RRF, however, dose of PD should be statistically and clinically more important to outcome. If one were to imagine a hypothetical study in anuric patients receiving just one exchange a day versus the usual full CAPD or APD prescription, it would be much more likely that there would be a difference in endpoints of morbidity and mortality.

Studies of PD in patients without renal function support the assumption that there is an effect of PD on outcome with respect to small solute clearance parameters (in many but not all studies) and ultrafiltration. However, in the studies that demonstrate this association of dose of PD and survival in anuric patients, it is not a continuous function. In other words, dose is important to outcome to a point, after which higher doses are not associated with further improvement in survival.

Many studies have suggested that small solute dosing targets, especially creatinine clearance, are difficult to obtain in the absence of renal function. (Whether the inability to reach these targets will affect patient outcome is a separate issue, discussed later.) A cross-sectional study of 147 PD patients receiving the standard four exchanges of 2 L found that only a minority could reach even urea targets [47]. In a subsequent study by the same group, increasing the dialysis volume was only modestly effective in enabling the patients to reach target [48]. Forty percent of patients were unable to reach Kt/V targets in a UK study, even with individualization of the dialysis prescription [49]. A small point prevalent study, however, of just under 50 anuric patients in a large Canadian PD program demonstrated that adequate Kt/V and creatinine clearance targets could be obtained with increased prescription of either CAPD or APD, especially in larger male patients. Once again, outcome measures were not examined [50]. A retrospective analysis of data on 122 functionally anuric CAPD and APD patients found that the majority of patients were able to reach the then-DOQI target for Kt/V urea, but only approximately 35% could obtain the target for creatinine clearance. Given that the renal contribution to the excretion of creatinine is more substantial than the renal urea excretion, it is perhaps not surprising that creatinine targets were harder to reach in this cohort without kidney function. Follow-up of the patients showed that 27 patients died, 30 were transferred to hemodialysis (mainly for peritonitis, not inadequate dialysis), and nine were transplanted. The rest remained on PD [51]. No relationship was found between small solute clearance parameters and technique survival. However, there was an overall patient survival advantage for those with Kt/V greater than a weekly Kt/V urea of 1.85 (RR mortality 0.54, $p = 0.10$). The peritoneal dose effect was statistically significant when adjusted for age, sex, the presence of diabetes, and multiple other co-morbidities.

Szeto et al. examined the effect of dose of PD and outcome in a single centre in Hong Kong [41]. One hundred and forty CAPD patients were followed prospectively for a median period of 20 months once they had become anuric. During that time there were 46 deaths, and actuarial patient survival at 24 months was approximately 70%. By multivariate analysis, independent predictors of survival included the presence of diabetes, duration of dialysis before anuria, serum albumin concentration, and the dose of PD, measured either by Kt/V urea or creatinine clearance. The authors concluded that peritoneal clearance does have an effect on clinical outcome when there is no renal clearance [41].

The NECOSAD database in the Netherlands recently reported on the outcome of 130 patients who became "anuric" (urine volume < 200 mL/day, a generous definition of anuria) over the course of the study [52]. The statistical approach can affect the outcome and is rather complex. Most of the patients were on CAPD, and not cycler dialysis. When the small solute parameters were analyzed as continuous variables, or divided into quintiles, there was no association with survival. However, as in the Baskharan study from Toronto, when a predefined cutoff Kt/V urea or creatinine clearance was used, it was found that values below a Kt/v urea of 1.5 or creatinine clearance of 40 L/week were associated with an increased risk of mortality. These values were lower than those in the Toronto analysis. Two-year survival was 67% in this cohort, compared with 84% in the whole NECOSAD group. Other predictors of survival included older age, more co-morbidity, longer duration of dialysis before "anuria," and low serum albumin. These were similar variables predicting outcome as were found in the Hong Kong study. The NECOSAD analysis also suggested that ultrafiltration volume was associated with better outcome, although again the statistical analysis for this is rather complicated [52]. Furthermore, given that the reanalysis of the CANUSA data showed that every 250 mL of urine output was associated with a 36% reduction in mortality [27], taking a 24-h urine output of less than 200 mL may have confounded the analysis with patients who received benefit of some residual renal function.

The European APD Outcome Study (EAPOS) prospectively examined outcome in anuric cycler patients in multiple centers [42]. Patients received a dosing regimen of APD to try to reach predetermined targets of a total weekly creatinine clearance of 60 L and a daily ultrafiltration of 750 mL. The cohort included 177 patients, 31 of whom died over the course of the study. In multivariate analysis, predictors of survival included age, co-morbidity, and malnutrition as assessed by Subjective Global Assessment. Increased ultrafiltration at baseline was associated with better survival, but dose of dialysis by small solute parameters did not predict survival. Interestingly, time-dependent analysis of residual renal function in this almost-anuric population came close to reaching statistical significance, again pointing to the powerful effect of even the smallest amount of renal function. Unlike the other studies cited, time on dialysis before entry into this study did not influence survival. The authors suggested that there is a minimum level of small solute clearance necessary to prevent uremic complications, but once that is reached, perhaps other risks such as volume overload or vascular disease become more important [42].

Indeed, the conclusion from the EAPOS is congruent with the other studies on anuric patients. A unifying hypothesis could be that the dose of PD in anuric patients is important to a point; higher doses may not have an impact on survival. However, this hypothesis does not directly address the following question: if residual renal function is so strongly predictive of survival in patients on PD and eclipses PD prescription, what should we do with the PD patient once the residual renal function is gone? Demonstrating, as these studies have, that there is a plateau effect of PD dose and outcome doesn't really address the possibility that this is a high-risk population who might be better served by a change to hemodialysis, with its attendant higher weekly small solute clearance, that might compensate for the loss of residual renal function. (Having said that, however, there is a small body of literature that suggests that residual renal function is important in patients in hemodialysis also [31], and that dose of hemodialysis may not affect outcome when there is significant RRF [53].) This is totally conjectural, however, and could only be addressed by a study that randomized anuric PD patients to either continuing on PD or changing to hemodialysis. This study is unlikely to be done, and there are likely important quality-of-life issues associated with a change of dialysis modality, especially if it entails moving from a home-based therapy to in-center hemodialysis.

Therefore, the anuric PD patient needs to be monitored closely, with particular attention paid to achieving a minimum weekly small solute clearance (Kt/V urea 1.5? 1.7? 1.85?) and maintaining sufficient ultrafiltration and dietary adherence to keep the patient euvolemic. Furthermore, since removal of middle molecular weight uremic toxins is time-dependent, anuric PD patients should receive dialysis 24 h a day, if at all possible, to maximize removal of these toxins.

Current Recommendations for Removal of Small Solutes in Patients on PD

The International Society of Peritoneal Dialysis (ISPD) commissioned a working group with representation from North America, Asia, Australia, and Europe to formulate recommendations for the delivery of adequate peritoneal dialysis, taking into account the more recent studies cited in this chapter. Their recommendations were published in 2006 [54]. The focus of the recommendations pertain to targets for the removal of both solutes and fluid. With respect to small solute removal, it is recommended that the total (renal and peritoneal) weekly Kt/V urea should be greater than 1.7. In the face of residual renal function, the renal and peritoneal Kt/V urea can be added together, although the contribution of renal and peritoneal clearances are likely very different from each other, and it is an oversimplification to simply add the two together. While it was felt that a separate recommendation for creatinine clearance wasn't

necessary, it was recognized that in patients on cycler a weekly minimum clearance of 45 L/1.73 M^2 should be reached. (The reason for adding a creatinine clearance target for the patients on cycler stems from the temptation to provide rapid cycles that could increase the removal of urea but compromise removal of more slowly-transported, larger uremic toxins.) Peritoneal dialysis should be carried out 24 h a day, except in special circumstances, because of the time-dependence for the transport of larger molecular weight toxins. Although a daily ultrafiltration target was not specified, it was emphasized that maintenance of euvolemia is an important part of adequate dialysis, and attention must be given to urine and ultrafiltration volume [54]. Within the confines of financial and adherence realities and limitations, the dose of peritoneal dialysis should be increased as a trial in any patient who is not doing well because of underdialysis or for uncertain reasons.

The National Kidney Foundation in the United States published similar recommendations in 2006 [55]. Furthermore, both the peritoneal and hemodialysis guidelines had sections on the preservation of residual kidney function. Specifically, it was recommended to try to avoid nephrotoxins and other renal insults in the dialysis patient with significant RRF (defined as $>$ 100 mL/day). Two small but carefully done studies have suggested that the use of angiotensin converting enzyme (ACE) inhibitors [56] or angiotensin receptor blocker (ARB) agents [57] may help to preserve RRF in patients on peritoneal dialysis. Therefore, the 2006 KDOQI iteration also recommends the preferential use of these agents for the treatment of hypertension in PD patients with RRF, and that "consideration" be given for the use of these agents in the PD patient without hypertension, in order to preserve the RRF [58].

The Australian guidelines put forward by CARI (Caring for Australians with Renal Impairment) published on the Internet in 2005 recommends that the weekly total urea Kt/V be ≥ 1.6, and that the creatinine clearance be no less than 60 L/week in high and high average transporters, and 50 L/week in low and low-average transporters (www.cari.org.au). The renal association from the United Kingdom has similar recommendations (1.7 and 50 L/week) and also recommends that if ultrafiltration does not exceed 750 mL/day in an anuric patient, consideration be given to a change in therapy (www.renal.org). The European Best Practice Guidelines published in 2005 have the same target Kt/V urea [59]. A minimum creatinine clearance of 45 L/week/1.73 M^2 was recommended for those patients on cycler. Finally, there is an ultrafiltration goal of 1 L/day for those patients who are anuric. [59] While it is important to emphasize the importance of maintenance of euvolemia, especially in patients without RRF, recommendations from groups other than those from Europe/United Kingdom eschewed an arbitrary ultrafiltration goal because of the variability of salt and water intake among patients.

Peritoneal Membrane Transport Characteristics

The first step in tailoring an individual patient's peritoneal dialysis prescription is to know that patient's peritoneal membrane transport characteristics. Unlike HD, where the physician has a wide menu of dialyzers to choose from for each individual patient, peritoneal dialysis patients are "born" with their membrane. A change in peritoneal dialysis dose can usually be accomplished only by changing dwell time, dwell volume, or the number of exchanges per day. At present there is no clinically proven way to alter membrane transport.

Solute clearance by PD is related to the dialysate to plasma ratio (D/P) of the solute multiplied by the drain volume (DV). Therefore, patients with small drain volumes tend to have lower clearances. It is important to point out that rapid transporters of creatinine/urea also tend to be rapid absorbers of dialysate glucose. Therefore, in these patients, although the D/P ratios of urea and creatinine at 4 h or longer dwells tend to be close to unity, their drain volumes tend to be small due to reabsorption of fluid once the glucose gradient is dissipated (Fig. 16.3). With dwell times associated with standard CAPD, rapid transporters may have drain volumes that are actually less than the instilled volume. For these patients, short dwell times are needed to reduce or minimize fluid reabsorption and optimize clearances. In patients who are slow transporters, peak ultrafiltration occurs later during the dwell and net ultrafiltration can be obtained even after prolonged dwells. In these patients the D/P ratio increases almost linearly during the dwell. It is not until 8–10 h that the D/P ratio reaches unity. For these patients dwell time is the crucial determinant of overall clearance, and they will do best with continuous therapies such as standard CAPD or CCPD, which utilize 24 h/day for dialysis and maximize dwell time/exchange. If a patient has a large body surface area he/she may need higher doses (i.e., large volumes of these therapies). Therefore, although a patient may have rapid transperitoneal solute flux, the amount of solute ultimately removed may be compromised by poor ultrafiltration and low drain volumes. On the contrary, a slow transporter may have solute removal not that different from the rapid transporter because of good ultrafiltration and large drain volumes. There are other ways to classify a patient's peritoneal membrane transport, but in the usual clinical setting the peritoneal equilibration test (PET) is the most practical.

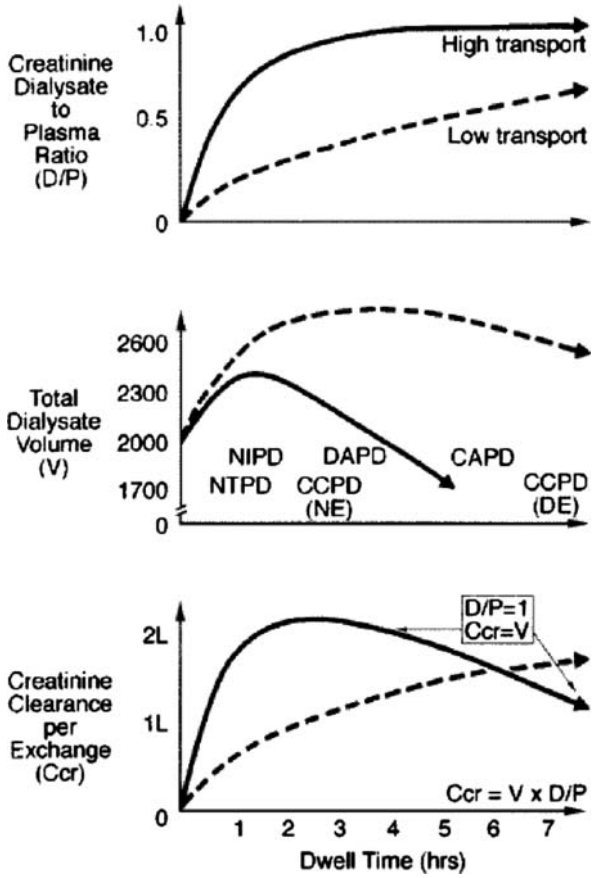

Fig. 16.3 Idealized curves of creatinine and water transport during an exchange with 2 L of 2.5% glucose dialysis solutions in patients with extremely low and high transport characteristics [60]

Mass transfer area coefficients (MTAC) [61–64] are more precise and more succinctly define transport. These define transport independent of ultrafiltration (convection-related solute removal), and hence are not influenced by dwell volume or glucose concentration. The practical use of MTAC for modeling a PD prescription requires additional laboratory measurements and computer models, but once these are obtained MTAC can be used in the clinical setting [64]. The standard peritoneal permeability analysis is another test to follow transport and ultrafiltration characteristics [65–67]. The major difference in this test is that it is better able to determine sodium sieving and can better differentiate the causes of ultrafiltration failure.

Influence of Body Size on Solute Clearance

It is intuitive that removing the same amount of solute from a 55 kg elderly female would represent *relatively* more clearance than the same amount of solute removed from an 80 kg muscular male. These patients have different metabolic rates. Therefore, the absolute daily clearance must be normalized for differences in body size (by V or volume of distribution for Kt/V and by BSA or body surface area for CCr). This modeling also predicts that, if one were to increase the instilled volume/exchange from 2.0 to 2.5 L or greater, under similar conditions total solute clearance should increase, and the instilled volumes needed to achieve small solute clearances can be predicted [68, 69]. However, using larger volume of dialysate may be complicated by higher intra-abdominal pressure, which may be uncomfortable for some patients and put patients at risk for complications related to this pressure Furthermore, larger dwell volumes are not very effective in increasing removal of middle molecular weight uremic solutes [70].

In a review of 806 PD patients, the median BSA was 1.85 m^2 (not 1.73 m^2), whereas the 25th percentile was 1.71 m^2 and the 75th percentile was 2.0 m^2 [69]. Despite this finding that most PD patients in North America are larger than the "standard" BSA of 1.73 m^2, based on clearances predicted by kinetic modeling, if one were able to individualize therapy (increased instilled volumes, daytime exchange for CCPD), the recommended acceptable target total solute

clearances should be achievable for most patients on PD. Those patients who are slow transporters and those who have large body surface areas (> 1.8 m^2) would need close observation once anuric.

Special Considerations

Rapid Transporters

As mentioned above, individual peritoneal membrane transport characteristics are important in determining total solute clearance and ultrafiltration rates in PD patients. Rapid transporters tend to optimize both solute clearance and ultrafiltration after a short dwell time (approximately 2 h) and therefore are likely to do well with shorter dwell therapies such as APD, with or without one or two daytime dwells. (The long daytime dwell, however, poses a challenge for the maintenance of euvolemia in the rapid transporter, discussed below.) Despite this relative ease in the ability to achieve recommended total solute clearance goals, these patients have been shown to have an increased relative risk of death and a decreased technique survival [71]. In the CANUSA Study, patients with a 4-h D/P creatinine of > 0.65 (rapid transporters) were compared to those with a 4-h D/P creatinine of < 0.65 (slow). The 2-year probability for technique survival was 79% among slow transporters compared to 71% for rapid transporters. The probability of 2-year patient survival was 82% among slow transporters versus 72% for rapid transporters, with a relative risk of death of 2.18 for rapid versus slow transporters using this definition for rapid transporters (D/P creatinine > 0.65).

Other investigators have made similar observations [72]. Nolph et al. [73] noted that rapid transporters (D/P > 0.81) had increased incidence of malnutrition. Heaf [74] noted increased morbidity in rapid transporters. These findings have not been confirmed in other studies [42, 43, 75].

The reason(s) for this increased relative risk in rapid transporters on peritoneal dialysis are unclear [76]. There may be a tendency towards malnutrition because of the increased peritoneal protein losses in rapid transporters. Many have shown that as the D/P ratio at 4 h increases, there tends to be increased protein loss. As dialysate protein losses increase, serum albumin levels decrease, and serum albumin correlates inversely with peritoneal membrane transport [77–79]. However, it has been noted that rapid transporters are hypoalbuminemic even before they start on PD and before peritoneal albumin loss can be implicated [80]. This would suggest that both the hypoalbuminemia and the rapid transport status are associated with some other factor, such as systemic inflammation, discussed below. Another way to explain the low levels of albumin may be secondary to overt or subtle volume overload. The typical dwells associated with CAPD are associated with problems with ultrafiltration in these patients. This volume overload may lead to increased blood pressure and/or increased left ventricular hypertrophy with its associated increased risks of death. Furthermore, to optimize ultrafiltration, these patients will probably increase the percentage glucose in their fluids, leading to better ultrafiltration, but increased glucose absorption. This increased glucose absorption may [81, 82] or may not [83] inhibit appetite. Another explanation is that rapid transport status is a reflection of chronic inflammation, and these patients have reduced survival as a result of the systemic inflammation, rather than because of any downstream effects at the level of the peritoneal membrane [84]. It has been suggested that rapid transporters change to nocturnal intermittent peritoneal dialysis (NIPD) with or without a short daytime dwell. This change maintains total solute clearance, while decreasing the need for hypertonic glucose exchanges, therefore decreasing the relative amount of glucose absorption [85]. There are no data, however, to evaluate outcome for these patients who change to NIPD, although there may be an increase in nutritional parameters. There may be a small but insignificant decrease in protein losses when changing from CAPD to NIPD [78, 85]. Conversely, patients on APD may lose more protein each day than those on CAPD [86].

The problem with changing to NIPD is that the prolonged period with dialysate dwell will dramatically reduce the time-dependent transport of middle molecular weight uremic toxins and toxins that transport slowly, such as phosphorus. Therefore NIPD should be considered only when there is significant residual renal function (GFR > 5 mL/min). Otherwise there is a sizable risk of inadequate dialysis (Other ways to deal with the long dwell of APD in rapid transporters is discussed below.).

Acid–Base Metabolism

An essential component of providing "optimal" dialysis is correction of metabolic acidosis. Chronic acidosis has a detrimental effect on protein, carbohydrate and bone metabolism. In PD patients, body base balance is self-regulated by feedback between plasma bicarbonate levels and bicarbonate gain/loss [84, 87, 88]. Dialysis must provide sufficient

replenishment of buffers to compensate for the daily acid load. Lactate (concentration 35–40 mmol/L) is the standard buffer in currently available PD solutions, although recently there has been more experience with bicarbonate-based solutions. Lactate is converted to pyruvate and oxygenated or used in gluconeogenesis with the consumption of H^+ and the generation of bicarbonate [89]. Some CAPD patients remain acidotic. With lactate-containing buffer solutions, buffer balance is governed by the relative amounts of H^+ generation, bicarbonate loss, lactate absorption, and lactate metabolism [90–94].

Ultrafiltration volume can affect bicarbonate loss [87]. Acid-base status is also related to peritoneal membrane transport type [95]. The D/P creatinine ratio from PET is positively correlated with lactate gain, dialysate base gain, and arterial bicarbonate concentration. Rapid transporters gain more lactate during the typical dwell and tended to have higher arterial bicarbonate levels. In 44 patients with metabolic alkalosis the mean D/P creatinine was 0.66 ± 0.12, whereas in those with metabolic acidosis the mean D/P creatinine was 0.59 ± 0.09 ($p < 0.005$). Most CAPD patients have stable mean plasma bicarbonate levels of about 25.6 mmol/L using a dialysate lactate of 35 mmol/L. Increasing dialysate lactate results in a higher serum bicarbonate level [96]. Lowrie and Lew noted no correlation between serum albumin levels and bicarbonate concentration in hemodialysis patients [97], and this was confirmed by Bergstrom [98]. Control of acidosis is important to prevent protein catabolism [99–101].

A recent survey of serum bicarbonate levels in PD patients showed that only consumption of the phosphate binder sevelamer hydrochloride was associated with a decline in serum bicarbonate concentration [102].

Other aspects of acid-base metabolism are discussed in the chapter 20 on noninfectious complications.

Normalization

Severely malnourished patients tend to have a lower ratio of total CCr to total Kt/V_{urea}. This is because malnutrition causes a relatively greater decrease in V than BSA (Table 16.2). Therefore, when normalizing Kt or CCr, the Kt/V is increased proportionally more than CCr. Total body water (V) can be estimated as a fixed percentage of body weight, or more accurately, by using anthropometric formulas based on sex, age, height, and weight such as the Watson [103] or Hume [104] formulas in adults (Table 16.3). These equations provide unrealistic estimates for V in patients whose weights are markedly different from normal body weight (NBW). BSA is usually calculated using the formula by Dubois and Dubois [105]. Jones [106] noted that when actual body weight (ABW) was used for normalization there was no difference in total solute clearance (Kt/V or CCr) between well-nourished and malnourished patients. However, when calculated V and BSA were determined using desired body weight (DBW), there was a statistically significant difference between the groups for both weekly Kt/V (1.68 ± 0.46 versus 1.40 ± 0.41, $p < 0.05$) and for creatinine clearance in L/1.73 m^2/week (52.5 ± 10.3 versus 41.6 ± 19.0, $p < 0.01$). These data suggest that, in malnourished, underweight individuals, if ABW is used to calculate V, the resultant V will be much smaller than that found if the larger DBW is used. In these instances, when Kt is divided by V, the resultant Kt/V may look inappropriately at target, despite progressive anorexia and weight loss in the patient [107, 108].

For well-nourished patients with a stable weight that is not markedly different from desired or ideal weight, the patient's actual body weight can be used in these equations for determinations of V and BSA. However, when markedly different from ideal, the choice of which weight to use in clearance calculations becomes important. One option is to use the patient's "desired body weight" during PD training and always use that weight in adequacy calculations, to avoid this problem if the weight changes significantly. DBW is expressed in kilograms, and is the midpoint of the range of body weights associated with the greatest longevity for normal individuals of the same age range, sex, and skeletal frame size as the individual in question. These body weights are published in the Metropolitan Life Insurance Company actuarial tables.

Table 16.2 Adequacy calculations: what weight should be used?

BW ratio	≤ 0.9	0.9–1.1	> 1.1
Percentage	19	33	48
BWa/BWd	0.82	1.01	1.37
Kt/V_a	1.95	2.08	1.94
Kt/V_d	1.74	2.08	2.25
CCra (L/week)	68.1	71.5	64.1
CCrd (L/week)	62.6	71.7	72.4

Table 16.3 Equations for normalization (calculating V for Kt/V or BSA for creatinine clearance)

V male (L)	$= 2.447 + 0.3362 \times$ weight (kg) $+ 0.1074 \times$ height (cm) $-0.09516 \times$ age (years)
V female (L)	$= -2.097 + 0.2466 \times$ weight (kg) $+ 0.1069 \times$ height (cm)
BSA	$= 0.007184 \times$ body weight $(kg)^{0.425} \times$ height $(cm)^{0.725}$

Source: [103, 105]

How to Monitor Dialysis Dose

The most accurate way to measure dialysis dose is to measure the total amount of the solute in question cleared from the body during a specific time interval. In practice, for CAPD, this means that 24-h collections of dialysate and urine should be obtained. Total solute clearance is calculated as described in the Appendix. An alternative would be to estimate the daily clearance either mathematically or with the use of computer-assisted kinetic modeling programs. It is important to remember that these estimations are truly approximations and should be used with this limitation in mind. Although there is a correlation with the actual clearance measured from 24-h collections, there is a high degree of discordance [109, 110]. Therefore, the "gold standard" for measurement of dialysis dose is to obtain 24-h collections of both urine and dialysate to document the delivered dose of dialysis. It has been suggested that these studies should be obtained quarterly and within 1 month of any prescription change [55]. However, if the patient has a lot of residual kidney function, it may not be necessary clinically to repeat these tests so often as long as the kidney function is being monitored monthly or bimonthly. Despite these recommendations, data from the United States suggest that adequacy studies are not done in many PD patients [68, 111, 112].

PET data are obtained in order to characterize the patient's peritoneal membrane transport characteristics (see above), not to determine clearance. The two tests are complementary to each other and are routinely used together for developing a patient's dialysis prescription and for problem solving.

Several studies have documented that an individual patient's peritoneal membrane tends to be stable over time [19, 25]. However, in some patients it may change. Therefore, peritoneal transport should be monitored to optimize clearance and ultrafiltration. PET is the most practical way to do this, and it is recommended that it be obtained if there is a suspicion of a significant change in membrane properties, such as new-onset difficulty with ultrafiltration. It has been shown that, over time, if there tends to be any change in transport characteristics, the D/P ratios are likely to increase slightly, associated with a small decrease in ultrafiltration. Alternatively, one can estimate D/P values for PET from D/P values on 24 h dialysate collections (Dialysis Adequacy and Transport Test, or DATT) when followed sequentially in an individual patient [113, 114]. These values tend to be slightly higher than the D/P for creatinine on the standard PET. The DATT is not recommended for work-up of ultrafiltration failure, but if the patient's dialysis prescription has not changed (i.e., instilled volume and percentage glucose), sequential DATT measurements do predict peritoneal membrane transport as long as instilled volume/exchange has not changed. Twenty-four-hour collections can also be used to calculate lean body mass (LBM), creatinine generation rates, and estimate protein intake.

Noncompliance

Noncompliance with a medical regimen is not uncommon and can adversely affect patient outcome. The degree of noncompliance with the dialysis prescription itself is easily documented in in-center HD populations [115], although its impact on outcome has been difficult to define. Certainly there is an element of noncompliance with a home therapy such as PD. Until recently there have been no simple ways to evaluate noncompliance in these populations [116]. It has been suggested that a value above unity for the ratio of measured to predicted creatinine production may be an indication of recent periods of noncompliance [117, 118]. These authors speculated that, if the patient had been noncompliant prior to collecting 24 h of dialysate and urine for adequacy studies, but was compliant on the day of collection, then a "washout" effect would occur. In such a case the creatinine production would be higher than would be predicted from standard equations, resulting in an elevated ratio of measured to predicted creatinine production. In other words, if a patient has been underdialyzing chronically and then increases the dialysis just before testing, there will be a disproportional amount of creatinine lost in the dialysate (similar to urinary creatinine excretion during recovery from acute renal failure). However, others have shown that the index is *not* a good indicator of compliance and that higher-than-expected creatinine removal may simply reflect good muscle mass and creatine generation [67, 119]. Nevertheless, noncompliance with the prescription is a real issue, as documented by patient questionnaires

[120] and by looking at patient home inventories [121]. Interestingly, noncompliance may be more of an issue in the United States than in other countries, such as Canada.

At present there is no definitive test, short of asking patients and looking at home inventories, to determine patient compliance. A patient who has, say, a sudden doubling of the serum creatinine in the absence of any change in RRF likely has stopped performing exchanges. More importantly, one should discuss compliance with the patient and have a heightened awareness of the problem. Be sure to design PD prescriptions with patients' lifestyle needs and abilities in mind. Five manual exchanges a day is not realistic for most patients. Automated therapies may help, but it is important to find out how much time the patient usually spends in bed, and what time they have to get up in the morning. For example, 9 h overnight is not a good fit for many people, who have to get to work or get their children off to school. A more patient-friendly prescription might entail 7 or 8 hours overnight, compensated by one exchange during the daytime. For example, the daytime exchange could be at lunchtime, after work, or after dinner. Education and importance of compliance with prescription should be emphasized.

Prescription Dialysis

Timing for Initiation of Dialysis

The NKF-DOQI Guidelines [55] and others [122] have highlighted the need to treat patients throughout the stages of chronic kidney disease (CKD) as a continuum. Data are emerging that suggest that the patient's clinical status, especially nutritional status and left ventricular functional status, at the onset of dialysis is a major predictor of eventual morbidity and mortality.

The traditional absolute indications for initiation of dialysis, such as pericarditis, encephalopathy, refractory hyperkalemia, nausea, vomiting and volume overload, raise little controversy. Weight loss and signs of malnutrition are other more subtle, "relative" indications for initiation. Interestingly, as opposed to stage 5 CKD where minimal target values for weekly total solute clearance have been established, minimal values for total solute clearance by residual renal function alone prior to initiation of dialysis have not been established. This seems paradoxical. In fact, in the CANUSA Study the mean GFR at initiation was approximately 3.8 mL/min [25]. Recent data demonstrates that the RRF at the start of dialysis is increasing over time, and the patients with the greatest co-morbidity have the most RRF at the start of dialysis. Presumably this is because they are not able to compensate for the decline in kidney function, where those patients with little or no co-morbidity can tolerate a very low glomerular filtration rate. Since there is compelling data for PD, and less so for HD that suggests that RRF is a predictor of long-term outcomes, it might follow that the degree of renal function at the start of dialysis could play a role in outcome. However, study of this is confounded by the association of more RRF at the start of dialysis with more co-morbidity, as noted above, and also that the amount of predialysis care and monitoring could be associated with an earlier start, with more renal function, onto dialysis. Furthermore, if the observation by Berlanga is correct, an earlier start onto PD might be associated with prolonged persistence of RRF and a survival advantage [123]. Finally, early referral can be associated with "lead time bias," wherein longer survival on dialysis may simply be a function of an earlier start onto the therapy, and not with an overall prolongation of life expectancy [124]. This guideline does not preclude the importance of quality-of-life issues, blood pressure control, treatment of anemia, and consideration of protein restriction and use of acetylcholinesterase inhibitors to prevent progression of disease. It still suggests individualization of therapy initiation. The recommendations are based on the following indirect evidence.

Outcome Data and the Confounding Effect of Early Start Dialysis, Co-morbidity, RRF, and Predialysis Education

Some databases suggest that outcomes are better for patients who start dialysis "early" than in those who start "late." Bonomini et al. [125] showed that the 5-year survival in 34 patients who started dialysis when their residual renal CCr was > 10 mL/min was 100% compared to an 85% survival in 158 patients starting dialysis with a CCr < 5 mL/min. Tattersall et al. [126] have shown that the level of renal function at the initiation of dialysis was an independent predictor of patient outcomes. Indeed, many studies have suggested that those referred late ($<$ 1 month prior to initiation of dialysis) had a higher hospitalization rate and cost [127], and morbidity and mortality rates on dialysis [128–133].

Taken in aggregate these studies suggest, at least in part, that outcome on dialysis is related to the level of residual renal function at the initiation of dialysis. One explanation for these observations may be the influence of residual renal solute clearance on the patient's nutritional status, and the ongoing, poorly understood anti-inflammatory effect of persistent kidney function.

Initial Prescription

When a patient presents with advanced CKD and PD is initiated, there are two alternatives for writing the initial prescription. These are based on the patient's residual renal function and symptoms. For those patients with minimal residual renal function (the definition of which is not evidence-based, but is taken to be < 100 mL/day) the initial prescription should consist of a "full dose" of PD in order to meet minimal total solute clearance goals. If the patient has a significant amount of residual renal function "incremental" dosage of PD can be initiated.

In both instances the initial prescription is based on the patient's body size (BSA) and amount of residual renal function (both potentially known variables at initiation of dialysis). At initiation, peritoneal transport is not known. Initial prescriptions are based on the assumption that the patient's peritoneal transport is average. Once an individual patient's transport type is known, his/her prescription can be more appropriately tailored. During training, transport type can be predicted from drain volume during a timed (4-h) dwell with 2.5% glucose [134].

Because peritoneal transport can change over first 1–4 weeks of therapy, it is recommended that baseline PET be delayed until after 4 weeks on PD.

"Incremental" Dialysis

One can use empirical prescriptions based on kinetic modeling for implementing PD using an "incremental" approach. These are also based on BSA and residual renal clearance. The 2006 KDOQI guidelines suggest that the total (peritoneal and renal) Kt/V urea be no less than 1.7. Incremental dialysis requires close monitoring and proactive adjustment of dialysis prescriptions and 24-h collection of dialysate and urine to document clearances. Residual renal clearance should be obtained every 1–2 months so that the peritoneal component can be modified if indicated to make sure total weekly Kt/V is 1.7 or higher. The argument for incremental dialysis and the suggestions that this approach could be better/more practical for PD are reviewed elsewhere [135]. Certainly, there are advantages to prescribing "incremental" dosing: the patient can gradually adapt to the constraints of performing the dialysis without being overwhelmed by "full dose" prescription; very often the use of smaller doses of PD will bring about remarkable improvement in symptoms without a major change in small solute parameters (again pointing to the benefits of PD that are not explainable by small solute kinetics); and, finally, the intriguing possibility that, in some patients, PD may be nephroprotective and itself slow the decline in residual GFR [123].

Pitfalls in Prescribing PD

There are some common pitfalls in prescribing the peritoneal component of total solute clearance. The following is a brief summary of some of these, and should be considered whenever a patient appears underdialyzed. Because PD is a home therapy, noncompliance with the prescription must always be considered as a reason for underdialysis [120]. Certainly, patients may be compliant with their prescription when bringing in their 24-h collections; however, if the patient is noncompliant at home, he/she may be underdialyzed on a daily basis. Home visits to monitor the amount of supplies on hand, and keeping track of monthly orders, may help sort this out [121, 136].

Some issues to consider in patients on standard CAPD are: 1) inappropriate dwell times (a rapid transporter would do better with short dwells); 2) failure to increase dialysis dose to compensate for loss of residual renal function; 3) inappropriate instilled volume (patient may only infuse 2 L of a 2.5-L bag) [137]; 4) multiple rapid exchanges and one very long dwell (patient may do three exchanges between 9 a.m. and 5 p.m., and a long dwell from 5 p.m. to 9 a.m., limiting overall clearances) [138]; finally, 5) inappropriate selection of dialysate glucose for long dwells, which may not maximize ultrafiltration.

In general, when the goal is to increase total solute clearance, it is best to increase dwell volume, not number of exchanges [139, 140] (Fig. 16.4). It is important to emphasize that the increased fill volume will increase small, but not

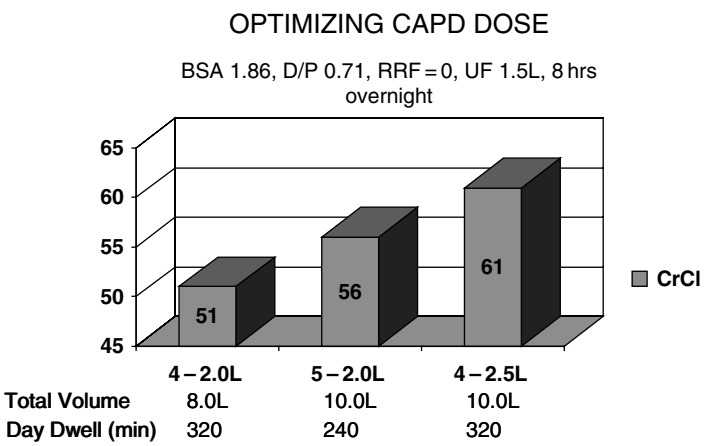

Fig. 16.4 Increasing the prescription from 4× 2.0 L to 5 × 2.0 L increased the clearance only 10%. Increasing the prescription from 4 × 2.0 L to 4 × 2.5 L increased clearance by 21%. This demonstrates the need, in CAPD, for 2.5 L fill volume [141]

large solute removal [70, 140] Increasing the number of exchanges decreases dwell time per exchange, making the therapy less effective for the average patient .

Other problems are specific for those patients on cycler therapy. The drain time may be inappropriately long (> 20 min), thus increasing the time the patient must be connected to the cycler, perhaps limiting the number of exchanges a patient would tolerate. Inappropriately short dwell times may also be prescribed, making the therapy less effective for the average patient in whom length of dwell is crucial. Failure to augment total dialysis dose with a daytime dwell ("wet" day versus "dry" day) could also result in underdialysis. Cycler patients typically "cycle" for 9 h per night. Therefore, the daytime dwell is long (15–14 h). During this long dwell (longer than the "long" night-time dwell for typical CAPD patients), diffusion stops and reabsorption often begins, compromising small solute clearance. Use of a midday exchange is an effective way to optimize both clearance and ultrafiltration in these patients (Fig. 16.5). Also, use of alternative osmotic agents such as icodextrin, which maintains ultrafiltration during long dwells, will be helpful [142]. These optimize both clearance and ultrafiltration without hypertonic glucose. [143, 144]. Finally, poor selection of dialysate glucose may not allow maximization of ultrafiltration, resulting in less total clearance.

When changing from standard CAPD (long dwells) to cycler therapy (short dwells), it is important to remember the difference in transport rates between urea and larger solutes and the effect that this change will have on the patient's overall clearance. These differences and their relevance for CAPD, CCPD, NIPD, and other modifications are reviewed by Twardowski [145]. Transport of urea into the dialysate tends to occur faster than for other solutes. Therefore, if total solute clearance targets are measured using urea kinetics, keeping Kt/V constant going from long to short dwells may decrease clearance of larger molecular weight uremic toxins [146]. There is also the risk of sodium sieving with more rapid exchanges, which will be discussed in the section on fluid management.

Knowledge of the individual patient's peritoneal transport characteristics and familiarity with the differences in dialysis needs for rapid versus slow transporters is imperative to avoid problems or confusion.

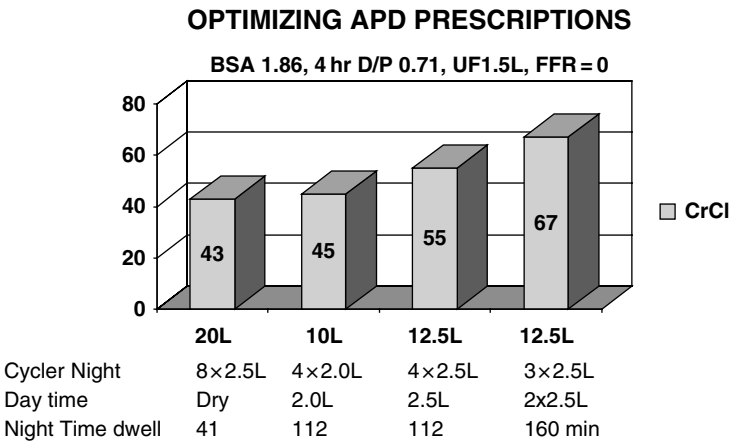

Fig. 16.5 A 10 L wet day (CCPD) delivers 8% more clearance than a 20 L dry day (NIPD). A 12.5 L prescription with a wet day and a daytime exchange improved clearance 57% over the 20 L dry day prescription. This demonstrates the need, in APD, for 2.5 L fill volume, wet day, and a daytime exchange [141]

Adjusting Dialysis Dose

Minimal established dialysis doses are reviewed above. When determining an individual patient's prescription, one should aim for a total solute clearance that is above this minimum, but also allow for other indices of adequate dialysis such as quality-of-life issues, blood pressure control, and dietary protein intake. If during routine monitoring or clinical evaluation of the patient the delivered dose of dialysis needs to be altered, this can easily be done if the patient's present transport characteristics (PET) are known. For instance, in a patient who is a slow transporter and thus clearance is critically dependent on dwell time, changing from standard CAPD (infused volume 8 L) to a form of cycler therapy using 2-h dwells, where the infused volume may be as high as 10–14 L may not always result in an overall increase in that patient's clearance because of the rapidity of the cycles sometimes prescribed in APD.

Once familiar with these relationships, to adjust the dialysate prescription the D/P ratios at the anticipated dwell time and the patient's drain volume for that dwell time should be known. By altering dwell time, the D/P ratio and the drain volume may change. By altering instilled volume, the total drain volume and therefore clearance will change. In general, increasing the instilled volume without changing dwell time will result in an increase in solute clearance.

Another means to tailor a dialysis prescription would be with the use of computer-assisted kinetic modeling programs [92, 147] that allow for ease in adjusting a patient's dialysis prescription. Baseline PET data, drain volumes, and patient weights are needed for input data. Use of these programs usually allows one to set targets for solute clearance, glucose absorption, and anticipated dietary protein intake. These computer simulations then produce a menu of prescriptions that should achieve these targets, and the one that would best suit the patient's lifestyle and meets guidelines can be chosen.

Tidal peritoneal dialysis is a form of automated dialysis in which, after an initial dialysate fill, only a portion of the dialysate is drained from the peritoneum, and this is replaced with fresh dialysate after each cycle [93, 94, 148]. This leaves some percentage of the dialysate in constant contact with the peritoneal membrane, which allows for ongoing solute removal. A typical tidal dialysis prescription would usually require 23–28 L of instilled volume, but preliminary studies suggest that tidal dialysis may be approximately 20% more efficient than nightly PD at dialysate flow rates of about 3.5 L/h [93]. Another advantage of tidal dialysis is that the residual volume may alleviate "fill" or "drain" discomfort, and may also be helpful if incomplete draining is causing the cycler to alarm frequently overnight [94].

Clinical Assessment of Adequacy

As mentioned at the beginning of this chapter, the clinical assessment of adequate dialysis does not just consist of any one laboratory measurement. It includes lack of signs or symptoms of uremia, as well as a patient's feeling of "well-being," control of blood pressure and anaemia and other biochemical parameters [149–151]. The minimal target dialysis dose should be delivered and an adequate PNA achieved. If the clinical judgement is that the patient is manifesting signs of uremia despite what appears to be adequate laboratory measurements of "dialysis dose," it would be prudent to increase the patient's dialysis dose if no other cause for this symptomatology is found. Certainly, a patient could be very compliant with the prescription during the period of dose monitoring but, because this is a home therapy, there may not be compliance during the rest of the therapy interval. Furthermore, there may be a subset of patients who require more than the recommended dose of dialysis for optimal well-being. Clinical judgment is important, since "one size fits all" should not apply to care of the patient.

Another explanation would be the effect weight loss has on calculation of V and the effect normalization of Kt in a malnourished patient has on Kt/V calculation (described in the section on discrepancy, above). Furthermore, if the dose of dialysis appears inadequate despite an adequate clinical assessment, these patients should be monitored very closely, and, once again, a trial of increased dialysis is recommended. In the end, however, patients usually enter dialysis therapy with a large burden of co-morbid disease that may not be ameliorated by more dialysis, and so clinical judgment must be used not to push the patient into an burdensome regimen which may not have any effect on outcome.

Volume Homeostasis

Patients with end stage renal disease (ESRD) have a high prevalence of co-morbidities such as coronary artery disease, left ventricular hypertrophy, hypertension, and left and right heart failure. These are all risk factors for an increased relative risk of a cardiovascular death [152]. Hypertension itself is an independent risk factor for all of these co-morbid

conditions and in patients with chronic kidney disease is in part related to plasma volume overload [153]. In patients on dialysis, although the data is less clear, plasma volume overload is thought to be a major factor in the development of hypertension [169]. One of the many functions of the normal kidney is to maintain volume homeostasis. Therefore it seems prudent that if one is discussing adequacy of any renal replacement therapy, one should consider the optimization of blood pressure and plasma volume as a part of the "adequacy" of the therapy.

The Importance of Volume Status

Observational studies of PD patients suggest that volume status (inferred by UF volume of presence of HTN) is related to patient survival (Table 16.4). Four studies found an association between fluid removal and mortality, while four studies found an association between fluid removal and BP control. Historically, textbook chapters and national guidelines on "adequacy" have not focused on volume control in PD because there are little to no high level studies (such as prospective randomized trials) that have evaluated the effect of achieving a certain ultrafiltration volume/day on a patients: Blood pressure control, volume status, and relative risk of death. However, recent circumstantial evidence from observational trials, have warranted formulation of national guidelines on maintenance of euvolemia and blood pressure control. This evidence will be reviewed here and includes the following: data that suggest that low transporters (who tend to have better PD ultrafiltration volumes) as opposed to high transporters have a lower relative risk of death; data that suggest that PD patients tend to be volume expanded; and data that suggest that greater volumes of daily fluid removal (PD, renal, or combined) is associated with an increased survival. Reasons for these observations will be examined. It is important to note that, in terms of why increased fluid removal/day is associated with a decreased relative risk of death, it is not known if it is the amount of volume of fluid removed per se (PD, renal, or combined) that is causative in reducing mortality, or if the fluid volume is a surrogate for something else (sodium removal, middle molecule removal, salt and water intake, etc). For instance, healthier patients may eat and drink more and hence need to have a higher UF volume.

Low Transporters Tend to UF Better and May Have a Lower Relative Risk of Death than High Transporters

Peritoneal membrane transport characteristics can affect the potential drain volume of any PD dwell. With standard glucose (dextrose)-containing dialysis solutions, the osmotic stimulus for transcapillary ultrafiltration dissipates during the dwell as the glucose is absorbed. If the dwell time is long enough, not only will transcapillary ultrafiltration stop, but lymphatic absorption will predominate, absorbing fluid and therefore decreasing potential drain volume. Peritoneal membrane solute transport type influences the rate of the glucose absorption and hence the expected drain volume per dwell. Rapid transporters (patients with higher D/P creatinine ratios) will be more prone to poor ultrafiltration and potential fluid retention as a result of rapid reabsorption of glucose. They also may be at a higher cardiovascular risk due to the greater systemic exposure to glucose than low transporters. As a result, in these patients,

Table 16.4 Effect of fluid removal on selected clinical outcomes

	Clinical outcome = Mortality		
Author/Year	Study Design	Predictor	
Jager, 1999	Prospective	PUF per 500 mL/24 h increase	TFR per 500 mL/24 h increase
Bargman, 2001	Prospective	UV per 250 mL/24 hr increase	
Brown, 2003	Prospective	TFR per 1,000 mL/24 h increase	
Ates, 2001	Retrospective cohort	TFR per 100 mL/24 h/1.73 m^2 increase	
	Clinical outcome = BP		
Author/Year	Study Design	Predictor	
Jager, 1999	Prospective	SBP 10 mm Hg increase	
Tonbul, 2003	Prospective	TFR 1086 mL vs. 1493 mL/24 h	
Woodrow, 2000	Prospective	PUF 1560 with 7.5% ico vs. 1410 mL 2.5% D	
Ates 2001	Retrospective cohort	Presence of hypertension	

Source: Modified from page S108, NKF-DOQI; From [27, 37, 42, 154–157]
PUF = peritoneal ultrafiltration/24 h, UV = urine volume/24 h, TFR = total fluid removed/24 h, SBP = systolic blood pressure

if the PD prescription is not managed correctly, they may become volume overloaded and theoretically may develop subsequent complications such as LVH and hypertension that may result in an increased risk of death.

Early observational studies suggested that higher membrane transport predicted a poorer outcome on CAPD [71, 158]. This was not confirmed in subsequent studies [71, 159]. A meta-analysis of studies published between 1987 and end of December 2005 that correlated membrane transport and relative risk of death was conducted. Twenty studies were identified, 19 of which were pooled to generate a summary mortality relative risk of 1.15 for every 0.1 increase in the D/P creatinine (95% confidence interval 1.07 to 1.23; $p < 001$) [58] (Fig. 16.6). It was concluded that higher peritoneal membrane status is associated with a higher mortality risk (increased mortality risk of 21.9, 45.7, and 77.3% in low-average, high-average, and high transporters, respectively) as compared to low transport status. On the other hand, studies that enrolled a greater proportion of patients on cycler therapy demonstrated a lower mortality risk for a given increase in D/P creatinine compared to studies that mainly enrolled CAPD patients. This is consistent with the reported observational finding that in patients all given the same CAPD (but not APD) prescription, those with high transport status were more likely to be hypertensive (100% versus 0%) and have LVH (100% versus 33%) than the low transporters on the same prescription ($3 \times 1.36\%$ glucose daytime dwells and $1 \times 3.86\%$ glucose overnight) [156] (Fig. 16.7). In these patients, when prescription was altered to increase ultrafiltration, blood pressure improved (discussed later). When these observations were noted, more attention was paid to individualizing the PD prescription for patients with high peritoneal membrane transport. Guidelines were developed that recommended limiting glucose exposure during long dwells, matching dwell time to transport type, and considering alternative osmotic agents that have a more favorable ultrafiltration profile during the long dwell that is independent of transport type (Fig. 16.8). With such maneuvers, it has been shown that patients with high membrane transport can be managed on PD without the increased mortality risk demonstrated in historical studies [160] (Fig. 16.9). As with hemodialysis or any therapy one should individualize therapy to achieve expected results. It turns out that patients starting PD now do so on cycler therapy in many parts of the world, so there may be little risk to baseline transport type if cyclers are considered and individualization of prescription with the goal of normalization of BP and euvolemia is attempted.

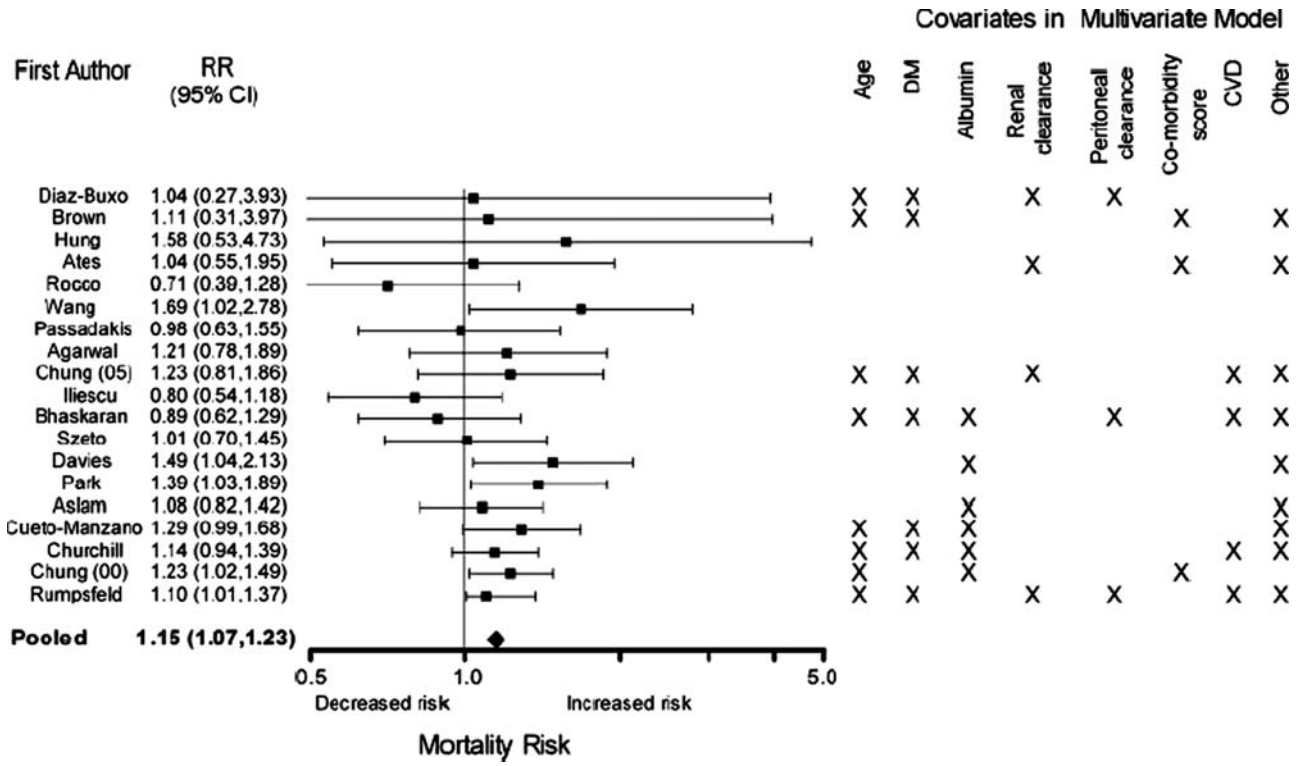

Fig. 16.6 Meta-analysis of the relationship between peritoneal membrane transport type and relative risk of death. Relative risk (RR) estimates and 95% confidence intervals (CI) for the ratio of the creatinine concentration in the dialysate to that in the plasma (D/P creatinine; per 0.1 increment) and mortality in peritoneal dialysis (PD) patients. From [58]

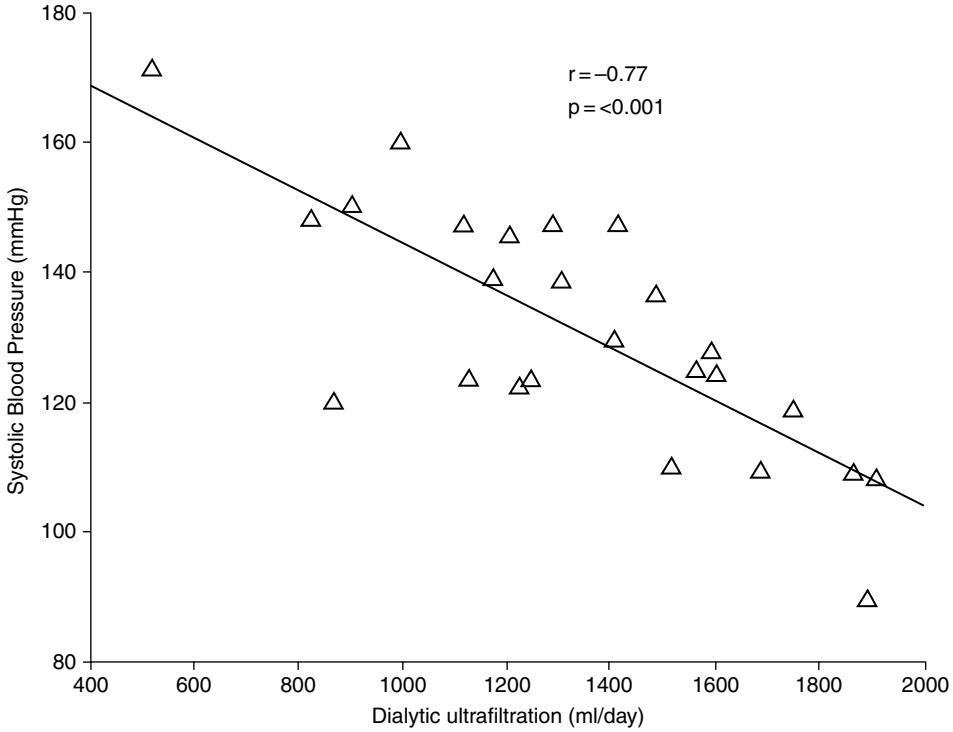

Fig. 16.7 Correlation between 24 h ambulatory BP reading and daily ultrafiltration in CAPD. Correlation between 24 h ambulatory BP reading and daily ultrafiltration in CAPD. From [156]

Peritoneal Dialysis Patients Tend to Be Volume Overloaded

Multiple observational studies have measured volume status for PD patients and compared it to patients on hemodialysis (HD). Using bioimpedance measurements (BIA) to determine intracellular and extracellular fluid spaces, it was noted that both total body water (TBW) and extracellular fluid volume (Vecf) was actually greater in PD patients than both before and after dialysis values in chronic hemodialysis patients and baseline values of healthy controls [160] (Fig. 16.10). Furthermore, the ratio of Vecf/TBW positively correlated with systolic BP and negatively correlated with serum albumin levels. These observations are somewhat counterintuitive in that PD patients are able to adjust their ultrafiltration (UF) on a daily basis because of the continuous nature of the therapy. Therefore, in theory

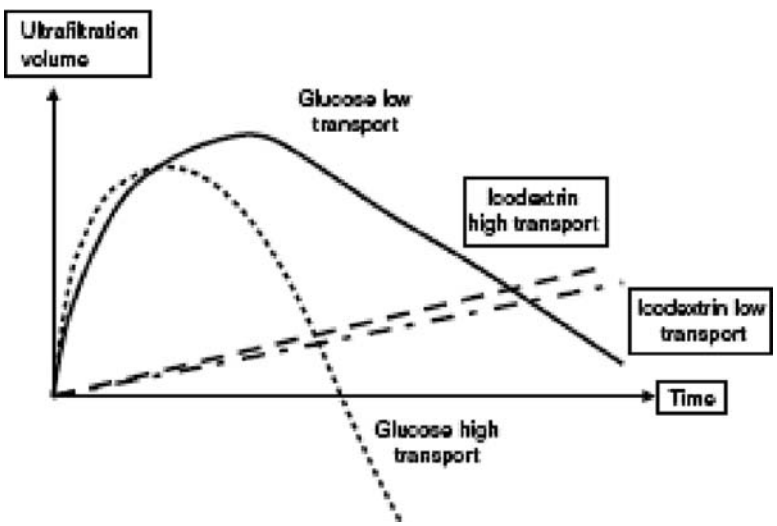

Fig. 16.8 Diagrammatic representation of ultrafiltration profiles related to transport type and osmotic agent. Theoretical constructs representing change in ultrafiltration profile with high and low transporters with glucose or icodextrin dwells. From [160]

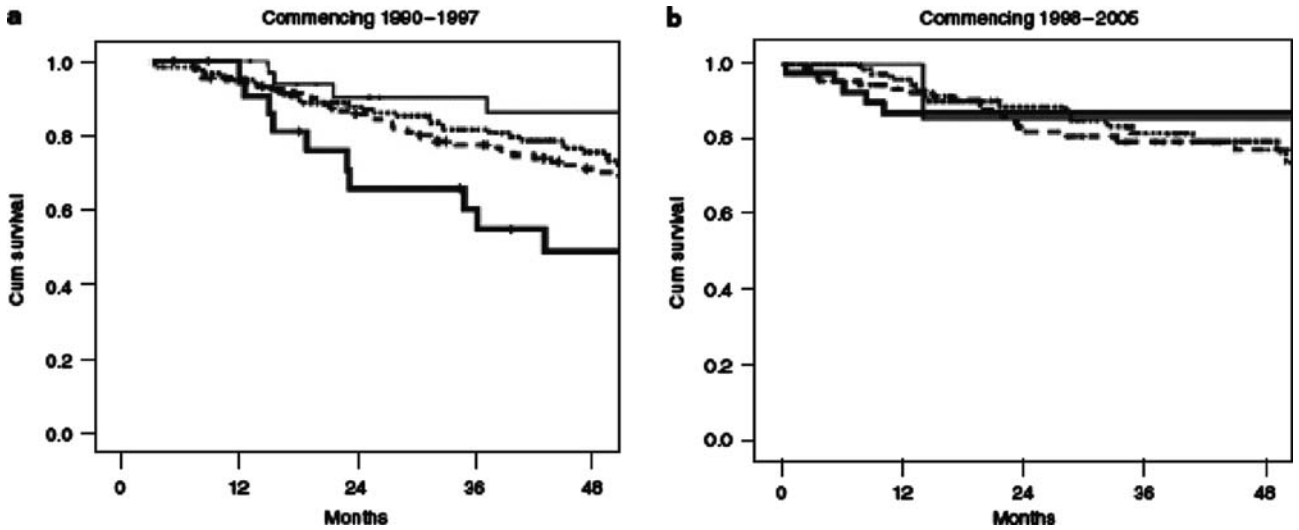

Fig. 16.9 Correlation between transport type and survival in two PD cohorts commencing therapy during different years. Survival on PD (patients censored at transplant or transfer to HD) according to transport category at start of treatment comparing 2 cohorts commencing therapy between (a) 1990–1997, $n = 320$ and (b) 1998–2005, $n = 300$. Low (solid line), low average (dotted line), high average (dashed line,) and high (solid bold line). In the first cohort, transport category was significantly ($p = 0.0009$) associated with survival, whereas in the more recent cohort transport type was not associated with survival. From [160]

they should be able to better attain a true "dry weight." Interestingly this observation is not an isolated one. Others have shown that CAPD patients have an increase in mean pulmonary artery pressure when compared to HD patients. In one study, pulmonary artery pressures were measured pretransplant in both PD and HD patients and found to be a mean of 22 + 7 mm Hg in 56 CAPD patients and 16.3 + 7.2 mm Hg in 296 HD patients ($p < 0.01$) [162].

In another study it was shown that CAPD patients ($n = 28$) had a considerable decrease in "dry weight" (66.6 + 2.3 kg on PD versus 62.4 + 2.4 kg on HD, $p < 0.05$) after transfer to hemodialysis [163]. This was associated with no change in systolic BP but a significant improvement in diastolic BP. These observations suggest that PD patients tend to be chronically plasma volume overloaded. Interestingly in hemodialysis patients, it has been noted that with chronic expansion of extracellular space, BP increases slowly over weeks to months [164]. Short term expansion of the extracellular space tended not to have a major effect on BP and slow reduction in dry weight was associated with a gradual decrease in blood pressure [165]. This suggests that acute volume expansion *per se* may not be the only

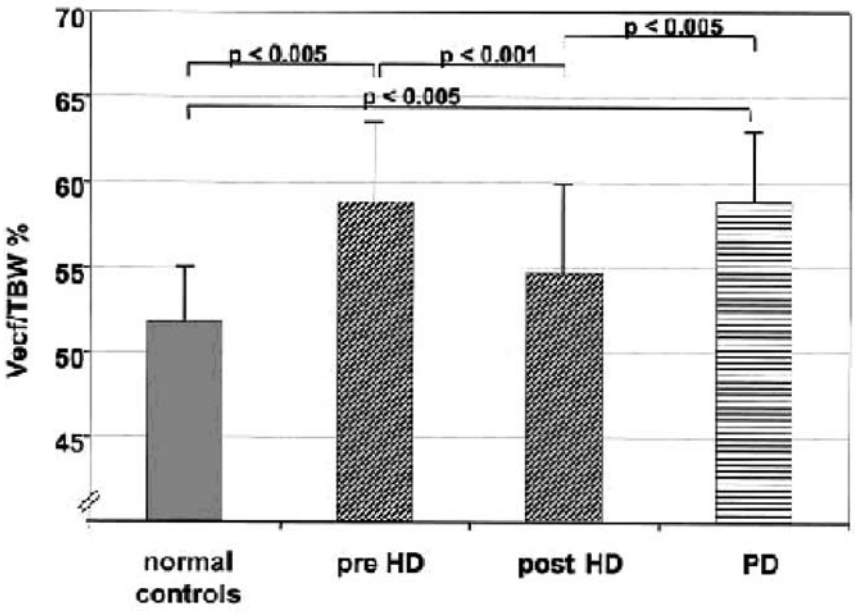

Fig. 16.10 Volume status in PD and HD (both pre- and post-dialysis). Ratio of Vecf/TBW in hemodialysis patients (measured pre- and post-dialysis) in PD patients and in healthy subjects. Measurements were performed after 20 minutes in the supine position using multifrequency bioimpedance. Where Vecf = volume of extracellular fluid and TBW = total body water. From [161]

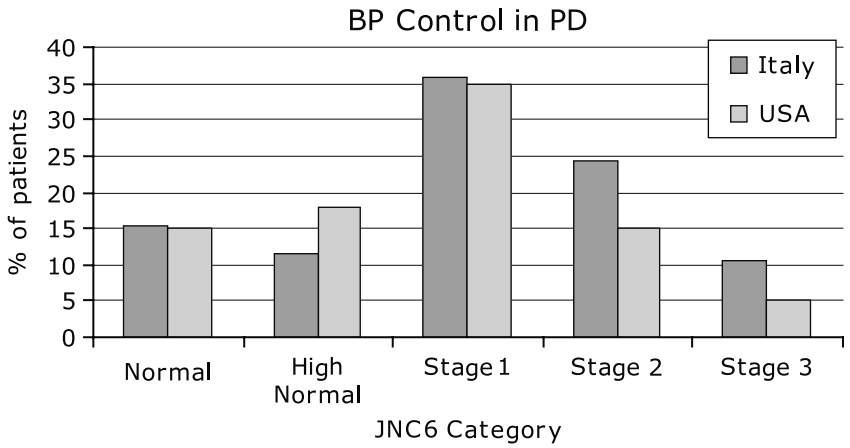

Fig. 16.11 Blood pressure control in PD patients. Blood pressure control in PD patients in Italy and the United States per Joint National Commission recommendations version 6. Modified from [68] and from [166]

mechanism that causes hypertension in ESRD patients. The increase in peripheral vascular resistance associated with chronic volume expansion may play a key role, and, therefore, close attention to dry weight and blood pressure needs to be addressed in every PD patient. Possible indirect evidence to support these observations is data that suggests that, historically, blood pressure control in PD patients has been suboptimal [68, 166] (Fig. 16.11). Furthermore it has been noted that long-term PD patients were more likely to have LVH than long- term HD patients [167]. In that study 51 CAPD patients were compared to a group of 201 HD patients. Left ventricular hypertrophy was more severe in CAPD patients than in HD patients ($p < 0.0001$) and CAPD patients were more likely to need antihypertensive medications (65 versus 38%, $p < 0.001$) despite CAPD patients being younger.

The Amount of Fluid Removal in Peritoneal Dialysis Patients (Peritoneal Ultrafiltration, Residual Renal Volume, or Both) Is Predictive of the Relative Risk of Death

The European Automated Peritoneal Dialysis Outcomes Study (EAPOS) reviewed the efficacy of automated peritoneal dialysis (APD) in anuric patients. Despite similar baseline co-morbidities, the study showed that patients who were below the predefined UF target of > 750 mL/day at the start of the study proved difficult to get above the UF target and had a significantly higher 2-year mortality risk [42].

Peritoneal membrane transport and small solute clearance did not predict survival. An important caveat about this study was that although EAPOS was an interventional study with a predefined minimal UF volume there was no randomization scheme, so any attempt to draw a cause and effect between UF volume and risk must be interpreted with caution. Therefore, a secondary analysis was conducted to see what other factors, if any, could be found in that database that were associated with the link between risk of death and UF volume (i.e., poor intake due to poor health; subtle volume overload with resultant hypertension; inability to increase UF due to co-morbidity such as hypotension; and, other unmeasured difference between groups) [168].

This analysis was unable to clearly define if there was a link with nutritional status. It did not find an association between UF volume, mortality, and blood pressure (BP) control. In fact, there was no relationship between BP control and survival. There were no data on other parameters such as inflammatory state. What was observed is that patients with decreased UF at baseline had a statistically significant lower UF capacity but similar peritoneal transport and a relatively lower use of hypertonic glucose.

Does a Targeted Increase in Peritoneal Ultrafiltration Improve an Individual's Relative Risk of Death or Any Other Surrogates for an Improvement in Death Risk?

Incident patients on PD need to be treated in such a way that prevents volume overload and development of LVH, and maintains control of BP. Can blood pressure or LVH be improved by an increase in ultrafiltration or fluid removal? In a report of CAPD patients who were originally all treated with the same prescription ($3 \times 1.36\%$ glucose during the daytime and $1\times$ overnight 3.86% glucose) and had a residual renal volume of < 200 mL/day, an increase in peritoneal

UF from a mean of 1,086 ± 256 mL/day to a mean of 1,493 ± 223 mL/day was associated with an improvement in systolic and diastolic BP (systolic BP 145 ± 13 versus 128± 5, $p < 0.001$) [156] (Table 16.5). In an open-labeled randomized trial that evaluated the effect of icodextrin dialysis fluid on extracellular water and left ventricular mass, it was found that an increase in ultrafiltration volume (744 + 767 mL versus 1,670 + 1,038 mL) was associated with a decrease in extracellular water and an improvement in left ventricular mass [167].

Another study showed that strict volume control (via sodium restriction and increased peritoneal ultrafiltration) could normalize BP in 37/47 patients on PD who previously needed antihypertensive therapy (47/78 at baseline) [170] (Fig. 16.12). In these patients, there was also a decrease in the cardiothoracic index. However, it should be cautioned that this intervention was associated with a decrease in urine volume (Fig. 16.13).

In summary, targeted optimization of fluid removal (in the cited studies mainly by PD ultrafiltration, although decreased sodium intake and increased urine volume may also play a role) has been shown to result in an improvement in surrogate clinical parameters associated with a lower relative risk of death (normotension, reduced LVH). This would suggest that optimization of volume status should be an important component of "adequacy" of peritoneal dialysis.

Table 16.5 Results of Ambulatory Blood Pressure Monitoring Parameters Before and After Changes in CAPD Regimens

	Before	After	Difference after intervention (%)	*p* Value
Daily ultrafiltration (mL)	1086±256	1493±223	42±20	<0.001
Mean body weight (kg)	67.3±8.9	65.5±8.7		0.001
Mean SBP (mmHg)	145±13	128±5	−11±5	<0.001
Mean DBP (mmHg)	97±10	81±3	−16±8	<0.001
Daytime SBP (mmHg)	159±11	138±6	−13±4	<0.001
Daytime DBP (mmHg)	103±11	86±3	−16±8	<0.001
Nighttime SBP (mmHg)	132±17	119±5	−10±9	0.02
Nighttime DBP (mmHg)	92±11	76±4	−17±11	0.002

SBP = systolic blood pressure: DBP = diastolic blood pressure.
Source: From [156]

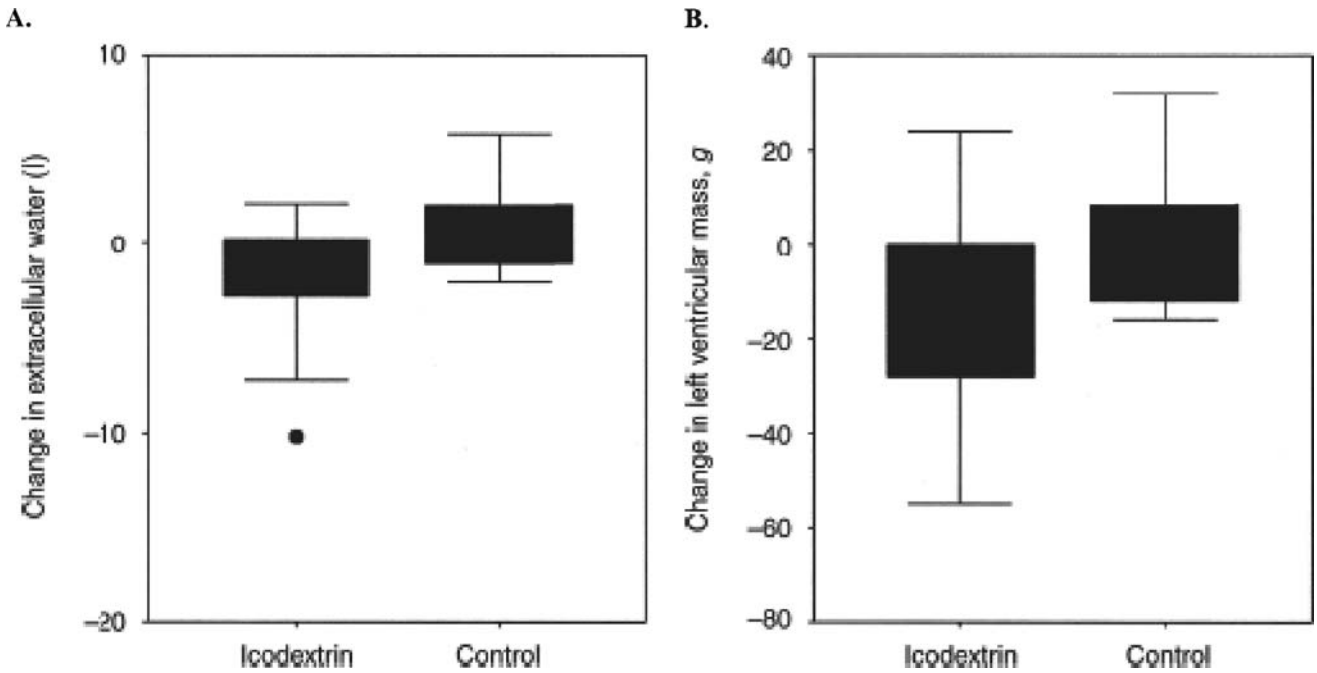

Fig. 16.12 Increased peritoneal ultrafiltration is associated with an improvement in LVH. Panel A: Change in extracellular water in the icodextrin treated and control groups. Box indicates the 25th and 75th percentiles (thick line is median value) and capped bars equal minimum and maximum value. Differences between icodextrin and controls at $p = 0.013$. Panel B: Change in left ventricular mass in the icodextrin-treated and control groups. Box indicates the 25th and 75th percentiles (thick line is median value) and capped bars equal minimum and maximum value. Differences between Icodextrin and controls at $p = 0.050$. From [169]

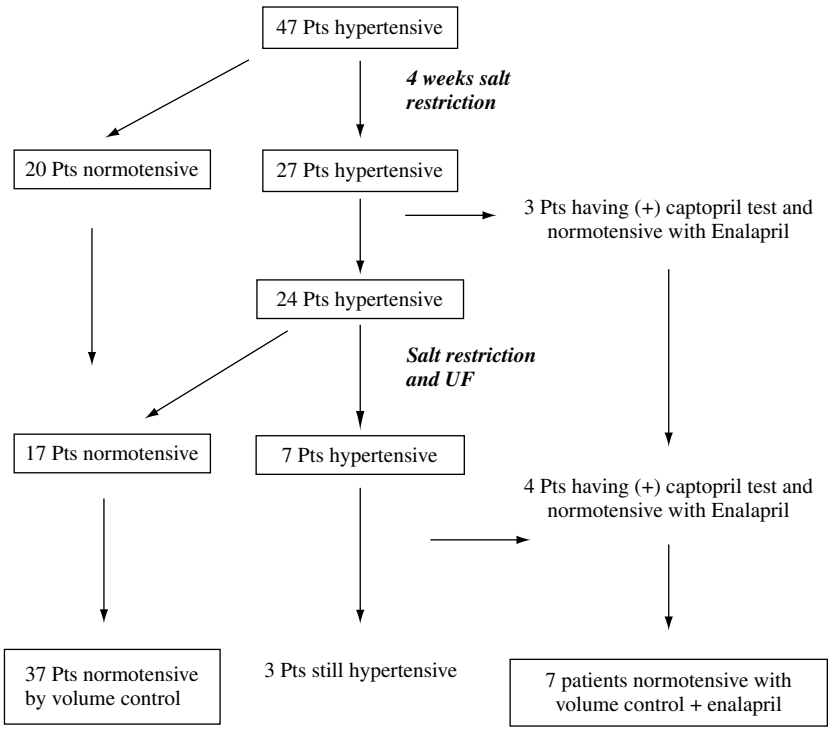

Fig. 16.13 Schematic outline of treatment plan for HTN in CAPD. From [170]

What is the Target Blood Pressure?

Hypertension is a common finding in the PD patient, with reported prevalence in PD populations of between 29 and 88% [166, 171]. Furthermore, uncontrolled hypertension due to volume overload is thought to contribute to higher left ventricular mass in CAPD patients [112]. The relationship between BP control and risk of death in ESRD patients is controversial. Some observational studies suggest that, in fact, there seems to be a "reverse epidemiology," where, in contrast to what is noted in the general population, the lower the systolic BP, the higher the relative risk of death [172, 173].

Others have shown a U-shaped curve, where in patients with both the lowest and highest post dialysis systolic BP have an increased relative risk of death [174]. This observation could be due to the fact that in the ESRD population we have a "selective" cohort and, in fact, patients with the lowest BP may have co-morbidities (congestive heart failure, malnutrition) that contribute to this increased risk, alternatively, this finding may be related to the hemodialysis procedure itself. PD patients would not have this reverse epidemiologic observation. In a prospective observational study of 125 PD patients where the mean BP was $131.2 \pm 17.4/83.4 \pm 9.8$ mm Hg, BP was found to be an independent predictor of mortality. Hypertensive patients (not defined) had a significantly worse 3-year survival than normotensives (60.5 versus 92.1%, respectively, $p = 0.0001$). Similarly, total ($p = 0.001$) and cardiovascular ($p < 0.01$) hospitalizations were significantly worse in hypertensive patients [37].

This study did not define a BP target. To examine the association between BP control and various clinical outcomes, 1,053 random PD patients from the USRDS DMMS wave 2 study were evaluated [175]. Using a Cox model and adjusting for covariates and a mean follow up of only 23 months, these authors found that the two lowest BP categories (systolic BP < 100 and systolic BP 101–110 mm Hg) were associated with an increased all cause and cardiovascular (CV) related mortality. They did not find a similar association for systolic BP. This study could not evaluate for the development of co-morbidities during follow up (new onset congestive heart failure), nor were they able to adjust for differences in confounding factors between group or over time. Higher systolic BP was associated with shorter duration hospitalization. They concluded that based on their data aggressive treatment of hypertension should be done with caution in the PD population, and again did not establish a BP target.

In the EAPOS study, there was no significant relationship between BP and survival when examined as a continuous variable (RR = 0.99/mm Hg, $p = 0.188$). When evaluated by tertiles, there was no significant difference by category ($p = 0.23$), although there was a tendency toward an earlier death in the lowest BP tertile [168] (Fig. 16.14). As a result of these studies, a "target" BP for PD patients cannot be recommended. In fact, there have been no prospective randomized trials done in an attempt to identify what BP should be targeted in an attempt to improve an individual

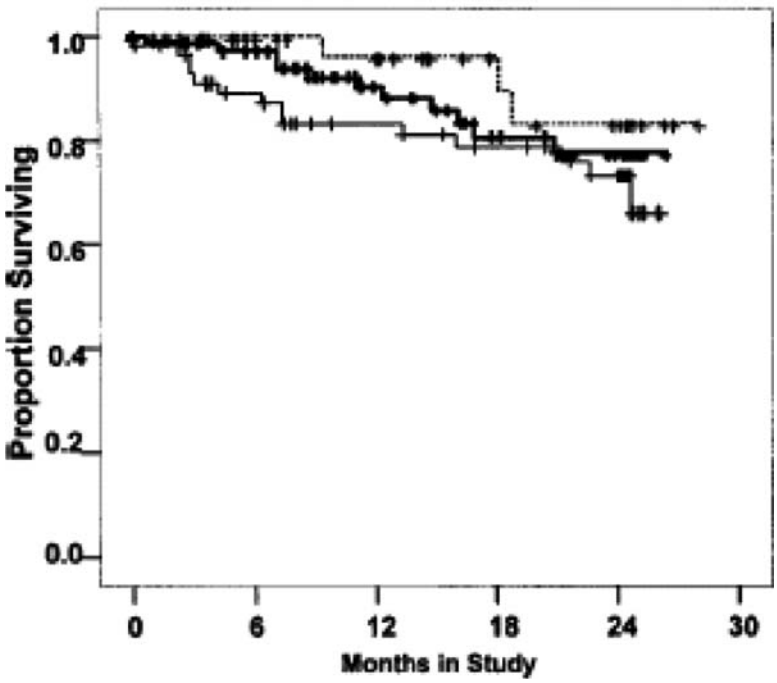

Fig. 16.14 Patient survival related to BP. Patient survival according to baseline systolic blood pressure (BP) divided into tertiles: BP < 126 mm Hg (solid light line); 126–150 mm Hg (solid heavy line); and > 150 mm Hg (broken line). There is no significant difference in survival (log rank test, $p = 0.23$), although the lowest BP group appears to have a disproportionate early death rate. From [176]

patient's outcome as there has been in the general population. Furthermore, there is little evidence to show which antihypertensive would be "best" to use in the PD patient for BP control. However, because there are data to suggest using an ACE or ARB for CV protection, preservation of residual renal function [56, 57, 177] or stabilization of peritoneal membrane transport characteristics, it is recommended that one consider giving preference to using these agents. NKF-DOQI guidelines did not give a target BP, but recommended that one try to control BP with less aggressive approaches than those used in the general population and that one should consider use of an ACE or an ARB. They further recommended that "one should optimize volume status because of the detrimental effect of volume overload on CHF, LVH and BP control," stating: "Each facility should implement a program that monitors and reviews peritoneal dialysate drain volumes, residual renal function and BP control on a monthly basis, and that some of the therapies one should consider to optimize extracellular water and blood volume include but are not limited to restricting dietary sodium intake, use of diuretics in patients with residual renal function and optimization of peritoneal ultrafiltration volume and sodium removal" [55].

What Daily Ultrafiltration Volume Should be Targeted?

Although there are no prospective randomized trials that have examined the relationship between peritoneal UF volume and risk reduction for hypertension, myocardial infarction, or stroke, there is a consensus based on cardiovascular literature that normalization of volume status and optimization of BP is desirable. As mentioned above, there is indirect evidence that blood pressure in ESRD patients is in part related to volume status. Therefore, it is reasonable to assume that if the patient is hypertensive they may be volume expanded. When there is lack of evidence for other secondary causes of hypertension, one should advise dietary salt and water restriction, slowly increase daily UF volume (monitoring intake and output) so that dry weight slowly decreases with a resultant improvement in the patients blood pressure.

While it is acknowledged that, in health, the kidneys play a key role in maintaining euvolemia, the practice of targeting a "minimal" UF volume (or if patient has significant residual renal function, total net fluid removal) as a "yardstick" of adequacy should be approached with caution. It may be prudent to achieve 1 L of UF/day. However this would only be appropriate if the patient drank at least 1 L of fluid a day. Similarly if the patient drank 2 L a day, a peritoneal UF of significantly less than that would be inadequate. Although studies reviewed above were able to show a UF volume below which a cohort had an increased relative risk, it is important to remember that these were not randomized studies and that patients with higher UF volumes may have "needed" them because they felt better and ate more.

At this point a specific drain volume can not be recommended. This must be individualized for each patient based on intake and residual renal volume. One should try to normalize BP by adjusting PD ultrafiltration volumes so that a

"dry weight" is achieved that allows normalization of BP with minimal to no BP medications used exclusively for blood pressure control. Certainly one may want/need to use an ACE inhibitor, ARB, or beta blocker for other clinical indications such as preservation of residual renal function, reduction of CV risk, treatment of angina, or rate control. In these situations, UF volume will need to be adjusted accordingly so that patients will not be symptomatic from low BP or hypovolemia.

How Is Optimal Volume Homeostasis Achieved in PD Patients?

Optimization of volume status in PD involves a group effort by the patient, the home dialysis nurses, the dietician, and the physician. It involves attention to sodium and water intake as well as sodium and water removal (by the kidneys and by peritoneal dialysis). Each facility should develop a program that reviews the patient's dietary sodium and water intake, BP readings, residual renal urine volume, and PD effluent volume on a monthly basis. The caregivers must be aware of the patient's peritoneal membrane transport type and their social constraints and desires. The NKF-DOQI 2006 publication, guideline #4 – Maintenance of Euvolemia – states that: "*Some of the therapies one should consider to optimize extracellular water and blood volume include, but are not limited to: restricting dietary sodium and water intake, use of diuretics in patients with residual kidney function, and optimization of peritoneal ultrafiltration volume and sodium removal*." [55] These therapies should be used in concert to individualize and optimize a patient's total body water and BP status.

What About Residual Kidney Volume?

Maximizing and maintaining residual kidney urine volume is an important way to augment daily fluid removal. As noted above, prospective randomized trials and observational studies have confirmed that there is a strong survival advantage for patients who have residual kidney function. The mechanism for this robust association with a reduction in mortality risk is unknown. It may be that residual kidney volume is a surrogate for other unrecognized systemic kidney functions, or it may be related to salt, solutes, or the urine volume itself.

An observational study [177] and two prospective randomized trials, one using an ACE inhibitor [56], the other using an ARB [57], have shown that use of these medications is associated with a preservation of residual kidney function. It must be noted that the patient numbers were small. However, although not well documented in these studies, residual renal volume was also maintained. Diuretics may be used to increase urine volume. A prospective randomized trial has shown that urinary sodium and water removal can be augmented and better maintained with the use of high-dose loop diuretics [39].

These studies suggest that it is important to monitor residual kidney function in patients on peritoneal dialysis. If hypertensive medications are need, preference should be given to the use of ACE inhibitors or angiotensin blockers. Avoid nephrotoxic agents when clinically possible. Finally, when attempting to optimize volume status, it would also be wise to consider the use of loop diuretics to augment urine volume.

How Do You Optimize Peritoneal Ultrafiltration?

To optimize a patient's UF, one must be aware of the overall treatment goals, the peritoneal membrane transport characteristics and the patient's quality of life, schedule, and treatment requests. The PD prescription can be onerous for the patient. Social factors and burnout are common causes of treatment failure. Therefore, prescriptions should always be reviewed and one should be sure they are consistent with the patient's personal and social needs. The implications of more frequent exchanges, longer overnight time connected to the cycler, or need for a mid-day exchange must be considered and discussed with the patient. If the prescription is decided without patient input and it is contrary to the patient's social desires or constraints, it is likely to fail and treatment goals – small solute removal, UF volume, and optimization of BP will not be achieved.

When appropriate, dietary sodium and fluid intake should be restricted. The patient's record of effluent volumes/dialysis solution used (% glucose/dextrose, icodextrin, or amino acids) should be reviewed. Special attention should be directed toward the "long" dwells of CAPD (overnight) and cycler therapies (daytime). To minimize any untoward side effects from glucose, the minimal percentage of glucose/dextrose solutions should be used when possible. At times this may mean changing the prescription to alter the potential UF profile of short dwells and long dwells to minimize

glucose absorption while maximizing UF. Drain volumes should be optimized for the long dwells of CAPD (night) and cycler (daytime) and when possible net UF should not be negative (i.e., no net fluid absorption) during these dwells. These principles are outlined in the 2006 NKF-DOQI guidelines [55].

In the previous chapters on the physiology of peritoneal dialysis (Chapter 6) and the principles of ultrafiltration (Chapter 6), the basic mechanisms of how the various osmotic agents stimulate transcapillary ultrafiltration, their theoretical ultrafiltration profiles and the role of competing forces such as lymphatic absorption of fluid are explained in detail. It is important to remember that osmotic forces (crystalloid for glucose and amino acids; colloidal for icodextrin) are used to induce transcapillary ultrafiltration. The magnitude of these forces can change during the dwell as the osmotic agent is absorbed and the rapidity of the absorption of the osmotic agent varies from patient to patient based on transport type and lymphatic absorption rates. Rapid transporters absorb the glucose faster than low transporters, hence the osmotic gradient for potential transcapillary ultrafiltration with any glucose dwell is mitigated more quickly in rapid transporters than in low transporters. One needs to be aware of transport type and dwell time per exchange in order to optimize ultrafiltration volumes. If a macromolecule is used as the osmotic agent (polyglucose/icodextrin), although it is very slowly absorbed by diffusion (hence only minimal difference in rate of disappearance of colloid osmotic gradient based on transport types), there can be a difference between rates of absorption based on differences in lymphatic absorption rates of the icodextrin and intraperitoneal fluid. In some patients, the actual UF will be less than expected if there is an increased rate of lymphatic absorption. These issues are most important during the long dwell, especially once residual kidney function is lost.

A special consideration during hypertonic glucose dwells is the difference between sodium and water removal (called sodium sieving). It is recognized that, during the process of transcapillary ultrafiltration, solutes (in this case sodium) can be removed at concentrations similar to that of plasma water (convective solute removal) if there is no resistance to their movement across the endothelial barrier. In order to optimize salt and water removal we need to know what pathways the water and solutes move through. Is the sodium concentration in the ultrafiltrate volume the same as in the ECF, or is some water being removed without solute? As mentioned in Chapter 6, there are three sets of pores via which solutes and water moves as they cross the endothelial barrier [63]. Large pores where macromolecules, water, and small solutes readily pass make up only about 3% of the total pore area, small pores where small solutes readily pass make up 95% of pore area, and ultra small pores or aquaporin water channels represent about 2% of the pore surface area. These aquaporins are water-only channels and it is here that as water moves from the capillaries to the dialysate that sodium is left behind or "sieved" [178]. Water that moves across these aquaporins is the equivalent of "free water."

Early on during a glucose-containing dwell, about 50% of the UF volume is via aquaporins and therefore sodium-free. The other 50% of the ultrafiltrate is via the small pores and therefore is sodium replete. As a result, early in the dwell dialysate sodium concentration will fall, but with longer dwell times sodium will move down its concentration gradient and eventually the D/P ratio of sodium will be near unity (D/P sodium about 1.0). The more hypertonic the solution, the more "free water" is removed early in the dwell. With icodextrin, because there is such a small transcapillary pressure difference across the aquaporin pores, very little of the UF volume is "free water." As a result, if one was to do multiple short overnight dwells (more than four exchanges over 8 h) with hypertonic solutions, the ultrafiltrate will be mainly free water and the serum sodium will increase slightly. The UF volume will be misleading as it will represent removal of mostly sodium-free water, and BP may not be controlled, whereas changing to APD with fewer overnight dwells followed by a daytime icodextrin dwell will likely result in an improvement in BP due to better sodium removal. Attention to these details will help optimize volume status and BP in PD patients.

Low Sodium Solutions

Lowering dialysate sodium allows for more diffusive removal of sodium independent of convective sodium removal. Although not currently available in the United States, many investigators have evaluated these solutions. This was first evaluated by Ahearn and Nolph. They found that using 7% dextrose dialysis solutions with sodium concentration of 100–130 mmol/L compared to 140 mmol/L resulted in increase sodium removal/exchange [179]. Others have found similar results. In one study the authors demonstrated that one could increase total sodium removal without any change in UF volume. Nine anuric patients were studied in a crossover trial in patients on APD. A dialysate sodium of 132 mmol/L was compared to one with a sodium concentration of 126 mmol/L. On the lower sodium solution, daily sodium removal increased to 94 mmol/L of UF compared to 32 mmol/L while on standard dialysate sodium. Four patients experienced an improvement in BP and three were able to discontinue their BP medications. There was no significant change in UF or body weight during the study [180]. In another study, the effects of ultralow-sodium dialysis solutions (Na 102 mmol/L) were compared to baseline (when at least one exchange was 3.86% glucose/4.25%

dextrose and one exchange with icodextrin) in five anuric PD patients [181]. Better sodium removal (80 ± 14 mEq versus 56 ± 15.9 mEq/day, $p < 0.05$), better BP control (mean BP 98 ± 5.5 mm Hg versus 109 ± 7.6 mm Hg, $p + 0.046$) with the ultralow-sodium solutions. Clearly these solutions may work but current data is limited and more studies are needed. For a further review of low sodium dialysate solutions, see [182].

What About Electrolytes and Other Issues?

As mentioned in the introduction to this chapter, "adequacy of dialysis" involves more than just small solute clearance. It theoretically involves replacing "all" the functions of the native kidneys. Some of these can not be replaced by dialysis and others require medications. It is known that the kidneys are important in bone and mineral metabolism. As such, peritoneal dialysis needs to be prescribed in a way that does not limit treatment of bone and mineral metabolism, acid base balance, anemia, and electrolyte control. These issues are discussed in other chapters of this book.

It is recognized that the calcium concentration of dialysis fluids can influence the ability to optimally treat the bone and mineral related complications of ESRD. Dialysis solutions need to be individualized as a part of this treatment program. In the past, it was common to use relatively high dialysate calcium concentrations (3.5 mEq/L) so that hypocalcemia would be prevented (this was in an era when aluminum-containing binders and calcium restriction were commonly used to prevent hyperphosphatemia). Once the toxicity of aluminum was recognized, nephrologists began to use calcium-containing binders. This was often associated with hypercalcemia and metastatic calcification. As a result, the approach to bone mineral metabolism has changed and one of these changes is to lower the dialysate calcium concentration. Most PD fluids now contain 2.5 mEq/L of calcium. These are more physiologic compared to the 3.5 mEq/L solutions and are less likely to result in positive calcium balance. However, if one is using multiple hypertonic dwells and not using calcium-containing binders, there is a small risk of negative calcium balance [183]. It has been shown that this is especially true at lower serum calcium levels (Fig. 16.15). Therefore, care must be taken to ensure that patients are on the appropriate amount of calcium supplement and that serum calcium and PTH levels are monitored as indicated.

Summary

When considering adequacy of dialysis, one must monitor small solute clearance, volume status, and blood pressure in addition to the clinical assessment of how the dialysis prescription is affecting the treatment of anemia, bone and mineral metabolism, and other co-morbid diseases. Periods of inadequate dialysis can result in subtle symptoms of uremia that are insidious in onset and may not be reversible. These can influence outcome in a negative way. To prevent this symptomatology and provide as close to optimal dialysis as possible, it is important to monitor dialysis dose and ultrafiltration volumes so that changes in dialysis prescription can be made proactively rather than reactively. When

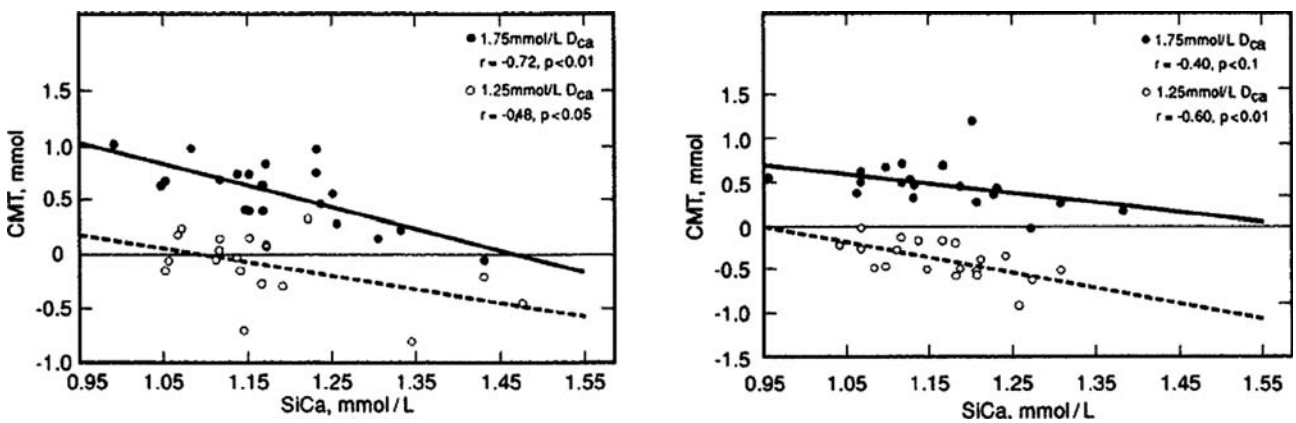

Fig. 16.15 Calcium mass transfer with dialysate fluids containing 1.25 and 1.75 mmol/L calcium. Cell A and B. Calcium (Ca^{2+}) mean mass transfer values (CMT, mmol) plotted against serum calcium levels (SiCa) with 1.25 and 1.75 mmol/L calcium in 1.5 g/dL dextrose (A) and 4.25 g/dL dextrose containing peritoneal dialysate (B) solutions. From [182]

tailoring PD prescriptions it is important that the prescribed dialysis dose be targeted to at least achieve these minimal doses and optimize replacement of as many other aspects or normal renal function as possible.

Appendix: Calculation of Dialysis Dose

The gold standard for determining the daily clearance of any solute is to measure the actual amount of that solute removed from the body during a day. For solute lost in the urine this is classically done by measuring the concentration of that solute (mg/dL or g/L) in a volume (V) of urine and dividing the product by the concentration of the solute in body fluids (mg/dL or g/L).

$$\mathrm{Creat_u} \times V_u \div \mathrm{Creat_p} = \text{daily renal creatinine clearance (L/day)} \tag{16.1}$$

where $\mathrm{Creat_u}$ is urinary creatinine concentration in mg/dL, V_u is volume of urine in L/day, and $\mathrm{Creat_p}$ is plasma creatinine concentration in mg/dL. To calculate the weekly renal creatinine clearance one would multiply the daily creatinine clearance (Eq. 1) by 7 days (Eq. 2):

$$(\mathrm{Creat_u} \times V_u \div \mathrm{Creat_p} \times 7 = \text{weekly creatinine clearance (L/week)} \tag{16.2}$$

To calculate daily renal urea clearance one would substitute urea for creatinine in Eq. 1 (Eq. 3) and use a similar substitution in Eq. 2 for weekly urea clearance, where $\mathrm{Urea_u}$ is the concentration of urea in urine in mg/dL and $\mathrm{Urea_p}$ is the concentration of urea in plasma in mg/dL:

$$\mathrm{Urea_u} \times V_u \times \mathrm{Urea_p} = \text{daily renal urea clearance (L/day)} \tag{16.3}$$

Calculation of residual renal creatinine clearance (RRCCr) for use in determination of total solute clearance is the sum of the daily renal urea and creatinine clearances divided by 2 (Eq. 4) (see above for rationale):

$$\mathrm{RRCCr} = (\mathrm{Eq.1} + \mathrm{Eq.3}) \div 2 \tag{16.4}$$

Urea kinetic modeling, as developed for HD, can also be applied to PD. This modeling uses the dimensionless term Kt/V, or total urea clearance divided by the volume of urea distribution (V). As with creatinine kinetics, the daily clearance of urea due to residual renal function is supplemental to that achieved from dialysis. The calculation of the residual renal function (RRF) contribution to total daily Kt/V is as follows. KT is the daily renal urea clearance in L/day (Eq. 3). Urea volume of distribution (V) is either estimated (60% of the patient's weight in kilograms if male, and 55% of patients weight if female) or preferably obtained from standardized nomograms or equation such as the Watson equation (Eq. 5A or 5B).

$$V\ \mathrm{male(L)} = 2.447 + 0.3362 \times \text{weight (kg)} + 0.1074 \times \text{height (cm)} - 0.09516 \times \text{age (year)} \tag{16.5A}$$

$$V\ \mathrm{female(L)} = -2.097 + 0.2466 \times \text{weight (kg)} + 0.1069 \times \text{height (cm)} \tag{16.5B}$$

$$Kt/V\ (\mathrm{RRF}) = \mathrm{Eq.3} \div \mathrm{Eq.\ 5A\ or\ 5B}\ \ Kt/V\ (\mathrm{RRF}) = [\mathrm{Urea_U} \times \mathrm{F_V} \div \mathrm{Urea_P}] \div V \tag{16.6}$$

To calculate total (urinary and dialysate) creatinine clearance or Kt/V, the contributions from residual renal function are added to the clearance from dialysis. Daily dialysate creatinine clearance (DialCCr) is calculated by modifying Eq. 1 to represent measurements obtained from 24-h dialysate collections. Dialysate creatinine concentration ($\mathrm{Creat_D}$) is substituted for urinary creatinine and total daily dialysate drain volume ($\mathrm{D}V_\mathrm{D}$) is substituted for urine volume (Eq. 7):

$$\mathrm{DialCCr\ (L/day)} = \mathrm{Creat_D} \times \mathrm{D}V_D \div \mathrm{Creat_P} \tag{16.7}$$

Total weekly creatinine clearance is the sum of daily dialysate (DialCCr) and residual renal (RRCCr) creatinine clearances times 7 days/week (Eq. 8):

$$\text{Weekly Creat Cl} = (\text{Eq. 7} + \text{Eq. 4}) \times 7$$

$$\text{Weekly Creat Cl} = (\text{DialCCr} + \text{RRCCr}) \times 7 \tag{16.8}$$

This value must then be adjusted for patient size, using a nomogram for body surface area (Eq. 8A). The recommended minimal dose for continuous therapy is = 60 L/week/1.73 m^2:

$$\text{Weekly Creat Cl} = (\text{Eq.8} \times 1.73\text{m}^2/\text{patients BSA}) \tag{16.8A}$$

or

$$\text{Weekly Creat Cl} = (\text{Eq.8} \times 1.73\text{m}^2/\text{Eq.9})$$

Where patient's BSA is calculated:

$$\text{BSA} = 0.007184 \times \text{body weight(kg)}^{0.425} \times \text{height(cm)}^{0.725} \tag{16.9}$$

Daily dialysate Kt/V is calculated in the following way. KT is simply the daily clearance of urea from dialysate. This is calculated by substituting Urea_D for Urea_u and the drain volume of dialysate ($\text{D}V_\text{D}$) for urine volume in Eq. 3 (see Eq. 10), and dividing this by the volume of distribution for urea, estimated using Eq. 5A or 5B or from a nomogram to get Kt/V (Eq. 11).

$$\text{Dialysate urea clearance/day} = \text{urea}_\text{D} \times \text{V}_\text{D} \div \text{urea}_\text{P} \tag{16.10}$$

$$\text{Daily dialysate } Kt/V = \text{Eq.10} \div \text{Eq.5A or 5B}$$

$$\text{Daily dialysate } Kt/V = \text{Dialysate urea clearance/day} \div |V \tag{16.11}$$

The daily dialysate Kt/V (Eq. 11) is then added to the daily residual renal Kt/V (Eq. 6) and multiplied by 7 to determine the total daily Kt/V (Eq. 12).

$$\text{Total daily } Kt/V = (\text{Eq.11} + \text{Eq.6})$$

$$\text{Total daily } Kt/V = Kt/V \text{ dialysate} + Kt/V(\text{RRF}) \tag{16.12}$$

$$\text{Total weekly } Kt/V \text{ is simply the total daily } Kt/V \times (\text{Eq.13}).$$

$$\text{Total weekly } Kt/V = \text{Eq.12} \times 7 \tag{16.13}$$

$$\text{Total weekly } Kt/V = \text{Total daily } Kt/V \times 7$$

As mentioned in the text, the minimal target weekly Kt/V for continuous therapy is considered to be 1.7.

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Chapter 17
Ultrafiltration Failure

S. Mujais and W. Smit

Definition

Fluid overload is an important problem in peritoneal dialysis (PD) patients, especially when residual urine production is absent. It may be caused by a high fluid intake, inappropriate PD prescription, noncompliance, or by a low drained volume. The latter can be due to mechanical problems, such as catheter dislocation or subcutaneous leakages, or to peritoneal membrane failure. When the diagnosis of ultrafiltration failure is based on a clinical definition, all the above causes of overhydration are included, which might lead to overdiagnosis. Underdiagnosis is also possible, for instance, when a patient with impaired peritoneal ultrafiltration remains in a good hydration status because of strict adherence to a severe salt and fluid restriction. Hence, when faced with a disruption of volume homeostasis, the clinician needs to determine where the fault lies: is it failure of the peritoneum to respond to an adequate osmotic stimulus, or the failure of the prescription to provide such an osmotic stimulus, or the failure of the patient to comply with dietary restrictions and guidelines. In addition, it can be argued that failure at the peritoneal level is also complex, as the response to the osmotic stimulus may be adequate, but overshadowed by other operative processes (such as lymphatic/tissue reabsorption) whereby the net observed ultrafiltration response is inadequate.

The implications of the above discourse are clinically relevant as they affect the interventions required to alleviate the consequences of fluid overload. They can be restated thusly: failure of volume homeostasis is not necessarily the result of inadequate peritoneal fluid removal. It can result from excessive salt/water intake. Failure of excess fluid removal does not obligatorily imply a pathologic alteration of the peritoneal membrane. It may be due to an erroneous prescription that does not offer optimal conditions for peritoneal ultrafiltration, or the operation of contrary mechanisms that thwart the effects of proper peritoneal membrane response.

The definition of peritoneal ultrafiltration failure has been debated. A common clinical definition refers to the inability to attain volume homeostasis despite the use of more than two hypertonic bags per day (4.25%/3.86% dextrose/glucose). However, others used a definition based on a standardized exchange and considered UFF to be present, for instance, when there was negative net ultrafiltration with a 1.36% glucose dwell [1]. In 2000, the International Society of Peritoneal Dialysis (ISPD) committee on ultrafiltration failure recommended a formal evaluation with a standardized test with 3.86%/4.25% glucose, and considered a net ultrafiltration of less than 400 mL after a 4-h dwell as indicative of UFF [2].

Although peritoneal ultrafiltration failure (UFF) can occur in any stage of peritoneal dialysis, it usually develops after a sustained period on PD [3, 4] and is therefore especially important in long-term PD. The proper incidence of ultrafiltration failure is difficult to determine because of the variability in case definition [5–12]. Prevalence as high as 31% for patients treated with PD for more than 6 years have been reported [13] and in a Japanese long-term study, drop-out because of UFF was as high as 51% after 6 years [14]. Both studies were based on clinical signs of UFF and not on a standardized test. Recently in a population of PD patients treated for more than 4 years, prevalence for ultrafiltration failure of 36% has been observed, based on a standardized peritoneal function test as advised by the ISPD committee [15].

This does not necessarily imply a failure in clinical management, as the therapeutic options have improved with wider use of cycler therapy and the availability of alternate osmotic agents such as icodextrin. Patients who have fluid management problems on standard continuous ambulatory peritoneal dialysis (CAPD) may do well with use of alternate osmotic agents such as icodextrin [16–22], or by transfer to automatic peritoneal dialysis (APD) [23].

S. Mujais (✉)
Medical Sciences, Research and Development, Astellas Pharma, US, Deerfield, IL, USA
e-mail: salim.mujais@gmail.com

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Table 17.1 Causes of volume homeostasis failure

Input dependent causes
Excessive salt/water intake
Output dependent causes
Uncompensated loss of residual renal function
Mechanical failure of dialysis procedure
Obstruction and other catheter malfunctions
Leaks
Inadequate provision of ultrafiltration conditions
Long dwells
Inappropriate tonicity
Mismatch of prescription and PET status
Exaggerated contrary mechanisms
Lymphatic/tissue reabsorption
Failure of peritoneal response
High transport status
Aquaporin deficiency
Loss of functional peritoneum

Classification

Table 17.1 offers a classification of causes of failure of volume homeostasis divided by the operative mechanisms. This is an etiologic classification that is useful as a framework for discussion of the various conditions. It divides the possible causes into groups based on a pathophysiologic approach and will be used in the discussion of the various entities. The linear approach to causation classification, however, does not always capture the complexity of clinical situations. It is not uncommon for causative mechanisms to coexist in the same patient. The most intuitively obvious example of mixed causality is the mismatch between fluid intake and dialysis prescription when the former is excessive and the latter is inadequate. More complex examples would be situations of ultrafiltration capacity failure due to high transport coupled with enhanced lymphatic/tissue reabsorption. Such occurrences of mixed causality are not rare in nephrology. They can be likened to mixed acid-base disorders and, like the latter, require a sharp diagnostic acumen coupled with a systematic approach to unravel their intricacies.

Diagnosis

The diagnostic approach needs to account for the frequency hierarchy of causes to be most efficient and practical. The more frequently occurring etiologies need to be addressed in a stepwise diagnostic scheme. Such a diagnostic approach is illustrated in Fig. 17.1.

In the work-up of fluid overload, it is important to consider reversible factors that can alter fluid balance first (Fig. 17.2). The clinical history may readily disclose the probable causation that can then be pursued with definitive diagnostic testing. A history of noncompliance with either dietary advice or PD prescription may direct the evaluation to more interventional pathways and preclude the need for expensive and tedious diagnostic work-up. Understandably, the detection and resolution of patient noncompliance are not easy tasks. Parallel evidence for no-compliance in

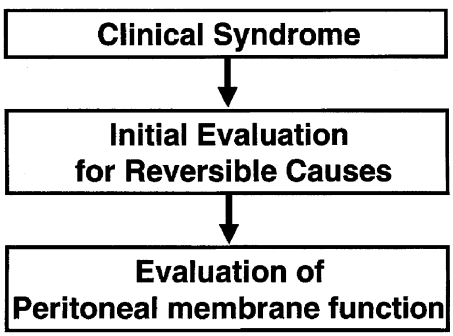

Fig. 17.1 Diagnostic approach for the clinical syndrome of volume overload

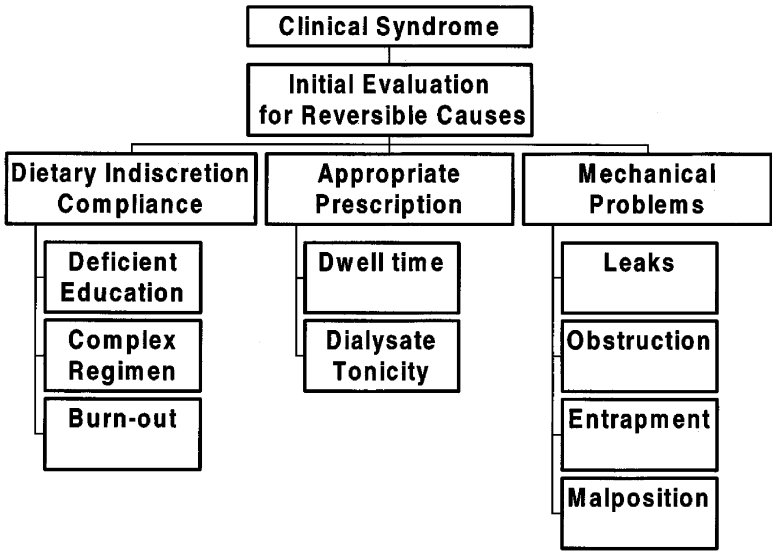

Fig. 17.2 Work-up of fluid overload. Initially the reversible causes should be considered. Patient compliance to diet and prescription must be evaluated, also an assessment of the prescription itself is useful. In addition several mechanical problem must be ruled out

other aspects of the therapy, or generalized evidence for nonadequacy of the therapy may be helpful. Concomitant small solute inadequacy and inadequate fluid removal are much less frequent due to true peritoneal membrane pathology. The clinical profile of the syndrome is also helpful when it is associated with a persistent reduction in drain volume. Reductions in drain volume due to mechanical problems have a more acute presentation. A positional dialysate flow suggests a malpositioned catheter, whereas sluggish outflow (and/or inflow) may result from a partially obstructed or entrapped catheter. Findings of edema localized to the abdomen or inguinal area on clinical examination can be important clues to the presence of a peritoneal leak.

At the time of the initial office evaluation, a quick "fill and drain" with 2 L of dialysate is beneficial in order to directly observe the nature and rate of in-flow and out-flow. The presence of fibrin clots may explain abnormalities with flow, which reduce the efficiency of drainage and volume removal and can often be resolved with intraperitoneal heparin. If incomplete drainage or positional drainage is observed, a flat-plate radiograph of the abdomen will assess the possibility of a malpositioned catheter. When an entrapped catheter or peritoneal leak is suspected, peritoneography or peritoneal computerized tomography are valuable in their diagnosis [24–27]. Diagnostic and therapeutic approaches to these conditions should be sought in the appropriate chapters in this volume.

The exclusion of rapidly resolvable causes of impaired fluid removal has diagnostic and therapeutic advantages. The causes discussed above can be frequently resolved with standard therapeutic approaches and the clinical syndrome hence resolved. Streamlining of the diagnostic approach is also aided by the exclusion of the mechanical causes. The next diagnostic step is to evaluate the ultrafiltration and transport functions of the peritoneal membrane.

Traditionally, peritoneal membrane function has been assessed by the peritoneal equilibration test (PET). The PET has been standardized both procedurally and interpretably to classify membrane function [28, 29]. It is directed, however, primarily at small solute clearance and although ultrafiltration capacity is closely linked to the latter, the traditional PET [29] does not address the issue of quantifying pathologic variations in ultrafiltration. For the purposes of diagnosing presence and causation of impaired fluid removal, the required test is one that will 1) measure ultrafiltration under optimal conditions (to avoid false-positive results); 2) evaluate small solute transport to aid in defining causation; and 3) have validated criteria that correlate with clinical behavior (to avoid both false-negative and false-positive results). The current PET does provide a thorough evaluation of small solute transport, but because of the modest osmotic challenge of a 2.5%/2.27% dextrose concentration utilized in the test, the osmotic drive for ultrafiltration is not optimal.

Therefore, a modification of the standard PET test was introduced by the group of Krediet [30], which offers a reasonable alternative and is recommended as the main test for determining the appropriateness of peritoneal ultrafiltration response (Fig. 17.3). The modification consists of replacing the 2.5%/2.27% dextrose solution of the standard PET with a 4.25%/3.86% dextrose solution, thereby satisfying the criterion of maximal osmotic drive defined above as required for proper evaluation of ultrafiltration capacity. A value of less than 400 mL of net ultrafiltration in a 4-h dwell correlates well with clinical behavior and avoids any false-positive results. An additional advantage of this approach is that it allows for determination of sodium sieving by profiling the changes in dialysate sodium concentration induced by osmotically

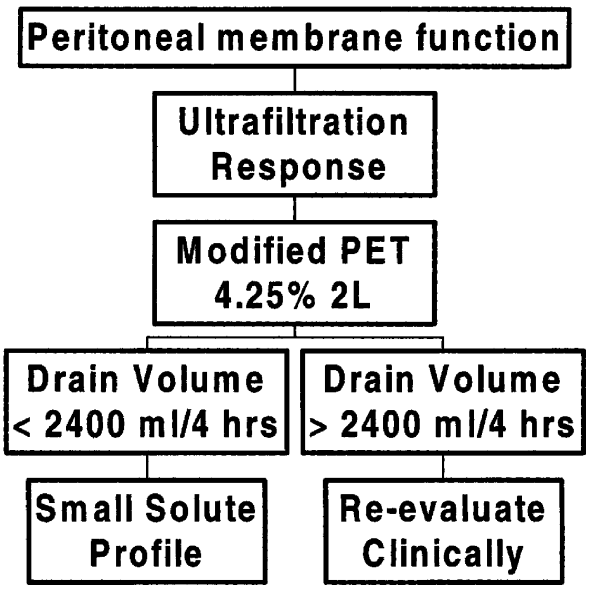

Fig. 17.3 Peritoneal membrane function testing with a 3.86%/4.25% dextrose solution indicates peritoneal membrane failure when the net drained volume is less than 400 mL after a 4-h dwell time

driven water flow. As water influx into the peritoneal cavity is mediated in part by aquaporins, the enhanced osmotic drive will draw water into the peritoneal cavity thereby diluting the sodium concentration. The greater the influx of water is via aquaporins, the greater the decline in dialysate sodium. Impaired aquaporin-mediated water transport will lead to obliteration of the decline in dialysate sodium. Hence, measurement of sodium sieving will allow better diagnostic discrimination of the causes of impaired ultrafiltration [31, 32]. The characterization of small solute transport with this approach correlates well with the results of the standard PET test with 2.5%/2.27% [33, 34].

After initial exclusion of mechanical, compliance, dietary, and other relevant clinical causes of impaired fluid removal, the patient needs to undergo an evaluation of ultrafiltration response. A PET using a 4.24%/3.86% dextrose solution is performed and dialysate and plasma sampling obtained as per usual. The modified test allows for both fluid removal and small solute profiles to be evaluated.

The primary intent of the test is to quantify the net ultrafiltration in response to a 4.25%/3.86% dextrose dialysis solution challenge. If net ultrafiltration is greater than 400 mL/4 h, the subsequent diagnostic sequence needs to focus on the following possible etiologies: 1) dietary indiscretion or dialysis noncompliance; 2) inappropriate prescription; and 3) recent loss of residual renal function for which no adjustments were made in prescription. If net ultrafiltration is less than 400 mL/4 h, the subsequent diagnostic sequence is dependent on an examination of the results of small solute profile measurement (Fig. 17.4). When using the values for net ultrafiltration volume indicated above, the physician

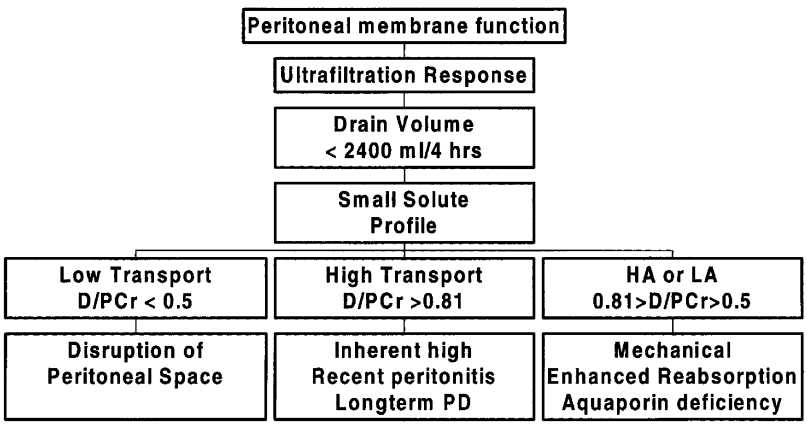

Fig. 17.4 Diagnostic sequence of ultrafiltration failure when the net drained volume is < 400 mL in a 4-h peritoneal function test using 3.86%/4.25% dextrose. Possible causes are given, according to the small solute transport status

should keep in mind the possibility of overfill of dialysis bags and account for this volume in their evaluation of the observed response. Pre- and postinfusion weighing of the dialysate solution bag and standardization of the flush before fill volume are important approaches to ensure accuracy.

Causes of Volume Homeostasis Failure

Input Dependent Causes

Excessive salt and water intake in end stage renal disease (ESRD) is so frequent that it invites neglect either because of familiarity or resigned frustration. Below the apparent simplicity of the clinical imperative to limit intake lies a complex web of factors that make the task very difficult. Patient-related factors such as established habits, difficulties in altering behavior, resentment and contrariness, and simple and pure gluttony are familiar to the practicing physician and so are the barriers to their modification. Resigned frustration with the latter, however, should not be allowed to become a pattern of clinical approach. The attention to intake issues has to focus additionally on three other aspects. First, is avoidance of being lulled by the impression that, because PD is a continuous daily therapy, the dangers of fluid overload are attenuated [35]. The potential advantages of PD are only real if they are used properly. The ability to control fluid removal on a daily basis is a significant advantage, but only as much as it is used appropriately. The tolerance of PD patients for greater food and fluid intake than hemodialysis patient should not be abused by neglect of proper dietary guidelines. Second, attempts at limiting salt and water intake should be balanced against provision of adequate nutrition. Salt and water are obligatory components of food and the zeal to control the former should not lead to restriction imposed on the latter that may hinder proper nutrition. Third, some physicians have used excessive fluid intake coupled with large ultrafiltration volume achieved with high glucose dialysate as a method of enhancing solute clearance. The contribution of ultrafiltration to clearance in PD is quite significant and the success of the above approach in the hands of expert users is testimony to this fact. Caution, however, is necessary when such an approach is used in both the selection and education of the patient in whom this approach is contemplated. Failure of the ultrafiltration to occur because of noncompliance with prescribed regimen, and excessive license in increasing intake by the unwary patient are risks to consider. In addition, the high glucose load that the patient will be exposed to with this regimen will not only have its effects on the metabolic status of the patient, but can also have negative effects on the peritoneal membrane.

Output Dependent Causes

Uncompensated Loss of Residual Renal Function

The contribution of residual renal function to fluid balance is major at the time of usual initiation of dialysis. Patients started on dialysis at a glomerular filtration rate of 5–10 mL/min/1.73 m^2 usually have over a liter of urine output per day. They are able to maintain such an output for over a year unless an intercurrent illness (peritonitis) or event (contrast dye study) causes a sudden loss of renal function. It is usually in such settings that a discrepancy between fluid balance needs and suitability of ongoing prescription arises most acutely. As renal function will inevitably undergo further declines in all patients, failure to adjust the dialytic prescription to the fluid balance requirements will lead to incipient fluid overload. The rate of loss of renal function varies among patients, and the impact of declining glomerular filtration rate (GFR) on urine output is also variable. GFR may decline without a perceptible change in urine output until advanced failure sets in. It is therefore useful to evaluate urine output on a quarterly basis and adjust prescription as needed.

Inadequate Provision of Optimal Ultrafiltration Conditions

From a clinical standpoint, inadequate provision of optimal ultrafiltration conditions can be reduced to two situations: a mismatch between prescription and PET status is best exemplified by use of long dwells in high transporters, and mismatch between dwell time and tonicity exemplified by use of low tonicity solutions in both high transport states and long dwells.

Long Dwells

Glucose is an unsuitable osmotic agent for long dwells because of its rapid absorption. By 4 h in patients with high transport, less than 25% of the original glucose concentration persists in the dialysate. Glucose concentration

continues to fall, albeit less dramatically, with further prolongation of the dwell. The two critical periods for ultrafiltration failure in a diurnal cycle of treatment are then the overnight dwell in CAPD and the daytime dwell in APD [23]. The former can be shortened by the use of an automated night-time exchange device and the latter by earlier drainage, either manually or by reattachment to the cycler for that function exclusively. Alternatively, and likely preferable from a quality-of-life standpoint, the use of alternate osmotic agents such as icodextrin would provide enhanced ultrafiltration at less disruption of lifestyle. When problems with fluid removal arise, examination of the long dwell first is worthwhile as this is the most vulnerable component of the therapy. Determining which patients have negative net ultrafiltration during the long dwell is a useful screening maneuver to adopt in PD clinics. With the use of 2.5% dextrose for a single long dwell in APD, three out of four patients may have negative net ultrafiltration. In high and high-average transporters, two out of every five patients may have a negative net long dwell UF with 4.25%. Icodextrin virtually eliminates negative net UF during the long dwell.

Inappropriate Tonicity

While improvements in fluid removal can be achieved by modifications in dwell time, and as discussed in another section, prescriptions with lower glucose content can be modeled and used, provision of appropriate tonicity for the chosen dwell duration and the peritoneal transport type is nevertheless necessary [23]. It is not uncommon to find patients labeled as having ultrafiltration failure when the cause of fluid excess is the reluctance of the physician to prescribe even 2.5%/2.27% dialysate. Indeed, the areas of the world where "ultrafiltration failure" is most frequently cited as a cause of technique failure are those that have the lowest utilization of solutions with tonicity higher than 1.5% glucose [14]. In the United States where "ultrafiltration failure" is seldom listed as a cause of technique failure, more than 50% of the dialysate used is in 2.5%/2.27% formulation. With the advent of icodextrin as an alternate osmotic agent, enhanced ultrafiltration without an increase in glucose exposure may be obtained.

Exaggerated Contrary Mechanisms

The peritoneal absorptive flow consists of two different pathways: 1) *direct lymphatic absorption* and 2) *fluid absorption into tissues*. The peritoneal fluid and protein absorption rates in animal experiments have been shown to be directly proportional to the intraperitoneal *hydrostatic* pressure. Hydrostatic pressure-driven convection is the most likely mechanism driving the fluid and protein transport into adjacent tissues.

Increased lymphatic/tissue absorption (or overall peritoneal fluid absorption) can lead to a low drain volume despite an adequate response to an osmotic challenge [31, 36, 37]. Lymphatic/tissue absorption of peritoneal fluid negatively influences the overall removal of water (decreases net ultrafiltration) and solute (partially negating the effect of diffusive and convective solute transport). Since the lymphatic/tissue absorption of peritoneal fluid does not alter the concentration of solutes in the dialysate, the D/P creatinine ratio remains unchanged even though net ultrafiltration can be significantly decreased. Measurement of fluid absorption from the peritoneal cavity can only be done with indirect methods. The disappearance rate (clearance) of intraperitoneally administered macromolecular tracers, such as radio-iodated serum albumin (RISA) [38, 39] or dextran 70 [40, 41], can be used. The disappearance rates of these tracers are constant in time [42] and independent of molecular size. This indirect measure can be applied as functional characterization of the effective lymphatic absorption rate. It implies that all pathways of peritoneal lymphatic drainage, both subdiaphragmatic and interstitial, are included in the definition. Lymphatic/tissue absorption rates average 0.95–1.0 mL/min in the upright position and thus contributes significantly to intraperitoneal volume balance. An overall increase in intraperitoneal pressure causes a decline in net ultrafiltration primarily by the increase in lymphatic/tissue absorption rate [43]. The relative contribution of increased lymphatic/tissue reabsorption to fluid removal problems is not definitively established. Proper assessment of frequency of the condition, however, will require further work. Impaired net ultrafiltration associated with the disappearance of intraperitoneally administered macromolecules was found in two out of the nine patients with ultrafiltration failure described by Heimbürger et al. [8]. Krediet and his group [31, 44] found a dextran disappearance rate exceeding 2 mL/min in about one-third of the patients with inadequate ultrafiltration (net UF $<$ 400 mL/4 h on 4.25%/3.86% glucose), often in combination with the presence of a large peritoneal surface area. There seems to be no evidence that the prevalence of this cause of impaired peritoneal fluid removal would increase with the duration of peritoneal dialysis, since lymphatic absorption rates appear to be stable over time [45].

Definitive proof of the condition requires identification of high macromolecule clearance from the peritoneal cavity to plasma as a surrogate marker for fluid removal by the lymphatic pathway [40, 46]. The point bears emphasis: clearance of macromolecules is used as an indicator of fluid clearance, but the two are not necessarily identical. In the absence of such a test, the diagnosis is made by exclusion of mechanical catheter problems, and aquaporin deficiency in patients with

low-average or high-average solute transport on the modified PET. The rate of lymphatic absorption is estimated by measuring the disappearance of macromolecules, such as albumin or dextran 70 from the peritoneal cavity (molecules too large for transcapillary transfer by either diffusion or convection). As described by Pannekeet et al. [43], this can be done by adding 1 g of dextran 70/L to a 2-L, 4-h 4.25%/3.86% dextrose dwell. The dialysate would be sampled at 0, 10, 20, 30, 60, 120, 180, and 240 min and the lymphatic or tissue absorption rate of dialysate would be calculated from the dextran clearance from the peritoneal cavity. Measurement of lymphatic flow is uncommon in clinical practice due to the complexity of the procedure.

Failure of Peritoneal Response

High Transport Status

The most frequent cause of peritoneal ultrafiltration failure is the presence of a large vascular surface area, characterized by a high D/P of creatinine or low D/D_0 glucose. It leads to high absorption rates of low-molecular-weight osmotic agents and therefore to a rapid dissipation of the osmotic gradient. A large peritoneal surface area can be anatomic or functional. In the first, neoangiogenesis in the peritoneum [47] leads to more vessels, so a larger surface for the transport of solutes is available. Functional enlargement of the vascular surface area can be present when more existing peritoneal microvessels are perfused (for instance, during PD-related peritonitis). Patients with a net ultrafiltration (< 400 mL/4 h with a 4.25%/3.86% modified PET) and D/P creatinine > 0.81, represent the largest group of patients with inadequate filtration due to peritoneal membrane characteristics. Patients can have an inherent high small solute transport profile at initiation of dialysis; they can have a transient fast transport status during peritonitis and there are patients who develop a high transport profile in the course of long-term peritoneal dialysis. These patients tend to have good small molecular weight solute transport, but have poor ultrafiltration during standard CAPD using glucose containing dialysate. If their dwell times are mismatched for their membrane transport characteristics, they often appear to have inadequate ultrafiltration as they lose residual renal function and no longer have urine flow to supplement net daily peritoneal fluid removal.

Inherent high transport

Fifteen percent of patients starting peritoneal dialysis display this transport profile. This proportion appears to be constant in various population groups and stable over medium periods of observation [48]. Patients in this group have very efficient membranes for small solute clearance, but may have difficulty in ultrafiltration particularly in long dwell cycles. These patients are at risk of high protein losses in the peritoneum. A high level of technique failure has been described on CAPD therapy, likely related to fluid management. Retrospective analysis also suggests higher mortality in this group [49–53]. Automated PD and icodextrin for long dwell are recommended therapeutic approaches in this group (see below).

Recent peritonitis

Impaired ultrafiltration with PD is a transient phenomenon during acute peritonitis [54]. The high solute transport rates during acute peritonitis lead to a rapid disappearance of the osmotic gradient. The infection-induced hyperpermeability is probably caused by increased secretion of vasoactive substances such as prostaglandins and cytokines [55] and an up-regulation of NO-synthase activity [56, 57]. These mediators are likely to increase the number of perfused peritoneal capillaries, leading to a functional increment of the vascular peritoneal surface area. This leads to an increase in transcapillary ultrafiltration rate during peritonitis, compared to the stable situation. In addition, vasodilatation leads to a reduced size-selectivity, resulting in a decreased restriction coefficient to macromolecules [58]. It is a common clinical observation for peritoneal dialysis patients to experience fluid retention during episodes of peritonitis [54, 59]. These patients often need a temporary change in their standard dialysis prescription (shorter dwell times or increased tonicity of fluids) to achieve net ultrafiltration. When compared to baseline, PET data during peritonitis reveal an increase in the D/P ratio for creatinine and a decrease in the D/D_0 ratio for glucose, usually accompanied by an increase in protein losses and a significant decrease in net ultrafiltration. Several studies have indicated that ultrafiltration during an episode of peritonitis can be satisfactorily achieved with the use of icodextrin [60, 61].

High transport during long-term PD

In long-term patients, the presence of a large vascular surface area, as judged from fast transport rates of small solutes, is by far the most frequent cause of ultrafiltration failure [62]. This fits well with the finding of an increased number of vessels in the peritoneal membrane of long-term PD patients [47, 63]. This peritoneal neoangiogenesis resembles the abnormalities

frequently observed in diabetic retinopathy. In PD the peritoneal tissues are exposed to extremely high glucose concentrations. This may explain the diabetiform alterations in the microvasculature, like reduplication of the capillary basement membrane and the marked increase in the number of microvessels [47], as well as the accumulation of advanced glycation end-products in the vascular walls [64]. Peritoneal equilibration testing shows an increase in D/P ratio for creatinine, a decrease in the D/D_0 ratio for glucose, and a smaller than usual decrease in dialysate sodium during the dwell. In contrast to the situation seen with peritonitis, where transport changes are usually transient, and protein losses are increased, the small solute transport changes in this group tend to be permanent and protein mass transport does not change.

These changes in peritoneal membrane function were originally described with acetate-containing dialysis solutions [5, 65], but have also been seen in patients who have only used lactate-containing dialysis. A history of recurrent peritonitis and extensive use of hypertonic exchanges has been observed in some, but not all, studies. The incidence seems to increase with time on peritoneal dialysis implicating repeated exposure of the peritoneum to dialysis solution as a cause.

The natural history of peritoneal membrane transport over time has been debated [3, 48, 66–70]. This is mainly due to noncomparability of the methods used. A small number of studies have used standardized 4-h dwell evaluations with examination of both ultrafiltration and solute transport, while a larger number utilized clearance monitoring. The latter may mask opposing directional changes in solute and fluid transport. The potential increase in solute clearance due to an increase in D/P creatinine may be masked by the potential decline due to lower ultrafiltration. The emerging picture, however, is that during long-term observations (greater than 2 years) some degree of increase in D/P creatinine does occur in patients on PD.

Aquaporin Dysfunction

This condition has first been described clinically in patients with severe peritoneal ultrafiltration failure, without signs of increased solute transport [32]. It is a rare condition to be present as the only cause of UFF, it is more frequently seen in combination with augmented small solute parameters. Impaired aquaporin function offers a very interesting model to understand peritoneal transport and its alteration by pathologic states. The peritoneal capillary membrane is not freely permeable to solutes but is a highly selective barrier, with the ability to impede diffusion and convection of relatively small molecules while restricting large macromolecules, but to a lesser degree than standard hemodialysis membranes. This suggests that the peritoneal capillaries contain populations of varying "pores," which alter solute transport. This has led, through computer simulations [71–76] and animal work [77–80], to the "three pore theory" of water and solute transport across the peritoneal membrane (mainly transcapillary movement of solute and fluid). This theory proposed three populations of pores. First a large number of transcellular pores (4–5 A radius). Second a large number of small pores (40–50 A) and third a small number of large pores (200–300 A). This theory predicted that 40–50% of the total ultrafiltrate is obtained through the transcellular path and therefore will be solute free, when driven by an osmotic pressure differential. Animal work and indirect human research has strongly pointed to the aquaporins being the water channel transcellular pores (ultra small pore). This assumption has been tested in rats and rabbits. Aquaporin-1 was inhibited by intraperitoneal administration of mercury-chloride and as a result almost complete blockage of the sieving of sodium was present [80, 81]. In humans, aquaporins have been demonstrated by in situ techniques to be present in the peritoneal capillary endothelium and mesothelium [82, 83]. The small pores are also involved in water transport through colloid osmosis and hydrostatic pressures which are in balance; these are also the pores through which most of the small solute transport occurs. Aquaporin dysfunction is that situation where there is damage to or diminished number of water channel ultrasmall pores, which can lead to deficient crystalloid induced ultrafiltration [32, 84].

The function of the ultrasmall pores or water channels can be estimated by the "sieving" of sodium during a hypertonic dwell [38, 85, 86]. The sodium concentration in dialysate decreases in case of free water transport. This is indeed observed in the initial phase of a 3.86%/4.25% glucose dwell, but not in a 1.5%/1.36% glucose exchange (see Fig. 17.5). The initial high osmotic pressure gradient in the 4.25%/3.86% glucose dwell will lead to osmotically driven fluid transport trough the ultrasmall pores, which leads to a dilution of the dialysate sodium concentration. The lowest dialysate sodium concentration is usually reached after 60 min. The lower osmolality of a 1.5%/1.36% glucose solution does not have the osmotic force to induce a fluid flow through these pores, so no sieving of sodium is observed. In case of a large difference between dialysate and plasma sodium concentration, diffusion of sodium from the circulation to the dialysate will take place. This will increase the dialysate sodium concentration and therefore a falsely decreased sodium sieving will be measured, incorrectly indicating loss of free water transport. To avoid this, a correction for sodium diffusion can be applied [87, 88].

Another way to assess aquaporin-mediated transport is to calculate the difference in net ultrafiltration obtained after a 4-h dwell with 1.5%/1.36% glucose and with 4.25%/3.86% glucose dialysate; 1.5%/1.36% glucose induces only a small crystalloid osmotic pressure gradient, and therefore limited transport through water channels. On the other hand, 4.25%/3.86% glucose induces a very high crystalloid osmotic pressure gradient and the net ultrafiltration

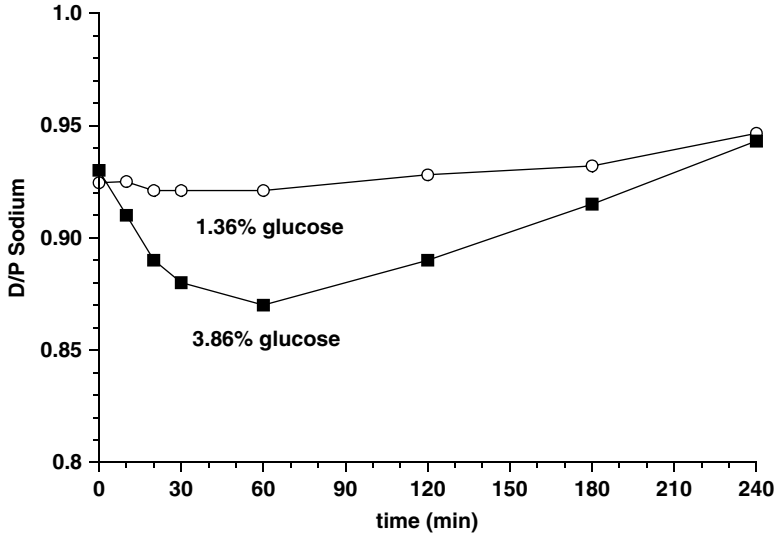

Fig. 17.5 Dip in dialysate over plasma ratio for sodium using a 3.86%/4.25% dextrose solution (closed squares) and a 1.36%/1.5% dextrose solution (open circles). The high osmolality of the first solution will induce osmotically driven "free water" transport, leading to dilution of the dialysate sodium concentration. This is not seen for the 1.36%/1.5% dextrose solution

obtained with it is therefore much more dependent on the number and function of water channels. Consequently, Δ ultrafiltration 4.25%/3.86%–1.5%/1.36% will decrease in situations with impaired aquaporin-mediated water transport. D/P Na^+ or ΔNa^+ are probably the simplest ways for rough assessment of aquaporin function.

Direct methods to calculate aquaporin mediated water transport have recently been developed. LaMilia and co-workers have described an easy direct measurement of free water transport [89], which has been refined [90–92] and tested with computer simulations by others [93]. In essence, this method uses a standardized 4.25%/3.86% glucose dwell and measures net UF after a shorter dwell period corresponding to the expected maximal sodium sieving time (60 or 90 min). By measuring directly net UF and sodium concentrations during this shortened dwell, the amount of actual free water transport can be calculated and hence one has a direct measure of aquaporin mediated fluid transport.

Loss of Functional Peritoneum

The combination of low drain volume in the face of adequate osmotic challenge and low small solute transport is very rare and reflects a major disruption of the peritoneal membrane and/or intraperitoneal fluid distribution. It is usually due to adhesions and the functional consequences may be related to fluid trapping in small spaces. Peritoneography may be helpful in making the diagnosis by identifying sequestered spaces. Poor UF in association with low transport is reported to occur in the advanced stages of peritoneal sclerosis [94–97]. It is important, however, to realize that a high transport rate has also been described prior to a diagnosis of peritoneal sclerosis [3, 65–67]. Unfortunately, no large prospective study of fluid problems in PD patients has been performed so it is not possible to state how often UFF together with low transport occurs. Because this condition results in both inadequate volume and inadequate solute removal, transfer to hemodialysis is required for adequate management in anuric patients [10]. In patients with residual renal function, management by peritoneal dialysis and oral loop diuretics may be successful. Whether restitution of peritoneal free space by adhesiolysis is warranted needs to be determined on an individual case basis.

A caveat on the diagnostic criteria is in order: patients with underlying low transport rate and leaks or mechanical problems or high lymphatic/tissue reabsorption may also present with the composite picture of low drain volume and low small solute transport. It is therefore important to exclude these latter causes before accepting low transport as the reason for the difficulty with peritoneal fluid removal.

Mechanical Failure of Dialysis Procedure

Catheter Malfunctions

Catheter-related problems contributing to poor drain volumes include obstruction, entrapment, or malposition [11, 12]. Catheter obstruction, either partial or complete, often results from fibrin plugs or build-up within the catheter

lumen but can be due to omentum obstructing the catheter ports or even a kinked catheter. These lead to sluggish or intermittent inflow/outflow of dialysate and thus alter the efficiency of fluid removal. Fibrin strands seen in the dialysate should raise suspicion of the problem. Treatment consists of aggressive "flushing" of the catheter with a dialysate-filled syringe and if this is unsuccessful, the use of fibrinolytic agents when fibrin-related occlusion is suspected.

The intra-abdominal portion of the catheter may become "entrapped" in a compartment formed by adhesions. This can lead to a reduction in intraperitoneal capacity resulting in pain on inflow once the compartment volume has been surpassed. With the use of peritoneography the compartment can be demonstrated. Treatment may be attained with surgical lysis of the adhesions if they are not too extensive.

Catheter malposition may occur because of improper placement, but this often results from the migration of catheters originally in good position [98]. A malpositioned catheter has positional outflow and does not drain the peritoneal cavity effectively, leading to an increase in residual volume. A normal residual volume (R) is approximately 200–250 mL [43] and can be measured from information obtained during the PET using the following equation:

$$\mathrm{R} = V_{\mathrm{in}}(S_3 - S_2)/(S_1 - S_3)$$

Where V_{in} = instillation volume, S_1 = solute concentration (urea or creatinine) in the pretest drain, S_2 = solute concentration of the instilled fluid (0 for urea or creatinine) and S_3 = solute concentration immediately following instillation [43]. An increase in residual volume dilutes the glucose concentration in the freshly instilled dialysate. This decreases the osmotic gradient and thus reduces the rate of transcapillary ultrafiltration without any significant effect on solute transport. Net ultrafiltration is decreased while the D/P creatinine ratio remains essentially unchanged. An increase in the calculated residual volume should raise the suspicion of a malpositioned catheter. However, the presence of this problem is often clinically apparent and the diagnosis is easily made with the aid of simple radiographic techniques (flat-plate of the abdomen) as peritoneal dialysis catheters have radio-opaque material imbedded within.

Leaks

Dialysate leaks from the abdominal cavity result in a decrease in drain volume and net fluid removal. In the case of external leaks, the impact is greater on drain volume. In leaks into the abdominal wall or pleural space, net fluid removal is diminished either because of accumulation in and reabsorption from the interstitial spaces or sequestration in the pleural space. Leaks into the interstitial space are commonly accompanied by abdominal wall edema with or without genital edema. Leaks can occur at anytime but are often seen shortly after the start of PD and usually occur at the catheter insertion site but can also be associated with an abdominal wall hernia or a history of multiple abdominal surgeries [24, 25, 99, 100]. Localized abdominal wall edema or subcutaneous fluid collections are often evident. Diagnosis is confirmed by utilizing radiographic techniques that include intraperitoneal infusion of a dialysis solution in which radiographic contrast has been added with computed tomography, or through the intraperitoneal infusion of radioisotope with peritoneal scintigraphy [24–27, 99–103], or by use of magnetic resonance imaging with or without contrast.

Peritoneal membrane function is not compromised and therefore peritoneal transport as evaluated by the PET is not changed compared to baseline. Leaks associated with hernias usually require surgical repair. Leaks occurring in the absence of a hernia usually represent a tear in the parietal peritoneum. In this situation there is frequently a history of multiple abdominal surgeries, pregnancies, recent corticosteroid usage, or abdominal straining (coughing, Valsalva maneuver). Small leaks may respond to peritoneal rest with hemodialysis support or the use of nighttime small volume peritoneal dialysis with cycler and a dry day without the need for surgical repair. Recurrence may require surgical repair.

Therapy

General Guidelines

A summary of guidelines for the prevention of fluid overload is presented in Table 17.2.

Routine Standardized Monitoring

Routine standardized monitoring of desired weight, course of residual renal function, and achieved ultrafiltration with current dialysis prescription should be emphasized in the care protocols of all patients on peritoneal dialysis. This

Table 17.2 Guidelines for prevention of volume overload in patients on peritoneal dialysis

General guidelines
Routine standardized monitoring including awareness of PET status
Dietary counselling concerning appropriate salt and water intake
Protection of RRF
Loop diuretics if RRF present
Enhanced compliance – Education
Appropriate prescription
Hyperglycemia control
Preservation of peritoneal membrane function
CAPD
Avoidance of long dwells with low glucose concentrations
Use of icodextrin for the long dwell
Use of night-time exchange device
Tailoring prescription to transport profile determined by PET
APD
Avoidance of long dwells with low glucose concentrations
Use of icodextrin for the long dwell
Use of short day dwells even when no additional exchange is needed for clearance

approach will allow for early detection of developing problems and early intervention with corrective measures. The volume status of patients on peritoneal dialysis should be used as a core indicator of dialysis adequacy. Constant re-evaluation by physicians and nurses of the patient's target weight in the light of blood pressure and other features suggestive of fluid overload is required. Particular emphasis should be placed on the desirability of normalizing blood pressure by using fluid removal alone, without antihypertensive drugs. Routine performance of PET with a view to identifying high and high-average transporters in whom monitoring of fluid status is particularly critical is highly encouraged. Use of icodextrin for the long dwell and utilization of APD may be preferred approaches in these patients.

Dietary Counseling

Avoidance of dietary indiscretion can be enhanced by detailed counselling and regular re-enforcement of taught guidelines. The tendency to be more liberal in dietary restrictions with peritoneal dialysis patients compared to patients on hemodialysis should be tempered by the need to maintain desired weight and reduction of cardiovascular risk. The general assumption that patients on peritoneal dialysis tolerate greater dietary salt and fluid indiscretion should not be construed as an endorsement for such indiscretion [104]. Tepid indifference that allows patients to hover close to mild edema may have pernicious long-term consequences. It is recognized that dietary interventions are the hardest to implement as they involve an elaborate process of education and lifestyle modification.

Protection of Residual Renal Function

Residual renal function (RRF) plays an important role in both small solute adequacy and volume control. The protective zeal that has become a cornerstone of nephrologic management in the pre-ESRD phase needs to be sustained after initiation of dialysis. This is particularly important in the context of the new directions in dialysis initiation where patients are started on dialytic therapy at higher levels of residual renal function than previously. Attention to the nephrotoxic potential of over-the-counter medications should become a component of regular patient interviews. Further, the use of aminoglycosides in the management of peritonitis should be limited to cases where no safer effective alternative is available. Protection from the nephrotoxic potential of contrast agents is limited by the obvious inability of using hydration methods. The promise of acetylcysteine or adenosine antagonists (e.g., aminophylline) has not been explored in this population and may be considered by inference until tested. Avoidance of nephrotoxic agents should be practiced rigorously.

Diuretic Use

Routine use of high-dose loop diuretics to maintain urine output in patients with residual renal function is a viable consideration. Usually large oral doses are needed (furosemide range 250–1000 mg) with or without addition of a

thiazide-like diuretic (metolazone 5–10 mg given 30 min prior to the loop diuretic). Urine volume can be successfully increased even in advanced renal failure by the use of large doses of loop diuretics alone or in combination with thiazides. While these agents do not help preserve RRF, they do increase urine output [105, 106]. The concern over the potential ototoxicity finds its origin in the experience with large intravenous doses. Oral administration seems not to carry the same risk.

Education and Enhanced Compliance

Emphasis should be placed in the initial training period on the education of the patient in the diagnosis and significance of fluid overload (e.g., awareness of importance of hypertension, peripheral edema, shortness of breath, etc.). Additionally, patients should be provided appropriate education in what the indications are to use more hypertonic PD solutions. Routine monitoring of patient compliance with PD exchanges and education of the patient in the importance of this issue are highly desirable.

Appropriate Prescription

Choosing the correct prescription for the peritoneal transport type of the patient is crucial. Patients with high and high-average transport can achieve adequate ultrafiltration using APD (four to five night cycles and long day dwell with icodextrin) and lower total glucose exposure than with CAPD [23].

Hyperglycemia Control

In diabetic patients, hyperglycemia can adversely affect the maintenance of an osmotic gradient across the peritoneal membrane. Control of the hyperglycemia may allow improved ultrafiltration without the need to use hypertonic glucose solutions unnecessarily. As glucose control is under current practice conditions mostly monitored and modified by the patients independently, education of the patient on the relevance of this activity to the adequacy of dialysis is important.

Preservation of Peritoneal Membrane Function

The most important therapeutic option is the prevention of ultrafiltration failure. Reduction of the occurrence of peritonitis can be achieved with appropriate patient training and retraining in aseptic techniques, the universal adoption of exit site antibiotic prophylaxis (either gentamicin or mupirocin creams) and the use of the widely applied double-bag system, which prevents extra disconnections [107]. The prevention of ultrafiltration failure in the long-term patients will depend largely on the possibility to reduce the peritoneal glucose exposure and the development of more biocompatible dialysis solutions. The first can, to some extent, be accomplished by preservation of the residual renal function. Therefore, nephrotoxic agents should be avoided, even when a patient is already on PD. In case of volume overload, the use of diuretics can lead to extra fluid removal by the kidneys, instead of increasing the osmolality of the dialysate. Alternative solutions that can replace glucose for one exchange per day are the glucose-polymer Icodextrin and amino-acids. Glucose polymers are attractive, because they are not hypertonic, exert their effect by colloid osmosis, and are taken up from the peritoneal cavity to a limited extent. They are therefore extremely useful in patients with an enlarged vascular surface area [16]. However, the use of icodextrin is limited to one exchange in the long dwell. Whether the agent can be used more than once daily and during shorter exchanges is under active investigation. Amino-acid-containing dialysis solutions are limited to one bag daily (separate exchange or mixed with glucose on the cycler) because of the increase in the nitrogen load. The use of more biocompatible dextrose-containing solutions seems to be promising in the preservation of the peritoneal membrane. Unfortunately, long-term patient-studies are still lacking. However, animal studies have shown that the use of more biocompatible solutions (lower content of glucose degradation products, higher pH, bicarbonate/lactate buffer) lead to less pathological alterations of the peritoneal membrane after long-term exposure compared to the conventional solutions [108, 109]. Temporary cessation of peritoneal dialysis has been used in a few patients with high small solute transport characteristics with some success and may be a reasonable option to consider if other approaches are unsuccessful [110–112]. Alternatively, reduction of peritoneal membrane glucose exposure may lead to some improvement in transport parameters [113].

Therapeutic Guidelines for Specific Diagnostic Categories

Failure of Peritoneal Response

Patients with peritoneal ultrafiltration failure should be treated according to the cause. Possibilities are summarized in Table 17.3

Fast Transport Status

In addition to the universal guidelines discussed above, therapeutic interventions in patients with high small solute transport need to address the basic pathophysiologic mechanism of rapid dissipation of the osmotic gradient. The latter phenomenon is particularly prominent during the long overnight dwell in CAPD and the daytime dwell in APD. The most appropriate intervention is the use of large molecular weight substitutes for glucose such as icodextrin [17–22]. Dialysis solutions containing icodextrin have been shown to be superior to glucose-based solutions in achieving net ultrafiltration during long dwells in majority of patients and particularly in high transporters. In areas where icodextrin dialysis solutions are not available, shortening dwell time is the preferred approach. In CAPD patients this can be achieved with the use of an automated night-time exchange device. This approach will shorten dwell time and has the additional benefit of improving small solute clearance with little impact on patient lifestyle. Alternatively, patients can be switched to APD where the use of short dwell times in the night phase enhances ultrafiltration. In patients on APD who do not have access to icodextrin, foregoing the daytime exchange and optimizing the night-time regimen may be sufficient [23]. If small solute clearance suffers, then a short daytime exchange with mid-day drainage will supplement night-time clearance without compromising ultrafiltration. If the preceding options are insufficient, then high glucose concentrations may be required. In a few patients adjunctive, temporary, or permanent hemodialysis may be required.

Preventive measures remain limited and speculative because of a lack of thorough understanding of the factors underlying high transport [114, 115]. In patients with inherent high transport, there are no clear associations with reversible conditions that can be therapeutically addressed. The possible association with higher indices of chronic systemic inflammatory response remains unproven. The clearest category for intervention is that of the transient small solute high transport rate associated with peritonitis. Approaches to reduce and prevent infections with improved connectology, patient training, and local prophylaxis have been successful, but more remains to be achieved. In patients who develop a high transport profile in the course of chronic peritoneal dialysis the approach is more a question of considered opinion rather than evidence-based. Reinforcing universal measures before relying on the chronic intensive use of 4.25%/3.86% glucose dialysate is generally preferable. Further, wherever available, use of icodextrin for the long dwell is recommended.

Loss of Functional Peritoneum

The combination of reduced solute clearance and diminished ultrafiltration represents a state of significant shortcomings in delivery of appropriate renal replacement by peritoneal dialysis. If therapeutic targets for either azotemia and volume homeostasis cannot be met, then adjunctive hemodialysis or permanent transfer to hemodialysis may be required in anuric patients. In patients with residual renal function, use of loop diuretics may allow achievement of adequate fluid balance while continuing on peritoneal dialysis.

Table 17.3 Therapeutic strategies in a patient with peritoneal ultrafiltration failure, according to the cause

Cause of Ultrafiltration Failure	Therapeutic Option
Fast transport status	• Avoid long dwells • Use icodextrin
Loss of functional peritoneum	• Transfer to hemodialysis when RRF is absent • Adhesiolysis if indicated
Aquaporin dysfunction	• Avoid hypertonic glucose • Use icodextrin • Temporarily discontinuation of PD?
Exaggerated contrary mechanisms	• Avoid large dialysate volumes • Avoid long dwells

Aquaporin Dysfunction

Adherence to the universal measures detailed above is necessary in all conditions whatever the underlying etiology of the impaired ultrafiltration. Patients with aquaporin dysfunction continue to have significant ultrafiltration via non-aquaporin pathways. This can be enhanced by the use of icodextrin in long dwells allowing for sustained fluid removal [19, 22, 115, 116]. For the glucose-based exchanges, increasing the dextrose concentration will not be beneficial.

Exaggerated Contrary Mechanisms

When enhanced tissue reabsorption results in reduced net ultrafiltration, interventions to maximise overall ultrafiltration are required to reach a state favorable to fluid removal. Ultrafiltration needs to exceed reabsorption to allow proper volume homeostasis. All interventions that maximize ultrafiltration (short dwell time, high tonicity of dialysate) need to be combined. As tissue absorption is a continuous process, and as ultrafiltration tends to decline with time, short cycle therapy is required to keep the balance of operation earlier than the convergence of the two processes. Adjusting cycle number and overall cycler time in APD, or cycle number in CAPD to the requirements of both ultrafiltration and solute clearance need to be done meticulously [23]. Also avoiding large dwell volumes can be beneficial, since large volumes will increase lymphatic absorption

Although there is a lot of promising investigative evidence that tissue absorption can be reduced [117–121], no pharmacological intervention can be recommended at this time for the lack of definitive clinical studies.

Future Prospects

Alternate use of current therapeutic options is a rich area deserving of consideration for the management of ultrafiltration failure in these challenging patients. Preliminary studies on the use of two icodextrin exchanges in a 24-h period suggest that this approach may be a successful option in this setting [122, 123]. In APD, the two exchanges are used sequentially during the long day interval, each dwelling for 7–8 h. In APD patients, a decrease in glucose exposure and a parallel decline in body weight have been observed [122]. In CAPD patients, one icodextrin dwell is used during the night and the other substitutes for a day dwell with extension of dwell time. Better blood pressure control and reversal of left ventricular hypertrophy have been achieved with such a regimen [123]. The use of two exchanges of icodextrin per day has resulted in modest asymptomatic changes in plasma oligosaccharides [122], but careful long-term studies are needed. Another area under exploration is the use of icodextrin as part of the solutions used on the cycler to allow for reduction in glucose exposure and possibly increased UF [124]. Such an approach would be particularly useful in very high transporters.

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Chapter 18
Quality of Life in Patients on Peritoneal Dialysis

M.S.Y. Thong and A.A. Kaptein

Quality of life (QL) issues are now recognized as important outcome measures in health care, cost-effective analyses of the efficacy of medical care and clinical trials, and therapeutic interventions for chronic conditions, including end-stage renal disease (ESRD). QL also factors in the decision-making process for dialysis treatment selection [1]. The past decade has seen a tremendous surge in research publications that have included measures of QL. A search on PubMed in March 2007 using the terms "quality of life" and "dialysis" yielded 1,951 publications of which 1,330 were published within the last 10 years. Hemodialysis (HD) is still the primary focus of treatment in many of these studies; only a relatively low number of studies examine quality of life in patients on peritoneal dialysis (PD). PD has less research compared to HD because it is a newer therapy and, until recently, has been limited to selected ESRD patients requiring dialysis.

With the increased incidence of ESRD worldwide due to an aging world population, and the increasing prevalence of co-morbid diseases [2–5], the demand for renal replacement therapy (RRT) is also on the rise. Advances in RRT techniques such as PD have not only improved survival [6] but PD is also now regarded as a viable option for the elderly and patients with more comorbid medical conditions [7–10]. Nevertheless, PD remains intrusive and burdensome on patients' lives. With patients on PD now living longer, their perceptions of the effect of PD treatment on their survival and quality of life should also be an important consideration in their clinical management.

Our chapter discusses 1) the complexity involved in the definition of QL; 2) the various instruments used in QL assessment with PD patients; 3) the psychometrics of QL instruments; 4) determinants of QL in PD patients, and 5) recommendations for future direction in the assessment of and interventions aimed at improving QL in PD patients.

Definition of Health-Related Quality of Life

Defining QL is complex as it can encompass a wide range of factors including psychological, cognitive, social, economic, political, cultural, spiritual, and physical factors [11]. The World Health Organization (WHO) [12] defines health as "a state of complete physical, psychological and social well-being and not merely the absence of disease or infirmity." While specifying the important domains of QL, the WHO definition is too broad and simplistic, implicitly covering dimensions such as education opportunities, social freedom, or economic development opportunities that are not of direct clinical relevance or concern when assessing treatment outcomes of chronically ill patients. Of pertinence to patients and health care providers are aspects of QL related to health or health-related quality of life (HRQL), namely the physical, psychological, and social functioning domains. However, the definition of HRQL in clinical research is still debated. Schipper et al. [11] conceptualized HRQL as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" (p. 16). Patrick and Erickson [13] defined HRQL as a "value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy." Wilson and Cleary [14] formulated HRQL as a continuum of biological/physiological factors at one end, and increasing in complexity to include measures of physical functioning and psychological well-being at the other end. The relationships between these factors are mediated by personal and environmental factors. Figure 18.1 provides a schematic representation of the relationships between the factors, as proposed by Wilson and Cleary [14].

This lack of consensus on the definition of HRQL is also present in ESRD research on this topic [15]. Early research into HRQL of dialysis patients had focused physical functioning as an outcome measure [16], before evolving into

M.S.Y. Thong (✉)
Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
e-mail: S.Y.M.Thong@lumc.nl

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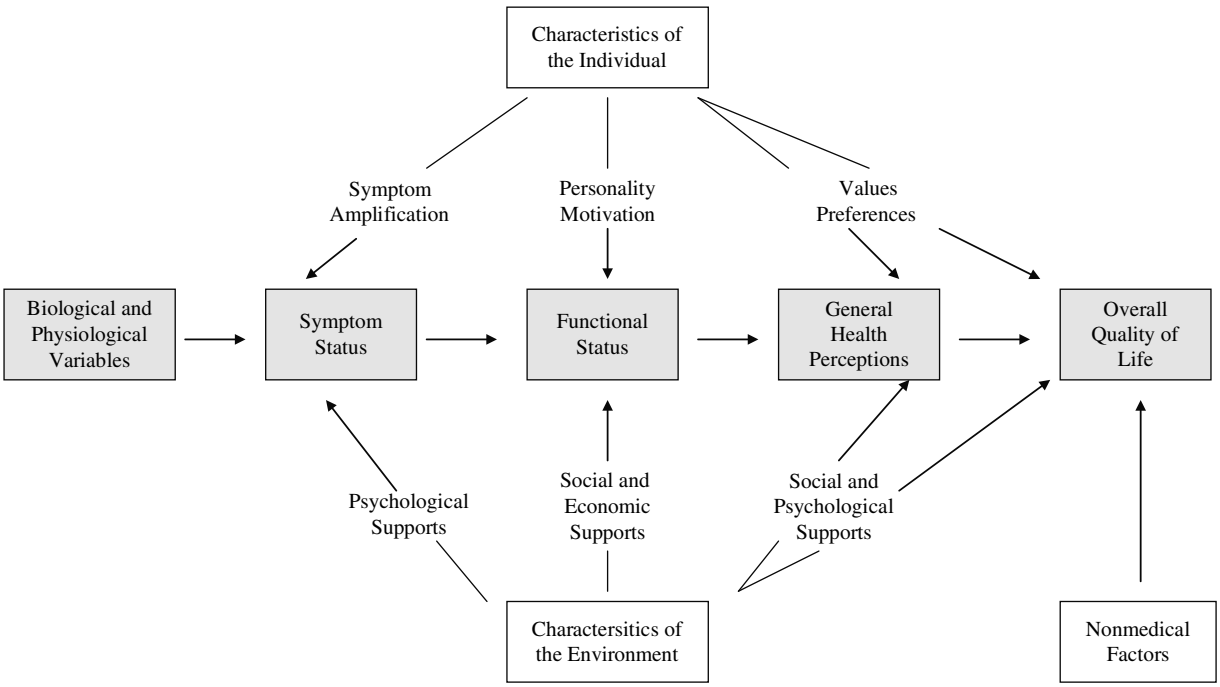

Fig. 18.1 Conceptual model depicting relationships between patient outcome variables in HRQL [14]

multidimensional assessments to include other aspects such as social and psychological functioning [17]. Recent studies have also addressed the perceptions of dialysis patients of their illness and treatment as determinants of HRQL [18].

A criticism of global health scores generated from multidimensional assessments is that they might not reflect a patient's actual HRQL [1]. For example, an ESRD patient with an amputation might describe poor physical functioning but who is otherwise having a better QL after starting dialysis, will have a low global QL score due to the poor physical functioning. Also most HRQL measures are not patient-centered as the domains being assessed might not be of critical relevance to the patients, or patients' choice of answers could be restricted [1, 16]. Kalantar-Zadeh and Unruh [16] envision a more patient-centered approach to HRQL assessment in which patients themselves determine the HRQL domains most salient to them, and information on these domains are then elicited, for example, via semi-structured interviews, as in the Schedule of Evaluation of Individual Quality of Life – Direct Weighted (SEIQoL – DW) [19]. The SEIQoL-DW assesses not only the level of patients' functioning, but patients nominate and rate the areas of HRQL of importance to them. Kalantar-Zadeh and Unruh [16] described that a small sample of dialysis patients using the SEIQoL-DW identified HRQL domains often not captured in the SF-36 as being important such as family, marriage, sexual functioning, and spirituality.

Psychometrics of HRQL Measures

Given the multidimensional and subjective nature of (health-related) quality of life, assessment of HRQL can be challenging, and selection of a suitable HRQL measure from the many that have been developed can be daunting. A HRQL measure can consist of a single item, such as a global health item [20] or more common are measures made up of several items or questions [21–23]. These items can be added up to form domains or dimensions, which are aspects of HRQL of interest that are being measured. Therefore, HRQL measures can also be single or multidimensional.

Distinction should also be made if a measure is used for discriminative or evaluative purposes [24]. A discriminative measure aims to differentiate HRQL between individuals or groups, while an evaluative measure is used to detect change in HRQL over time. An example of both a discriminative and evaluative measure is the Short-Form 36 (SF-36) [23]. A comparative study using the SF-36 showed that patients with a kidney transplant, HD, and PD had poorer HRQL compared with the normal controls, but that kidney transplant patients reported better HRQL when compared with either HD or PD patients [25]. The SF-36 has also been used in large cohort studies such as the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) to assess changes in HRQL in dialysis patients over time [26].

Depending on the purpose of its use, the hallmarks of a good HRQL measure are its reproducibility and its accuracy in measuring what it claims to measure [27]. Both the reproducibility and accuracy of a measure can be evaluated on its psychometric properties such as reliability, validity, responsiveness, interpretability, and ease of administration.

Reliability

Reliability refers to the consistency of a measure. There are several estimates of reliability. Internal consistency refers to the homogeneity of a measure and is indicated by the correlation between items in the scale, or within a scale domain [28]. When using an observer-rated or proxy-assessed measure of HRQL, the inter-rater or interobserver reliability of the measure should be determined to ensure a consistency of ratings that different raters and observers might give to the phenomenon being observed [29]. The kappa statistic is often used to determine agreement for measurements collected on nominal or ordinal scales, while the intraclass correlation indicates agreement for measurements made on a continuous scale [30, 31].

Test-retest reliability refers to the consistency of results when the measure is repeatedly administered at different time-points to the same individual. As is with inter-rater reliability, test-retest reliability can be established with the kappa statistic. Multi-item measures should have good internal consistency reliability to ensure there is agreement between items on the measured domain. Internal consistency is indicated when a commonly used estimator, the Cronbach alpha is above 0.70 [32].

Validity

A HRQL instrument is considered valid if it measures what it is designed to measure. Types of validity include criterion validity, content validity, and construct validity. Criterion validity is the most difficult to establish with HRQL measures as it requires the measure to be compared to a "gold standard", for which none exists in HRQL assessment. Content validity refers to the comprehensiveness of the items in sampling the domain of interest [33]. Construct validity is established by comparing results between different measures that are supposed to measure similar constructs, and the extent these results are consistent with theoretically hypothesized relationships between the measure and the patient group [27, 34].

Responsiveness

When using HRQL as an outcome measure of therapeutic efficacy, it is of clinical interest to determine treatment effects on HRQL over time. Therefore, a responsive HRQL measure has to be sensitive in detecting clinically relevant changes over period of follow-up. Related to the sensitiveness of a measure, is the issue of floor and ceiling effects. Presence of such effects especially at the baseline measurement reduces the responsiveness of the measure, as it will be less sensitive in detecting changes in patients' HRQL [35]. Responsiveness can be evaluated with the effect size, standardized response mean and/or the responsiveness statistic [1, 36].

Interpretability

Interpretability refers to the ease from which clinically meaningful information can be derived from quantitative HRQL results [27, 33]. A score obtained in a discriminative study should signify whether that individual has normal, mild, moderate, or severe impairment in HRQL. Likewise, in evaluative studies, changes in HRQL score (even if small in magnitude) should be interpretable in terms of its clinical significance. The baseline measurement should be considered when interpreting change in patients' HRQL scores [37]. A small change in a patient with very low baseline functioning might be more clinically important compared to a higher functioning patient registering the same magnitude of change.

Method of Administration, Length, Cost of Administration

The mode of administration is an important consideration when collecting HRQL data as it can influence the response rate. Table 18.1 summarizes the strengths and weaknesses of the various methods of data collection. Interviewer-conducted (either in person or via the telephone) assessments often generate higher adherence compared to self-assessments as response burden is reduced [27]. Nonresponse bias in interviewer assessment is minimized compared to

Table 18.1 Modes of administration of HRQL measures

Mode of administration	Strengths	Weaknesses
Interviewer	Good response rate; minimizes missing items and errors of misunderstanding	Resource-intensive, high cost; decrease willingness to reveal problems or sensitive issues; limited format of instrument
Telephone	Minimizes missing items and errors of misunderstanding; less resource-intensive than interviewer-conducted assessment	Under-reporting of sensitive issues
Self	Cost efficient; involves patient with research and clinical care, empowerment	Issue of noncompliance, missing items, misunderstanding
Proxy	Reduce response burden on target group	Possible differences in perceptions from target group
Computer-based	Able to tailor individual questionnaires by branching, time efficient, assess vulnerable subgroups	Limited by access to computers

Source: Adapted from [27, 43].

self-reports as HRQL information from vulnerable subgroups such as the elderly, severely ill, disabled, or those with language/literacy difficulties can be collected [38]. Data quality in interviewer assessments can be better than that of self-reports as interviewers can prompt or probe for further details [39]. Another advantage of interviewer assessment is that longer questionnaires are also more feasible as respondent burden is reduced. A randomized trial with community-dwelling elderly women on length of questionnaire and response rate demonstrated that an increase in length of questionnaire decreased the response rate [40]. However, interviewer-conducted assessments are resource-intensive, incurring higher costs and requiring more time. A study comparing mailed surveys and telephone interviews on the SF-36 reported that telephone interviews were 77% more expensive than the mailed survey [41]. There is also a possibility of underreporting of sensitive items in interviewer assessments [41]. Self-reports are cost-efficient and afford a modicum of response anonymity to sensitive questions. Although response rates to mailed questionnaires are higher, these mailed self-reports have also more missing data [41]. Computer-based adaptive HRQL measures, using multimedia technology, could bridge the gap of assessing vulnerable groups, collect precise and practical information for clinical use, and remain cost-effective [42–44].

Measuring HRQL in PD Patients

Health Profiles

A wide variety of health profiles used to evaluate HRQL in ESRD patients have been adequately discussed in other reviews [16, 17, 34, 45, 46]. Health profiles provide a description of the health status of an individual based on several HRQL domains. Component scores or a total HRQL scale score are often generated from health profiles. Health profiles can be generic or disease-specific.

Generic Measures

Generic assessments have been developed for a wide application to different population groups and allow for comparison of HRQL among different (healthy) populations or patients with chronic diseases [27]. As generic assessments are by definition not designed to assess HRQL issues specific to a disease, they are less sensitive in detecting changes in HRQL due to treatment [47].

SF-36

The SF-36 [23] is a generic multidimensional HRQL instrument developed for use with various populations [48–50]. The SF-36 has 36 items measuring eight dimensions of HRQL: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, social functioning, mental health, vitality, body pains, and general health perceptions. Items in each subscale are added together to form subscale scores, which are transformed to

a 0–100 scale, with higher scores indicating a better HRQOL. The eight subscale scores can be further combined into the physical (PCS) and mental (MCS) component summary score.

The SF-36 is widely applied in comparative studies of HRQL in ESRD patients, and with the general population [51–53]. The psychometrics of the SF-36 are sound. Studies with ESRD patients show that it has good internal consistency [26, 53, 54]. A large study comparing the HRQL of 16,755 HD and 1,260 PD patients using the SF-36 reported that similar PCS were found in both HD and PD groups, while PD patients scored higher on the MCS compared with HD patients [51]. Shorter versions, the SF-12 and SF-8 have since been developed [28, 55]. The SF-12 has been used with dialysis patients [56, 57].

Nottingham Health Profile (NHP)

The NHP provides a brief assessment of perceived health for use with various populations [58]. It consists of two parts. Part 1 has 38 yes/no items assessing six domains: physical mobility, pain, social isolation, emotional reaction, energy, and sleep. Examples of items include: "I am tired all the time," "Things are getting me down," "I feel I am a burden to people." Weighted scores with a range of 0–100 are calculated for each domain, and higher scores are indicative of more problems in the domain. The second part assesses the impact of health on seven life areas. Both parts can be used independently and Part 2 is not scored. A small number of comparative studies with PD patients have used the NHP [25, 59–63]. A Dutch study comparing the HRQL of HD and PD patients in The Netherlands and in Curacao showed only slight differences in HRQL between the groups as measured with the NHP [59].

Sickness Impact Profile (SIP)

The SIP was developed to assess changes in behaviors as a consequence of illness [64]. It consists of 136 items descriptive of activities of daily living, divided into 12 categories. Patients endorse statements that best describe them that day and that are related to their health. Examples of SIP items are: "I walk more slowly," "I am going out less to visit people," "I act irritable and impatient with myself, for example, talk badly about myself, swear at myself, blame myself for things that happen." Endorsed items are scored with a numeric scale value reflecting level of dysfunction; higher scale scores indicate greater dysfunction. In addition to individual category scores, an aggregate psychosocial score can be derived from four categories, while a physical aggregate score is calculated from three categories. The SIP can be administered by an interviewer or as a self-report, and takes 20–30 min to complete. Although the SIP is a reliable and valid instrument [28], and has been used with ESRD patients [65], a study comparing the psychometrics of the SIP and the NHP in a small sample of dialysis patients reported that the NHP was more feasible to administer as it was shorter and easier to understand, and that the internal consistency of the NHP was slightly better compared with the SIP [66]. Also, the responsiveness of the SIP to detect change has not been well demonstrated [28]. A short version of the SIP consisting of 68 items is also available and has been proven to be reliable [67].

Disease-Specific Measures

Specific instruments were developed to assess aspects of HRQL of a disease of interest that are not or inadequately assessed in generic measures. The decision to use a disease-specific or a generic instrument depends on the research objectives, as both types of measurements can be complementary [68]. Disease-specific measures in ESRD such as the Kidney Disease Quality of Life (KDQOL) [21] include both generic and disease-specific HRQL aspects. A search on PubMed showed that no HRQL instruments had been developed specifically for PD patients.

Kidney Disease Quality of Life

The Kidney Disease Quality of Life (KDQOL) instrument is a self-report questionnaire consisting of 134 items [21]. It has the SF-36 as its generic core and is supplemented with items of relevance to the HRQL of dialysis patients. Disease-specific items assess symptoms/problems, effects of kidney disease on daily life, burden of kidney disease, cognitive function, work status, sexual function, quality of social interaction, and sleep. Included are also items relating to social support, encouragement from dialysis staff, patient satisfaction with care, and a global rating of health. A shorter version, the KDQOL-SF was subsequently developed in view of the length of the original version. The KDQOL-SF includes the SF-36 supplemented with 43 disease-specific items from the domains identified in the original version [69]. The KDQOL-SF is easy to administer, requiring approximately 16 min for completion. The KDQOL-SF is a validated

and reliable instrument [70–73], used widely with both PD and HD patients [74–76]. The HRQL of a small sample of PD patients showed deterioration over a follow-up of 2 years in the KDQOL dimensions of physical health, mental health, kidney disease issues, and patient satisfaction [77].

CHOICE Health Experience Questionnaire (CHEQ)

The CHOICE Health Experience Questionnaire (CHEQ) was recently developed for the Choices for Health Outcomes in Caring for End-Stage Renal Disease (CHOICE) study [78]. The CHEQ is a self-report designed to measure HRQL, and also to discriminate between dialysis modality and dialysis dose on HRQL. It includes the generic measure SF-36, with an additional six disease-specific domains (diet, freedom, time, body image, dialysis access, and symptoms). The CHEQ consists of 83 items and requires approximately 25 min completion time. Although the reliability and validity of CHEQ have been established [78], this instrument has not been used by other research groups.

Utility/Preference-Based Measures

Utility or preference-based measures were designed for cost utilities purposes and assess patients' preference and values for a health state [79]. Patients' health preferences are combined into a single indicator, usually a numeric representation of a health between 0 and 1, with 0 being death and 1 having optimal health [80, 81]. Often regarded as interchangeable, the terms "HRQL" and "health status," however, are conceptually different. A meta-analysis on the relationship between HRQL and health status concluded that patients determine their HRQL and health status differently [82]. Rating of HRQL is influenced by mental health while physical functioning is more important in patients' perceptions of their health status. While utility measures are useful in the analysis of treatment effects and its cost-effectiveness, they might be inappropriate measures for HRQL [82]. Utility measures are synonymous with the biomedical approach of disease, while health-related quality of life measures are reflective of a biopsychosocial perspective [83].

EuroQol/ED-5D

The EuroQol/EQ-5D provides a descriptive profile from which an index value of health status is derived [84]. It consists of five items measuring the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels of severity. Furthermore, patients can rate their health on the Visual Analogue Scale (VAS), which is a picture of a thermometer calibrated on a scale of 0 ("worst imaginable health state") to 100 ("best imaginable health state"). The EuroQol/EQ-5D is easy to administer and is reliable [85] for use with PD samples [76, 80, 86]. A Swedish study using data collected with the EuroQol concluded that PD had a more favorable cost-utility ratio compared with HD for ESRD patients who have no contraindications to either of the dialysis therapies [87].

Time Trade-Off

The Time Trade-Off (TTO) [88] is a utility instrument that measures the number of life years a person will (hypothetically) exchange for improvement in HRQL. It can be assumed that patients with poor HRQL will be more willing to have shortened life years in return for improved HRQL compared to patients with good HRQL. However, studies suggest weak to poor correlations between health profiles such as the SF-36 and the TTO in dialysis patients [80, 89]. PD patients measured on the SF-36 had poor HRQL, while high TTO scores indicated that these patients valued their health status highly [80]. This suggests that the SF-36 and the TTO measure different aspects of HRQL as impaired physical and mental functioning might not be reflected in the value patients place on their health [80].

Proxy Assessments

Proxy reports refer to information collected on behalf of the patient from their family/caregivers or from the clinical staff. Proxy reports are useful when the patients are too old or young, severely ill, or have communicative difficulties or cognitive impairments [39]. However, the reliability of proxy reports on a subjective concept like patients' HRQL has been debated [90]. A study on agreement between nephrologists, nurses, and patients on patients' health rating over time

showed lower correlations between ratings by patients and clinical staff as compared to ratings between clinical staff [90, 91]. In general, proxy reports tend to underestimate the HRQL of patients [90, 92, 93]. Agreement between proxy and self-reports are usually low for HRQL domains with greater subjectivity and less visibility such as pain intensity, affect, or fatigue. Accuracy improves when rating patients' physical functioning or symptoms [93, 94]. Proxy assessments of overt aspects of physical functioning like mobility and activities of daily living, or of symptoms such as nausea and fatigue show higher agreement probably because these aspects provide visual cues to patients' experience [90].

Karnofsky Index

Originally developed for use with cancer patients undergoing chemotherapy, the Karnofsky Index (KI) [22] is a proxy assessment widely used to evaluate physical functioning in ESRD patients [95, 96]. The KI is scored on a range of 0–100 on 11 scales, with higher scores indicative of better functioning. The KI is not a true measure of HRQL as it is limited by its narrow focus on physical functioning, and that it is a proxy assessment [16]. A study on agreement between two nephrologists using the KI with HD patients reported a low kappa score of 0.29 [95].

Determinants of HRQL in PD Patients

PD has been a lifesaver for many patients with ESRD. However, the burdens of the disease and its therapy can still impact negatively on the quality of life. While biological/physiological factors such as serum albumin levels, anemia, and residual renal function have been previously studied for their association with HRQL in PD patients, research is now also focusing on the more complex psychological aspects of patients' personality and perceptions on their HRQL. As illustrated in Fig. 18.1, biomedical factors are only distal correlates of HRQL. The perception of patients of biomedical issues mainly determine (HR)QOL, for example, poorer self-ratings of health have been associated with higher morbidity and mortality [97–99].

Clinical Factors

The study of biological and physiological factors and their association with HRQL in PD patients has particular resonance with clinicians and clinical practice. However, the relationships between clinical factors and HRQL are not as robust as expected [100], because HRQL is largely determined by the perceptions of the patient [18, 101–104]. Nevertheless, research into some clinical factors such as hemoglobin, glomerular filtration rate, and nutrition has shown some association with HRQL in dialysis patients.

Hemoglobin/Anemia

The management of anemia with recombinant human erythropoietin has been associated with improved HRQL in dialysis patients [105, 106]. Increased oxygen transport following normalized hemoglobin levels has been associated with better cognitive and physical function [107]. As part of a multicenter randomized trial, a Swedish study showed that dialysis patients with normalized hemoglobin levels had improved QL on all domains as measured by the Kidney Disease Questionnaire at 48 weeks from baseline [108].

Glomerular Filtration Rate (GFR)

PD preserves residual renal function better than HD [109]. An association between a decline in GFR and HRQL has been suggested, although results are inconclusive. The Modification of Diet in Renal Disease (MDRD) study showed that renal deterioration and symptom severity were correlated with declining QL in HD patients [110]. Results from the Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) trial suggest that improving small solute clearance was not associated with improved HRQL in PD patients [111]. From the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), Termorshuizen et al. suggest that residual renal function and peritoneal clearance should not be considered as equivalent [112]. The authors found a 12% improved survival of PD patients with every 1 mL/min/1.73 m^2 increase in rGFR while no effect of peritoneal clearance on survival was found. This difference in effects of rGFR and peritoneal clearance was also noted on several HRQL dimensions as measured by the SF-36 and the KDQOL.

Nutrition

Protein-energy malnutrition (PEM) is a common occurrence in dialysis patients, consistently associated with poor outcomes [113–115]. An Italian study found that increasing levels of serum albumin correlated positively with physical functioning, with a 30-point difference measured on the SF-36 physical functioning subscale between the lowest and highest levels of serum albumin [53]. Mittal et al. [116] reported that for every 1 g/dL increase in serum albumin, the physical functioning score on the SF-36 improved by 1.8 in their sample of PD patients. Kalender et al. [117] found that increased serum albumin was associated with better physical functioning. Conversely, an increase in the inflammation marker C-reactive protein (CRP) correlated with both poorer physical and mental functioning for HD patients. However, there was no relationship between serum albumin and CRP levels on HRQL in PD patients. HD patients who were depressed had significantly poorer nutritional status compared with nondepressed patients [118].

Psychosocial Factors

As quality of life is by definition a subjective entity, major determinants of HRQL are individual characteristics such as personality and perceptions. As illustrated in Fig. 18.1, biomedical factors translate, partly, into HRQL issues via psychological and social processes.

Personality

A study on personality factors and mortality in a group of predialysis patients who were followed for a mean of 49 months found that a 1-point increase in conscientiousness was associated with a 6.4% lower mortality risk, and a 1-point increase in neuroticism was associated with a 4.8% increase in mortality [119]. Conscientiousness reflects a patient's self-discipline, self-control, dependability, and the will to achieve, while neuroticism infers generalized emotional distress or chronic negative affect [120]. Dialysis patients with higher conscientiousness scores showed better medical adherence compared with patients who had a lower conscientiousness score [121]. Personality qualities could also implicitly influence adherence to a dialysis training program [122]. This study found that poorer adherence to a dialysis training program by incident PD patients was associated with an increased risk of peritonitis. Research with other patient groups suggests motivation and self-efficacy as important factors in adaptation to treatment demands [123–125]. For example, two PD patients with similar clinical prognosis will have different levels of functioning if one of them is more determined to be self-sufficient and have control of their treatment.

Having a sense of humor can be protective against the rigors and stress of dialysis. A small study suggests that dialysis patients with a sense of humor lowered their mortality risk by 31%, after accounting for demographics and clinical variables [126].

Perceptions of Illness/Well-Being, Satisfaction

Psychological factors such as perceptions of illness and satisfaction levels can also determine HRQL. Leventhal's Self-Regulation Model (SRM) postulates that a person, when confronted with an illness, will create a perception or cognition of the illness as an (mal)adaptive mechanism [127, 128]. With its focus on the psychological aspects of HRQL, the SRM can be considered an extension to the model outlined in Fig. 18.1, which exemplifies the biomedical approach to measuring HRQL in chronic illness. The SRM has been well tested and studies with other chronic illnesses suggest possession of positive illness perceptions [129–131] is associated with better well-being [132].

Studies with mainly HD samples suggest that patients who perceive having more control and fewer consequences due to their disease had better health outcomes [101–104]. Patients with negative perceptions of their illness have increased risk of depression [133], poorer adjustment to the disease and treatment [134], and have poorer HRQL [18].

Patients who perceive ESRD as a negative intrusion into their lifestyle are more likely to have poorer treatment compliance [135] and higher symptom burden [136]. Symptoms are subjective perceptions of physical, emotional or cognitive changes experienced by the patient [14, 137]. Correlations between symptoms and clinical variables are often low [26, 77, 138], and the clinical pathophysiology underlying symptoms is still unclear [139]. A negative correlation between physical symptom distress and HRQL has been well-demonstrated in ESRD patients [26, 138, 140]. Common symptom complaints such as pain, fatigue, itch, poor appetite, poor sleep and "restless legs", and sexual dysfunction, have been associated with reduced HRQL in PD patients [100, 141–144]. Patients who report feeling more pain and regard it as a negative intrusion into their lives were more likely to express pessimism and anxiety [141], and a decrease in their HRQL [145].

Affective symptoms such as depression are common in dialysis patients. Nearly 50% of a sample starting dialysis met the diagnosis of depression, when measured on the Beck Depression Inventory (BDI) [146]. Among chronic PD patients, prevalence of depression varies between 25 and 50% [113, 116, 147]. However the diagnosis of depression in dialysis patients is confounded by the similarities in somatic symptoms of depression with those of uremia, such as fatigue, poor appetite, sleep disturbances, and cognitive disturbances [148]. It has been suggested that the Cognitive Depression Index (CDI) [149], a subset of the BDI assessing only the affective aspects of depression such as guilt, hopelessness, irritation, and suicidal ideation, is a more reliable instrument of depression among dialysis patients [149]. Variation in depression prevalence could also be explained by the use of different assessment methods. In a study comparing agreement in depression diagnosis, 45% of the sample was depressed using the BDI cut-off score of 11, while only 12% met the criteria of the Diagnostic and Statistical Manual of Mental Disorders – 3rd Ed. (DSM-III) for depression [150]. Despite its prevalence depression in patients with PD is under-researched [151, 152] and undertreated. Watnick and colleagues [146] reported that only 16% of patients who meet the criteria for depression at the start of dialysis received treatment for their depressive symptoms. However, patients' resistance could also hamper treatment for their depression. A study into the feasibility of pharmacotherapy for depression in PD patients found that less than half of those eligible agreed to receive treatment [147]. Depressed patients have a higher risk of malnutrition, peritonitis, poorer treatment compliance, and poorer psychological adjustment to disease and treatment, which in turn could affect HRQL [134, 152–156]. A 10-point decrease in the mental component score (MCS) of the SF-36 was associated with a 28% increase in mortality risk [157].

Patients who perceive having more control over their illness and treatment reported better physical functioning [104], and improved affective state over time [134]. A study with PD patients who were given no choice in treatment modality reported poorer mental and affective states compared with those who had elected for PD [158]. Patients with adequate predialysis care and a planned start to dialysis are more likely to choose for PD, and present with better mental and physical functioning compared with patients with an unplanned dialysis initiation [159]. PD patients who are more satisfied with the level of care provided by the dialysis team report having better HRQL [160].

Having access to social support has been linked to better health outcomes and survival in ESRD patients [161–164]. We found that patients who perceive an insufficiency in social companionship and daily emotional support had a higher mortality [165]. Being able to reciprocate socially is also associated with better survival in dialysis patients [163].

Demographics

HRQL is also mediated by factors such as patients' demographics. There are suggestions of racial and cultural differences on HRQL in PD patients. Black male patients reported having less satisfaction with care they received compared with whites [166]; in addition, white patients perceived their HRQL better than their Asian counterparts [74, 166]. Another study found that Indo-Asian patients had lower acceptance and adjustment to their illness compared with white patients [167]. Gender differences have also been observed in the HRQL of PD patients. Female PD patients reported higher sexual functioning, as measured on the KDQOL, when compared with males [166]. Male PD patients scored lower on all four dimensions of the KDQOL (physical health, mental health, kidney disease issues, and patient satisfaction) compared with female PD patients [77]. The association between socioeconomic status and HRQL in dialysis patients has not been widely investigated. A small follow-up study that examined socioeconomic status on HRQL of HD patients concluded that patients in the high socioeconomic status group had improved HRQL scores on the SF-36 after 6 months' follow-up compared with those in the low socioeconomic status group [168]. PD patients with lower socioeconomic status had a higher risk of developing dialysis-related peritonitis compared with those from a higher socioeconomic status [169].

Functioning

Functioning, in particular physical functioning has been also studied for its association with HRQL in PD patients. Functioning could be determined by perception of symptom burden. For example, complaints of fatigue and poor sleep [170–172] could result in poorer level of physical functioning. Poorer physical functioning, as measured by decreased participation in social and leisure activities, and activities of daily living, has been associated with poorer HRQL [171, 173], and higher morbidity and mortality [174].

The impact of dialysis on work participation and HRQL should also not be overlooked. Compared with the general population, patients on dialysis are less likely to have employment [175] due to treatment restrictions [171, 175]. Dialysis patients with employment report having better HRQL compared with those without work [176–178]. Patients

who perceive that their health and dialysis treatment are limiting their ability to work, are less likely to be employed, resulting in a self-fulfilling prophecy [177]. A study suggests that the poorer cognitive functioning in dialysis patients could also compromise their ability to work [179].

HRQL Between Different Categories of Dialysis Patients

Patients on dialysis have consistently lower HRQL when compared with the general population, especially in physical functioning [104, 176, 180]. Comparative studies suggest that HRQL also differs within dialysis patients, such as PD versus HD, or between PD patients either on continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD). However, evidence to suggest one mode of dialysis is better than the other in impacting on/improving HRQL is still inconclusive.

PD Versus HD

Studies into the efficacy of dialysis modality on HRQL show mixed results. Some studies suggest that both PD and HD patients had similar HRQL [86, 181]. A small study using a questionnaire developed by a committee of clinicians experienced in dialysis, reported that PD patients scored higher than HD on measures assessing family life, independence, religion/spirituality, energy level, and living situation [182]. This study also included a free-text section in which patients identified positive and negative aspects of their treatment. Positive aspects of PD treatment frequently cited were: improved strength/energy, being alive and well, ability to perform therapy at home, able to perform treatment during sleep, and increased independence. Patients cited problems with supplies, frequency/length of treatment, bloating/pain, interference with sleep, and changes in routine as negative aspects of PD treatment. A large study with 16,755 HD and 1,260 PD patients reported that PD patients scored higher on the mental processes of the SF-36 after adjusting for demographic and clinical variables [51]. However, comparisons of these results are difficult, given the cross-sectional design of the studies and the use of prevalent patients.

A randomized controlled trial would be an ideal study design to overcome the methodological issues of these previous studies. The only randomized trial investigating HRQL of PD and HD patients compared the mean quality-adjusted life year (QALY) scores between the two treatment modalities, and found a small difference favoring HD patients after 2 years' follow-up [183]. However, these results could be confounded due to the small sample of 38 patients. The Netherlands Co-operative Study on the Adequacy of Dialysis (NECOSAD), a longitudinal observational study using incident dialysis patients, suggests that PD patients have a more pronounced decline in the SF-36 physical function scores over 18 months follow-up compared with HD patients [100]. Results from the Choices for Healthy Outcomes in Caring for End-stage Renal Disease (CHOICE) study indicate that HRQL in both modalities improved but on different domains. PD patients fared better than HD patients in terms of finances, while HD patients reported better physical functioning, general health perception, and sleep compared with PD patients after 1 year of treatment [184]. The Dialysis Morbidity and Mortality Study (DMM) Wave 2 reported that after 1 year, PD patients had more favorable evaluations of the effects of kidney disease, the burden of kidney disease, staff encouragement, and satisfaction with care compared with HD patients [185]. In a meta-analysis of 61 studies, PD patients were characterized by a better well-being and less distress than HD patients [186].

However, the differences in HRQL between the modalities could be due to inadequate adjustment for case mix [187] or other factors such as differences in HRQL scores prior to start of dialysis, which make comparison between the modalities difficult. Korevaar et al. [188] demonstrated that, even after extensive adjusting for case mix, the HRQL scores just before start of dialysis were different for patients who would start with PD compared with those who would start with HD. Patients who eventually start with PD had higher HRQL as measured with the SF-36 at this predialysis phase compared with the pre-HD patients. They concluded that future comparative studies on HRQL between these two modalities needed to include the baseline HRQL at or before the start of dialysis to reduce possible selection effects.

The differences in HRQL could also suggest that both modalities might not be comparable [189]. A model of integrated care has been suggested in which PD and HD should be regarded as complementary modalities on a continuum for patient care rather than as "competitive alternatives" [190]. Patients starting dialysis who have no contraindications for either HD or PD are more likely to choose PD over HD [191], probably because PD allows for greater autonomy and freedom in lifestyle, such as employment [189]. In their editorial, van Biesen et al. [190] recommend that PD should be the initial therapy for patients with no contraindications, as its advantages include

better renal function preservation, and better quality of life and survival in the first few years of dialysis compared with HD. In this model of integrated care, transfer to HD will be closely monitored when problems of PD such as patient burnout, infections, or dialysis inadequacy compromises the well-being of the patient.

CAPD Versus APD

Investigations have also been done on possible differences in HRQL of patients on different modes of PD, for example, HRQL differences between patients on continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). A small randomized study comparing the HRQL benefits of CAPD and APD with the SF-36 showed that APD patients reported having significantly more time for work, family, and social activities compared with CAPD, although there was a tendency of more sleep problems with the APD sample than that of the CAPD [192]. In another study, APD patients were found to have better mental health, and less anxiety and depression compared with CAPD patients [193]. Although APD is a more costly option than CAPD, the associated HRQL benefits such as better mental health and maintenance of employment could offset its higher cost [192].

Pediatric PD Patients

Peritoneal dialysis (PD) is the dominant mode of therapy for pediatric patients requiring dialysis. Two-thirds of pediatric patients are on PD [194]. However, research on the HRQL of pediatric ESRD patients is limited compared with the adult ESRD population. No long-term, prospective study has been conducted on this pediatric population [195]. As with the adult population, there is also a lack of consensus on the definition and measurement of HRQL in the pediatric population. Studies often compare the HRQL of children with a chronic illness to their healthy peers, although knowledge on the normative process of children adapting to a chronic illness is sparse [196].

When assessing HRQL in pediatric PD patients, issues important to adult PD patients like employment, sexual functioning, and death are less relevant to pediatric patients. Of more concern to the pediatric patient are issues like growth, academic performance, exercise, self-reliance, and functional and psychological/emotional development [197–199]. Children on dialysis have to contend with a lifelong reliance on a machine for their survival, differentiating them from their peers during this pivotal stage of their personal development. Complications with treatment could result in missed school attendance, affecting not only their academic and functional development, but also further isolate them from their peers [195]. Children on dialysis who experienced greater functional impairment as a consequence of their illness were more likely to be depressed, anxious, and exhibit more behavioral problems [200].

Elderly PD Patients

Studies suggest that HRQL of dialysis patients is negatively associated with age, especially in the domains of physical, cognitive, and affective functioning [60]. A possible explanation for this differential age effect on HRQL of dialysis patients could be that measures used in previous studies reflect the domains of more relevance to younger patients and have poorer validity for use among older patient groups as more weight tends to be allotted to physical health. This, together with confounding by age and co-morbidity, could result in lower HRQL scores for the older patients [201]. Using the patient-centered measure, Schedule for the Evaluation of Individual Quality of Life – Direct weighting (SEIQoL-DW) instrument to assess QL domains of importance to dialysis patients, McKee et al. [201] noted that while both young and old dialysis patients had similar nominations on the domains of family and marriage/relationships, only the younger patients nominated work opportunity/standard of living. Among the older patient group, the top-nominated domain was leisure activities.

Comparative studies of age effects on HRQL have often used both HD and PD patients [87, 135, 202]. To our knowledge, only one study has looked at the effect of age in younger and older PD patients. In this retrospective study, younger (between 40 and 60 years of age) and older (over 70 years of age) nondiabetic PD patients had similar rates of PD-related complications, and older patients were more likely to have better adjustment to treatment and having comparable or better physical and social state at 1-year follow-up compared with younger patients as reported on the Karnofsky Index and with patient interviews [203].

Caregivers' HRQL

Successful adaptation to PD treatment especially for the elderly is also very much dependent on the availability of caregivers. De Vecchi et al. reported that 12% of younger and 43% of older PD patients in their study required assistance with their dialysis at one year of follow-up [203]. Few research has looked into the issues of caregiver distress and burnout, although caregivers of dialysis patients have poorer HRQL compared with the general population [204, 205]. Caregivers of PD patients, when compared with HD caregivers, fared worse on the physical aspect, and the mental components of the SF-36 – vitality, social aspect, emotional aspect, and mental health [205]. A Spanish study reported similar findings in which younger caregivers of elderly dialysis patients who perceived having insufficient social support, reported experiencing greater feelings of burden, and poorer HRQL, and have a higher risk for clinical depression [204]. A study exploring the coping strategies of dialysis caregivers and their HRQL suggest that male spousal caregivers showed less optimistic, supportive, and palliative coping compared with female spouses. In general, spouses with emotive, evasive, and fatalistic styles of coping had poorer HRQL [206]. A questionnaire has been recently developed to assess burden of care among caregivers of PD patients [207]. Although the validity and reliability of this questionnaire has been reported, it has not been used by other research groups.

Withdrawal from Treatment

As medical care becomes more patient-focused, the recognition of the patient's autonomy to withdraw from treatment when the perceived discomforts of treatment exceed its benefits is also increasing [208]. Withdrawal from dialysis is a common occurrence and accounts for approximately one in five deaths among dialysis patients [209, 210]. Patients who withdraw from dialysis have been characterized as being older, with higher level of physical and cognitive impairments, and more co-morbid conditions [211, 212].

This high prevalence of deaths due to dialysis withdrawal coupled with the inclusion of older and sicker ESRD patients into dialysis programs highlights the need for better communication between clinicians and their patients regarding end-of-life issues [213, 214]. A small qualitative study with HD patients identified the following domains as being important for quality end-of-life care: avoiding inappropriate prolongation of dying, strengthening relationships with loved ones, relieving burden, having a sense of control, and receiving adequate pain and symptom management [215]. Family's perspectives elicited on ESRD deaths showed that approximately 75% of family members perceived that the patients were in pain during the last week of life [216]. A majority of family members reported that patients described the pain as moderate to severe and occurring most or all of the time. Nearly half of the family respondents felt that relief of pain should have been of greater importance for the patient. The Renal Palliative Care Initiative (RPCI) has been developed to integrate palliative medicine into nephrology [217]. The RPCI, a collaborative work between Baystate Medical Center and eight dialysis centers from the Connecticut River Valley, proposed interventions in symptom assessment, symptom treatment guideline, morbidity and mortality conferences, spiritual care, advance care planning, hospice referral, and bereavement services.

Improving HRQL

Improvement in physical functioning through exercise rehabilitation has been shown to improve HRQL in dialysis patients [218]. A small study of PD patients in Hong Kong showed improvements in the KDQOL domains of burden of kidney disease and physical functioning after undergoing a 12-week exercise program [219]. Another study compared the benefits of exercise coaching during predialysis or after start of dialysis [220]. Patients were offered a 1-year program consisting of 6 months exercise coaching and a further 6 months of follow-up. The authors concluded that exercise rehabilitation offered at predialysis stage was more beneficial for patients' HRQL rather than after start of dialysis.

Besides exercise rehabilitation, ensuring that PD patients have continued good social support from the start of dialysis is also crucial for improving HRQL. Clinical care providers could tailor intervention programs to improve social support based on patients' needs, such as recommendations to appropriate programs like self-help groups [221] or psycho-educational programs [154, 222–224] designed to promote self-efficacy in coping with dialysis. Besides providing relevant medical information regarding lifestyle changes due to dialysis, clinical care providers should also highlight to patients and family/caregivers the relational dynamics involved in lifestyle changes [225]. Patients and

their family/caregivers could be made aware of potential conflicts that could arise when communicating encouragement and support for lifestyle change.

Given the chronic nature of PD treatment, clinical care providers should encourage patients to be an active participant in the self-management of their day-to-day care. Self-management refers to the health promotion and patient education programs developed to encourage behavior change and assist in adjustment to a chronic illness [226, 227]. Christensen et al. [228] reported on the efficacy of a behavioral self-regulation intervention for adherence in patients on HD, in which patients divided into small groups, discussed a self-regulation protocol with psychologist-trainers. The target behavior was adherence to fluid restrictions, which was a major self-regulatory task in these patients. Encouraging results from this study should spur further development of such self-regulatory–based interventions in patients on PD.

Future Trends and Conclusions

The evaluation of HRQL in PD patients has evolved from survival to include more complex psychosocial factors. As HRQL assessment becomes more patient-centered, evaluation of patients' perceptions of their health and illness should be an integral part of the evaluation process.

As more patients with ESRD are being offered PD as the first-line treatment, HRQL assessment tools specific to PD patients across the different age spectrum should be developed. This would allow for a more comprehensive understanding by clinical care providers of HRQL issues important to this patient group, which can then be used to improve patients' care. Clinical management of chronic illnesses is moving towards a model of collaborative care [229], whereby patients and clinicians work in partnership for the benefit of improving patients' HRQL through a complementary offering of both traditional and self-management education programs. For example, a randomized controlled trial comparing the effects of self-management interventions versus traditional care on morbidity and mortality of PD patients could be initiated.

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Chapter 19
Peritonitis

L. Fried and B. Piraino

Peritonitis remains a major complication of peritoneal dialysis, accounting for much of the morbidity associated with the technique. Peritonitis accounts for 15–35% of hospital admissions and is the major cause of transfer to hemodialysis (technique failure) [1–7]. High peritonitis rates are associated with mortality, either as a primary or contributing factor [8–11].

In the early 1980s, peritonitis incidence was high, with rates as high as 6.3 episodes/patient year [12]. With improvements in connection technology and institution of prophylactic measures, the rates declined to less than 0.5 episodes/patient year (Fig. 19.1) [4, 13–15]. However, many patients continue to experience frequent peritonitis. There is variability in peritonitis rates by both program and by individual patients. The two most common ways of expressing overall rates are the average number of episodes per single patient year and the average number of months between episodes (Table 19.1). Overall rates mask different outcomes based on patient demographics and the organism involved [2, 16–18]. In small programs, overall peritonitis rates can be skewed by a few individuals with high rates. In these cases, median rates can be useful (Table 19.1) [17]. In larger programs with low peritonitis rates, low overall rates can mask the cases of individuals with high rates. Examining both overall unit rates and individual peritonitis rates is important. This chapter will review the pathogenesis, diagnosis, treatment, and clinical course of peritoneal dialysis-associated peritonitis. Table 19.2 shows the definition of terms used in the chapter.

Pathogenesis

Pathogens

The most common organisms producing peritonitis are summarized in Table 19.3. Most episodes are due to a single organism [19, 20]. In contrast to surgical peritonitis and spontaneous bacterial peritonitis, the most common organisms are Gram-positive [20]. Table 19.3 shows rates (versus percentages) to highlight that the wide variability in reported rates is mainly due to differences in the rate of coagulase-negative staphylococcal peritonitis. With declining coagulase negative *Staphylococcus* rates secondary to changes in connection technique and *Staphylococcus aureus* due to exit site prophylaxis [21] (Fig. 19.2a), the proportion of infections secondary to Gram-negative organisms is increasing [22]. However, the actual rate per year of Gram-negative peritonitis is relatively constant [15, 23, 24] (Fig. 19.2b). Although unusual, fungi are important causes of peritonitis as the sequelae are serious. Fungal peritonitis is predominantly due to *Candida* species, though many species have been reported [25–30]. Anaerobic peritonitis is uncommon and suggests bowel perforation [31–33]. Multiorganism infections that involve more than one Gram-negative organism also suggest bowel perforation. However, polymicrobial peritonitis with Gram-positive organisms can result from touch contamination or a catheter infection [34]. Mycobacterial peritonitis is rare, but may be more common in countries where mycobacterial infections are endemic [35].

Routes of Entry

The routes of entry for peritonitis are summarized in Table 19.4.

L. Fried (✉)
VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania
e-mail: Linda.Fried@va.gov

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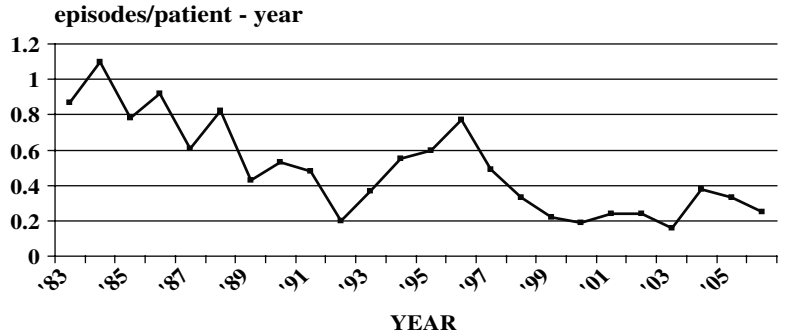

Fig. 19.1 Peritonitis rates over time at the University of Pittsburgh PD Program

Table 19.1 Methods to express peritonitis rates*

1. Rates can be calculated for the program or for an individual patient
a. Number of total peritonitis episodes divided by time period at risk, expressed as episodes/dialysis year
b. Months of peritonitis dialysis at risk, divided by the total number of episodes, expressed as interval in months between episodes
To convert from a or b above to the other, divide 12 by the interval or rate
2. As percentages of patients per period of time who are peritonitis free
3. As median of individual patient rates for the individuals in the program

*Adapted from [145]

Table 19.2 Definitions*

Peritonitis	100 WBC/μL, >50% polymorphonuclear cells
Exit-site infection	Purulent drainage from the exit site. Erythema may or may not indicate infection
Tunnel infection	Erythema, edema, or tenderness over the subcutaneous portion of the catheter (often occult)
Catheter infection	Exit-site and/or tunnel infection
Catheter-related peritonitis	Peritonitis in conjunction with a catheter infection with the same organism or evidence of infection at both sites, though one site may be culture negative
Relapsing peritonitis	Peritonitis with the *same* organism within 4 weeks of stopping antibiotics
Recurrent peritonitis	Peritonitis with a *different* organism within 4 weeks of stopping antibiotics
Refractory peritonitis	Failure of the effluent to clear after 5 days of appropriate antibiotics
Peritonitis related mortality	Mortality secondary to sepsis from peritonitis, with active infection (e.g., positive culture, cell count), during hospitalization for peritonitis or within 14 days of peritonitis episode

*Adapted from [232]

Contamination

The most common source of peritonitis is contamination at the time of the exchange, leading to infection with predominantly Gram-positive skin flora ("touch contamination") [36]. The organism involved is mainly coagulase-negative *Staphylococcus*, though diphtheroids, *Corynebacterium* and *Bacillus* are also seen [37]. The Y-set with flush-before-fill technique decreased the incidence of peritonitis from touch contamination [22, 37–41]. This has decreased coagulase-negative *Staphylococcus* peritonitis as well as other Gram-positives, but has had no effect on the incidence of *S. aureus* [34, 39]. Some patients' skin is colonized with Gram-negatives, which may be related to prior antibiotic use [42]. In these patients touch contamination can lead to Gram-negative peritonitis. In one study the Y-set decreased the incidence of *Acinetobacter* peritonitis, indicating touch contamination as a route of infection [39].

It has been suggested that contamination from mouth organisms (e.g., *Streptococcus* species) can occur in individuals who do not wear a mask during connections, but this is not well studied [43]. Another potential source of peritonitis due to contamination are from bites to the tubing by domestic animals. *Pasteurella* infections have been described most commonly with cats, but there are also reports of peritonitis from hamster tubing bites [44–50].

Table 19.3 Organisms producing peritoneal dialysis peritonitis*

	Episodes/patient-year
Gram-positive	
Staphylococcus epidermidis	0.06–0.4
Stapnylococcus aureus	0–0.15
Streptococcus	0.03–0.14
Enterococcus	0.01–0.04
Other Gram-positive	<0.01–0.02
Gram-negative	0.09–0.24
Pseudomonas aeruginosa	0.01–0.18
Other pseudomonas	0.01–0.02
Klebsiella	0.01–0.02
Escherichia coli	0.01–0.04
Other Gram negative (e.g., *Pasteurella, Morganella, Citrobacter, Acinetobacter, Proteus, Serratia, Enterobacter, Streptophonomonas*)	Each individually <0.01
Polymicrobial with at least one Gram negative	0.02–0.04
Fungal	<0.01–0.07
Mycobacterial	<0.01
Sterile	0.06–0.20

*Adapted from [11, 13, 15, 24, 37, 42, 53, 189, 231, 234, 240, 323–328]

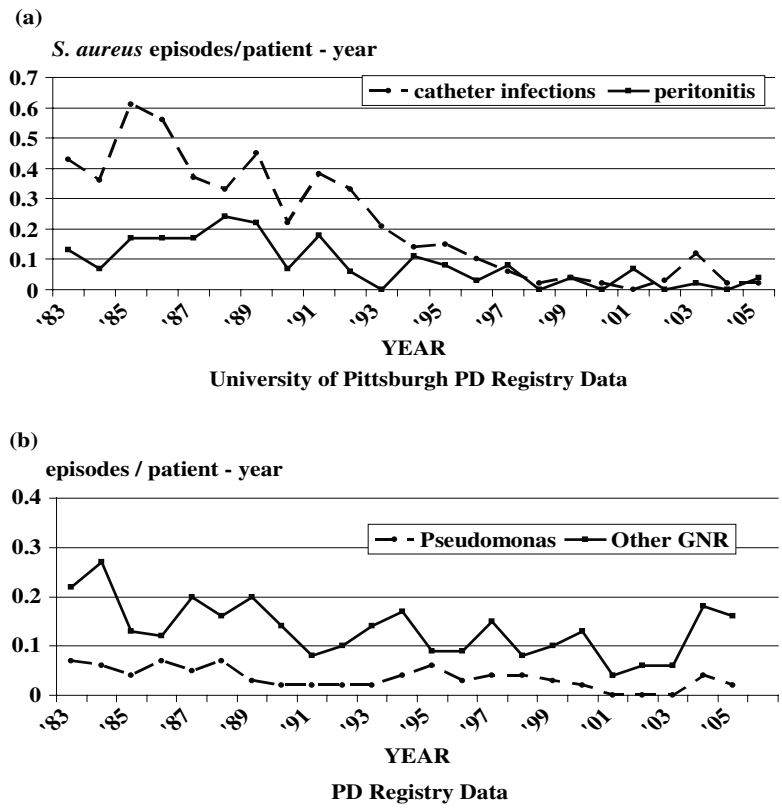

Fig. 19.2 Organism-specific rates over time at the University of Pittsburgh PD Progam. (**a**): *Staphylococcus aureus* catheter infections and peritonitis, (**b**): *Pseudomonas aeruginosa* and other Gram-negative peritonitis

Table 19.4 Routes of entry for peritonitis

Contamination
Catheter-related
Enteric
Hematogenous
Gynecological

Catheter-Related

Catheter infections previously accounted for 10–25% of peritonitis episodes prior to implementation of exit site antibiotic prophylaxis [19, 51–53]. Exit-site and tunnel infections predispose patients to the development of peritonitis, presumably through contiguous spread along the catheter surface [54]. In a trial examining the risk factors for peritonitis, the development of an exit-site infection doubled the risk of subsequent peritonitis [22]. Prior to the introduction of the Y-set, 64% of those with a history of an exit-site infection developed peritonitis, versus 45% without [55]. The most common organisms causing exit-site infections are *S. aureus, Pseudomonas*, and coagulase-negative *Staphylococcus* [56]. Tunnel infections are predominantly caused by *S. aureus*, followed by *Pseudomonas* [52]. In contrast, coagulase-negative *Staphylococcus* is an unusual cause of tunnel infection, catheter-related peritonitis or catheter loss [52, 56]. In a study evaluating catheter-related infections, none of the coagulase-negative *Staphylococcus* peritonitis episodes associated with an exit-site infection required catheter removal versus 76% with other organisms [52] (Fig. 19.3). Peritonitis associated with tunnel infections is generally refractory to treatment without removal of the catheter. Except in the case of coagulase-negative *Staphylococcus*, the treatment failure rate was still high even when there was an exit-site infection without clinical evidence of a tunnel infection, suggesting occult tunnel infections. Catheter infections can also produce relapsing peritonitis, recurrent peritonitis with the same organism within 2–4 weeks of stopping antibiotics. This can be due to the presence of a tunnel infection or alternatively to bacterial colonization of a biofilm [57, 58]. Biofilm formation is ubiquitous and does not necessarily result from infection [59]. Recurrent peritonitis in association with a biofilm is most often due to coagulase-negative *Staphylococcus*, while recurrent peritonitis due to a tunnel infection is generally due to *S. aureus* or *Pseudomonas aeruginosa* [60].

Enteric

Gram-negative peritonitis is caused by intestinal flora but the path of entry into the peritoneal space is not always obvious. Infection can result from abdominal perforation, instrumentation, or other abdominal processes [33, 61–68]. However, in many cases an etiology of the infection is not found [69]. A recent study indicating that Gram-negative peritonitis is reduced with use of gentamicin prophylaxis for routine exit site care is suggestive that some Gram-negative peritonitis occurs via the exit site entrance [21]. It is also quite possible that some peritonitis due to enteric organisms is from touch contamination, as skin flora can contain Gram-negative organisms [70, 71]. Enteric organisms may enter the peritoneal cavity by transmural migration across the gastrointestinal tract without overt gastrointestinal pathology [72]. Diverticulosis appears to increase the risk of transmural migration, as can acute treatment of

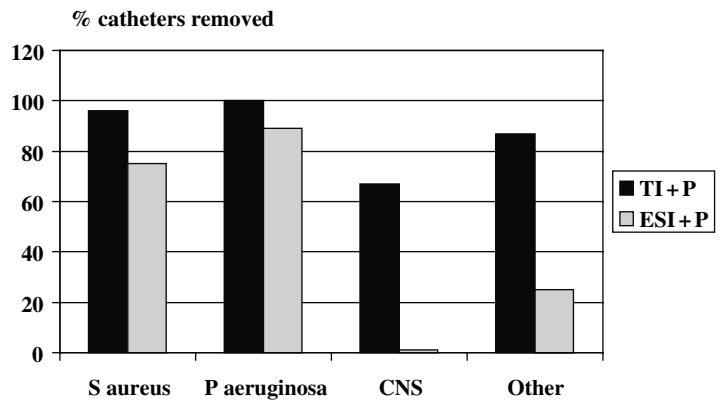

Fig. 19.3 Catheter removal by organism. From Gupta et al., [52]. Reprinted with permission. TI = Tunnel infection, ESI = exit-site infection, P = peritonitis, CNS = coagulase negative *Staphylococcus*

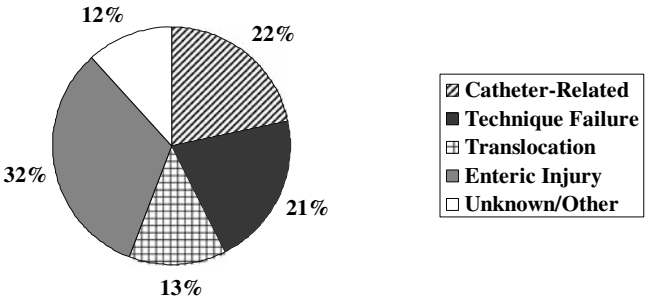

Fig. 19.4 Etiology of peritonitis involving enteric organisms, including *Streptococcus* sp. and *Torulopsis*. Data derived from [67]

constipation [73, 74]. However, the presence of multiple Gram-negative organisms or an anaerobe suggests perforation [31]. Figure 19.4 summarizes the etiology of peritonitis involving enteric organisms.

Hematogenous Spread

Bacteremia can lead to peritonitis, though it is an uncommon cause. Invasive procedures or dental work can produce transient bacteriemia and peritonitis [65, 75, 76]. Routine gastrointestinal endoscopy is associated with bacteriemia in 2–6% of procedures, though esophageal dilation and variceal sclerotherapy have a significantly higher frequency [77, 78]. Dental procedures can lead to peritonitis from mouth organisms such as *Streptococcus* sp. [75, 76]. These cases are potentially preventable with prophylactic antibiotics given at the time of invasive procedures, including dental.

Gynecological

In rare cases, ascending infections from uterine and vaginal sources can lead to peritonitis. This can lead to infections with vaginal flora, including yeast. Cases have been reported with gynecological procedures, vaginal leak of dialysate, and the use of intrauterine devices [79–85].

Predisposing Factors

Risk Factors

Studies examining risk factors for the development of peritonitis identified higher rates for children, African Americans, Native Canadians, and those with a history of substance abuse or lower socioeconomic status [19, 86–91]. The higher rate in children is mainly due to Gram-positive organisms [61]. Age (in adults), diabetes, and gender do not appear to be significant risks, although this is controversial [19, 91–93]. Low serum albumin at the start of dialysis, perhaps signifying inflammation or poor nutrition, has been found to be a risk factor [93, 94]. Immunosuppression is also a risk factor. Prior steroid use is not consistently a predictor, but HIV-positive patients have higher peritonitis rates [19, 95, 96]. In addition, the proportion of Gram-negative and fungal infections is higher in HIV-positive patients [95–97]. Prior antibiotic use is also a risk for fungal peritonitis [28, 30, 98–100]. Gastric acid inhibitors may increase the risk of Gram-negative peritonitis, as can constipation [73, 74]. Upper respiratory tract infections may predispose children to peritonitis, though the reason for this is not clear [76]. The strongest dialysis-related factors are the type of connection system and staphylococcal nasal carriage.

Recent studies suggest that depression may be a risk factor for the development of peritonitis [101]. The reason is not fully delineated but might be due to carelessness in doing the connection by the depressed patient, or alteration of the immune system due to depression, or both. This potential risk factor, and interventions to decrease it, requires further study.

Connection System

The Y-set was introduced in the late 1970s in Europe but did not gain widespread use until the mid- to late 1980s [41, 102]. This system uses a flush-before-fill technique that flushes sterile dialysate into the drain bag after connection to the patient's catheter, but before dialysate is infused into the peritoneum [41, 102]. This decreases the possibility of bacteria from touch contamination reaching the peritoneal cavity. This improvement dramatically decreased the

peritonitis rate when compared to the standard spike system [22, 38, 40, 41]. The Canadian CAPD Clinical Trials Group performed a randomized multicenter trial comparing a standard spike to the Y-set [22]. The Y-set reduced the peritonitis rate by 60%. The twin bag system with a preattached drain bag, requiring only connection at the catheter, further reduces peritonitis rates [103–105]. However, contamination remains a leading cause of peritonitis in many programs and is possibly related to training methods. A structured approach to training is probably best [106]. This requires more formal studies. The very low rates of peritonitis reported from Japan indicate that culture and training may be important in preventing peritonitis [107]. These centers show that rates as low as one episode every 50 months or more are possible.

Continuous cycler peritoneal dialysis is currently a popular form of PD in the Western world. Some studies have found that continuous cycling peritoneal dialysis (CCPD) patients have a lower peritonitis rate than CAPD [108–110] but others have shown this is not the case [111–113]. This is presumably secondary to the decreased number of connections between the system and peritoneal catheter. In the United States some cycler systems require the patient to "spike" bags, which is a potential source of contamination. It is also important not to reuse cassettes or tubing in automatic peritoneal dialysis (APD), as this increases the infection rate [114, 115]. A modification using an assist device to spike the bags on CCPD may further lower peritonitis rates [116]. No controlled studies between CAPD with the twin bag system and CCPD with this modification have been performed.

Staphylococcal Carriage and Exit Site Prophylaxis

Nasal carriage increases the risk of *S. aureus* exit-site infections and subsequently peritonitis [117–121]. Phage typing of *S. aureus* from those with peritonitis or exit-site infection found that in most cases the isolates were the same as from the nares [117, 122, 123]. Zimmerman et al. found that 83% of all *S. aureus* peritonitis episodes were associated with *S. aureus* catheter infection or colonization of the exit site with *S. aureus* [124]. This is consistent with a failure of the Y-set to reduce *S. aureus* peritonitis.

Compared to noncarriers, carriers have a 2–6-fold higher incidence of *S. aureus* peritonitis [15, 117, 121, 125]. Immunosuppressed patients appear to be at particular risk of *S. aureus* peritonitis, regardless of carriage status [126]. Diabetics appear to have an increased rate of nasal carriage [118, 126]. However, it is controversial whether diabetics have an increased risk of *S. aureus* peritonitis after accounting for the higher carriage [118, 125–127]. Treatment strategies that treat nasal carriage (nasal mupirocin or cyclical rifampin) or treat the exit-site to prevent *S. aureus* exit-site infection (mupirocin or gentamicin), dramatically reduce the incidence of *S. aureus* peritonitis (see below, Prevention) [21, 128–132]. Gentamicin compared to mupirocin, both applied daily to the exit site as routine care, decreased both exit site infections and peritonitis, and virtually eliminated *P. aeruginosa* as well as *S. aureus* PD-related infections. This approach has not been compared to intranasal application of mupirocin [21].

Clinical Presentation

The usual symptoms are cloudy fluid and abdominal pain (Table 19.5) [20, 42, 76]. The presentation can vary from cloudy fluid with no pain to a severe illness [42, 133]. In children, cloudy fluid is almost universal, though the incidence of abdominal pain may be less than in adults [76]. The initial presentation in children may be fever alone [76]. The abdominal pain is typically generalized and is often associated with rebound. Local abdominal tenderness could indicate a potential intra-abdominal etiology.

Early studies found that 98–100% of cases presented with cloudy fluid [20, 42, 76]. However, 6% presented with abdominal pain, in the absence of cloudy fluid or elevated cell count [134]. Usually, this represents a delay of

Table 19.5 Clinical presentation* (percentages)

Cloudy fluid	98–100
Abdominal pain	67–97
Abdominal tenderness	62–79
Rebound tenderness	35–62
Fever	34–36
Chills	18–23
Nausea	30–35
Vomiting	25–30
Diarrhea	7–15

*Adapted from [20, 42, 76]

Table 19.6 Differential diagnosis of cloudy effluent

Infectious peritonitis, including culture-negative peritonitis
Eosinophilic peritonitis
Encapsulating peritoneal sclerosis (EPS)
Chylous ascites
Malignant ascites
Pancreatitis
Chemical peritonitis

leukocytosis, and when re-examined, the dialysate cell count has increased [134, 135]. This delay may be secondary to slower cytokine response to infection [134]; therefore, PD patients with abdominal pain should be considered to have peritonitis until proven otherwise. Cloudy fluid can, in rare cases, represent malignancy or chylous ascites [134, 135]. These cases can be differentiated by cytology and dialysate triglyceride levels. The differential diagnosis of cloudy effluent is outlined in Table 19.6.

The presentation is somewhat dependent on the organism involved and the etiology of peritonitis. Episodes due to coagulase-negative *Staphylococcus* and other skin organisms such as *Corynebacterium* are generally milder than episodes with *S. aureus, Streptococcus*, fungi, or Gram-negative organisms [133, 136, 137]. Peritonitis from bowel perforation or other abdominal processes often produces severe symptoms, but the initial presentation may not differ from typical peritonitis [31–33, 138]. Some investigators have found that the presence of free air associated with peritonitis, or alternatively, increasing free air (as free air results from introduction of air during an exchange) to be a clue to bowel perforation [138, 139]. Tunnel tenderness indicates a tunnel infection, but the sensitivity of the physical examination for tunnel infections is low [140]. Since tunnel infections are generally associated with exit-site infections, the presence of an exit-site infection in a patient with peritonitis should trigger a suspicion of catheter-related peritonitis.

Diagnosis

Cell Count

The usual criteria for peritonitis are 1) cloudy fluid; 2) dialysate white blood cell count $>100/\mu L$; 3) polymorphonuclear cells (PMN) $>50\%$; and(4) positive culture [20, 26]. The culture is not always positive and is dependent on the technique used for culturing the effluent (see below). Most but not all patients have abdominal pain. In the absence of peritonitis the cell count is usually $<30/\mu L$ and is predominantly mononuclear [134, 141, 142]. Some authors have found that PMN $>50\%$ is a better criterion that the total cell count, especially in patients already on antibiotics [141, 143, 144]. Short dwell times can also decrease the number of white cells seen and in this case, PMN $>50\%$ may also be a better criterion [145]. Antonsen et al. found that if the cell count is not done within 4–6 h of collection the number of leukocytes can decrease by 25–30% [146]. The leukocyte count is more stable if samples are sent in EDTA tubes. A number of studies have described the use of leukocyte esterase reagent strips to rapidly diagnosis and elevated leukocyte count in peritoneal fluid [147–150]. This may be useful for units far from a hospital or laboratory.

Tuberculous peritonitis may present with a predominance of lymphocytes, but neutrophil predominance is more common [35, 151–155]. Occasionally, eosinophil predominance is seen in the effluent (eosinophilic peritonitis). Rarely, this is due to fungal peritonitis [156, 157], but in most cases cultures for bacteria and fungus are negative. However, a recent report found that in approximately half of the cases, the eosinophilia was due to infection with a spectrum of organisms similar to the overall distribution in the unit [158]. In many cases the peritoneal eosinophilia occurs early after the initiation of PD and is felt to represent a reaction to the plasticizers in the PD catheter or plastic dialysate bags [159, 160] or inadvertent entrance of air at the time of the exchange [161]. Icodextrin has also been associated with peritoneal eosinophilia [162, 163]. Blood eosinophilia may also be seen in setting of peritoneal eosinophilia [164–166]. In most cases the eosinophils resolve without treatment [159, 164, 167]. Persistent cases may respond to steroids or a mast-cell-stabilizing antihistamine [168–171].

Culture

The handling of the dialysate is important in establishing the etiological agent. Culturing a large volume improves the diagnosis [172]. Blood culture techniques improve the yield of culture and our the standard technique [145, 173–176]. In general, at least 10–20 mL of dialysate should be cultured using blood culture media. Culturing the sediment after

centrifuging 50mL of dialysate is ideal and further decreases the proportion of culture-negative peritonitis [145]. Blood cultures are rarely positive; therefore, routine culturing of the blood is not necessary unless the patient presents with a septic picture. Cultures are generally positive within 24–72 h, though coagulase-negative *Staphylococcus* may grow more slowly [177]. Fungal cultures might take longer than the routine time in many laboratories and a high index of suspicion is needed, especially if the patient is not responding to antibiotics. The growth of mycobacteria is slow, resulting in a delayed diagnosis. Peritonitis due to mycobacteria may be difficult to diagnose but should be suspected if routine cultures are negative, the peritonitis fails to resolve with the usual antibiotics, the patient seems to be chronically ill, and if there is evidence of mycobacterial infection elsewhere. In some cases laparoscopy with biopsy is needed to make a diagnosis. Polymerase chain reaction for tuberculosis can also aid in the diagnosis [178–180].

The use of Gram stain is predominately useful for an early diagnosis of fungal peritonitis, but is much less useful to diagnose bacterial peritonitis [145]. It is important not to base antibiotic therapy solely on the Gram stain. In many cases where Gram-positive cocci were seen, another organism was found, or the culture was negative [181]. However, Gram stains can yield an early diagnosis of fungal peritonitis, which can allow prompt initiation of appropriate treatment and catheter removal [29].

The exit site and tunnel should always be carefully examined in a patient presenting with peritonitis. If drainage from the exit site is present, this should be cultured. Clinical examination of the tunnel often underestimates the presence of a co-existent tunnel infection when exit site infection is present [140]. Ultrasound may be beneficial in diagnosing an occult tunnel infection. The width of a normal tunnel is approximately 6 mm [182]. In the presence of a tunnel infection, ultrasound of the tunnel can show decreased echogenicity around the tunnel, indicating a fluid collection [140, 183]. In patients with an exit-site infection a positive ultrasound indicates a high risk of catheter loss [184, 185]. However, the accuracy of ultrasonography is operator dependent and the indications for use of ultrasound in evaluating the patient with peritonitis have not yet been determined. Vychytil et al. proposed that the indications for tunnel ultrasound in the setting of peritonitis are peritonitis in patient with an exit site infection, infection with *Staphylococcus aureus*, and relapsing/persistent peritonitis [186].

Differential of Culture-Negative Peritonitis

The incidence of culture-negative peritonitis has decreased with improvement in culture techniques. The culture negative rate should be less than 20%; higher rates suggest issues with culture technique [145]. Reculturing sometimes yields an organism [187]. There is debate about the causative organism in these cases, but most studies implicate Gram-positive organisms and the incidence has decreased with the use of the Y-set [37, 188, 189].

Another etiology of culture-negative peritonitis is the use of antibiotics at presentation either surreptitious or for another infection. One study found that in one-third of the culture-negative cases there was antimicrobial activity in the dialysate [190]. Though antibiotic use is a potential cause of negative cultures that should be explored with patients, it is notable that this study had a particularly high rate of culture-negative peritonitis. Culture-negative peritonitis can also be secondary to unusual or difficult-to-culture organisms, such as mycobacteria or some fungi. These cases do not respond to antibiotics, though there may be an early response of mycobacterial infections to quinolones [191].

Pancreatitis can also present as abdominal pain with an increased cell count. Peritoneal fluid amylase >100 U/L can help differentiate pancreatitis from usual peritonitis [192]. However, other abdominal processes, such as ischemic bowel and small bowel perforation, can also produce an elevated amylase in the dialysate [192, 193]. Rare causes of culture-negative peritonitis are chemical peritonitis from medications (Vancoled brand vancomycin, amphotericin, thrombolytics) or presence of endotoxin in the dialysate [194–202]. Icodextrin can also lead to cloudy effluent [163, 203–205]; if this is suspected, stopping the icodextrin will resolve the cloudy effluent.

Treatment

Initial Regimen

Once cultures have been sent, antibiotics should be started promptly. Hospitalization is generally based on severity of illness, such as hypotension, need for intravenous fluids, and parenteral narcotics. Pain control is important and is often neglected [206]. Intraperitoneal antibiotics are generally preferred as this route may be more effective than the intravenous route, and certainly results in high local levels [207]. There are many published antibiotic regimens for PD peritonitis. In an effort to standardize the treatment of PD peritonitis the Advisory Committee on Peritoneal Management of the International Society for Peritoneal Dialysis reviewed the literature and published guidelines. The

guidelines are periodically updated as new information on peritonitis and its treatment becomes available. In 1993, the committee's recommendation for empirical antibiotics was vancomycin plus ceftazidime or an aminoglycoside [208]. However, as concern for vancomycin-resistant organisms increased, the committee updated the recommendations in 1996 to decrease the routine use of vancomycin, and recommended first generation cephalosporins with an aminoglycoside [209]. The most recent update in 2005 recognized that this general recommendation was not adequate for programs with high rates of methicillin-resistant organisms [145]. Methicillin resistance varies from program to program. Therefore, the updated guidelines recommend that the choice of empiric antibiotics be made in light of the patient's and program's history of microorganisms and sensitivities.

Figure 19.5 summarizes the guidelines' initial empirical therapy. The guidelines advocate the use of a drug that covers Gram-positive organisms plus an antibiotic for Gram-negative coverage, including *Pseudomonas*. The actual choice of which antibiotics to use should be based on program organism sensitivity patterns. If there is a high prevalence of methicillin resistance, the recommendation is vancomycin plus a second medication for Gram-negative coverage. The Gram-negative coverage can be obtained with an aminoglycoside, cefepime, aztreonam, or ceftazidime. In general, although both oral and intravenous quinolones have good peritoneal penetration, they do not cover a large proportion of isolates and should not be used for empiric therapy alone, unless local sensitivities support its use. Short courses of intermittent aminoglycosides appear to be safe for empiric antibiotic use, but prolonged or repeated courses should be avoided. If an aminoglycoside is used, it should not be administered in the same exchange as a penicillin, as they are not compatible.

Subsequent antibiotic therapy is based on the culture results (see Table 19.7 for dosing of antibiotics [25, 145, 208, 210]. Both continuous and intermittent therapy dosing are given, and there are not enough data to recommend one regimen over another. Intermittent dosing is more convenient, and may be associated with less toxicity from the aminoglycoside. Once-daily dosing is also applicable to APD, where the antibiotics can be given in the long day dwell (at least 6 h), although few data exist. A randomized multi-center trial in children, many of whom were on cyclers, demonstrated that intermittent administration was as effective as continuous with use of vancomycin or teicoplanin [211]. However, there is concern that intermittent dosing of cephalosporins will lead to periods overnight where the antibiotic level is below the minimal inhibitory concentration (MIC), especially in the presence of significant residual renal function [212]. This theoretically can lead to induction of resistance [213].

Subsequent Regimen

Gram-Positive Organisms

If a Gram-positive organism, especially coagulase-negative *Staphylococcus* or other skin organism, is isolated, the patient should be questioned about a break in technique and a review of connection technique should be made. If *Pasteurella* grows, then the patient should be questioned about cats in the area of the dialysis procedure, as this is often due to cats playing with the tubing. Touch contamination can also lead to polymicrobial Gram-positive peritonitis, which has a better prognosis than polymicrobial Gram-negative peritonitis. The course for various Gram-positive organisms differs and is summarized below.

Coagulase-Negative Staphylococcus and Other Gram-Positive Skin Organisms

If the organism isolated is a diphtheroid, *Corynebacterium* or *Bacillus*, a first-generation cephalosporin for 14 days is generally sufficient. In the case of coagulase-negative *Staphylococcus,* the course depends on whether the organism is methicillin-resistant. Methicillin-sensitive organisms can be treated with cefazolin and the cure rate is equivalent to vancomycin [214]. The cure rate for methicillin-resistant organisms is much lower with cefazolin (versus vancomycin) [214]. If cephalosporins are the empirical therapy the patient should be changed to vancomycin once methicillin-

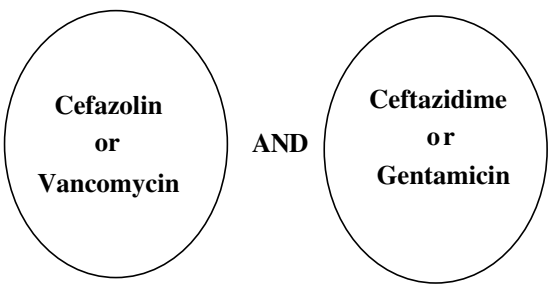

Fig. 19.5 Approach to empiric antibiotic therapy for PD-related peritonitis according to the International Society for Peritoneal Dialysis 2005 guidelines [145]

Table 19.7 Dosing of commonly used intraperitoneal antibiotics for peritonitis*

	Intermittent**	Continuous closing**
Cephalosporins		
Cefazolin	15 mg/kg 20 mg/kg for APD	500 mg load then 125 mg/L
Cephalothin	15 mg/kg/day	500 mg load then 125 mg/L
Cefepime	1 g/day	500 mg load then 125 mg/L
Cephadrine	15 mg/kg/day	500 mg load then 125 mg/L
Ceftazidime	1000–1500 mg/day	250 mg load then 125 mg/L
Ceftizoxime	1000 mg/day	250 mg load then 125 mg/L
Ceftriaxone	1 g/day	250 mg load then 125 mg/L
Aminoglycosides		
Amikacin	2 mg/kg	25 mg load then 12 mg/L
Gentamicin	0.6 mg/kg	8 mg load then 4 mg/L
Netilmicin	0.6 mg/kg	8 mg load then 4 mg/L
Tobramycin	0.6 mg/kg for CAPD For APD 1.5 mg/kg load then 0.5 mg/kg in long dwell	8 mg load then 4 mg/L
Penicillins		
Ampicillin	Data on i.p. not available	125 mg/L
Oxacillin	Data on i.p. not available	125 mg/L
Nafcillin	Data on i.p. not available	125 mg/L
Amoxicillin	Data on i.p. not available	250—500 mg/L load then 50 mg/L
Quinolones		
Ciprofloxacin	Data on i.p. not available (can give p.o. 500 b.i.d.)	50 mg/L load then 25 mg/L
Other antibiotics		
Vancomycin	15–30 mg/kg, up to 2 g/day every 5–7 days	1 g load then 25 mg/L
Clindamycin	Data on i.p. not available	300 mg/L load then 50 mg/L
Imipenem/cilistatin	1 g b.i.d.	500 mg/L load then 200 mg/L
Teicoplanin	15 mg/kg every 5–7 days	20 mg/L
Aztreonam	1,000 mg	1000 mg/L load then 250 mg/L
Ampicillin/sulbactem	2 g every 12 h	1000 mg/L lad then 100 mg/L
Quinupristin/dalfopristin	25 mg/L in alternate bags given in conjunction with 500 mg iv bid	500 mg/l load then 200 mg/L

*Adapted from [25, 145, 208, 210]b
**If significant residual renal function (urine output >100 mL/day), dose should be increased by 25%. i.p., Intraperitoneal; p.o., per os.; APD, automated peritoneal dialysis

resistant organisms are identified. Coagulase-negative staphylococcus can cause biofilm and inadequate antibiotic levels may lead to relapsing peritonitis [215]. The systemic level of vancomycin is generally about twice the level in the effluent and this should be remembered in determining dosing interval. Redosing should occur once the serum level reaches 15 μg/mL to avoid relapse [145, 216].

Staphylococcus aureus

In the majority of cases, *S. aureus* peritonitis is associated with a catheter infection or colonization [122, 124, 137, 217]. The peritonitis tends to be severe and patients often require hospitalization [133, 137]. If *S. aureus* catheter infection is present in conjunction with *S. aureus* peritonitis, the catheter should be removed promptly. Once the culture returns, the subsequent antibiotic regimen also depends on whether the organism is methicillin sensitive. If the organism is methicillin sensitive, the antibiotics can be switched to an anti-staphylococcal penicillin or the first-generation cephalosporin be continued [145]. If vancomycin was used empirically, the antibiotics should be switched to avoid prolonged vancomycin use. Rifampin, for up to 1 week, can be added if desired, or if the response to treatment is slow [145]. If the organism is methicillin resistant, the antibiotics should be changed to vancomycin (or teicoplanin). The vancomycin should be dosed approximately every 5 days with more frequent dosing for those with residual renal function. Trough vancomycin levels can help guide therapy with redosing when the level falls to less than 15 μg/mL [145, 216]. Treatment failure for MRSA is higher than for methicillin-sensitive staphylococcal infections [120]. Antibiotics should be continued for 21 days [145].

Streptococcal

Most cases of Streptococcal peritonitis are secondary to *S. viridans*, followed by *Enterococcus*. Streptococcal peritonitis tends to be more severe with much more pain than episodes due to coagulase-negative *Staphylococcus* [136]. Beta-hemolytic streptococcal peritonitis can be particularly severe, leading to shock and death [42, 218]. Nonenterococcal streptococcal peritonitis responds well to ampicillin and first-generation cephalosporins [145]. The response to these antibiotics appears to be better than the response to vancomycin [145]. Antibiotics should be continued for 14 days [145]. Pain, often severe, must be adequately treated [206].

Enterococcal infections are slower to respond to antibiotics. If sensitive, ampicillin 125 mg/L in each exchange is the preferred antibiotic, to avoid selection of vancomycin-resistant *Enterococcus* (VRE) [145]. Once-daily, low-dose aminoglycosides may be synergistic. *Enterococcus* is part of the gastrointestinal flora; peritonitis should lead to consideration of work-up for abdominal pathology [67, 219]. The incidence of VRE varies from unit to unit, but is a growing problem [220–225]. The prevalence is increased by prior use of antibiotics, especially vancomycin, and hospitalization [221–223]. Linezolid or quinupristin/dalfopristin should be used. Quinupristin/dalfopristin is not effective against *E. faecalis* [145, 224]. Prolonged courses of linezolid can lead to bone marrow suppression and neurotoxicity [145, 224].

Gram-Negative Peritonitis

General Considerations

Once the organisms and the antibiotic sensitivity have been determined, the antibiotics should be adjusted if possible to avoid long-term aminoglycosides, given the risk of ototoxicity and vestibular toxicity [226, 227]. The choice of antibiotics should be based on sensitivities. The aminoglycosides may differ in risk of ototoxicity and vestibular toxicity, and the risk of toxicity may increase with repeated courses [228, 229]. A review in patients without renal failure found that the risk of ototoxicity was 14% for amikacin, 8% for gentamicin, 6% for tobramycin, and 2.5% for netilmicin [229]. The risk for vestibular toxicity was similar for gentamicin, amikacin, and tobramycin at around 3–4%, with netilmicin around 1.5%. However, there are few data for patients on PD. In a study examining the development of ototoxicity using tobramycin, hearing declined in 25% but improved in 17.5% [230].

The most common organisms isolated in non-Pseudomonal Gram-negative peritonitis are *Klebsiella, Escherichia coli*, and *Enterobacter* [69, 231]. The presentation is more severe than that seen with coagulase-negative *Staphylococcus*. Gram-negative peritonitis is associated with higher rates of death, hospitalization, catheter loss, and transfer to hemodialysis than peritonitis with Gram-positive organisms [2, 16, 69, 232]. This is also true for episodes not associated with abdominal perforation.

In uncomplicated episodes the antibiotics should be continued for 2 weeks [145]. Infections with *Acinetobacter* and *Stenotrophomonas* (formerly *Xanthomonas)* can be difficult to treat. *Acinetobacter* is associated with high prevalence of antibiotic resistance and relapse, and is best treated with two antibiotics for 3 weeks [233, 234]. *Stenotrophomonas* also produces serious infections and should be treated with two antibiotics for a duration of 3–4 weeks [145, 235].

Multiple enteric pathogens or the presence of an anaerobe suggest intra-abdominal pathology and the need for surgical evaluation [31, 236]. If a patient with single-organism peritonitis is not responding to appropriate therapy, this should also prompt an evaluation [237]. Patients may initially respond to antibiotics but then deteriorate [67]. Unlike the case with routine peritonitis, bacteremia is not uncommon with peritonitis associated with abdominal processes [68, 238]. In cases of an enteric source of peritonitis (e.g., due to cholecystitis), the recommended antibiotics are metronidazole with ampicillin and ceftazidime or an aminoglycoside [145].

Pseudomonas

Unlike other Gram-negative organisms, *Pseudomonas aeruginosa* peritonitis is commonly associated with catheter infections [239, 240]. Both current and prior episodes of *Pseudomonas aeruginosa* exit-site infection predispose to peritonitis. One study found that 22% of patients with a history of *Pseudomonas* exit-site infection developed peritonitis after resolution of the exit-site infection [241]. If a patient presents with *Pseudomonas* peritonitis, the exit site and tunnel should be examined for infection, which can be subtle. If present, the likelihood of cure without catheter removal is low, and the catheter should be removed [52, 145]. Peritonitis should be treated with two anti-pseudomonal antibiotics [145]. The duration of antibiotics should be 21 days.

Fungal

The optimal treatment of fungal peritonitis is not known. The mortality rate associated with fungal peritonitis is high in children and adults, varying from 20–45% [27, 28, 30, 242–244]. There are reports of successful treatment of fungal

peritonitis without catheter removal, but most patients will ultimately lose their catheter [27, 29, 30]. Larger series have found a cure rate without catheter removal of approximately 10% using fluconazole [245–247]. However, the mortality is high if the catheter remains in place. In the largest reported series, Wang et al. examined the outcome of 70 cases of fungal peritonitis. The treatment regimens varied over time, though most received fluconazole with or without flucytosine [244]. The survival in those whose catheter was removed 71 versus 9% in those whose catheter was not removed, though the series was uncontrolled. The survival was even better if the catheter was removed within 24 h of diagnosis. Similarly, Goldie et al. found that the survival was better if the catheter was removed within 1 week of diagnosis (85 versus 50%) [28]. In that study, the treatment regimen was mainly amphotericin based.

Given the poor outcome, the 2005 guidelines recommend removing the catheter promptly for fungal peritonitis [145]. There are no controlled trials of antifungal therapy. Possible agents are amphotericin, caspofungin, fluconazole, and voriconazole. Amphotericin (0.5 mg/kg/day intravenously ± 1–2 mg/L intraperitoneally) was used in older series, but more recently the azoles have been used [28, 244, 248, 249]. The azoles can be given orally, intravenously or intraperitoneally. However, resistance to azoles has been reported and therefore sensitivities should be checked if possible. 5-Fluorocytosine, where available [50 mg/L intraperitoneally or 1 g per os q.d.), is often added for synergy [142, 214]. If fluorocytosine is used, it is necessary to monitor serum levels to avoid bone marrow toxicity. Therapy should generally be continued after catheter removal for an additional 10 days [145]. Some patients, after catheter removal and treatment, may be able to return to PD but the incidence of adhesions is high and most will need to remain on hemodialysis [29, 244]. The ability to return to PD might be improved by prompt removal of the catheter and antifungal therapy, but this is controversial [244, 250].

Mycobacterium

Mycobacteria are rare causes of peritonitis that require a high index of suspicion for diagnosis. Acid-fast bacilli smears are usually negative, though the ability to detect positive smears can be enhanced by centrifuging 100–150mL of dialysate and examining a smear from the pellet [145]. Cultures, when obtained, are positive, but growth is slow, delaying the diagnosis [35, 154]. The number of reported cases is low, but the disease may respond to standard antimycobacterial therapy [35]. In general, treatment is based on regimens used for extrapulmonary tuberculosis (rifampin, isoniazid, pyrazinamide, ofloxacin plus pyridoxine) [145]. Streptomycin and ethambutol are avoided due to toxicity in end-stage renal disease [145]. CAPD continuation is occasionally possible but ultrafiltration failure may occur [35, 251]. Many patients will have had their catheter removed for unresolving peritonitis before the diagnosis is made. Peritonitis with non-tuberculous mycobacterium, mainly *M. fortuitum*, has been reported and can respond to appropriate antibiotics [252].

Culture-Negative

If, after 96 h, the culture is negative but the patient is responding to therapy (elevated cell count has resolved) and the Gram stain did not reveal a Gram-negative organism, the original antibiotics regimen can be continued, but aminoglycoside should be discontinued. Antibiotics should then be continued for a total of 14 days [145]. If the patient is not responding, the Gram stain and culture should be repeated and special culture techniques should be used for unusual organisms [145, 187]. If this does not reveal an etiology for the apparent failure of antibiotics, the catheter should be removed.

Follow-Up

General

Clinical response is generally seen in 3–5 days, though this is organism-dependent. The dialysate leukocyte count in uncomplicated peritonitis normalizes in 4–5 days [12]. If there has been no improvement by 96 h, re-evaluation is essential. Reculturing might yield an organism not covered by the chosen antibiotics. The patient should be assessed for intra-abdominal pathology or enteric source; the catheter should be evaluated for infection. Unresolving peritonitis predicts a poor outcome and catheter removal is imperative [253, 254].

Catheter Removal

The indications for catheter removal during peritonitis are listed in Table 19.8. Usually, a period of 2–4 weeks between catheter removal and insertion of a new catheter is advocated, to avoid reinfection [145, 255, 256]. However, this requires temporary transfer to hemodialysis, which can be inconvenient for the patient and problematic for young

Table 19.8 Indications for catheter removal during peritonitis

Remove catheter
Refractory
Enteric associated with intra-abdominal process
Fungal
Consider simultaneous replacement of catheter
Relapsing
Catheter-related

children [257]. Experience is growing on simultaneous removal and replacement of catheters for relapsing or recurrent peritonitis [257–265]. To do this safely, the peritoneal WBC count should be less than 100/μL and antibiotics continued for 10 days after the WBC normalized or 7 days after surgery [263]. This simultaneous technique appears to be more successful for Gram-positive peritonitis than for *Pseudomonas* or fungal peritonitis [260, 262]. In one small series a dialysate WBC count <200/μL at the time of the procedure predicted success with *Pseudomonas* infections [259]. In many cases hemodialysis was avoided with the simultaneous procedure [260, 263, 265].

Delayed removal of the PD catheter in refractory peritonitis to 10 days or longer, leads to a very high risk of patient death (approximately 1/3) and to peritoneal membrane failure when the patient attempts return to PD [266] (Fig. 19.6).These results suggest that if the patient is failing to respond to appropriate antibiotics by 5 days, the catheter should be removed more expeditiously [254]. This approach is associated with a considerably lower morbidity.

Relapsing Peritonitis

In relapsing peritonitis, peritonitis with the same organism recurs after completion of antibiotics. Most cases are secondary to the presence of a subcutaneous tunnel infection or involvement of slime layer on the intra-abdominal catheter [58]. In rare cases relapse is secondary to the presence of an abdominal abscess [58]. Relapse may also be secondary to inadequate treatment of the prior infection. Underdosing of antibiotics increases the risk of relapse. Mulhern et al. found that in patients treated with once-weekly vancomycin a low trough level predicted relapse (9/14 with 4-week mean trough <12 mg/L relapsed versus 0/17 > 12 mg/L) [216]. It is important to consider a patient's weight (and hence volume of distribution) and residual renal function when dosing antibiotics. In cases of relapsing peritonitis, the catheter should be removed and as discussed above the catheter can generally be replaced as a simultaneous procedure, allowing the patient to avoid HD or minimize time on HD.

In some cases relapse is secondary to harbouring of bacteria in a catheter biofilm. Once a tunnel infection has been ruled out, the cases may respond to intraperitoneal thrombolytics in addition to antibiotics. Urokinase, streptokinase, and, more recently, tissue plasminogen activator have been used, though urokinase is not currently readily available [267–271]. This treatment is most successful for coagulase-negative *Staphylococcus* or culture-negative peritonitis [271]. The cure rate has been reported to be 50–65% in selected patients, though this is lower than with catheter removal [194, 268–270]. In addition, a recent randomized trial of the use of intraperitoneal urokinase in individuals with peritonitis resistant to empiric antibiotics did not reveal a benefit [272]. If the peritonitis does not respond, the catheter should be removed. This can be replaced as a single procedure if the effluent can first be cleared of white cells.

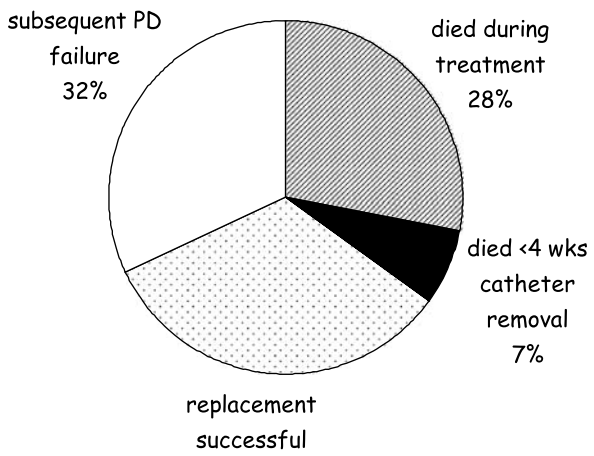

Fig. 19.6 Outcome of peritonitis episodes that fail to respond to antibiotics. Outcomes listed are died during initial therapy before catheter was removed, died within 4 weeks after catheter was removed and before new catheter could be reinserted, attempt at reinsertion of PD catheter unsuccessful and successful reinsertion of PD catheter with resumption of peritoneal dialysis. Data derived from [266]

Outcome and Sequelae

Resolution

From 60 to 90% of episodes resolve with antibiotics [133, 254, 273–275]. The rates of resolution are higher in the absence of an exit-site or tunnel infection. Catheter removal rates are higher for *S. aureus* and Gram-negative infections [52]. The higher rate of catheter removal for *S. aureus* is secondary to catheter infections, as the rate of removal in the absence of a catheter infection is similar to coagulase-negative *Staphylococcus* [69].

Abscess Formation

Abscess formation occurs in less than 1% of episodes of peritonitis [276]. The patients tend to present with abdominal pain, nausea, vomiting, and peripheral leukocytosis [276]. The organisms reported are Gram-negative, fungus, and *S. aureus* [58, 276]. CT scan or ultrasound is helpful in making the diagnosis. The disease responds to drainage.

Transfer to Hemodialysis (Technique Failure)

Peritonitis is a major cause of technique failure in PD patients, accounting for 30–80% of permanent transfers [4, 277, 278]. The data on whether technique failure secondary to peritonitis has declined with the decline in overall peritonitis rates are conflicting [7, 279]. The Y-set reduced peritonitis, but did not significantly impact technique survival in all studies [4, 189]. Peritonitis from coagulase-negative *Staphylococcus* and other skin organisms tends to be less severe, and as a result reduction in touch contamination has less of an impact on technique survival. Severe episodes of peritonitis are associated with decreasing albumin from increased protein losses, poor intake and inflammatory response [18, 280]. This is associated with a worse long-term outcome. Prompt transfer to hemodialysis is appropriate in severe, poorly responding episodes of peritonitis.

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is an uncommon but serious complication of PD. The frequency is variable but tends to increase with longer time on PD [281–284]. This entity is not infectious, but patients present with abdominal pain, nausea and vomiting, bowel obstruction and malnutrition and sometimes low grade fever [281, 285]. A loss of ultrafiltration is seen [281, 285]. The disease can present after transfer to hemodialysis or transplantation as ascites. Recurrent peritonitis may be a predisposing factor, but this is not a consistent finding. Nomoto et al. found that those with EPS had a 3.3 times higher peritonitis rate than those without, but Hendriks et al. found that the rates were not different [285, 286]. In a recent study by Yamamoto et al., the two independent risk factors associated with EPS were membrane transport characteristics and number of peritonitis episodes [284]. The pathogenesis is a fibrotic reaction of the peritoneum. It may not be recurrent peritonitis alone but a severe episode that is important [287], especially after a fairly long period on PD. This is supported by Davies et al., who found that ultrafiltration tends to decline with time on PD and is worsened and accelerated by severe or closely spaced episodes of peritonitis and to use of higher dextrose dialysate [288].

Death

Peritonitis results in death in 1–6% of episodes [9–11, 289]. The immediate cause of death is often cardiovascular [9] and patients with cardiovascular disease appear to be at increased risk of death after peritonitis [18]. The mortality rate for Gram-negative and fungal peritonitis is significantly higher (4–10% for Gram-negative, 20–45% for fungal) [9, 28, 69, 232, 242, 244] (Fig. 19.7). Mortality associated with bowel perforation approaches 50% [67, 68]. In contrast, the mortality associated with coagulase-negative *Staphylococcus* peritonitis is less than 1% [232]. There is a high mortality rate in the first year after transfer to hemodialysis, which may be related to poorer nutrition in those with severe peritonitis episodes [4]. Lower albumin levels are associated with increased mortality after peritonitis [290], but this may be related to the increased protein losses with severe peritonitis and not pre-existing malnutrition. Elevated C-reactive protein levels also predict death after peritonitis [9], so another explanation for the reason lower albumin predicts death is inflammation.

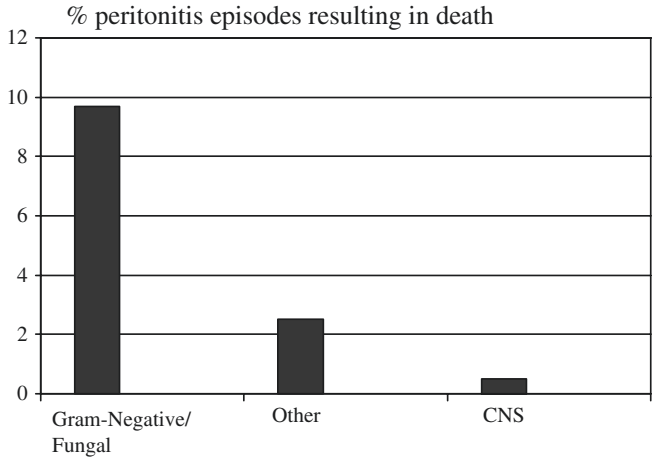

Fig. 19.7 Mortality of peritonitis by organism. Rates expressed as percentage associated with death per episode. CNS = Coagulase-negative *Staphylococcus*. Data derived from [232]

Prevention

General

Training of patients in the PD technique by experienced nurses is critical. Dryden et al. found that a preventative program decreased the risk of exit-site infection (10-fold), peritonitis rate (2-fold), and catheter loss (4.5-fold) [291]. The program was directed at *S. aureus* nasal carriage, intensive training of nurses, and aseptic techniques for catheter insertion and care. A recent study found that a standardized training curriculum reduced exit site infection rate (0.22 versus 0.38 episodes per patient year ($p = 0.003$), with a trend toward lower peritonitis rates (0.33 versus 0.44 episodes per patient year, $p < 0.10$) [106]. In terms of training, patients should be instructed to wear masks during exchanges. Careful hand-washing with antibacterial soap, and complete drying of the hands, decreases the skin bacterial count by 95–99%, thus reducing the potential transfer of bacteria [292]. The room where exchanges are performed should be isolated from heavy traffic. Pets should be excluded from the room in which exchanges are performed as bacterial transmission from pets has been reported [44–50]. The ISPD web site has a video program on teaching nurses how to instruct patients on the proper PD technique, freely available without charge to all at ispd.org.

Tubing changes should be performed by nurses, not patients [293]. Connection technology for CAPD using a twin-bag system or APD should be utilized. In areas where prespiked APD bags are not available, the spike assist device for APD may also decrease rates [116]. Aggressive nutritional intervention in children may decrease the peritonitis rate [294]. We provide prophylaxis for technique-related contaminations with cefazolin or cephalexin, as well as prophylaxis for invasive procedures [295].

Prevention of Catheter-Related Peritonitis

The use of prophylactic antibiotics at the time of insertion is recommended by the ISPD guidelines [145]. There have been four randomized prospective trials. Gadallah et al. randomized catheter procedures into three groups: vancomycin (1 g intravenously approximately 12 h before catheter placement, $n = 86$), cefazolin (1 g approximately 3 h before catheter placement, $n = 85$) or no antibiotics ($n = 83$) [296]. One patient developed peritonitis in the vancomycin group within 14 days of the procedure versus 6 in the cefazolin group and 10 in the group who did not receive antibiotics. This suggests that vancomycin may be more effective than cefazolin. Two other studies showed a benefit of preoperative antibiotics using cefuroxime (1.5 g intravenously, 250 mg intraperitoneally) or gentamicin (1.5 mg/kg intravenously) [297, 298]. In both cases the incidence of peritonitis was lower in the first month after insertion. In contrast, Lye et al. found no benefit using gentamicin (80 mg) and cefazolin (500 mg) [299].

No particular catheter has been definitively shown to have lower infection rates than the standard silicon Tenckhoff catheter. Double-cuff catheters should be utilized, with a downward or lateral directed exit site [19, 256, 300]. Swimming should be avoided after catheter insertion, until the catheter is healed, and swimming in lakes and ponds completely avoided. Exit-site infections should be treated promptly. We have found that patients with untreated well water at home are at increased risk for *Pseudomonas* exit-site infections, and we instruct these patients to use bottled water for exit-site care.

Specific Organism Prophylaxis

Dental Procedures

Oral procedures have a high incidence of transient bacteremia, though the inoculum is generally low [77]. Peritonitis after dental procedures has been reported in children and adults [75, 76]. Though there are no prospective trials, we would recommend prophylaxis prior to dental procedures, using American Heart Association guidelines [295].

Staphylococcus aureus

S. aureus nasal carriage increases the risk of peritonitis as well as exit-site and tunnel infections [117–119, 121, 301]. There have been a number of studies examining the effect of prophylaxis on peritonitis; these regimens are summarized in Table 19.9. All the regimens decrease the rate of infection. The results of the randomized trials using mupirocin or rifampin (versus no treatment) in adults are shown in Fig. 19.8. In a study directly comparing exit-site mupirocin to cyclical rifampin every 3 months, both were equally effective but the incidence of side-effects was greater with the rifampin [131]. A recent randomized controlled trial of exit site mupirocin versus exit site gentamicin found similarly low *Staphylococcus aureus* catheter infection rates (0.06 versus 0.08 episodes/pt year for mupirocin versus gentamicin, respectively) [21]. The low rate of *S. aureus* catheter infections was accompanied by a low rate of *S. aureus* peritonitis in both arms as well. The overall peritonitis rate was lower in the gentamicin group compared to the mupirocin group due to a decrement in other organisms (0.34 versus 0.52 episodes/patient year) (Fig. 19.9).

In two studies utilizing mupirocin at the exit site versus no treatment, all patients were treated regardless of nasal carriage status [131, 132]. In contrast, the nasal mupirocin trials treated carriers only [121, 130, 302]. Most of the nasal mupirocin trials required subsequent surveillance cultures and retreatment of those who became recolonized [121, 130]. The recolonization rate is high after mupirocin or rifampin treatment, with 40–55% recurrence at 3 months and 60% at 12 months [130, 303, 304]. The Mupirocin Study Group, in contrast, initially screened patients for nasal carriage (two-thirds positive cultures) and then treated identified carriers with nasal mupirocin for 5 days every month regardless of subsequent nasal culture results [302]. Given the cost of frequent cultures, this may be a more economical approach but did not reduce *S. aureus* peritonitis rates, just exit site infection rates. The definition of carrier varied between the studies, but a conservative definition is one positive of three serial cultures [131]. Persistently positive nasal cultures (two or more out of three) are associated with a greater risk of infection, but the staphylococcal peritonitis rate is still elevated with one positive culture (compared to noncarriers) [119]. Exit site prophylaxis may be preferred as one study found that the strains of S. *aureus* isolated from the exit site may not be the same as the nose, indicating that the nose is not the only source of colonization [122]. Since publication of the studies demonstrating efficacy of mupirocin, a number of studies using historical controls have found that mupirocin is effective at decreasing exit site infection and peritonitis rates [304–307].

Table 19.9 *Staphylococcus aureus* prophylactic regimens

	Reference
Rifampin (carriers)	
Adults:	
600 mg/day × 5 days every 3 months	[129, 131]
Children:	
300 mg/day for children <30 kg, 600 mg/day for >30 kg	[303]*
20 mg/kg/day in two divided doses	[128]**
Exit-site mupirocin	[131, 132]
Daily as part of routine exit-site care for all patients (not studied in children)	
Nasal mupirocin	
2% b.i.d.–t.i.d. × 5–7 days for carriers with retreatment for recolonization based on cultures (adults and children)	[121, 130, 304]
2% b.i.d. for 5 days each month in carriers	[302]
Anti-Pseudomonal antibiotics, covering Staphyloccocus (not studied in children)	
0.1% gentamycin cream daily as part of routine exit-site care for all patients	[21]
0.5 mL (1 mg) ciprofloxacin otologic solution daily as part of routine exit-site care for all patients	[318]

*Pediatric trial; the rifampin was given with nasal bacitracin

**Pediatric trial; the mupirocin was given with cloxacillin

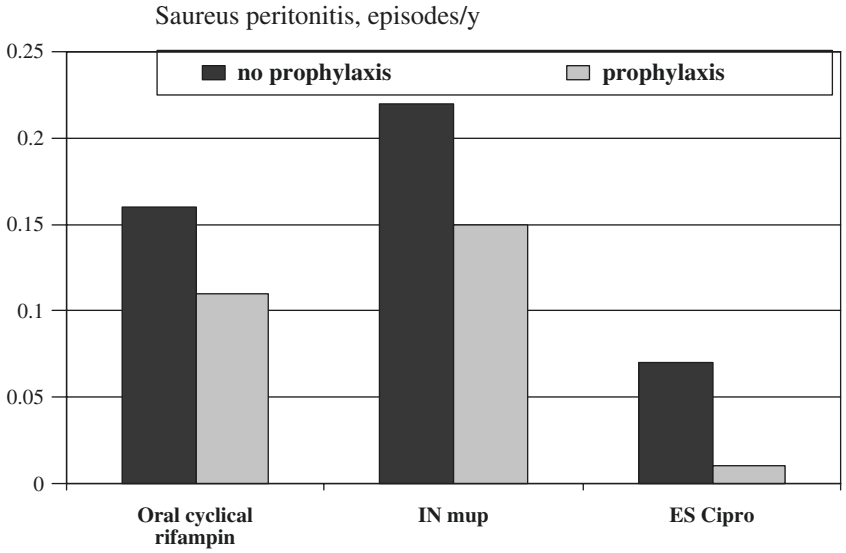

Fig. 19.8 Effect of staphylococcal peritonitis prophylaxis on peritonitis rates. Trials shown are randomized trials in adult trials only rifampin or mupirocin vs. no treatment or placebo. Data derived from [129, 302, 318]. ES mup = Exit-site mupirocin, IN mup = intra-nasal mupirocin

There are few side-effects associated with mupirocin, mainly nasal irritation and discharge for the nasal route [302]. Exit-site mupirocin ointment can degrade polyurethane and should be avoided with these catheters, which are rarely used [308]. Increased antibiotic resistance to mupirocin has been reported, though the prevalence varies among programs. Perez-Fontan found an increasing prevalence of mupirocin resistance over time [309]. In that program, mupirocin treatment was intermittent and based on surveillance cultures. Increased courses of mupirocin were associated with an increased prevalence of resistance. Resistance was not associated with an increased peritonitis rate, but there was an increase in exit site infection, raising the concern that in the future, mupirocin will be less effective. Mupirocin appears to be less effective for MRSA [310, 311].

Given the high morbidity associated with *S. aureus* peritonitis, each dialysis unit should establish a prophylactic regimen to prevent this infection. This might be cyclical intranasal application of mupirocin, daily exit-site mupirocin, or daily exit-site gentamicin. All appear to be effective in reducing *S. aureus* infections in PD patients, and the latter in addition reduces Gram-negative infections.

Fungal

Prior antibiotic use increases the risk of fungal peritonitis [22, 28, 98]. This introduces a potential target group for prophylaxis. Six trials have studied the effect of prophylaxis, though only one was a prospective, randomized trial. Five

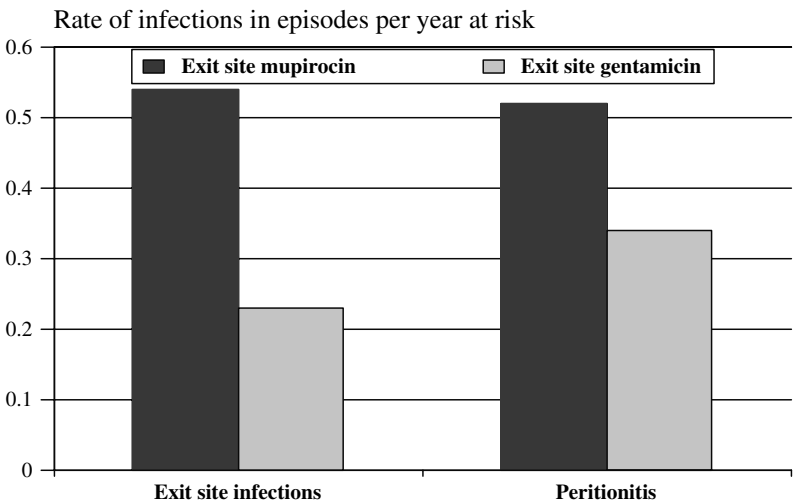

Fig. 19.9 Comparison of exit site infection rate and peritonitis rates with exit site mupirocin vs. exit site gentamicin. Data derived from [21]

trials utilized oral nystatin: 500,000 U tablet q.i.d., 500 IU t.i.d., or in children 10,000 U/kg/day in three divided doses during the antibiotic course [312–316]. Lo et al. randomized patients to either nystatin tablets during antibiotic courses or to control [313]. There was a decreased incidence of *Candida* peritonitis (1.9 versus 6.4 per 100 peritonitis episodes and 0.66 versus 1.43 per 100 antibiotic prescription for any indication) with prophylaxis. Two of the trials utilized ketoconazole (10 mg/kg per day in children) or fluconazole (200 mg on day 1, then 100 mg/day) [315, 317]. These studies, which had retrospective controls, also found a decreased incidence of fungal peritonitis. Two studies using either retrospective controls or compared one dialysis unit utilizing prophylaxis with another that did not, did not find that nystatin was effective [312, 314]. However, both of these units had low baseline fungal peritonitis rates and prophylaxis may be more effective when baseline rates are high. No side-effects of the prophylactic regimens were reported.

Gram-Negative

As most pseudomonal peritonitis is due to catheter infection, prophylaxis is possible. Two studies have investigated exit site antibiotics as a preventive measure to prevent peritonitis. Bernardini et al., randomized 133 individuals to exit site mupirocin or gentamicin cream [21]. The catheter infection rate and the peritonitis rate were lower in the gentamicin group. Of note, there were no pseudomonal exit site infections or peritonitis episodes in the gentamicin group, versus 6 catheter infections (0.11 episodes per patient year) and 2 peritonitis episodes (0.04 episodes per patient year) in the mupirocin arm. Both the pseudomonal and nonpseudomonal Gram-negative peritonitis rates were lower with the gentamicin, suggesting that some Gram-negative infections are related to catheter infections. Montenegro et al. randomized 164 individuals to exit site care with soap and water only versus exit site care with soap and water plus application of 1 mg ciprofloxacin (0.5 mL otologic solution) [318]. Ciprofloxacin reduced overall, Staphylococcal and Pseudomonal exit sites infection rates. Similar to the gentamicin trial, there were no episodes of Pseudomonal infections in the treated group.

Unfortunately, despite the morbidity and mortality associated with non-pseudomonal Gram-negative peritonitis, there are few effective interventions to reduce the incidence. Trials utilizing neomycin, cotrimoxazole, or cephalexin were not effective in decreasing peritonitis [319–321]. Constipation, a possible inciting event, should be avoided with a bowel regimen. Prophylactic antibiotics should be administered for endoscopic and gynecological procedures. The abdomen should be drained prior to procedures. Further research aimed at preventing non-pseudomonal Gram-negative peritonitis is necessary.

Quality Improvement

The ISPD guidelines state that a center's rate should be no more than 0.67 episodes per patient year (1 episode per 18 months) [145]. Each dialysis program should monitor individual patient and overall peritonitis rates. The presumed cause and organism patterns should be evaluated as part of a continuous quality improvement (CQI) program. Interventions directed at the cause of peritonitis should be made to prevent future episodes. CQI can involve training processes, retraining, exit site prophylaxis and treatment of contaminations. Borg et al. found that with a multifaceted quality improvement project, they were able to decrease the peritonitis rate from 1.6 episodes/patient year in 1998 to 0.3 episodes/patient year in 2002 [322]. Individuals with high peritonitis rates can be problematic. Technique should be reviewed and the patient retrained. A careful evaluation for an occult tunnel infection should be performed and consideration made for changing the catheter. If these maneuvers are not effective in decreasing the peritonitis episodes, then one should consider transfer to hemodialysis. With the maneuvers stated above, hopefully centers can achieve very low peritonitis rates and thus decrease the morbidity associated with these infections.

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Chapter 20
Noninfectious Complications of Peritoneal Dialysis

J.M. Bargman

Peritoneal dialysis is associated with a collection of complications unique to the modality but not involving infection of the peritoneal fluid, catheter, exit site, or tunnel. Some complications are related to increased intra-abdominal pressure, such as abdominal hernias and leaks of dialysis fluid. The long-term presence of dialysis fluid in the peritoneal cavity can result in a rare syndrome of encapsulating peritoneal sclerosis and other mechanisms of damage to the peritoneal membrane. Other complications are similar to those encountered in hemodialysis patients. Examples of these include dialysis-associated amyloidosis and acquired cystic disease of the kidney. This chapter will address these and other noninfectious complications of peritoneal dialysis.

Hernias

The presence of dialysis fluid in the peritoneal cavity leads to increased intra-abdominal pressure (IAP). Pressure within the abdomen increases in proportion to the volume of dialysate instilled [1–3]. The supine patient generates the lowest IAP for a given volume of intraperitoneal fluid. Even in the supine patient on automated peritoneal dialysis, intraperitoneal pressure correlates with the volume of instilled dialysate [4, 5]. Intermittent events such as coughing and straining result in transient high pressures. In addition, patients who are older, and those who are more obese, generate higher IAP for a given activity [1, 3].

In accordance with Laplace's law, the tension on the abdominal wall increases with the instillation of dialysate, as a result of the rise in IAP and the larger radius of the abdomen. Increased abdominal pressure and abdominal wall tension place mechanical stress on the supporting structures of the abdomen and can lead to hernia formation in those with congenital or acquired weakness or defects in the abdomen. The areas of weakness are probably very important in the pathogenesis of hernias. Indeed, the IAP in patients with hernias is no different from the pressure measured in those without hernias [6].

A host of hernias has been described in peritoneal dialysis (PD) patients [7–13]. The most common hernia is incisional or through the catheter placement site [10, 14, 15]; in other reports, inguinal or umbilical (Fig. 20.1) hernias occur most frequently [8, 16, 17]. Asymptomatic hernias are probably quite common and may not be detected until some complication such as bowel strangulation occurs. Different centers report a cumulative incidence of 10–15% of hernias in their PD patients [12]. A variation of hernias is the rare development of cystocele or enterocele [18], again likely related to the increased IAP. Patients with hernias tend to be older, female, multiparous, those who have experienced a higher frequency of postoperative leak at the time of catheter insertion, and those who have undergone a previous hernia repair [10]. Those with smaller body habitus may be predisposed, perhaps because the dwell volumes are not adjusted down proportionate to the body size [19]. The mean time for development of hernia is 1 year and the risk increases by 20% for each year on continuous ambulatory peritoneal dialysis (CAPD) [10]. Patients with polycystic kidney disease may be predisposed to hernia formation and leaks either as a result of higher IAP caused by the large kidneys or as a manifestation of a generalized disorder of connective tissue [20–23].

A major potential area of weakness is the abdominal incision for the implantation of the dialysis catheter. When this incision is made in the midline there is a predilection for incisional hernia to develop because this is an anatomically weak area [17]. Change to a paramedian incision through the rectus muscle has resulted in less perioperative leaks and hernia formation [24], although a recent meta-analysis did not report a difference in catheter complications after a paramedian versus central incision [25].

J.M. Bargman (✉)
University of Toronto General Hospital, Toronto, Ontario, Canada
e-mail: Joanne.Bargman@uhn.on.ca

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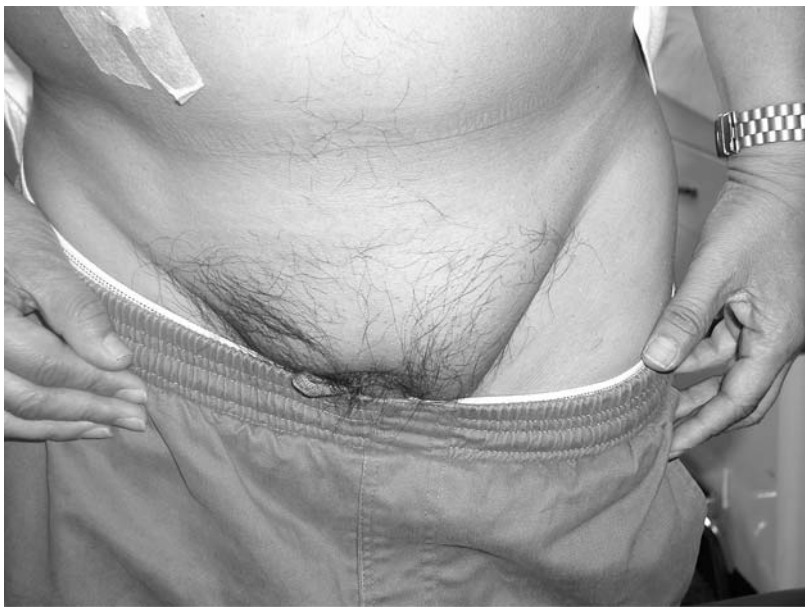

Fig. 20.1 Umbilical hernia in a peritoneal dialysis patient

Another area of potential weakness for herniation is the processus vaginalis. After the migration of the testes in fetal life, the processus vaginalis normally undergoes obliteration. Frequently this does not occur in the general population (and in males more than females), and the increased abdominal pressure during PD may push bowel, and dialysis fluid, into the processus vaginalis, resulting in an indirect inguinal hernia. Male pediatric patients may be predisposed to this complication, and if they develop a unilateral inguinal hernia, both sides should probably be repaired prophylactically [11].

Most hernias present as a painless swelling. Sometimes the patient may report a 'pop' during exertion when the hernia develops acutely. Rarely, bowel has been reported to herniate through the diaphragm at the foramen of Morgagni and present as a retrosternal air–fluid level or juxtacardiac mass [26].

The most worrisome complications are incarceration and strangulation of bowel. This can occur through almost any kind of hernia, but especially a small one [14, 27, 28]. Umbilical hernias may have a particular predilection for bowel strangulation [12]. Hernias may present as a tender lump, recurrent Gram-negative peritonitis, bowel obstruction, or perforation. Bowel incarceration or strangulation can mimic peritonitis [8], even without the supervening development of peritonitis, and this complication must be kept in mind, particularly if the site of herniation itself is not obvious (Fig. 20.2).

With the recent trend of emphasis on adequacy of small-solute transport, many patients are being prescribed larger volumes of dialysate such as 2.5 and 3.0 L fill volumes. As discussed, increased fill volumes are associated with increased IAP. It remains to be seen whether the higher fill volumes will lead to an increased incidence of hernias and dialysate leaks [23, 29, 30]. The higher pressures secondary to the larger volumes may possibly be offset by the growing trend of automated dialysis, wherein the patient dialyses mostly in the supine position. Two recent reports found no increase in the incidence of hernia with larger dialysis volumes, although there was also an increase in the use of cyclers, which may have confounded the effect [31, 30].

Treatment of Hernias

Hernias warrant surgical repair. Hernias diagnosed before the start of PD can be repaired at the time of catheter insertion [13, 32–36]. Although large ventral hernias carry little measurable risk of bowel incarceration [37], they are unsightly and are prone to enlarge. The defect in the abdominal wall integrity with these hernias also serves as a source of leak of dialysis fluid into the abdominal wall and surrounding structures (see below). The smaller hernias, especially umbilical hernias, should be repaired because of the risk of bowel incarceration and strangulation.

It is not usually necessary for the patient to be converted to hemodialysis around the surgical repair of a hernia [35, 38]. The patient can be maintained temporarily on "low-pressure" PD (smaller volumes in CAPD, day dry in APD) postoperatively to allow time for wound healing. For example, the CAPD patient would carry out their normal regimen up to the time of surgery. They should be drained for the surgical repair. Patients could be left without dialysis

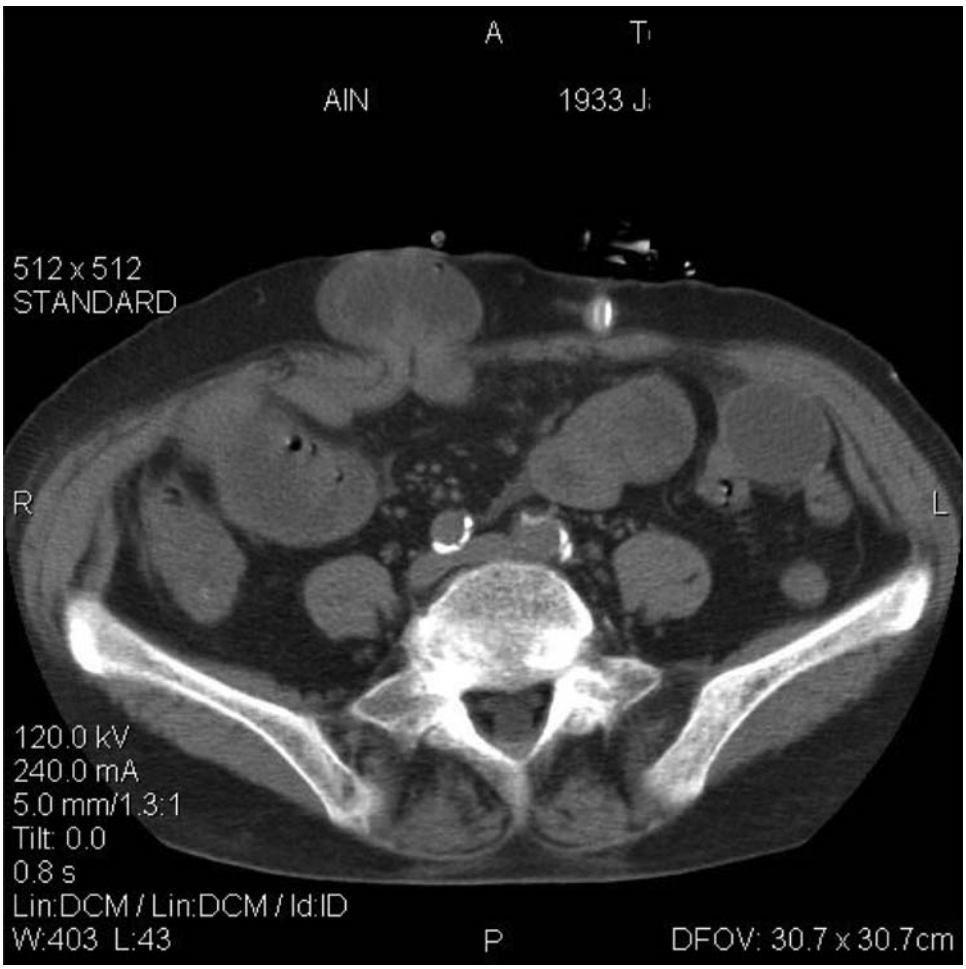

Fig. 20.2 Computerized tomographic (CT) scan of the abdomen in a patient with advanced sclerosing encapsulating peritonitis. Note the thickened, dense peritoneal membrane binding the bowel to the posterior aspect of the peritoneal cavity

for a day or two, and then start on 1-L exchanges. In the patient on cycler PD, 24–48 h after the repair they could restart night cycles, with a lower volume, and remain without dialysis during the daytime when they are ambulatory and thus subjected to higher IAP [38, 39–42]. Patients typically do not eat and drink a lot around the surgery, and we have not seen hyperkalemia as a result of using less than the usual PD prescription [38]. In the end, the decision about dialysis should be a medical one, but the risk of transient underdialysis must be weighed against the risk of insertion of an acute line for hemodialysis and the upheaval associated with the hemodialysis procedure itself.

Conventional hernioplasty may be followed by the insertion of an overlying polypropylene mesh to reinforce the hernia repair [39, 43–45]. The addition of the mesh may afford a quicker return to full-volume dialysis [40, 46]. Subsequent development of peritonitis does not appear to be complicated by mesh infection [43]. In the malnourished patient, even low-tension repair with a mesh can fail with recurrence of hernia [47]. If hernias recur, other options include changing the patient to night-time cycler dialysis, in which the patient dialyzes supine (and hence under lower IAP) with smaller daytime dwell volume, or, in the CAPD patient, using lower volumes of dialysate but with more frequent exchanges.

Genital and Abdominal Wall Edema

Edema of the *labia majora* or scrotum and penis is a distressing complication of PD. Early reports suggested that up to 10% of CAPD patients could experience genital edema [48–51], although more recent reports document a lower incidence of this complication [52, 53]. It appears that women have a much lower incidence of genital edema compared to men [52, 53]. This disparity may be the result of the processus vaginalis being patent more often in males; alternatively, labial swelling may not be as noticeable compared to swelling over the penis and scrotum. On the other hand, rarely

dialysate can dissect through the pouch of Douglas, the vaginal vault, or even travel through the Fallopian tubes and present with leakage through the vagina [54–57].

Two mechanisms have been suggested to explain genital edema [48]. First, dialysate can track through the soft-tissue plane from the catheter insertion site, from a soft-tissue defect within a hernia, or from a peritoneo-fascial defect. In any of these cases, genital edema can be associated with edema of the anterior abdominal wall and settle over the penis or *mons pubis*. Secondly, dialysis fluid can travel through a patent processus vaginalis to the labia or scrotum where it may leak into the surrounding soft tissue. This has been particularly described in young boys on PD [11]. If bowel accompanies the dialysate through the processus vaginalis, there will be an associated inguinal hernia; in fact, the presence of scrotal edema may suggest a clinically occult indirect inguinal hernia [58].

The presence of abdominal wall edema suggests that the origin of the peritoneal leak is proximal to the inguinal region in one of the potential sites listed above. On clinical examination, the patient should be standing. Asymmetry of the abdomen may indicate dialysis leak into the abdominal wall. Moreover, when the dialysate has dissected into the superficial structures of the abdomen, the abdominal wall can look pale and boggy. The skin indentations made by an elastic waistband, underwear, or by the catheter lying across the abdomen look deeper and more prominent than usual.

Diagnosis

Usually the patient who develops genital edema will bring it to medical attention. Sometimes they may misinterpret this development as indicative of general fluid overload and try to ultrafilter more fluid. The patient may complain of diminished effluent return, which in this case is not the result of a high transporter state. The patient should be carefully examined, and abdominal wall edema or asymmetry can be better appreciated when the patient stands only in their undergarments.

A CT scan with intraperitoneal instillation of dye in the dialysate may demonstrate the source of leak, especially a patent processus vaginalis or a clinically occult hernia [26, 59–65]. MR scanning may also be helpful if these facilities are available [66, 67], and since the study can be carried out with the dialysate used as the tracer, gadolinium, with its attendant risks, is not needed [68].

Treatment of Genital and Abdominal Wall Edema

Treatment of genital edema includes bed rest, scrotal elevation if symptomatic, and the use of frequent low-volume exchanges by cycler, if possible [48]. If this is not possible, and the patient needs dialysis, they should receive hemodialysis temporarily. In the case of abdominal wall leaks, cessation of PD for a week or two, or conversion to nocturnal PD (with dry days), for 2 weeks may be sufficient to allow healing of the leak [69]. Many or most patients can resume CAPD or could be converted to PD with lower IAP, such as with smaller volumes or by cycling in the supine position [70]. It is unclear whether antibiotics should be given prophylactically in the case of pericatheter leaks, but they are recommended in some centers [71].

There is some experience with infiltration of the catheter cuff in situ with fibrin glue to stop pericatheter leakage [72, 73]. If the source of leak is through the catheter tract, it should be discussed with the person responsible for insertion of the catheter. It is possible that not enough attention is being placed on the proper positioning and securing of the deep cuff (see Chapter 14).

Radiological and Isotopic Diagnosis of Hernias and Genital Edema

Computerized tomographic (CT) scanning can be helpful in diagnosing leaks and the cause of genital edema. Different agents (iopamidol, diatrizoate) have been employed in various volumes of dialysis fluid. It makes sense to use the largest volume tolerable in conjunction with manoeuvres to raise the IAP in order to facilitate fluid egress from the peritoneal cavity [59]. Peritoneal installation of radiocontrast dye with CT scanning detects more leaks and hernias compared to plain peritoneography without CT scanning [59, 62, 74, 75]. CT scanning can demonstrate collections of dialysate/dye in the anterior abdominal wall, which can track inferiorly and collect in the genitalia. Alternatively, dye can be visualized in the processus vaginalis as a cord-like structure and subsequent cuts can follow this inferiorly to the labia or scrotum. Within the scrotal sac it can often be discerned whether the contrast/dialysate forms a hydrocele or whether the fluid has dissected through the tunica vaginalis into the scrotal wall itself. We have rarely seen patients present with intermittently diminished effluent return, unchanged peritoneal transport parameters, and normal rapid

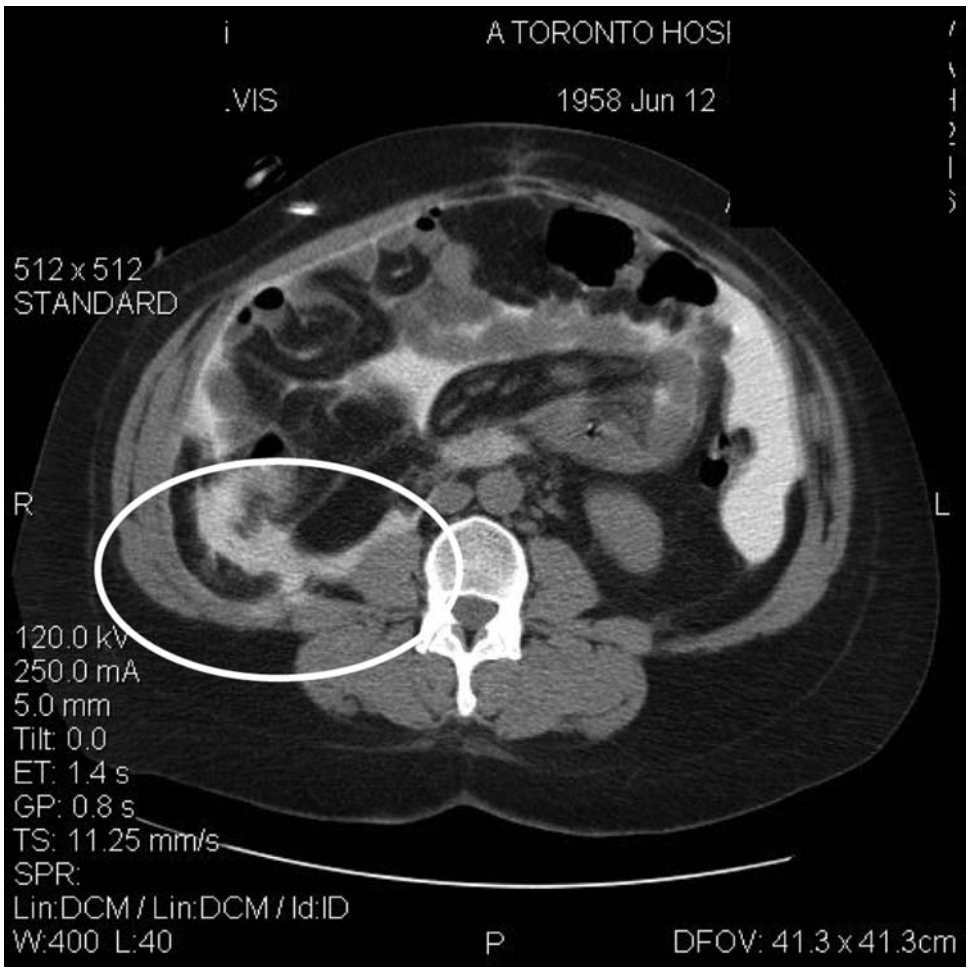

Figure 20.3 Advanced acquired cystic disease of the kidneys shown by CT scan. This long-term PD patient had small, shrunken kidneys at the start of dialysis. Reproduced from [330], with permission

inflow and outflow of a dialysate exchange. Physical examination does not reveal abdominal protuberance or tissue edema. CT scanning shows that the dialysate is leaking retroperitoneally. Presumably this is a slow leak, which explains why a rapid in and out exchange returns normal volumes (Fig. 20.3). It has been suggested that the patient should be taken off PD for a few weeks and then rechallenged. In the time off PD, the source of the leak (e.g., a tear in the peritoneum) may seal itself and PD can be resumed successfully [76].

Abdominal scintigraphy with technetium 99 m has proven successful in identifying and locating the site of abdominal leaks or a patent processus vaginalis [77–81].

Different radioligands have been used with the tracer including DTPA, albumin colloid, and tin colloid. One to five millicuries are injected into 0.5–2 L of dialysate [82–84]. It has been suggested that the patient sit up and lean forward to increase the IAP and hence to encourage the radiolabeled dialysate into the leaking sites [85]. Delayed images after ambulation (to raise the IAP) may be necessary to detect the leak [86, 87]. In addition, multiple projections should be taken in order to separate an abdominal wall leak from the peritoneal dialysate directly posterior to it [86]. While the dose of isotope may seem hefty, much of the radiation is drained out of the body with the dialysate after the study. Therefore, the net dose of radiation is only a fraction of that originally instilled in the peritoneal cavity [88].

Hydrothorax

Increased IAP can result in leak of dialysis fluid from the peritoneal cavity, across the diaphragm, and into the pleural space. The accumulation of dialysis fluid in the pleural cavity is called hydrothorax [89 90] (Fig. 20.4). It is not clear how often hydrothorax occurs in patients receiving PD. Most studies estimate that the incidence is less than 5%, which

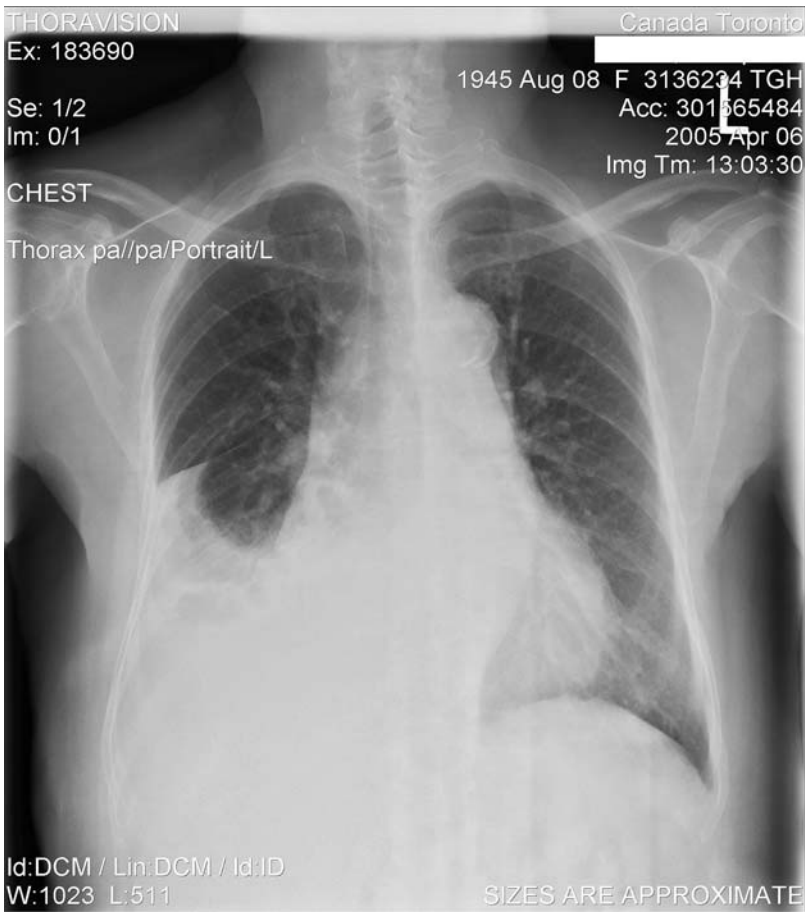

Fig. 20.4 Radiograph of the cervical spine in a long-term CAPD patient who developed destructive spondyloarthropathy. Analysis of resected vertebral tissue revealed amyloid composed of β_2-microglobulin

would make it less frequent than abdominal hernias [91–93]. In one study the incidence was as high as 10% [94]. However, it is possible that hydrothorax does occur even more frequently, but does not come to medical attention if the patient is asymptomatic or if minor complaints of shortness of breath are overlooked.

Pathogenesis of Hydrothorax

A source of communication must be present to allow flux of dialysis fluid from the peritoneal into the pleural cavity. Autopsy studies have revealed localized absence of muscle fibres in the hemidiaphragm. These missing muscle fibers are replaced with a disordered network of collagen. One or more defects in the tendinous part of the hemidiaphragm have been observed [95].

When hydrothorax has been investigated by surgery or pleuroscopy, "blisters" or "blebs" have sometimes been noted on the pleural surface of the diaphragm. Presumably these represent the areas of deficiency in the usual support structures of the diaphragm described at autopsy [96]. With the installation of dialysis fluid into the peritoneal cavity these blebs can be seen to swell, weep, and even rupture, thus providing the pathway for the movement of dialysate into the pleural space. Others have suggested that there may be congenital defects that predispose to communication between the peritoneal and pleural cavities [97].

As with hernias and genital edema, this complication of the peritoneal boundary has been suggested to be more prevalent in those with polycystic kidney disease [98].

In pediatric patients receiving PD who develop hydrothorax, diaphragmatic eventration rather than hernia has been described at surgery [99, 100].

It is likely that these defects in the musculotendinous part of the diaphragm are not rare occurrences but, in a manner similar to patent processus vaginalis, come to medical attention only when there is fluid in the abdominal cavity under increased pressure. This explains why hydrothorax has been described in patients on PD and in those with liver disease or ovarian cancer and ascites.

The extent of the deficiency in the hemidiaphragm varies among patients. Those with a preexistent clear connection between peritoneal and pleural space probably correspond to those patients who develop hydrothorax with their first-ever infusion of dialysis fluid. In contrast, there are patients who develop hydrothorax months to years after starting PD. Presumably, those patients have attenuated tissue separating pleural from peritoneal space, and it may take repeated exposure to raised IAP [101–103] or an episode of peritonitis to remove the barrier between the two cavities. Such may be the case in a patient who presented with acute massive hydrothorax and was found to have amyloidosis within the hemidiaphragm [104].

It has been suggested that in a subset of patients with hydrothorax there is a one-way communication between peritoneal and pleural cavities. This phenomenon might explain the persistence of hydrothorax after drainage of dialysis effluent. Postulated mechanisms for one-way flow include a valve-like defect in the diaphragm, or the action of the hepatic capsule to tamponade backflow of dialysate from the pleural to the peritoneal space.

In rare instances, dialysis fluid may flux into the pericardial space, particularly if communication between the two cavities had been established by previous pericardiocentesis [105–107].

Diagnosis of Hydrothorax

The majority of patients with hydrothorax are women. The reason for this sexual predominance is not clear, although stretching of the hemidiaphragm from previous pregnancy has been suggested [96]. The pleural collection is almost always on the right side, a phenomenon also noted with Meigs syndrome, hepatic ascites, and menses-associated lung diseases [108]. It may be that the presence of the heart and pericardium prevent flux of fluid across the left hemidiaphragm [96]. There are isolated reports of PD hydrothorax on the left side, or both sides, but this is much less common [109].

Finally, patients whose renal failure is the result of autosomal dominant polycystic kidney disease may have a higher risk of developing hydrothorax on PD. Possible explanations include higher than average IAP resulting from the space occupied by the large kidneys, or perhaps greater inherent weakness of the diaphragm as a part of a generalized membrane defect seen in this condition [98].

Small pleural effusions can be asymptomatic and may be first detected incidentally on routine chest radiographs. Larger pleural effusions can lead to respiratory embarrassment and so usually are symptomatic.

The shortness of breath that results from the pleural effusion can be mistaken for congestive heart failure. The patient may choose more hypertonic dialysis solutions in an effort to increase ultrafiltration. In the patient with hydrothorax, however, increased ultrafiltration will lead to even greater IAP with further flux of dialysate into the pleural space, worsening the symptoms. Therefore, a history of a patient complaining of dyspnea that appears to worsen with hypertonic dialysate should suggest the possibility of hydrothorax, particularly if effluent returns are less than normal (i.e., they are trapped in the pleural space). Indeed, in a patient new to peritoneal dialysis, when residual kidney function is the greatest, the complaint of shortness of breath should mandate the consideration of PD hydrothorax.

Physical examination is consistent with pleural effusion, with absent breath sounds and stony dullness to percussion in base of the affected lung. Tension hydrothorax has rarely been reported [110, 111].

Chest X-ray shows a pleural effusion on the right side in most patients. Clearly other causes for pleural effusion should be ruled out, including local parenchymal lung disease, congestive heart failure or pleuritis. The scenario wherein a patient develops a large right-sided pleural effusion with the first few dialysis exchanges is strongly suggestive of hydrothorax. However, in a patient on CAPD for months who develops peritonitis, fluid overload, and pleural effusion, making the correct diagnosis can be more difficult.

In the patient in whom the etiology of the pleural effusion is uncertain, a thoracentesis can be helpful in making the correct diagnosis. If the pleural fluid is composed of dialysate, the glucose concentration is very high (usually greater than 40 mmol/L) and the fluid has a low protein concentration consistent with a transudate. However, if the fluid is sampled after it has dwelled in the pleural cavity for hours, it is possible that glucose has diffused out of the cavity and so may not be very high. It has been suggested that, regardless of dwell time of the pleural fluid, the glucose concentration should still be more than 50 mg/dl (about 3 mmol/l) l greater than a simultaneous blood glucose [112].

It has been suggested that the dye methylene blue can be instilled in the peritoneal cavity before the pleural tap, and blue staining of the pleural fluid provides evidence of peritoneal–pleural communication. However, intraperitoneal methylene blue can lead to chemical peritonitis that is very painful; furthermore, the blue staining may be so faint as not to be appreciated in the pleural fluid, leading to a false-negative result. Even when the diagnosis is certain,

thoracentesis should also be used in patients who are short of breath from the hydrothorax. Evacuation of one or more liters of fluid leads to significant improvement in the patient's respiratory status.

In the absence of thoracentesis, the presence of a peritoneal–pleural communication can be confirmed by isotopic scanning. In different studies, between 3 and 10 mCi of technetium-labeled macroaggregated albumin or sulphur colloid has been instilled into the peritoneal cavity along with the usual volume of dialysis fluid. The patient should move around to ensure mixing of the radioisotope and dialysate and to raise the IAP. Subsequent scanning detects movement of the isotope above the hemidiaphragm [113, 114]. This usually is detectable in the first few minutes, but sometimes late pictures (up to 6 h) need to be taken. This method is convenient but not absolutely foolproof. Defects have been found in the diaphragm at surgery in patients in whom isotopic scanning was negative.

Other studies have reported the use of contrast peritoneography using diatrizoate and iopamidol, but experience with these nonisotopic methods is limited. Magnetic resonance imaging without the use of gadolinium has also used been to detect dialysis leaks, including those into the pleural space, in PD patients [68]

Treatment of Hydrothorax

Thoracentesis is recommended for the immediate treatment of hydrothorax if respiratory compromise is present. Otherwise, simply discontinuing PD often leads to rapid and dramatic resolution of the pleural effusion [93]. In a small number of patients the effusion is slow to resolve, suggesting that there may be a one-way or ball-valve type communication between peritoneal and pleural space, as previously discussed. In this instance, thoracentesis may be helpful to hasten the resolution of the pleural effusion.

Subsequent treatment depends on whether the patient chooses to continue on peritoneal dialysis. The occurrence of hydrothorax occasionally is so distressing to the patient that he or she may request transfer to hemodialysis. In this case, the communication between peritoneal and pleural space should be of no consequence and nothing further needs to be done once the effusion has resolved.

If the patient is going to continue with PD there are a number of different options [115]:

Temporary Hemodialysis (2–4 Weeks) with Subsequent Return to CAPD

Especially in the presence of peritonitis, there may be a transient loss of the integrity of the cell layers overlying a diaphragmatic defect. If PD is temporarily discontinued and the mesothelium allowed to reconstitute itself over the defect, it is possible that the peritoneo–pleural communication may become resealed. It is less likely that this would be effective in those patients demonstrating pleural leak with the first dialysis, but even this phenomenon has been reported after a 2-month hiatus on hemodialysis. It has been suggested that the dialysate in the pleural space may act as a sclerosing agent and prevent subsequent leaks [116].

Temporary Hemodialysis with a Return to a PD Regimen with Lower IAP

Patients who experience hydrothorax on CAPD are sometimes able to resume PD by cycler. Even though the supine position might be thought of as conducive to the movement of fluid into the pleural cavity, it appears to be more than compensated by the reduction in IAP afforded by this posture [117]. In other words, the movement of fluid from the peritoneal to pleural space is pressure-driven, not positional. The use of smaller dialysis volumes with more frequent exchanges is helpful in minimizing the increment in IAP [117, 118].

Obliteration of the Pleural Space ("Pleurodesis")

Previous studies have reported the successful obliteration of the pleural cavity. In this instance the leaves of the pleura stick together and prevent the reaccumulation of pleural fluid [119, 120].

There are various agents used to induce pleurodesis. Oxytetracycline (20 mg/kg) has been administered via a thoracostomy tube [93, 115, 121–123]. It is important that the patient remain supine, up to 24 h, and assume different positions, including head-down, to ensure exposure of the agent to all the pleural surfaces. The patient should also receive analgesia, as this procedure can be painful. Talc has also been reported as a successful agent for pleurodesis [100, 124–126]. Obliteration of the pleural cavity has also been accomplished by the instillation of 40–100 mL of autologous blood [127–130]. The patient should be maintained, if possible, on hemodialysis for a few weeks to allow the pleurodesis to take place [128, 131]. More than one installation of blood may be necessary, but the benefit of the

blood is that it appears to be a relatively painless procedure compared to the use of talc or tetracycline [127, 128]. There are reports from Japan of the use of OK-432, a hemolytic streptococcal preparation, and the use of *Nocardia rubra* cell wall skeleton to effect pleurodesis [93]. Finally, a combination of aprotinin-calcium-chloride–thrombin and "fibrin glue" instilled in the drained pleural cavity was reported to successfully prevent recurrent hydrothorax in a patient who had previously failed treatment with other agents [132]. As with any intervention, there is a risk of infectious complications [133].

Operative Repair

At thoracotomy or visual-assisted thoracoscopy [134–139], a communication between peritoneal and pleural space may be visualized. Sometimes the "blebs" or blisters are quickly recognized and these can be sutured and reinforced with Teflon felt patches [96]. It is recommended that 2–3 L of dialysate be infused into the peritoneal cavity through the dialysis catheter. The diaphragm is inspected from the pleural side for seepage of dialysate through holes or blisters. It is important that the surgeon be patient as it may take time for the seepage to be recognized [140]. The defects can be patched, oversewn, or the visualize pleural space simply pleurodesed.

In the case of eventration of the diaphragm, as reported in the pediatric literature, surgical repair can be effected by plication with nonabsorbable suture. These patients are able to return to PD successfully [99, 141].

In summary, hydrothorax is a well-described but relatively uncommon complication of PD. Diagnosis is relatively simple once the possibility of peritoneal–pleural communication has been entertained. Thoracentesis may be necessary to confirm the diagnosis and is mandated by respiratory embarrassment. If the patient is willing to continue with PD, several treatment options are available.

Other Respiratory Complications

The effects of CAPD on respiration can be divided into those related to the effect on the mechanics of breathing engendered by the physical presence of dialysis fluid in the peritoneal cavity, and those resulting from the carbohydrate loading from absorption of glucose, which can affect intermediary metabolism and change respiration in a substrate-driven manner. Sleep apnea is increasingly recognized in end-stage renal disease patients and will be discussed separately.

Changes in Pulmonary Function Resulting from Altered Mechanics of Breathing

Early studies of PD suggested that this procedure compromised respiratory function [142]. However, these and other studies were reported in acutely ill subjects, and many other factors could have affected the integrity of the lungs, pleura, and respiratory muscles. Later studies of stable patients on chronic PD demonstrated that 2 L of dialysis fluid in the abdomen resulted in reduction of most lung volumes, including the functional residual capacity (FRC) [143–145]. These changes can persist or normalize after only 2 weeks on CAPD [146].

It has been suggested that, as the FRC decreases to less than the closing volume, small airways will collapse and cause ventilation–perfusion mismatch and arterial hypoxemia. At the outset of dialysis, instillation of dialysate is associated with an average 5 mm Hg fall in arterial Po_2 in the sitting position and an average 8 mm Hg decrease when the patient is supine. These changes are seen in association with a fall in FRC. When these patients are restudied a few months later, there is no longer a decrement in arterial Po_2, despite a similar fall in FRC. It has been suggested that some long-term adjustment takes place, such as redistribution of blood away from the more poorly ventilated lower segments of the lungs [144]. Other studies have not confirmed arterial hypoxemia in patients on PD [143, 146, 147], although arterial hypoxemia has been reported in both hemodialysis and PD patients with polycystic kidney disease while ambulatory, which was improved in assuming the supine position [148]. A recent study examined whether pulmonary function tests done as part of preoperative risk assessment changed if the peritoneal cavity was filled with dialysis fluid. These investigators found no statistical difference in the test results and suggest that this testing can be done with the peritoneal cavity filled or empty [149].

The changes in lung volumes have not been found to be any more severe in patients with chronic obstructive airways disease [146], and it has been advised that obstructive airways disease should *not* be regarded as a contraindication to the use of PD [150]. It has been demonstrated by total-body plethysmography that the presence of 2 L of dialysis fluid has no effect on airways resistance [151]. Indeed, it is conceivable that the presence of dialysis fluid in the abdomen can

facilitate pulmonary function. This change may be explainable by altered diaphragmatic contractility secondary to stretch of the diaphragm caused by the dialysate [152]; that is, with increased length of the muscle fibers there is improved muscle function. Explained in another way, the presence of the intraperitoneal fluid increases the upward curvature of the diaphragm. The radius of the new curve is smaller. Laplace's law dictates that the diaphragm generates more pressure for a given amount of muscle tension when the radius is smaller. Therefore, the contractility of the diaphragm may increase in the presence of intraperitoneal fluid [153]. This effect is analogous to the benefit that the patient with obstructive airways disease achieves by holding a pillow tightly against the abdomen. However, there is an upper limit to this relationship, after which the diaphragm loses efficiency and compromise of ventilation occurs [153]. More sophisticated testing, including electromyographic recording of the diaphragm using intragastric and intraesophageal catheters, has confirmed that diaphragmatic strength is significantly improved when the abdomen is filled with dialysate. This parameter was measured as the maximum transdiaphragmatic pressure. The improvement in strength again was suggested to be a result of an adaptive change in the diaphragm's force–length ratio as a result of tonic stretch from the intra-abdominal dialysate [154].

A study of pulmonary function in predialysis, PD, hemodialysis, and renal transplant patients showed that the diffusion factor for carbon monoxide, while reduced in all the groups, was significantly lower in the group of patients on CAPD, with a mean carbon monoxide diffusing capacity (DLCO) just under 70% of predicted value. The authors postulated that this surprising finding was most likely the result of subclinical pulmonary edema (potentiated by the low serum albumin in the CAPD group) or else the result of interstitial fibrosis caused by repeated episodes of pulmonary edema [155]. However, another intriguing possibility is that the raised intraabdominal pressure (IAP) leads to reflux, chronic aspiration, and the consequent development of restrictive lung disease. In a related way, reflux has been implicated as a major cause of chronic cough in patients on PD [156–158].

Substrate-Induced Changes in Respiration

The nature and availability of energy substrate can alter intermediary metabolism and affect ventilation. This relationship has been described in patients undergoing total parenteral nutrition, where hypercaloric glucose and amino acid solutions produce significant increase in minute ventilation, carbon dioxide excretion, and oxygen consumption [159]. A theoretical treatment of substrate absorption during CAPD predicts that the absorption of glucose and, to a lesser extent, lactate would drive intermediary metabolism and lead to the changes in respiration described above. The increase in metabolically driven ventilation could prove dangerous to the patient with lung disease [159].

Studies in patients on CAPD confirm increased minute volume, oxygen consumption, and carbon dioxide excretion compared to controls [160]. This suggests that the lactate and glucose absorbed are incorporated into the Krebs cycle. Moreover, because some of the glucose is metabolized in a manner that does not require oxygen, but does produce carbon dioxide, the respiratory quotient increases. In the normal situation, however, the arterial P_{CO_2} does not increase, because the patient is stimulated to hyperventilate and "blow off" the extra carbon dioxide. In the patient who is too ill to hyperventilate, this may not be the case. Cohn and co-workers described a patient with systemic lupus erythematosus and renal and respiratory failure who developed acute respiratory acidosis each time a high-glucose dialysis solution was used. The acidosis would abate when the dialysis was changed to one with a lower concentration of glucose. The authors suggested that the carbohydrate loading led to lipogenesis, a process associated with a respiratory quotient (CO_2 produced per O_2 used) as great as 8. In the patient with compromised ventilatory status and respiratory muscle dysfunction, the extra carbon dioxide could not be exhaled quickly enough, and so hypercapnia ensued. The use of dialysis solutions with lower glucose concentration resulted in less net glucose absorption and hence less substrate-driven carbon dioxide production [161].

Sleep Apnea

Obstructive sleep apnea is characterized by repeated bouts of apnea that each last for 10 s or more. Often the apnea is recognized by snoring with the resumption of breathing, and by its sequela of excessive daytime somnolence. The apneas can result in arterial hypoxemia and hypercapnia, which in turn can lead to pulmonary arterial and systemic hypertension. The apneic periods are broken by the arousal reaction, accompanied by sympathetic outflow. This sympathetic response or other responses are probably responsible for the association between cardiovascular and cerebrovascular disease and sleep apnea.

Both hemodialysis and PD patients often report disturbances of sleep, including nonrestorative sleep, early wakening, and daytime sleepiness. The contribution of sleep disturbances in general, and obstructive sleep apnea in particular, to these symptoms is unknown. In addition, whether PD confers an additional insult to sleep by the presence of dialysate (or dialysate exchange by automated cyclers) during sleeping time is unknown. Unlike conventional hemodialysis, PD effects solute flux during the sleeping hours. Besides the potential disturbance of 2 or more liters of dialysate in the peritoneal cavity, potential sleep-enhancing molecules might be dialyzed out during a long overnight dwell [162].

Studies on sleeping patterns in patients on PD suffer from small numbers, and the patients who are recruited report significant sleep disturbances. Therefore, results from these studies are probably not generalizable to the PD population as a whole In the subset of patients reporting these disturbances, polysomnography demonstrates a high prevalence (>50%) of obstructive sleep apnea [163, 164]. This prevalence is comparable to that of a cohort of self-selected hemodialysis patients with sleep disturbances [163]. While the prevalence appears excessive, it is in a self-referred group with sleep disturbances. It is still not clear whether there is a truly higher general prevalence of sleep apnea in dialysis patients, and, if so, what it is about the renal failure that should lead to this association. A survey of Asian PD patients with sleep disturbances found that they were more likely to have anxiety and suffer from somatic complaints such as bone pain and arthralgia [165].

Studies in PD patients suggest that the presence of the dialysate in the peritoneal cavity does not confer additional disturbance of sleep unless that patient has obstructive sleep apnea. In the small numbers of apneic patients there was striking arterial hypoxemia when the patients slept with dialysate *in situ* (P_{O_2} 78 ± 7 mm Hg) than when they slept without dialysis fluid (P_{O_2} 92 ± 4 mm Hg). Sleep as a whole was also more disturbed with dialysate in the peritoneal cavity [163]. Again, whether the difference is the result of the physical presence of the dialysate, with attendant changes in intra-abdominal or diaphragmatic pressures, or a metabolic effect of the dialysis fluid is unclear. A small survey of sleep disturbances in PD patients showed that interruptions in sleep were mostly due to treatment-related effects, such as cycler alarms [166]. A recent study examined sleep disturbances in a cohort of Chinese night-cycler and conventional CAPD patients. These disturbances were found to be more prevalent in the latter cohort. Concurrent examination of fluid volume status suggested that the cycler patients had better control of hypervolemia, and it was postulated that avoidance of fluid overload at night with the use of night-cycling dialysis may lead to improved mechanics of ventilation both at the lung level and also in the upper airway [167]. However, as recently pointed out, careful attention to volume status in CAPD patients may help to improve sleep apnea, and patients should not be changed to nocturnal cycler dialysis solely for this indication [168].

Acid–Base and Electrolyte Disorders

Disorders of Water Metabolism

In patients on PD the serum sodium concentration will depend on the relative amount of salt and water ingested and the net salt and water flux across the peritoneal membrane. Renal excretion may contribute in those with residual renal function. Sodium flux into the peritoneal cavity in the PD patient is caused by diffusion and convection. Because sodium is sieved by the peritoneal membrane, the fluid entering the peritoneal cavity by osmotically driven flow is hyponatremic, that is, more water than salt flows from plasma to peritoneal compartment [169, 170]. In theory this sodium sieving should leave the patient with a relative water deficit; the patient should become hypernatremic. However, hypertonicity is a powerful stimulant of ADH secretion, which in turn stimulates thirst. The patient will drink water or some other hypotonic fluid until tonicity is restored. In fact, patients on CAPD may occasionally demonstrate plasma sodium concentrations slightly lower than normal [171]. There are a number of reasons for the relative water excess, including increased water intake or low sodium concentration in the dialysis solution. Hyponatremia may also be a marker for intracellular potassium depletion associated with catabolism and malnutrition [172–174].

The use of icodextrin dialysate leads to retention of osmotically active byproducts in the extracellular fluid and leads to water flux out of the intracellular compartment and mild hyponatremia. Infants undergoing PD and fed normal infant formula may be prone to hyponatremia because sodium losses from ultrafiltration are greater than sodium gained from ingestion of formula. Moreover, the proprietary infant formulas have a high water to sodium ratio, leading to water accumulation and hyponatremia [175].

In a study of insulin-dependent diabetics with hyperglycemia, those on hemodialysis were able to nearly normalize the serum tonicity, whereas PD patients remained hypertonic owing to continued loss of water in excess of solute into

the dialysate. In hyperglycemia the increased extracellular glucose effects osmotic flux of water from the intracellular compartment to the extracellular fluid compartment, which brings the extracellular osmolality towards normal. The fall in serum sodium concentration resulting from this movement of water into the extracellular compartment can be predicted. Patients on hemodialysis, however, demonstrate a greater fall in serum sodium concentration than do hyperglycemic patients not on dialysis. On the other hand, patients on PD behave more like the nondialysis patients. One explanation is that the hemodialysis patient drinks water in response to increased plasma osmolality, and in the absence of ongoing osmotic diuresis, is able to lower plasma tonicity. In contrast, the patient on PD undergoes continuous loss of water in excess of sodium (see above), and in this way mimics the effect of the osmotic diuresis seen in hyperglycemia with normal renal function. The excess loss of water can perpetuate the hyperosmolar state [176].

Disorders of Potassium Metabolism

Hypokalemia is found in 10–36% of CAPD patients [177, 178]. Ongoing losses of potassium in the dialysate may contribute to hypokalemia in some patients. However, on a mass balance basis, it is not predicted that a significant amount of potassium would be removed by peritoneal dialysis. For example, if the serum potassium concentration is 4 mmol/L, even if potassium equilibrates in the dialysate fluid (and extra potassium is not removed from intracellular sources), each 2-L exchange would be expected to remove, at most, 8 mmol. Therefore it would be expected that PD patients would have a predilection for *hyper*kalemia. Given that this is not the case, other factors must play a role. One confounding factor may be poor nutritional intake, particularly of potassium-replete foods such as fruits and vegetables. An examination of hypokalemia in a single American PD unit concluded that African-American status was the strongest predictor of hypokalemia. This finding was ascribed to avoidance of fruit and vegetables as the result of ethnocultural food preferences [178]. Furthermore, poor nutritional status is associated with intracellular potassium depletion, which can lead to flux of extracellular sodium and potassium into the cells, resulting in hyponatremia (discussed above) and hypokalemia [174]. A recent survey of Asian PD patients confirmed an association between hypokalemia and poor nutritional status and co-morbidity [179]; besides poor oral intake, the intracellular potassium deficit may have played a role. In this study, dose of dialysis and the amount of residual kidney function did not correlate with hypokalemia, which reconciles well with the limited amount of potassium that can be removed by these mechanisms. On the other hand, another center reported increasing prevalence of hypokalemia as they increased their dose of PD dose for adequacy targets [180]. Finally, the stimulation of insulin secretion by absorption of glucose in the dialysis fluid may drive potassium into cells [181].

Potassium supplementation should be monitored in dialysis patients because of the absence of renal reserve in some patients to excrete excess potassium. Although hypokalemia is reported to reflect a total body potassium deficit of hundreds to thousands of millimoles, I have been struck by the observation that oral potassium chloride supplements (one or two tablets daily, each tablet 8–10 mmol) have a dramatic effect in normalizing the serum potassium. This suggests that there may be an intracellular block to potassium uptake, so that the supplements stay in the extracellular compartment, but this explanation does not fit with all the other factors, discussed above, that tends to move potassium into cells. Therefore, the explanation remains elusive.

Potassium chloride can be added to the dialysate to diminish the concentration gradient for diffusion of potassium into the dialysis fluid to stop potassium loss, or can be added in high enough concentration to allow potassium to diffuse from the dialysate to the patient. In the acute setting, up to 20 mmol/L of KCl can be added to the dialysate with a low incidence of side-effects. This dose has been reported co increase the plasma potassium concentration by an average 0.44 mmol/L over 2–3 h. However, the effect of this hyperkalemic solution on the peritoneal membrane is unknown, so this treatment should be used only in urgent settings [177].

Acid–Base Balance

In health the kidneys help to maintain acid–base balance via excretion of acid and generation of new bicarbonate. As the kidneys fail, however, net acid excretion diminishes and metabolic acidosis develops. It is important, therefore, that any form of dialysis provide replenishment of buffer.

In the early years of PD, bicarbonate, the obvious choice, was employed as a buffer. However, bicarbonate reacts with calcium chloride, leading to precipitation of calcium carbonate. Therefore, other less reactive buffers had to be used, and experience has accumulated principally with lactate. Dialysate containing glucose must be kept at pH 5–6 to reduce caramelization and the generation of glucose degradation products (GDPs). Serum lactate remains low in

patients receiving lactate-containing dialysate. The patient receiving lactate also shows normal serum bicarbonate levels [182–187], suggesting that adequate amounts of lactate are being absorbed and converted to bicarbonate. In PD patients, gain of alkali from ingested food and absorption from the dialysate just matches daily acid production, so that these patients are in acid-base balance [184]. A recent survey of acid-base balance in PD patients demonstrated that the major correlate with a mildly reduced serum bicarbonate concentration was the concomitant use of the phosphate binder sevelamer hydrochloride [186], although this association has not been confirmed by other investigators [187].

Rapid transporters have been reported to have higher systemic pH and plasma bicarbonate concentration compared to slow transporters. One explanation is that the rapid transporters have a greater net gain of lactate, which is subsequently utilized as buffer [188]. Mujais et al. also reported that the serum anion gap varied inversely with transport status in CAPD, but not APD, patients [185].

The potential advantages of bicarbonate-based, neutral-pH dialysis solutions are discussed in Chapter 11.

Patients on PD may develop metabolic or respiratory alkalosis. The metabolic alkalosis can result from contraction of the extracellular fluid volume over a fixed bicarbonate mass, as reported in the treatment phase of hyperglycemia [189, 190] or with the frequent use of hypertonic dialysis solutions [191]. In patients with respiratory alkalosis the normally functioning kidneys defend against alkalemia by excreting bicarbonate. The PD patient without residual renal function has no such mechanism. Furthermore, the constant infusion of buffer in the patient with respiratory alkalosis can lead to serious alkalemia [192, 193].

Respiratory alkalosis may appear during the initial stages of dialysis. In the acidotic patient commencing dialysis, the infusion of buffer will correct the extracellular acidosis. However, because the bicarbonate anion crosses the blood–brain barrier relatively slowly, the cerebrospinal fluid bathing the respiratory center will remain relatively acid. This cerebrospinal fluid acidosis will continue to stimulate respiratory drive and maintain hyperventilation in the face of now-normal extracellular fluid pH. This complication is less likely to occur in PD, however, because the conversion of lactate to bicarbonate occurs slowly enough to allow cerebrospinal fluid equilibration with extracellular fluid.

Cardiovascular Complications (See Also Chapter 23)

The reduction in blood pressure seen in many PD patients on first glance seems like a major benefit of this modality. However, low blood pressure can have deleterious effects. Diabetic patients have been reported to experience exacerbation of peripheral vascular disease during CAPD. Risk factors for the worsening of peripheral perfusion include smoking, previous symptoms of peripheral vascular disease, and absent limb pulses. It has been suggested that the lowered blood pressure on CAPD compromises blood flow to the ischemic limbs [194]. The use of erythropoietin in diabetic PD patients has been identified as a particular risk for the development of peripheral vascular disease [195]. It is not clear whether this complication also holds for diabetic patients on hemodialysis or whether it is unique to PD.

The elevated IAP caused by the presence of dialysis fluid in the peritoneal cavity has the potential to affect cardiac function. In cirrhotic patients, drainage of ascitic fluid produces a fall in right and left atrial pressure with improvement in cardiac function [196]. There is no consensus on the influence of peritoneal dialysate on cardiac function. Studies have been unable to document a decrease in cardiac function with infusions of as much as 3 L of dialysate [197], whereas others have reported up to a 20% decrease in cardiac index with 2 L of intraperitoneal fluid [198, 199]. Perhaps what makes the most sense physiologically was a study that found that it was the subgroup of patients with LVH who showed echocardiographically detectable changes in function with the infusion of large (3 L or more) volumes of dialysate [200]. The reduction in LV systolic function was felt to be the result of reduction in preload, because a significant decrease in the LV internal diameter in diastole was found. It is predicted that the subgroup of patients with LVH are the patients in whom cardiac function is affected by preload reduction. In other words, the patients with LVH and diminished LV compliance would be vulnerable to a decrease in LV preload resulting from decreased venous return [200]. However, decreased venous return could not explain the reduced cardiac output in all the patients. Some of these patients had no change in right heart pressure. In these patients increased cardiac surface pressure from the bulging of the diaphragm into the thoracic cavity may have compromised cardiac function [200]. In this regard it is interesting to note that inferior attenuation on cardiac thallium-201 imaging has been noted in patients holding 2 L of PD fluid. The elevation of the diaphragm as a result of increased IAP was thought to be the cause of the abnormal scan, as opposed to myocardial disease [201].

In summary, it appears that the presence of intraperitoneal dialysate usually does not exert a clinically significant effect on the cardiovascular system, although there is a potential for such an effect with the use of large (3 L or more) volumes in patients with diminished cardiac compliance.

Gastrointestinal Complications of PD

Pancreatitis

Risk of Pancreatitis in PD Patients

Peritoneal dialysate can gain access to the lesser sac of the peritoneal cavity *via* the epiploic foramen. The posterior surface of the lesser sac serves as the anterior surface of the pancreas. Therefore, any constituent of the dialysate has the potential to irritate the pancreas. Proposed irritants include the high glucose concentration of dialysis fluid, unidentified toxic byproducts of the dialysate, bags, or tubing [202], acidity of nonbiocompatible dialysate [203] and, of course, the infected dialysate of peritonitis [203]. Rechallenge with peritoneal dialysate after an episode of pancreatitis has resulted in a recurrent episode of pancreatitis [204]. In addition, there may be a predilection for pseudocyst formation [203].

Other risk factors for pancreatic inflammation in patients on CAPD include hypertriglyceridemia, which is prevalent in these patients. In addition, patients with adynamic bone disease are prone to hypercalcemia when given calcium supplements and vitamin D, and the elevated serum calcium is another risk factor for acute pancreatitis.

Despite all the potential risk factors outlined above, it still remains controversial whether acute pancreatitis occurs more frequently in CAPD patients compared to those on hemodialysis. In a review of the literature, Gupta et al. concluded that in fact, acute pancreatitis was not more common in CAPD patients, and that previous reports to the contrary were the result of reporting bias [205]. However, given the potential for contact between PD fluid and the pancreas, and the frequency of at least transient episodes of hypercalcemia in CAPD patients, there remains a strong theoretical risk for a predisposition toward acute pancreatitis in this population compared to those of hemodialysis. In this regard many reviews of the incidence of pancreatitis among dialysis and transplant patients concluded that this complication was more common in PD patients [206–208].

Diagnosis of Pancreatitis

Diagnosis of acute pancreatitis may be difficult. It should be considered in cases of 'culture-negative' peritonitis, especially if the abdominal pain fails to resolve or localizes in the epigastrium. Hiccoughs may be present [209]. The serum amylase will rise with pancreatitis, except in those dialyzing with icodextrin (*see below*). However, because patients with chronic renal failure can have elevated serum amylase levels, there is overlap between the elevated levels seen in patients with renal failure and pancreatitis and those with renal failure alone [203]. Serum amylase values greater than three times the upper limit of normal are suggestive of acute pancreatitis. A review of the literature concerning pancreatitis in PD patients shows that the amylase level was elevated in 18 of 23 patients. In the 18 the mean increase was 8.5 times the upper limit of normal [205]. In the other five patients, however, the serum amylase was normal. In summary, it seems that a markedly elevated serum amylase is strongly suggestive of acute pancreatitis, but normal or near-normal levels do not rule out this diagnosis.

It is important to remember that patients dialyzing with the glucose-polymer fluid icodextrin may have inappropriately low levels of serum amylase during pancreatitis. Metabolites of icodextrin interfere with the serum assay for amylase [210]. In these patients, alternative methods, such as the use of serum lipase, should be used to help with diagnosis.

It has been reported that an increased amylase level in the dialysis effluent (greater than 100 U/L) indicates acute pancreatitis or other intra-abdominal pathology compared to the lower levels seen with dialysis-associated peritonitis [211]. However, this has not been confirmed in other centers [205].

The dialysis fluid is usually clear with pancreatitis, and the lack of cloudy fluid should suggest a cause of the abdominal pain other than peritonitis [212]. Brown-black dialysis effluent has been reported in the face of hemorrhagic pancreatitis as a result of the presence of methemalbumin [213]. The fluid has occasionally been reported to be cloudy because of the presence of fibrin or triglycerides [214]. Dialysate leukocytosis with sterile culture has occasionally been described in pancreatitis. Pancreatitis may also occur simultaneously or as a complication of PD peritonitis [202, 203].

Ultrasound and CT scanning can demonstrate an engorged, edematous pancreas [203, 204], or pseudocyst formation. Unfortunately, these radiological studies are also frequently normal [202, 203]. The mortality is high and part of the reason may be that time to diagnosis may be delayed on the assumption that the abdominal pain is the result of bacterial peritonitis. In fact, the diagnosis may be made for the first time at post-mortem examination. Mortality is higher in patients with acute hemorrhagic pancreatitis (in which case the presentation may be with hemoperitoneum and abdominal pain), and conversely, the persistence of clear dialysis fluid throughout the course of pancreatitis is a good prognostic sign [215].

Hepatic Complications

In CAPD patients receiving intraperitoneal insulin, a unique hepatic lesion can develop. A layer of fat may be deposited under the hepatic capsule exposed to the peritoneal cavity [216–219]. Occasionally these fatty deposits will be more nodular in shape, rather than like a 'rind' of fat that is more typically seen [220]. The thickness of this fatty layer correlates with the degree of obesity, as well as the size of the dose of intraperitoneal insulin. Patients who are rapid transporters appear to have larger amounts of fat deposits [221]. It has been proposed that the administration of insulin in the peritoneal dialysate leads to increased concentration of this hormone at the capsule and at the level of the subcapsular hepatocytes. In the face of relative peripheral insulin deficiency and obesity, free fatty acids are delivered to the liver where they are re-esterified in the presence of the high insulin levels under the hepatic capsule. Pathologically, there may be associated steatonecrosis, but liver function usually remains normal. However, it is important that this complication be kept in mind. One of our CAPD patients on intraperitoneal insulin underwent CT scanning for abdominal pain and was reported to have 'metastatic carcinoma' of the liver. However, the abnormality was distributed just under the liver capsule across the surface of the liver exposed to the dialysate. A needle biopsy confirmed that the lesion was not cancer, but the above-described subcapsular steatosis. If the patient changes from intraperitoneal to subcutaneous insulin, the steatotic lesions regress [220, 222].

The liver is at risk for abscess formation as a result of dialysis-associated peritonitis. This diagnosis should be considered in cases of persistent peritonitis. Ultrasound of the liver may be normal and exploratory laparotomy may be necessary. Needle aspiration and drainage under CT guidance is a less invasive alternative.

Other rare complications reported include portal vein thrombosis as a complication of *Staphylococcus aureus* peritonitis in a patient with alcoholic cirrhosis [223] and ascites after discontinuation of PD. In the latter case, infection of the dialysis fluid should be ruled out with paracentesis. Another suggested cause for post-PD ascites includes portal hypertension, although in other instances the pathogenesis remains obscure [224, 225]. Post-PD ascites remains a puzzling condition, but thankfully usually resolves over the first year after discontinuation of this type of dialysis.

Other Gastrointestinal Complications

Many patients on CAPD complain of abdominal bloating and reflux. It has been assumed that the cause of these symptoms is the increased IAP and volume. It might be expected that the increased abdominal pressure dynamics across the esophageal–gastric junction and leads to esophageal reflux or spasm. One study using manometry to measure esophageal pressures and peristalsis found no increase in esophageal pressure or pressure at the lower esophageal sphincter when 1.5–2.5 L of dialysate was instilled in the peritoneal cavity [226]. Symptomatic patients (nausea, vomiting, epigastric fullness) were found in another study to have reduced lower esophageal sphincter pressure compared to asymptomatic CAPD controls [227]. The combination of increased IAP seen in PD, diminished lower esophageal sphincter pressure, and delayed gastric emptying [228] is certainly a risk for the development of reflux symptoms. Collection of dialysis fluid in the lesser sac of the peritoneal cavity can push on the stomach and aggravate gastroesophageal symptomatology further. Gastroesophageal reflux may also be responsible for cough, especially at night, in many patients on PD [156–158].

Treatment includes frequent small meals, avoidance of foods that reduce sphincter pressure (chocolate, alcohol), decreased dialysis volumes, and the use of histamine-2 blockers and proton-pump inhibitors. Pro-motility agents may be helpful, including oral domperidone and intraperitoneal erythromycin [229].

The small bowel is vulnerable to catheter-related perforation. This complication results from pressure necrosis from the dialysis catheter. Small bowel perforation of this type has been reported not only in patients with an unused PD catheter, but also in patients actively receiving CAPD [230]. Perforation of the jejunum considered unrelated to the PD catheter has also been reported [231].

There are rare reports of ischemic colitis and necrotizing enteritis as complications of PD [212, 232, 233]. The likeliest cause is hypotension with consequent hypoperfusion of the bowel. However, the development of ischemic bowel in a normotensive 6-year-old child on PD with improvement upon transfer to hemodialysis suggests PD itself may play a role in the bowel ischemia [233]. Marked gastrointestinal bleeding from dilated submucosal vessels in the bowel have been reported in association with the use of hypertonic dextrose solutions. No such bleeding occurred when the patient changed to hemodialysis. It was suggested that PD provoked mesenteric vasodilation which promoted the gastrointestinal bleeding [234, 235]. Conversely, angiodysplastic bleeding has been reported to stop when hemodialysis patients are transferred to PD [236, 237]. Bleeding from vascular ectasia of the stomach has also been reported in patients on PD, and should be suspected if there is persistent erythropoietin-resistant anemia [238, 239].

Finally, free air in the peritoneal cavity, or pneumoperitoneum, usually presents as free air under the diaphragm. In nondialysis patients, this radiological sign suggests perforation of an abdominal viscus and usually leads to laporatomy. However, air can be infused along with dialysis fluid, particularly with "flush before fill" systems. Therefore, many PD patients have the incidental finding of pneumoperitoneum [240, 241]. One review found that almost four percent of their PD population had pneumoperitoneum on routine chest radiographs [242]. If the finding is the result of the concomitant accidental infusion of air along with dialysis fluid, the outcome is benign and the air should gradually resorb. However, in the PD patient who presents with abdominal pain, pneumoperitoneum is hard to interpret. Previous reports suggest that the larger the volume of free air, the greater the likelihood of viscus perforation [240]. Unfortunately, this relationship has not been substantiated in other reports [241, 243]. Clearly the interpretation of the free air must be taken in clinical context: free air under the diaphragm on a chest X-ray in a well PD patient is little cause for concern, but even a small amount of free air in a patient with abdominal pain must at least suggest the possibility of perforation of an abdominal viscus, and not automatically be dismissed as air infused during a dialysis exchange [244].

Encapsulating Peritoneal Sclerosis

Clinical Presentation

This rare and devastating complication consists of progressive inanition, vomiting, and, most importantly, intermittent bowel obstruction [245]. The small intestine is bound or encapsulated by a thick fibrous layer, rendering the peritoneal surface opaque. The fibrous layer resembles a "thick shaggy membrane" or a "fruit rind" that may or may not peel off the bowel relatively easily [246]. The bowel so exposed may appear normal [246]. A different form of sclerosing peritonitis has been described in which the diffuse sclerosing process extends transmurally with incorporation of the inner circular muscular layer and myenteric plexus of the small bowel in the fibrosing process [247].

The prevalence of sclerosing peritonitis varies among different units. Some variability in the data may be accounted for by the definition used for sclerosing peritonitis in each center. Patients with this syndrome have a generally poor outcome, with high mortality, probably on the basis of severe malnutrition and recurrent bowel obstruction. The diagnosis of bowel obstruction may be delayed because the fibrosing process does not allow the bowel to distend and display the typical radiological findings [248].

Encapsulating peritoneal sclerosis (EPS) appears to be a distinct and devastating syndrome and the name should not be used interchangeably with "peritoneal sclerosis." The latter term should be reserved for the finding of nonencapsulating sclerosis and fibrous adhesions sometimes associated with outflow problems or ultrafiltration failure. This condition is seen in patients who have had prolonged PD, previous abdominal surgery or recurrent episodes of peritonitis, and may be present at the initiation of dialysis. Indeed, the lack of rigorous differentiation between these two entities may confuse any attempt to define etiological factors, particularly among different dialysis centers. It is also important to keep in mind that many long-term PD patients will have thickening of the peritoneal membrane, but this finding alone does not constitute EPS.

Calcifying Peritonitis

Marichal et al.[249] described two patients on CAPD who developed recurrent abdominal pain and incomplete bowel obstruction. Radiographs revealed multiple calcifications that had an eggshell pattern on the loops of the small bowel. One of the patients came to laparotomy, where the intestinal loops were found to be free, in contrast to the appearance in sclerosing encapsulating peritonitis (EPS). Pathologically, the parietal peritoneum showed fibrous thickening and few cells. Also seen were bands of ossification and calcium deposits. The authors called this entity "progressive calcifying peritonitis." Other interesting aspects of these patients included the fact that they dialyzed with acetate buffers, and one of the patients had hyperparathyroidism and recurrent hemoperitoneum. The patients had a benign course compared to that of EPS, and once PD was discontinued bowel function improved [249].

The relatively benign outcome was substantiated by a report from Australia of a long-term CAPD patient with similar features, extensive plaque-like calcification on visceral and parietal peritoneum, and again hemoperitoneum. This patient had elevated levels of parathyroid hormone and increased calcium–phosphate product. After surgical excision of some of the plaques the patient was able to return to PD [250].

However, the optimistic outlook for calcifying peritonitis has been tempered by a report of a long-term CAPD patient who developed extensive peritoneal calcification but whose course was more typical of SEP. This patient had recurrent ileus which did not improve with transfer to hemodialysis. She ultimately sustained bowel infarction and died [251].

The etiology of calcifying peritonitis remains obscure. In the original report acetate was implicated as a cause [249] but subsequent patients dialyzed with lactate buffer. As in the more sinister EPS (see Chapter XX), it is possible that the calcification is a reaction to multiple episodes of bacterial peritonitis. It has been suggested that hemoperitoneum could accelerate the calcification, because iron in the peritoneal cavity can serve as a nidus for precipitation of calcium [252]. Not all the patients had hemoperitoneum, however, and women with recurrent hemoperitoneum associated with menses are not known to develop this complication.

Perhaps the likeliest cause is a disorder in the phosphate–calcium–parathyroid hormone axis, or a deficiency of inhibitors of calcification. Some of the patients had markedly increased levels of parathyroid hormone, and it is conceivable that the peritoneal calcification was a manifestation of calciphylaxis or calcinosis [253, 254]. On the other hand, calcifying peritonitis has been reported in patients years after parathyroidectomy. In this setting it has been suggested that after parathyroidectomy the bone reverts to a low-turnover state. Administration of calcium and vitamin D analogues can results in extraosseous or metastatic calcification, one consequence of which could be peritoneal calcification.

Calcifying peritonitis has been reported so infrequently that it is difficult to provide any recommendations for management. It is advisable to avoid hypercalcemia or marked elevations of the calcium–phosphate product. It is possible that the development of calcifying peritonitis may be an indication for parathyroidectomy if the level of hormone is markedly increased, particularly if there is uncontrolled hypercalcemia.

From the available reports it is not clear whether calcifying peritonitis is in itself an indication for transfer to hemodialysis, although the original report implied that bowel motility improved once PD was stopped [249].

Hemoperitoneum

Presentation and Etiology of Hemoperitoneum

Peritoneal dialysis affords a “window” into the peritoneal cavity. Intraperitoneal bleeding is likely to occur frequently in physiological and pathological settings, but is not detected. With drainage of the dialysis effluent, peritoneal bleeding will be readily apparent by the appearance of bloody effluent known as hemoperitoneum.

The presence of blood in the dialysis effluent can be distressing to the patient and a source of concern to the physician. As little as 2 mL of blood can render 1 L of dialysis fluid noticeably blood-tinged.

Hemoperitoneum has a wide differential diagnosis, as shown in Table 20.3. A common and benign cause of blood in the peritoneal cavity is menstruation. In retrospective reviews of hemoperitoneum, menstrual bleeding is the single most common cause, accounting for more than one-third of the benign episodes [255, 256] The majority of regularly menstruating women on CAPD experience recurrent hemoperitoneum [257].

There are two mechanisms by which menstruation could lead to hemoperitoneum. If there is endometrial tissue in the peritoneal cavity it will shed simultaneously with the intrauterine endometrium, and so bloody dialysate will occur simultaneously with menstrual flow. The alternative mechanism is that the shed uterine tissue and blood both moves out of the uterine cervix and refluxes in retrograde fashion through the Fallopian tubes into the peritoneal cavity. The peritoneal bleeding may start a few days prior to the appearance of blood per vagina [258]. It has been suggested that the timing of menstrual pain matches the appearance of peritoneal blood rather than vaginal menstrual flow, so that the peritoneal blood may be an important cause of dysmenorrhea [258].

Women of reproductive age may also experience hemoperitoneum coincident with ovulation at mid-cycle [255, 259]. It is suggested that the source of blood is bleeding from the ovary with the rupture and release of the ovum. Other ovarian sources of bleeding include ruptured cysts, which can bleed sufficiently to necessitate transfusion [260, 261].

The episodes of hemoperitoneum associated with menstruation and ovulation are recognized by their periodicity and occurrence in women of reproductive age. While this cause of blood in the dialysate is considered benign, there are potential complications. The blood loss can exacerbate the anaemia of chronic renal failure, and for this reason alone anovulant therapy may be indicated. A reported association between hemoperitoneum and *Staphylococcus epidermidis* peritonitis suggests that the bloody dialysate may provide a rich growth medium for intraperitoneal bacteria. Moreover, the retrograde movement of blood from the uterine cavity through the Fallopian tubes may passively carry

Table 20.1 Reported causes of hemoperitoneum

Gynecological
Menstruation [284, 285, 288]
Ovulation [285]
Ovarian cysts [282, 285–287]
Neoplastic
Renal cell carcinoma [299]
Adenocarcinoma of colon [299]
Polycystic diseases
Polycystic kidney disease [294]
Polycystic liver disease [300]
Gastrointestinal
Catheter-induced splenic injury [289, 302]
Hepatic metastases [290]
Hepatoma [291, 292]
Spontaneous splenic rupture in chronic myelogenous leukemia [303]
Colonic perforation in dialysis amyloid [304]
Spontaneous rupture of splenic infarct [305]
Acute cholecystitis [281]
Post-colonoscopy [281, 282]
Intraperitoneal connective tissue pouch [306]
Pancreatitis [282]
Hematological
Idiopathic thrombocytopenic purpura [282, 293]
Anticoagulation therapy [282]
Diseases of the peritoneal membrane
Sclerosing peritonitis [282, 298]
Peritoneal calcification [275]
Radiation-induced peritoneal fibrosis [297]
Miscellaneous
Leakage from extraperitoneal hematoma [282, 295, 307]
Post-pericardiocentesis [308]
Angiomyolipoma of kidney [309]
IgA nephritis [310]
Mixed connective tissue disease [311]
Extracorporeal lithotripsy [296]
Spontaneous rupture of umbilical vein [312]

bacteria into the peritoneum and lead to peritonitis. Other investigators, however, have been unable to document an increased frequency of peritonitis in relation to menstruation-generated hemoperitoneum [255].

In the patient who is not menstruating, hemoperitoneum must be carefully investigated. There are a number of surgical causes of blood in the peritoneal cavity, including cholecystitis, injury or rupture of the spleen [262–264], after colonoscopy [265] pancreatitis [255]. In these instances it should be apparent that the patient has a painful abdomen, and the localized tenderness in concert with the bloody effluent should mandate an urgent surgical consultation. Surgical causes of hemoperitoneum may also present less acutely. We cared for an elderly man with asymptomatic hemoperitoneum who upon investigation had adenocarcinoma of the colon with serosal invasion. Primary and metastatic tumors of the liver can present with hemoperitoneum [266–269] as can hepatic rupture [270].

Hemoperitoneum has been observed in patients with coagulation disorders [255], polycystic kidney disease, post-colonoscopy [255], colonic perforation as a consequence of dialysis-associated amyloidosis [271], leakage from a hematoma outside the peritoneal cavity [255, 272] in patients with tuberous sclerosis [273], and with concurrent cytomegalovirus infection [274] and that seen after extracorporeal lithotripsy for kidney stones [275]. Trauma from the intraperitoneal portion of the catheter can also lead to bleeding [276, 277], including bleeding from the outer wall of a gravid uterus [278, 279].

Recurrent hemoperitoneum may be a harbinger of disease of the peritoneal membrane itself. Bloody effluent has been described in patients with peritoneal calcification in association with hyperparathyroidism [250], in patients with radiation-induced peritoneal injury [280], and as the presenting abnormality in patients who develop encapsulating peritoneal sclerosis [255]. We looked after a young man who had been on PD for many years and developed

asymptomatic hemoperitoneum. Investigations at the time were unhelpful, but within the year he developed classic encapsulating peritoneal sclerosis.

In patients with polycystic kidney disease, bleeding into a cyst can be associated with hematuria or hemoperitoneum. A patient with polycystic kidney disease on peritoneal dialysis was reported to have bloody effluent [281]. In this case, however, the bleeding was painless, which is unusual if a kidney cyst had ruptured into the peritoneal cavity. Moreover, there was associated leukocytosis of the dialysis effluent. These unusual features led to further investigations, which revealed that the patient had renal cell carcinoma [281]. Similarly, hemoperitoneum has been observed with rupture of acquired renal cysts [282]. Rupture of hepatic cysts [283].and ovarian cysts [260] can also result in hemoperitoneum.

Management of Hemoperitoneum

The patient with hemoperitoneum is at risk of the intraperitoneal blood coagulating in the catheter lumen. Therefore, use of intraperitoneal heparin 500–1,000 U/L has been recommended for as long as the dialysate still has visible blood or fibrin. In our experience the intraperitoneal heparin does not worsen the bleeding or lead to systemic anticoagulation. In some instances of hemoperitoneum the use of rapid exchanges with dialysate at room temperature leads to rapid resolution of the bleeding. It is postulated that the relatively cool dialysate induces peritoneal vasoconstriction, and this leads to hemostasis [284].

Women of reproductive age should be instructed about hemoperitoneum, because it is a common occurrence in this group and can be very frightening if it is not anticipated. All other cases of hemoperitoneum warrant appropriate investigation, including imaging procedures and surgical consultation if indicated.

Chyloperitoneum

The pathological influx of chylomicrons rich in triglycerides into the peritoneal cavity is referred to as chylous ascites, or as chyloperitoneum in the patient on PD. This phenomenon results from the interruption of the lymphatic drainage from the gut to the main lymphatic trunks. Compromise of the integrity of these lymphatic channels is most commonly the result of neoplasm, particularly lymphoma.

After a fatty meal, long-chain fatty acids are incorporated into chylomicrons, which enter the lymphatic circulation. Therefore, chyloperitoneum is an intermittent event occurring after the ingestion of fat and clearing some time afterwards. Because medium-chain triglycerides are not absorbed through the lymphatic channels, chylous ascites has been treated by prescribing a diet in which fat is delivered in this form, thus obviating the need for lymphatic drainage of triglyceride.

In the patient not on PD, chylous ascites is likely to present as increasing abdominal girth and peripheral edema. For the patient on PD, chyloperitoneum presents as milky-white effluent that can be mistaken for peritonitis.

The diagnosis is suggested by the white, milky appearance of the dialysate in conjunction with the absence of any indication of peritonitis. Lipoprotein electrophoresis shows lipid staining at the origin, characteristic of chylomicrons [285]. When the dialysate is separated into layers upon standing, the supernatant stains positively for fat with Sudan black, and dissolves with ether [285 286]. The triglyceride level of the dialysate is greater than the plasma triglyceride level, a characteristic of intestinal lymph.

The etiology of chyloperitoneum is obscure. In every case there must be communication between the peritoneal lymphatics and peritoneal cavity. The dialysis catheter or its trochar could sever a lymph vessel. Chyloperitoneum has been reported spontaneously in the neonate [287] as a complication of tuberculous peritonitis [288], as a complication of superior vena cava syndrome [289] and around peritoneal catheter insertion [285, 286]. Interestingly, chyloperitoneum was reported in five Japanese patients given a calcium channel-blocker called manidipine [290]. We puzzled over a CAPD patient who presented with recurrent episodes of cloudy peritoneal dialysate associated with low peritoneal cell counts and sterile bacteriological cultures. Investigation revealed extensive retroperitoneal lymphoma and the episodes of cloudy dialysate represented chyloperitoneum [291]. It has also been reported with other intra-abdominal malignancies [292].

Chyloperitoneum should be part of the differential diagnosis of recurrent cloudy fluid (especially if it is intermittently cloudy) or of "culture-negative" peritonitis. Its diagnosis warrants further investigation into the cause. Temporary cessation of PD and a diet of medium-chain fatty acids may be helpful until its resolution [285, 287]. Octreotide has also been reported to resolve chyloperitoneum in a PD patient [293].

Acquired Cystic Disease of the Kidney

Incidence and Pathogenesis

Acquired cystic disease of the kidney is the term used to describe the progressive replacement of renal parenchyma by cysts in patients with chronic renal failure. This phenomenon was initially described in patients receiving chronic hemodialysis [294]. Although it has been suggested that a retained uremic toxin or one unique to hemodialysis stimulates cystic transformation in the end-stage kidney, it has become clear that acquired cystic disease of the kidney is not unique to the subset of the population with chronic renal failure that receives hemodialysis. This complication has been reported in patients with renal failure who have never undergone dialysis and in patients on PD who were never exposed to hemodialysis [295–297]. Indeed, the acquired cystic disease in patients who have received only PD can be so prominent it can be mistaken for polycystic kidney disease [298]. These observations suggest that factor(s) in the uremic milieu are probably responsible for cystic transformation, rather than something particular to the dialysis process itself.

As in the hemodialysis literature, there is great variation reported for the prevalence of this condition. This variation is the result of the method used to diagnose the cysts, i.e., post-mortem examination of the kidneys versus ultrasound, the particular population being studied, and the criteria used for making the diagnosis. In a review by Ishikawa, the reported prevalence of this condition in CAPD patients varied from 3 to 100% with a mean prevalence of 41%. Methods of diagnosis included ultrasound, CT scanning, magnetic resonance imaging, and post-mortem studies [299]. In comparing the prevalence of acquired cysts in hemodialysis and CAPD patients, a number of confounding factors need to be recognized. Cystic transformation has been reported to be more common in males than in females [300]. Moreover, it has been associated with increasing age [300] and with longer duration of dialysis [301]. (The latter factor perhaps explains why acquired cysts were described earlier in hemodialysis than in PD patients, because there is a greater prevalence of long-term hemodialysis patients.) When corrected for the duration of dialysis there appears to be no difference in the prevalence or severity of cysts [301, 302]. Therefore, any comparison must take into account the patients' age and sex and duration of dialysis before the actual mode of dialysis can be implicated in facilitating cystic change. A pathologic study of renal cystic and neoplastic transformation confirms the association with male sex, duration of dialysis, and hemodialysis [303]. With these limitations in mind surveys of dialysis patients suggest that the prevalence of acquired cystic disease of the kidneys averages about 40–50% and is independent of the mode of dialysis [299, 300, 304].

Risk of Neoplastic Transformation

In dialysis patients with acquired renal cysts, there is a small but significant risk of the development of renal malignancy. The prevalence of renal cancer will again vary depending on the method of detection. One review noted a prevalence of 1.3% for renal malignancy in a dialysis population with acquired cysts [305], which is a two-fold risk compared to renal failure patients without cysts [306]. In CAPD patients, however, the incidence was 0.4%, or two out of 475 patients examined in one group analysis [299]. Overall, there are few reports of renal cell malignancy complicating acquired cysts in patients, and two rare instances of metastatic disease. In one case the renal neoplasm was a poorly differentiated transitional cell carcinoma, and analgesic abuse could not be effectively ruled out as a causative factor [307]. In another instance, however, renal cell carcinoma was confirmed in a nephrectomy specimen with acquired cystic disease and subsequently hepatic metastases occurred [306].

The lower incidence of renal neoplasia in PD patients with acquired cystic disease, when viewed in an optimistic light, might reflect the better-preserved immune function seen in these patients compared to those receiving hemodialysis. In other words, tumor surveillance may be more effective as a result of improved immune function. This is suggested by the observation that transplant patients (on immunosuppression) have a greater propensity to metastatic disease of renal cell carcinoma than patients on dialysis [308], and that acquired cystic disease of the native kidneys may more readily undergo neoplastic transformation in patients who have received a kidney transplant [309]. On the other hand, it may simply be that the index of suspicion is lower in those managing patients on PD consequent to the paucity of reports of renal neoplasms in this group.

Many reports of neoplastic transformation in dialysis patients with acquired renal cysts conclude by advising "regular" or annual surveillance by ultrasound. However, this approach must be tempered by consideration of the enormous cost involved to do this compared to the low incidence of renal cancer and even lower incidence of metastatic

disease in the population of PD patients. Perhaps, as suggested by Ishikawa [299], only those at high risk should be screened; that is, men on long-term CAPD with extensive cystic transformation of the kidneys.

There have been reports of spontaneous hemorrhage into the cysts of PD patients with acquired cystic disease of the kidneys [310]. This may occur less frequently than in hemodialysis because of the reduced need for systemic anticoagulation.

Pruritus

More than half of dialysis patients suffer from pruritus during their time on renal replacement therapy [311, 312]. The itch is severe in only a small minority of dialysis patients, but can be distracting enough as to be an unacceptable burden. Dialysis patients have committed suicide because of intractable itch. There appears to be no significant difference in the prevalence of pruritus between patients on hemodialysis and PD [313].

The etiology of uremic pruritus remains obscure [314]. Hyperparathyroidism and abnormalities in divalent iron metabolism have been implicated in uremic pruritus. It has been observed that itching will often dramatically improve in hyperparathyroid dialysis patients after removal of the parathyroid glands [315]. However, the correlation between parathyroid gland hypersecretion and pruritus is not tight; although studies have demonstrated that patients with itch overall have higher levels of parathyroid hormone, there is no correlation between the severity of pruritus and levels of the hormone. Moreover, studies of skin mineral content in pruritic and nonpruritic dialysis patients have been conflicting [313]. A recent survey in Japan found that hemodialysis patients with pruritus were more likely to be male, with higher levels of β-2-microglobulin, blood urea nitrogen, calcium, and phosphorus [316].

The role of histamine is also not well elucidated. It is recognized to cause itching and allergic skin reactions and has long been suspected to play a role in uremic pruritus. Mast cells, which release histamine, have been found in increased numbers in the skin of uremic patients. However, other studies could not confirm the increase in skin mast cells, or the relationship between plasma histamine levels and itch [317]. Examination of the use of erythropoietin for uremic itch in hemodialysis patients found a correlation between symptomatology and plasma histamine levels [318].

There are theoretical reasons why pruritus might be less prevalent and less severe in patients on CAPD compared to those on hemodialysis. Reactions with the extracorporeal circuit, including the sterilizers and plasticizers, are known to be immunogenic and can sometimes produce hypersensitivity reactions. If middle molecule retention is important in the pathogenesis of pruritus, it might be anticipated that the better clearance of these molecules by PD may afford protection against pruritus [319]. Finally, improved divalent ion metabolism and control of hyperparathyroidism with CAPD might also be expected to correlate with a reduced prevalence of pruritus. An older study of severe pruritus in dialysis patients found a lower prevalence in CAPD compared to hemodialysis [320]. However, other surveys have been unable to document any difference in this complaint between the two dialysis modalities [317]. Plasma histamine levels were not different among CAPD, hemodialysis or predialysis patients, and there was no correlation between these levels and the extent of itch [317]. Perhaps the intervening appearance of high-flux dialyzers and more careful management of calcium and phosphate have resulted in a more equal distribution of pruritic complaints among hemodialysis and PD patients related to other, as yet unknown, factors.

Patients with chronic renal failure often have dry skin, and this can contribute to pruritus. One study reported a correlation between hydration of the stratum corneum of the skin and complaints of itch in hemodialysis and PD patients. The dryness may be amenable to treatment with skin emollients [321].

Trying to study the treatment of pruritus is fraught with hazard. Measurement is confounded by its subjective nature, the absence of animal models, and the lack of validated measurements. The effect of treatment is subjected to bias on the part of investigator and patient [322]. It is likely that the placebo effect is significant.

Measures to relieve pruritus include skin moisturizers [321], activated oral charcoal, cholestyramine, intravenous lidocaine, antihistamines, ketotifen (which stabilizes mast cells), cromolyn soldium (also stabilizes mast cells) [323], and erythropoietin [318]. A recent study of gamma-linoleic acid suggested that this T-cell modifying drug reduced uremic pruritus [324]. A recent report suggests that gabapentin may be helpful [325]. Similarly, a well-conducted trial of nalfurafine, a kappa-opioid receptor antagonist, was found to significantly reduce severe pruritus [326, 327].

Parathyroidectomy may be helpful in those with advanced hyperparathyroidism. Careful attention should be paid to optimizing serum phosphorus levels.

Many studies have reported relief of pruritus with ultraviolet phototherapy, the mechanism of action is unknown, but is confined to the ultraviolet B spectrum [328, 329]. Postulated mechanisms of action include inactivation of pruritogens, reduction of skin phosphorus content, or alternation of signalling in cutaneous nerves. A meta-analysis of published trials of therapy for uremic pruritus found that only ultraviolet B phototherapy fulfilled the criteria for clinically significant improvement [322]. While noting that many of the studies were flawed, the authors concluded that this phototherapy was the treatment of choice in moderate to severe uremic pruritus. The effects of lidocaine, charcoal, and nicergoline were statistically, but not clinically, significant, and the effect of the bile acid sequestrant cholestyramine was clinically insignificant [322].

Insofar as pruritus may be a surrogate for underdialysis or impaired middle molecular clearance, it has been observed that pruritic patients have a worse outcome than patients without itch [316]. Therefore, other parameters of dialysis adequacy should be closely monitored in these patients.

Calciphylaxis

This rare and unusual skin condition has been reported in end-stage renal disease patients, including those on PD [330–335]. It has been increasing in frequency in the last two decades. One theory for the increased frequency is the routine use of calcium carbonate or acetate as phosphate binders [336] and the more prevalent use of vitamin D analogues. We have also noted a strong association with the use of warfarin: Matrix GLA protein, which protects the endothelium from calcification, is regenerated by a vitamin K-dependent process. It follows that patients may be rendered deficient in this vascular-protective protein if they are taking warfarin. Any patient who develops calciphylaxis while on warfarin should have this medication stopped.

This syndrome usually presents with *livedo reticularis* and progresses to the formation of cutaneous ulcers and necrotic eschars. There may be simultaneous development of lesions around several areas of the body (Fig. 20.5). There is a predilection for the torso and thighs. Women appear to be affected more frequently than men. This syndrome is different from slowly progressive gangrene of the digits secondary to vascular calcification, and the two syndromes should *not* be grouped together as "uremic calcemic arteriolopathy."

The etiology is obscure, although it occurs most frequently in patients with renal failure. Many patients have severe hyperparathyroidism and an abnormal calcium-phosphorus product. It is held that the calcium and parathyroid abnormalities sensitize the patient, and when a "challenging agent" is introduced the patient responds with vascular and soft-tissue calcification [337]. We reported a patient on PD with lupus who received ultraviolet light therapy for pruritus which we postulate served as the "challenger" for her subsequent development of calciphylaxis [338]. Treatment includes meticulous local care of the skin and subcutaneous lesions with timely debridement. There are anecdotal reports that urgent parathyroidectomy may be life-saving in the subset of patients with hyperparathyroidism [339]. Careful attention to calcium and phosphorus levels is a reasonable strategy. Hyperbaric oxygen therapy has been

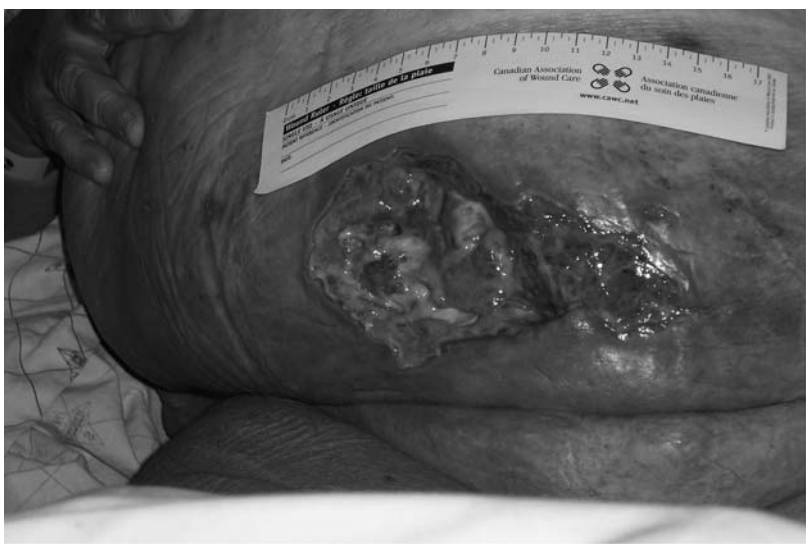

Fig. 20.5 An example of calciphylaxis in a peritoneal dialysis patient. Note the typical features including ulceration and necrosis of the abdominal wall in an obese female. The lesions healed with hyperbaric oxygen

helpful [330, 340–342] and there are now reports of the use of sodium thiosulphate [343], cinacalcet [344], and bisphosphonates (reviewed in [345]).

Dialysis-Associated Amyloidosis

Amyloid deposits in the bones and joints of long-term hemodialysis patients were described in the 1980s. This interesting syndrome of hemodialysis-associated amyloidosis included carpal tunnel syndrome, subchondral bone cysts, spondyloarthropathy [346], and pathological fractures [347, 348]. This amyloid is composed of β_2-microglobulin (B_2M) [349]. Since then, pathological studies have revealed that B_2M amyloid can deposit in tissues outside the musculoskeletal system, including skin, soft tissue, and viscera [350, 351].

This protein is a B cell product and is present on almost all cell membranes. It is measurable in plasma. These levels may be the result of production by lymphocytes, or from normal cell turnover and release of membrane constituents. It is freely filtered at the glomerulus and absorbed and catabolized in the proximal tubule. With renal insufficiency the filtration and catabolism of B_2M decreases and plasma levels increase. It is unclear whether the damage associated with accumulation of B_2M is uniquely linked to the amyloid structure, or whether other mechanisms might exist [352].

Since the musculoskeletal syndrome was originally described exclusively in long-term hemodialysis patients, many factors related to hemodialysis were postulated to play a role in the formation of B_2M amyloid. First, B_2M levels were markedly elevated in long-term hemodialysis patients, especially in those patients using small-pore membranes and those with negligible endogenous renal function. Secondly, the stimulation of the immune system by the repeated interface of blood with artificial membranes was postulated to lead to increased production of B_2M [347].

Serum levels of B_2M are also very high in patients receiving peritoneal dialysis, although not as high as levels in hemodialysis patients using conventional membranes [353, 354]. Explanations put forth to explain the discrepancy include better clearance of this middle molecule by the peritoneal than by the older types of hemodialysis membrane [355], the lack of immune stimulation using the peritoneal membrane and, in long-term patients, better preservation of endogenous renal function [356].

However, by the mid-1980s presumptive evidence of B_2M amyloidosis in CAPD patients began to emerge. The prevalence of carpal tunnel syndrome, subclinical median mononeuropathy, bone cysts, discitis, and cervical spondyloarthropathy suggested that PD patients were not protected from this articular complication [357]. Subsequently B_2M amyloid was isolated from the tenosynovium of a long-term CAPD patient undergoing surgical release for carpal tunnel syndrome [358]. Finally, post-mortem studies in long-term PD patients confirmed the deposition of this type of amyloid in the intervertebral discs of the lumbosacral spine, the synovium of the scapulohumeral joint, hip and wrist, and the capsules of the shoulder joint and periarticular tissues [359–361].

The prevalence of dialysis-associated amyloidosis is difficult to reconcile among various surveys. Some studies report the prevalence of carpal tunnel syndrome or bone cysts as a surrogate for amyloid deposition, which may not necessarily be accurate and could underestimate the true prevalence of this condition [357, 362, 363]. The most accurate way to diagnose B_2M amyloidosis is at post-mortem, although, in this case, the amyloidosis, while present, may not have been associated with morbidity during life. One post-mortem analysis has demonstrated a high prevalence of B_2M amyloid deposition in CAPD patients [364]. In this study eight of 26 CAPD patients and 13 of 26 hemodialysis patients had tissue evidence of B_2M amyloid. When adjusted for duration of dialysis there was no statistical difference between the two modalities although the trend was still for more amyloid deposition in the hemodialysis patients [364]. Unfortunately, no data were available about the residual renal function in these patients.

A worrisome manifestation of B_2M amyloidosis is destructive cervical spondyloarthropathy. Again this complication had hitherto been documented only in long-term hemodialysis patients [365]. However, in our institution a patient who had received CAPD for 13 years developed this spondyloarthropathy, complicated by a compressive myelopathy. The cartilage removed at the time of fusion grafting was positive for amyloid composed of B_2M (Fig. 20.6) [366].

In summary, levels of B_2M in patients on PD are lower than those in patients receiving hemodialysis with conventional membranes. However, these levels are still much higher than those seen in controls. The relative paucity of reports of dialysis-associated amyloid in CAPD patients does not necessarily reflect a proportionately lower incidence of this arthropathy. There are fewer long-term PD patients compared to hemodialysis patients and residual kidney function is preserved for a longer time. The level of suspicion for this complication may not be as

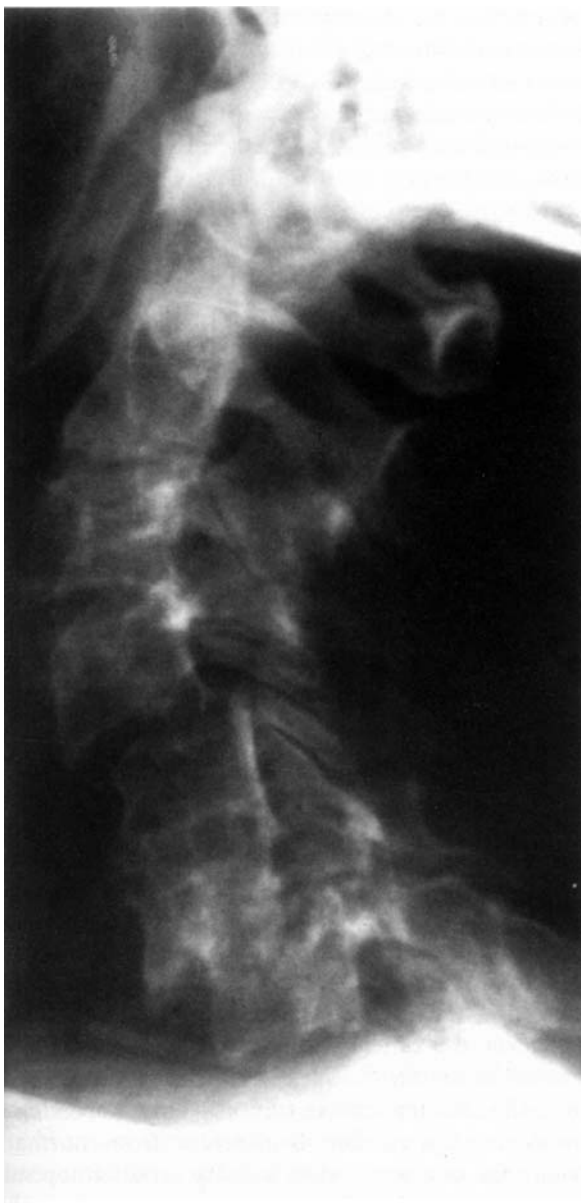

Fig. 20.6 Radiograph of the cervical spine in a long-term CAPD patient who developed destructive spondyloarthropathy. Analysis of the resected vertebral tissue revealed amyloid composed of β2-microglobulin

high in those treating CAPD patients. When adjusted for duration of dialysis the prevalence is likely higher than previously thought.

Tendonitis, Tendon Rupture, and Calcific Periarthritis

Spontaneous tendon rupture can occur in dialysis patients and may be associated with hyperparathyroidism and osteodystrophy. This complication has been described mainly in patients undergoing hemodialysis. However, we have seen a young patient on CAPD with rupture of the quadriceps femoris tendon. Bilateral rupture of the tendon of the long head of the bicep muscle has also been described [367] and was attributed to the strain of the spiking and hanging of the 2-L bag.

Lateral epicondylitis or "spike elbow" has also been described in CAPD [368]. This inflammation may be an overuse syndrome caused by the repetitive insertion of the spike with a twisting and pushing motion.

Calcific periarthritis has also been well described in patients on dialysis, although again it has been more frequently reported in patients on hemodialysis. Deposits of hydroxyapatite, calcium pyrophosphate dihydrate (CPPD), or calcium oxalate [369] can accumulate around the joints and lead to acute attacks of synovitis or periarticular

inflammation. This syndrome has been associated with an elevated calcium-phosphorus product and hyperparathyroidism [370]. In PD patients there is no association between inflammatory arthritis or periarthritis and PTH-induced subperiosteal resorption. These findings suggest that the calcific periarthritis may be related to factors other than parathyroid overactivity or increased calcium-phosphorus product.

Back Pain

The instillation of dialysis fluid into the peritoneal cavity can lead to alteration in spinal mechanics in the upright posture. In the patient with lax abdominal musculature the abdomen protrudes under the weight and volume of dialysate, and this swings the center of gravity anteriorly. The normal lumbar lordosis is inappropriately accentuated.

Many patients entering PD programs are elderly or have been deconditioned by years of illness and poor nutrition. Moreover, some patients have had treatment with corticosteroids or have undergone previous abdominal surgery. It is not surprising, therefore, that the abdominal musculature is often weak, leading to the alteration in spinal mechanics outlined above. In addition, the elderly uremic patient may be at risk of degenerative disc disease, spondylolysis, spondylolisthesis. and osteoporosis. Therefore the combination of intraperitoneal fluid, poor abdominal muscle tone, and intrinsic disease of the spinal column may culminate in back pain. This pain may be the result of paraspinal muscle spasm, posterior facet disease, or sciatica [371]. With the recent emphasis on adequacy of small-solute clearance, many centers are using higher instilled volumes of dialysate, such as 2.5 –3.0 L. The trend may be expected to aggravate posterior facet syndromes in predisposed individuals, especially if they are ambulatory with these larger volumes.

Treatment includes simple back education, where the patient learns the appropriate way to stand, bend over, and lift to minimize strain on the back. Pelvic tilt exercises are simple and can be performed by patients on PD [371]. Judicious use of skeletal muscle relaxants or anti-inflammatory agents may be necessary for short-term relief of symptoms, although the risk of nonsteroidal anti-inflammatory agents to residual kidney function must be taken into account.

In the patient complaining of persistent back pain, further evaluation is warranted. This includes vertebral radiographs to evaluate the bony structures. The opinion of a rheumatologist or physiotherapist may be necessary. Again, though, it is important to let the rheumatologist be aware of the importance of residual kidney function even in patients on dialysis.

The dialysis regimen can be changed to APD. Dialysis in the supine position removes the lordotic stress on the lumbar vertebrae and paraspinal support tissues. Moreover, larger dialysis volumes can be used overnight and smaller volumes during the day. It is advisable to keep some fluid in the day dwell for adequacy considerations, but that will depend on the individual patient and circumstances. With this regimen the adverse effect of intraperitoneal fluid on spinal mechanics is minimized and the patient may be able to perform PD despite abnormal spinal mechanics.

Oxalate Metabolism and Kidney Stones

Oxalate is freely filtered at the glomerulus and secreted in the proximal tubule. As renal function deteriorates, oxalate retention and hyperoxalaemia supervene. The retained oxalate is deposited as the poorly soluble calcium salt in kidney, bone, hyaline and fibrocartilage, myocardium, lungs, central nervous system, and blood vessels (reviewed in [372]). Chondrocalcinosis and pseudogout can be caused by calcium oxalate as well as calcium phrophosphate dihydrate in patients with end-stage renal disease [369].

In patients on CAPD, plasma levels of oxalate are three to five times higher than in controls and are equivalent to predialysis levels in hemodialysis patients [373]. Because of its low molecular weight (90 Da) it is rapidly cleared during hemodialysis and levels fall about 40%. On the other hand, CAPD clears about 300 μmol/day, which approximates the amount synthesized daily. Therefore, CAPD can maintain steady-state plasma levels of oxalate, but at levels much higher than normal [373–375]. Previous studies of oxalate removal by PD should be interpreted in the light of the finding of rising oxalate levels in the drained effluent, suggesting ongoing production of oxalate *ex vivo* in the dialysate [375]. Furthermore, although clearance of oxalate is greater per unit time with hemodialysis, total weekly elimination is similar with CAPD because of the longer time of dialysis [376]. In young patients with oxalosis, a combination of hemodialysis and equilibration (long dwell) PD may be the best combination to keep blood oxalate levels under control until liver/kidney transplantation can be arranged [377].

Ascorbic acid supplements cause a further increase in plasma oxalate levels. One hundred milligrams of oral ascorbic acid results in nearly a 20% increase in plasma levels of oxalate. In patients on CAPD who take vitamins, the benefit of vitamin C supplements should be weighed against the potential hazard of further elevating plasma

oxalate levels. Pyridoxine supplementation does not appear to lower significantly the plasma oxalate or oxalate generation rate in PD patients not taking vitamin C [378].

A significant number of patients on CAPD will pass kidney stones. In one survey [379], 10 of 186 CAPD patients (5.4%) passed renal calculi after 6–9 months on CAPD. Half of these stones were composed of calcium oxalate monohydrate and the rest were made of protein matrix alone or calcium apatite. Metabolic investigation of CAPD patients has demonstrated that, while the total excretion of calcium and oxalate is necessarily diminished, the urinary concentration of oxalate is significantly elevated compared to normals, and the ionic calcium concentration in the urine is lower than normal. However, the calcium oxalate activity product is in the "labile" region and varies according to the urinary ionized calcium concentration. This dependence upon urinary calcium is different from normals, where the calcium oxalate activity product depends upon the concentration of both urinary oxalate and calcium. Therefore, although the urine ionic calcium concentration is low in renal failure, relative increases in this level will significantly influence the activity product and lead to crystallization. The administration of 1,25-dihydroxy vitamin D3 correlates with the urine ionized calcium concentration [379] and could be considered a risk factor for stone formation. Interestingly, intraluminal lithiasis should be kept in mind as a rare cause of obstruction of the PD catheter. Impaction of a calcium-struvite calculus in the intraperitoneal tip of the catheter lumen has been described. The authors suggested that a fibrin clot could have adhered to the catheter and served as a nidus for mineralization in this patient with an elevated calcium-phosphate product [380].

Transplantation

Outcome of Allografts in PD Patients

As CAPD grew in popularity, more data became available on the outcome of renal transplantation in these patients. Two reports from the early 1980s led to concern. A significant increase in the helper to suppressor T-lymphocyte ratio in patients on long-term CAPD was associated with an increased incidence of graft rejection when compared to hemodialysis patients [381] Similarly, a second study found decreased graft survival in patients previously receiving CAPD when compared to those on hemodialysis. This decreased survival was apparent as early as 1 month post-transplant. Again, the patients who had been on PD had a higher ratio of circulating helper T lymphocytes and did not display the T-cell lymphopenia found in the hemodialysis patients [382]. Although the implication is that the increased ratio of circulating T lymphocytes is linked with graft rejection, it has not been demonstrated that the ratio of helper to suppressor T lymphocytes bears any consistent relationship to graft outcome. Unlike hemodialysis patients, CAPD patients did not benefit from pretransplant blood transfusions [382]. Indeed, a fall in panel reactive antibodies was noted in three children with their conversion from hemodialysis to PD, which was attributed to a reduced need for blood transfusion during the latter treatment [383].

Since these two reports, many centers have compared patient and graft outcome in their PD and hemodialysis patients. Many of the studies consisted of small numbers of PD patients, which limits the power of statistical analysis and increases the chance of beta error. However, as pointed out [384], even the studies involving large numbers of PD patients have shown similar, if not identical, graft and patient survival. It is conceivable that the intense immunosuppressive therapy given to transplant patients negates any modest innate difference in immunocompetence between the two dialysis modalities. An analysis of more than 500 patients who survived the first 6 months after transplant demonstrated that duration of dialysis prior to transplant was an important predictor of survival (the more years of dialysis, the higher the mortality), but that modality of dialysis could not predict patient survival [385]. Interestingly, Spanish investigators reported that patients receiving a kidney transplant had a higher incidence of delayed graft function if they were on hemodialysis rather than peritoneal dialysis [386]. The hemodialysis patients had received more blood transfusions beforehand and the kidneys they received had longer cold ischaemia time, and both these factors may have contributed to the delayed graft function. If a patient receives a run of hemodialysis just before receiving the kidney, there may be stimulation of inflammatory cytokines as a result of blood flowing through the extracorporeal circuit, and the patient may be volume-depleted [387]. Both of these factors could contribute to compromising the immediate function of the transplanted kidney. Moreover, the hemodialysis cohort received more immunosuppressive therapy and suffered more late infections compared to those on CAPD pretransplant [386]. More recent analyses support the finding that patients proceeding to renal transplantation from PD, compared to from HD, have a lower incidence of delayed graft function and the need for dialysis postoperatively [388–391]. The exception may be in pediatric patients [392] where modality did not have an impact. Whether the decreased incidence of delayed graft function in adults translates into overall better graft survival is unclear. Data from the United States Renal Data

System suggested a lower incidence of delayed graft function, but higher incidence of early graft loss, in PD patients [393]. The study of Bleyer et al. suggested that despite the difference in delayed graft function, at one year there was no difference in transplant function [394]. However, more recent data from the USRDS over the 1990s suggests that there was better graft and patient survival in patients who were on PD compared to hemodialysis at the time of renal transplantation [395].

There has been a question of a higher incidence of arterial and venous thrombosis of the renal allograft in the perioperative period in patients who were on CAPD compared to those on hemodialysis. A report from the Netherlands documented graft thrombosis in 7.3% of CAPD patients receiving kidneys compared to 3.6% of hemodialysis patients [396]. No obvious reason could be found for the increased thrombosis. In contrast, a review of more than 800 kidney transplants conduced that, if anything, there was a trend towards a higher rate of thrombosis of the allograft in hemodialysis patients [386]. Data from the USRDS reported a higher incidence of graft thrombosis in patients coming from PD compared to HD [393, 397]. In the pediatric patient, where graft thrombosis remains a significant cause of graft loss, peritoneal dialysis continues to be associated with a higher risk of this complication [398].

Other Risks Unique to the PD Patient

The PD patient may face extra risk of infection from the peritoneal cavity and catheter. Previous episodes of peritonitis have been postulated to leave a nucleus of infection that could develop into overwhelming sepsis. The development of peritonitis could pose a life-threatening complication in patients receiving immunosuppressive drugs. The incidence of peritonitis in the post-transplant period does appear to be significant, varying from 5 to 35% if the patient needs to resume PD because of graft nonfunction [399–401]. Peritonitis is easily managed by antibiotics, lavage, and catheter removal if necessary [402], although in one patient it led to death from sepsis [403]. The simultaneous administration of cytotoxic agents does not hamper the response of bacterial peritonitis to antibiotic therapy.

Most centers electively remove the PD catheter about 2–3 months post-transplant, although some remove it at the time of transplant, especially living donor transplants, and haemodialyze the patient as needed thereafter [404]. Because of the risk of bowel perforation, an unused catheter should be flushed regularly and removed no later than 2–3 months after successful transplantation.

Post-transplant ascites has been reported in children [405] and adults who were on CAPD before the transplant. In adults the ascites lasted up to 50 days, but ultimately resolved [406].

Finally, there is the risk of mechanical problems in the PD patient undergoing transplant. The catheter exit site can be close to the transplant bed. (Initial implantation sites of PD catheters should be chosen with this potential problem in mind.) If the PD peritoneum has not been disrupted during transplant surgery, PD can be performed postoperatively, if necessary. There have been reports of drainage of dialysate through the transplant incision [403, 400] and through the site of a transplant nephrectomy [407]. This complication is managed by temporarily stopping PD and proving antibiotic coverage.

Cancer

While cardiovascular and infectious complications comprise the major causes of death in dialysis patients, it is unclear whether there is a higher incidence of cancer and cancer-related deaths in this population. It is possible that, as part of a change in immune function in the dialysis population [408], there is impaired tumor surveillance. Unfortunately, many of these studies are hampered by small sample size, selection bias, and perhaps a bias in favor of increased diagnosis in a more closely monitored population [409]. For example, a survey of hemodialysis patients in Japan showed a higher incidence of cancer in patients dialyzing at university-affiliated hospitals rather than private hospitals. The authors suggested that closer follow-up and higher autopsy rates were responsible for this difference [409]. Studies in hemodialysis patients on the whole demonstrate no real consensus as to whether there is a greater risk of malignancy [410].

Cancer appears to be a relatively rare cause of death in dialysis patients, according to North American registry data. This is because cardiovascular and infectious etiologies eclipse malignancy in this population. There may be some exceptions. Patients with failed renal transplants have a higher incidence of skin cancers, lymphoma, and other malignancies secondary to chronic immunosuppression. Dialysis patients with lupus nephritis who also received immunosuppression with drugs such as cyclophosphamide or chlorambucil may be at increased risk for neoplasia. The risk of cancerous transformation of acquired renal cysts has already been discussed.

A cohort of greater than 800,000 dialysis patients in the United States, Australia and New Zealand, and Europe were compared to the general population with respect to cancer frequency. This analysis suggested a higher risk of neoplasia in patients younger than 35, and overall there was a greater risk of cancer of the kidney [303, 411–413], bladder, thyroid, and other endocrine organs in dialysis patients. Furthermore, excess cancers were seen where a viral etiology is known or suspected, such as cervical, tongue and liver cancers. There was no difference in the higher incidence between those on HD versus those on PD [414].

Analysis of cancer screening of dialysis patients suggests that many of the commonly used tests may have diminished yield in dialysis patients [415]. In combination with the accelerated death rate from cardiovascular disease, the authors suggest that routine cancer screening would not extend the life expectancy of a dialysis patient. Their theoretical treatment using optimal, inexpensive screening tests resulted in a net gain in life expectancy of 5 days or less from screening for breast, cervical, colorectal and prostate cancer [416].

As a public health policy issue cancer screening may not be worthwhile, especially in the elderly patient with significant comorbidity [417]. It still may be good medical practice to employ screening in young, high-risk patients such as those with a failed kidney transplant, or those who have received chronic immunosuppressive therapy for other reasons.

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Chapter 21
Protein-Energy Malnutrition/Wasting During Peritoneal Dialysis

J.J. Carrero, O. Heimbürger, M. Chan, J. Axelsson, P. Stenvinkel, and B. Lindholm

Defining the Problem and Its Magnitude

The kidneys play a key role in maintaining fluid and electrolyte homeostasis, excretion of metabolic waste products, and regulation of various hormonal and metabolic pathways. Even a slight reduction in renal function may therefore have metabolic and nutritional consequences. Patients with chronic kidney disease (CKD) display a variety of metabolic and nutritional abnormalities and a large proportion of the patients demonstrate signs of protein-energy wasting (PEW) [1, 2], and these problems become more severe when patients reach the stage of end-stage renal disease (ESRD) [2, 3], a condition that, by definition, means the need to start life-saving renal replacement therapy by dialysis or kidney transplantation.

PEW is the consequence of multiple factors related to CKD and the development of a state of uremia with its subsequent disturbances in protein and energy metabolism; hormonal derangements; increased catabolism due to acidosis and inflammation; reduced food intake because of anorexia, nausea, and vomiting caused by uremic toxicity; and numerous other causes linked to intercurrent or underlying co-morbidity. As a result, ESRD patients starting dialysis are often suffering from PEW.

In this chapter, we will use the term "PEW" to underline that the nutritional problems as regards protein and energy metabolism in ESRD are usually due both to insufficient nutritional intake and accelerated breakdown of protein and energy stores due to increased net catabolism. We will focus on the problems pertaining adult peritoneal dialysis (PD) patients; however, the problems are often essentially of the same nature in the late and early stages of CKD as well as in patients undergoing hemodialysis (HD).

When dialysis therapy begins, accompanied by reduction of uremic symptoms and liberalization of the diet, some patients may show improved nutritional status [4]. However, many of the indicators of malnutrition that are present at the onset of therapy remain abnormal and some aspects of malnutrition may become even more severe. With PD therapy some of these factors, but far from all, can be partly or fully corrected. On the other hand, additional metabolic and nutritional problems may be induced by the PD procedure *per se*, including dialytic losses of proteins, amino acids, water-soluble vitamins and other essential small molecular solutes, metabolic alterations induced by the glucose absorption from the dialysate, as well as suppression of appetite by glucose absorption from dialysate and abdominal discomfort induced by the dialysate [5].

Prevalence of Protein-Energy Wasting in PD

Several reports have shown a high prevalence of PEW in PD patients, with 18–56% of PD patients showing anthropometric and biochemical evidence of malnutrition [3, 4, 6–11]. Whereas the prevalence and severity of PEW is clearly related to residual renal function [12, 13], the choice of dialysis modality does not seem to play a major role. A few studies have compared the prevalence of malnutrition in PD and HD patients, and in most of these studies no major differences were found [14, 15]. The serum albumin levels among PD patients are often found to be lower than in HD patients, possibly due to the protein losses in dialysate; however, this is not a consistent finding [4]. A common finding is that there is a larger gain in body fat in PD compared with HD patients [4], most likely due to the impact of glucose absorption from the dialysate, and the absence of the intermittent catabolic stimulus associated with the HD procedure.Thus,after initiation of PD, there is improvement of nutritional status with weight gain [16], improved

J. J. Carrero (✉)
Karolinska Institutet, Division of Renal Medicine and Baxter Novum, Stockholm, Sweden
e-mail: juan.jesus.carrero@ki.se

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anthropometric parameters [4, 17], and a rise in plasma proteins [4, 16, 17], indicating an increased net anabolism. Detailed prospective studies using anthropometrics [4, 18], dual energy X-ray absorptiometry (DEXA) [19], and the combination of total body potassium and tritium dilution [20] have all shown that, whereas lean body mass (LBM) seems to be stable, body fat mass may increase considerably in some patients, at least during the first years of treatment with PD. In addition, part of the reported weight gain may be due to increased body water [5].

Implications on Outcome

PEW is an important risk factor for morbidity and mortality in PD patients [4, 8, 18, 21–23], and cachexia has been reported to be a cause of death in such patients [24, 25]. The relation between nutritional status and outcome was studied in detail in the CANUSA study [10, 26], a prospective cohort study of nutrition and adequacy involving 698 PD patients from 14 centers in Canada and the United States. Age, insulin-dependent diabetes, a history of cardiovascular disease, and country (United States versus Canada) were significant demographic risk factors for death, and low serum albumin levels, presence of PEW (as assessed by subjective global assessment; see below), and low normalized protein intake (as assessed from urea kinetics as the protein equivalent of nitrogen appearance rate, nPNA) were significant nutritional risk factors for death [27]. When serum albumin and subjective global assessment were included in the Cox proportional hazards model together with the demographic risk factors, the predictive power of the model increased whereas the additional inclusion of nPNA did not result in any additional increase in the predictive power of the model [26].

However, it should be kept in mind that the relationship between PEW and mortality and increased morbidity (usually assessed as hospitalization rate) is not necessarily a cause-effect one. In addition to uremia, a large proportion of dialysis patients have complicating diseases such as diabetic vascular complications, severe cardiovascular disease (CVD), and other systemic diseases with unfavorable prognosis. Such sick patients may be anorectic and wasted, and PEW may thus be a marker of illness [28–34]. Instead, CVD is by far the most common documented cause of mortality in the dialysis population, while PEW is a reported direct cause of less than 5% of deaths [35]. Although inflammation is often intertwined with PEW (*vide infra*), uremic malnutrition may also predict death independent of inflammatory status [36]. The impact of inflammation on the development of PEW and atherosclerosis are further discussed later in this chapter.

Detecting Malnutrition

Signs of Protein-Energy Wasting in PD Patients

Assessment and monitoring of nutritional status are essential to prevent, diagnose, and treat uremic malnutrition [37]. Common signs of PEW in ESRD patients (Table 21.1) are reduced muscle mass as assessed by anthropometric methods, low serum concentrations of albumin, transferrin, prealbumin, and other liver-derived proteins. However, recent studies have identified additional factors influencing the nutritional status that constitute a new challenge to physicians and dietitians for management of PD patients. Examples of such additional factors are co-morbidities such as diabetes (which requires integration of another special diet) and psychosocial issues (e.g., aging, depression, and dependence). These additional signs of PEW that should be also evaluated when assessing the nutritional status of the patient are summarized in Table 21.2. Patients should be also encouraged to be proactive to report any decline in oral intake and physical function. This self-awareness and reporting of signs of deterioration should be part of the education program that would overall contribute to the early detection and management of this condition.

Methods of Diagnosing Protein-Energy Wasting in PD Patients

In order to prevent and treat PEW in dialysis patients, it is important to appropriately assess the nutritional status and to identify patients at risk [15, 38–40]. Validation of nutritional status may be based on clinical evaluation, anthropometric measurements and various biophysical and biochemical methods. Based on the complex nature of nutrition, involving several different components like fat mass, lean body mass, plasma proteins, etc., at different stages of malnutrition (Fig. 21.1), there is no single best nutritional marker. Instead, several nutritional markers should be

Table 21.1 Common signs of protein-energy malnutrition/wasting in PD patients

Dietary intake
Poor appetite
Protein protein intake (estimated by nPNA[a]) <0.8 g/kg SBW[b]/day
Total caloric intake <35 kcal/kg SBW/day
Anthropometrics and body composition
Body mass index <20 kg/m^2(severe <18 kg/m^2)
Weight loss by 10–15% or more in dry weight
Reduction in anthropometrics (handgrip strength, skinfold thickness and midarm muscle circumference; <15th percentile = moderate; <5th percentile = severe malnutrition/wasting).
Low percentile (<85%) of standard body weight
Decreased lean body mass and body fat mass
Subjective Global Assessment (SGA; B or C)[c]
Total body nitrogen and total body potassium are low
Biochemical signs
Low essential plasma amino acids.
High nonessential plasma amino acids.
Low serum urea and creatinine, potassium, and phosphate[d]
Low (<3.5 g/dL) serum albumin[e]
Low insulin-like growth factor –1 (<300 ug/L), transferrin (<200 mg/dL), prealbumin (<30 mg/dL), cholesterol (<150 mg/dL)

[a]nPNA, protein equivalent of nitrogen appearance in urine and dialysate, normalized to actual or desirable body weight
[b]SBW, Standard body weight
[c]B, mild to moderate malnutrition/wasting; C, severe malnutrition/wasting
[d]Needs to be interpreted in relation to metabolic status and solute removal rates
[e]Note that serum albumin is *not* a reliable nutrition marker

Table 21.2 Additional factors to be considered when evaluating nutritional status and implementing appropriate dietary measures

Co-morbidities:
Diabetes
Hypertension
Obesity
Dyslipidemia
Cardiovascular disease
Other medical conditions affecting nutritional status, e.g., disease of the gastrointestinal tract, cancer
Life-cycle:
Aging and age-related issues, e.g., poor dental status, taste changes
Menopause
Physical:
Deconditioning, inactivity
Functional status
Sarcopenia
Psychosocial issues:
Lifestyle and behavior:
Attitude
Perceived illness and need for intervention
Self-efficacy
Depression
Cognitive state, ability to shop and prepare meals
Cultural factors, health and food interest
Dependence: living or consuming meals alone
Economic and income factors
Family and social supports
Educational:
Education and literacy levels
Clarity and quality of instruction

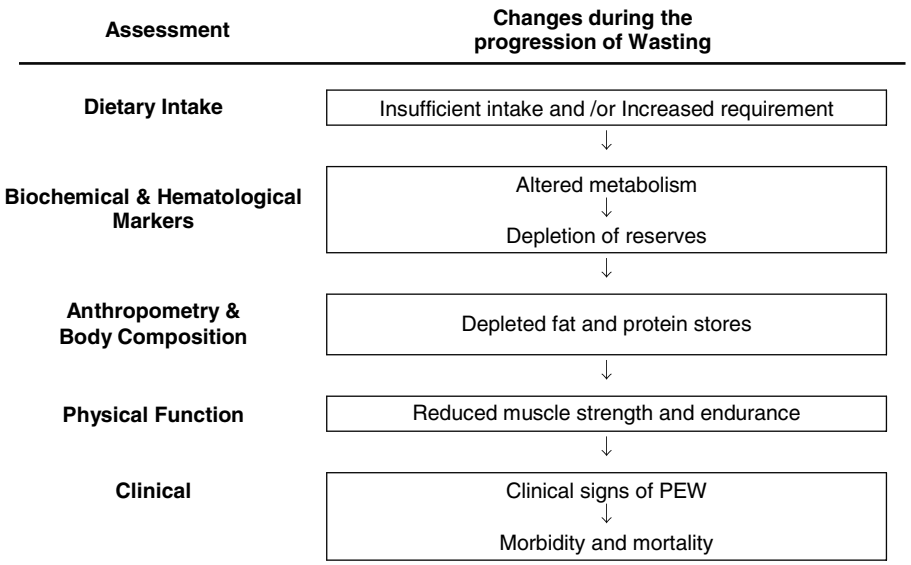

Fig. 21.1 Monitoring of Nutritional Status
Note: Combining the use of SGA at any stages is useful to indicate the degree and progress of malnutrition

evaluated together in PD patients as well as in other patients with CKD. Serum albumin and the method of subjective global assessment of nutritional status (SGA) [1, 3, 41, 42] are the most commonly used methods to identify PEW in these patients. However, serum albumin cannot be considered as a reliable nutritional marker (see below).

Subjective Global Assessment (SGA) of Nutritional Status

SGA has been widely used in both dialysis patients [3, 41, 42] as well as in patients with ESRD starting dialysis therapy [1]. SGA has been demonstrated to have good correlations to other nutritional markers in dialysis patients [3, 41] as well as to have a high predictive value for mortality in patients starting dialysis therapy [26]. However, one potential problem with SGA is its subjective nature, which may reduce its reproducibility; therefore, small differences in SGA score must be interpreted with great caution. In general, SGA may differentiate severely wasted patients from those with normal nutrition, but it is not a reliable predictor of degree of malnutrition [43]. Validation studies in other renal populations have confirmed the usefulness of SGA for continuous monitoring [44, 45]. However, though SGA is commonly used for the follow up of PD patients, validations of SGA in the PD population are still warranted. Furthermore, the definition of SGA may vary between different studies in CKD patients and there is a need to establish the validity and reliability of different SGA versions among these patients [46]. Malnutrition-Inflammation Score (MIS) is a quantitative assessment tool based on SGA, which adds some biochemical markers as serum albumin. In a recent study, this score proved to correlate well with clinical, nutritional, inflammatory, and anthropometric parameters and anemia indices in PD patients [47]. A validated nurse-performed nutrition-screening tool (NST) developed for HD patients has also shown to be valuable in identifying nutritionally at-risk patients [48]. This may also benefit the PD units to prioritize patients needing dietitian intervention, especially in facilities that do not have on-site or regular dietetic support.

Anthropometrics and Other Commonly Used Body Composition Measurements

Other common methods are anthropometry (such as skinfold thickness and calculation of midarm muscle circumference, MAMC), handgrip strength, bioimpedance (BIA), and DEXA (Table 21.3). Measurements of actual body weight, height, and frame size are easy to obtain and can be used to provide estimates of normal body weight, body mass index, and other height-to-weight indices. In ESRD patients, the pre-uremic weight for a patient may represent a target weight. Weight gains or losses in ESRD patients are influenced by the fluctuating state of hydration in these patients, which is a consequence of dialytic therapy, use of diuretics, and fluctuating fluid intake. Handgrip strength is not only a marker of lean body mass but also provides important prognostic information [1, 42, 49], at least in males [23]. Bioimpedance is affected by fluid status and may therefore be a less reliable tool in dialysis patients. DEXA

Table 21.3 Advantages and disadvantages of available techniques to measure body composition in PD patients

Method	Advantage	Disadvantage
Dual-energy x-ray absorptiometry	Direct measurements of bone mineral content/density, fat body mass and body compartments (truncal body mass)	Lean body mass may be influenced by hydration; cost and availability
Anthropometrics	Easy to perform; noninvasive; reproducible to 90% confidence level	Interobserver error; less sensitive
Bioelectrical impedance	Noninvasive; quick	Indirect method; influenced by hydration and electrode site; more sensitive to changes in the limbs than to changes in the trunk
Creatinine kinetics	Low cost; ease of calculation	Influenced by catabolism, residual renal function and hydration, meat intake and changes in creatine metabolism; large intra-patient variability
Total body potassium	Noninvasive; accurate; reproducible	Cost; relatively insensitive to change over time; low availability
Total body nitrogen	Very accurate; reveals subtle changes	Cost; lack of availability; does not distinguish inert nitrogen from muscle nitrogen

is increasingly used and is now considered as a practical tool to estimate lean body mass and fat mass [1], although skinfold thickness may be a better method to assess subcutaneous fat [50]. However, estimation of truncal fat mass by waist circumference [51] or DEXA [52] is of particular interest because of its link with adipokine-related inflammation and the metabolic syndrome.

Creatinine kinetics (CK) has also been used to calculate LBM in PD patients from creatinine excretion in the urine and dialysate. However, the estimated LBM from CK is usually markedly lower than with other methods such as total body potassium [53], anthropometry [54, 55], bioimpedance [54, 56], or DEXA [56–58]. Furthermore, LBM estimated from CK is dependent on the creatinine content in the diet (mainly related to the meat content), and the metabolic degradation of creatinine, which is poorly understood in uremia [53, 59, 60]. Finally, the variation in LBM with repeated measures of LBM using CK is unacceptably high [53]. Therefore, CK is not a good method for monitoring of LBM in PD patients.

Biochemical Diagnosing Methods: Serum Albumin, Other Plasma Proteins, and Amino Acids in ESRD

Serum albumin has by far been the most commonly used marker of nutritional status in ESRD patients [28]. However, serum albumin levels in ESRD patients are influenced by several other factors [28, 33, 61]; a low serum albumin level mainly represents the acute phase response, fluid overload, and albumin losses in dialysate and urine, and only to a lesser extent reflects a poor nutritional status [28, 61, 62]. The same is true also for other plasma proteins such as prealbumin, transferrin, and retinol-binding protein [63]; as for serum albumin, there is considerable overlap between serum levels of these proteins between wasted and well-nourished patients [1]. While they predict clinical outcome, this is mainly because they are also negative acute phase proteins [1]. Plasma amino acid levels are also abnormal in ESRD patients in whom the levels of essential amino acids are low while nonessential amino acids are often high, and dialysis does not reverse these abnormalities [7, 42].

The plasma insulin-like growth factor (IGF)-1 level in nonuremic patients is more sensitive and more specific than other nutrition-related serum proteins. IGF-1 has also been shown to be a sensitive marker of wasting in both HD and PD populations. In a large cohort of ESRD patients prior to the commencement of PD therapy, IGF-I appeared to correlate well with markers of PEW and sarcopenia; however, IGF-I was also influenced by age [64]. As a disadvantage, IGF-1 concentrations have wide confidence limits in normal people, making it difficult to identify wasted patients and, in renal failure, levels may be either artificially lowered or raised because of alterations in IGF-binding proteins.

A multidisciplinary team approach including both biochemical and nonbiochemical diagnosing methods is likely the key for a successful identification of patients at nutritional risk. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommends a range of routine measures to be performed and frequency of performance in order to identify the development or progression of PEW [65]; serum albumin and post drained body weight are recommended to be measured monthly; standard body weight (%) and nPNA are recommended to be measured every 3–4 months, while SGA and diet interviews should be performed every 6 months.

Causes of Protein-Energy Wasting

A variety of causes contribute to impaired nutritional status in ESRD patients. When dialysis therapy begins, the uremic symptoms are reduced, the diet is less restricted and most patients may show improved nutritional status. However, anorexia may persist in PD patients and many of the catabolic factors found at onset of therapy remain abnormal (Table 21.4). Furthermore, the dialytic procedure induces additional catabolic factors (Table 21.4), in particular dialytic losses of proteins (5–15 g/24 h) and hence increases the protein requirements above those for nondialyzed uremic patients. However, despite the increased nutritional requirements, ESRD patients often maintain a low nutritional intake because of anorexia, nausea, and vomiting, caused by uremic toxicity (due to underdialysis), medications and unpalatable diets, infections, and other complicating illnesses. In addition, PD patients may experience aggravated anorexia due to absorption of glucose or amino acids from the dialysate as well as abdominal discomfort induced by the dialysate (Table 21.5).

The observation that PD patients seem to have a decreased utilization of ingested protein and increased protein requirements, compared to healthy subjects indicates that several metabolic factors that are not fully corrected by the treatment, as well as effects of the treatment *per se*, may enhance net protein catabolism and impair the utilization of dietary protein (*vide infra*). Furthermore, many PD patients are physically inactive due to several factors such as fatigue, anemia, and intercurrent diseases. Physical inactivity may result in muscle-wasting and a negative nitrogen balance [66].

Anorexia

Anorexia, defined as the loss of the desire to eat, is relatively common in PD patients, contributes largely to PEW, affects quality of life, and is associated with an increased risk of morbidity and mortality [67, 68]. In a cross-sectional

Table 21.4 Catabolic factors present in ESRD and PD patients that may contribute to PEW

Factors due to uremia per se
Anorexia caused by increased circulating levels of anorexins like cholecystokinin, leptin, and proinflammatory cytokines.
Abnormal protein and amino acid metabolism.
Metabolic acidosis
Decreased biologic activity of anabolic hormones, such as insulin and IGF-1.
Increased circulating levels of pro-inflammatory cytokines and catabolic hormones, such as parathyroid hormone.
Abnormal energy metabolism, carbohydrate intolerance, and impaired lipid metabolism
Other catabolic factors
Fluid overload and congestive heart failure.
Co-morbidity such as cardiovascular disease, diabetes, chronic obstructive pulmonary disease, infections, and chronic inflammation
Gastrointestinal problems.
Physical inactivity.
Factors related to peritoneal dialysis
Losses of proteins, amino acids, and other essential nutrients in dialysate.
Suppression of appetite by glucose absorption from dialysate and abdominal discomfort.
Infectious complications, such as peritonitis and exit site infection.

Table 21.5 Anorectic factors present in PD patients

Induced by the PD procedure
Abdominal discomfort induced by the dialysate
Absorption of glucose from the dialysate
Peritonitis
Other causes
Uremic toxicity (underdialysis)
Increased circulating levels of anorexins such as cholecystokinin, leptin, TNF-α, and other cytokines
Reduced circulating levels of orexigens such as neuropeptide Y
Unpalatable or inadequate diets
Gastropathy (particular in diabetes)
Medications
Psychosocial factors such as poverty, loneliness, and depression

comparison, PD patients were found to have blunted hunger and lower fullness profile scores as compared to the controls. Interestingly, PD patients normalize their mean appetite perception at a lower level of nutrient intake than controls as assessed by 3-day dietary record [69]. Considering all evidence that the requirements for protein are increased in PD patients and that an adequate energy supply is crucial for optimizing utilization of ingested protein, low protein and energy intakes must be especially harmful in such patients.

Low Protein Intake

A large proportion of PD patients ingest a considerably lower amount of protein than the recommended intake of 1.0–1.2 g/kg body weight/day [8, 11, 70–72]. This may be especially harmful as energy intake also has been reported to be low in spite of the additional supply of energy from the amount of glucose absorbed from the dialysate [15]. Metabolic studies indicate that the utilization of protein is greatly dependent on the energy intake, so that a low-energy intake reduces utilization, whereas a high energy intake has a protein-saving effect [73]. In PD patients, the nitrogen balance is strongly correlated to the total energy intake [15]. About 70% of the 24-h peritoneal glucose load is absorbed from dialysate in PD patients with normal peritoneal transport characteristics [74]. Thus, 100–200 g of glucose will be absorbed per day, averaging about 8 kcal/kg BW/day (varying between 5–20 kcal/kg BW/day), which should be advantageous regarding the utilization of protein [74]. However, despite glucose uptake, many PD patients have a total energy intake below 35 kcal/kg BW/day [75–77]. Considering that many patients on PD ingest less than 35 kcal/kg BW/day, energy deficiency may be an important factor contributing to poor utilization of dietary protein [78].

Anorectic Factors

The cause(s) of anorexia among PD patients are multifactorial and include the release of neurotransmitters (e.g., serotonin), neuropeptides (e.g., neuropeptide Y, orexin), the concentrations of gut-to-brain signaling factors (e.g., cholecystokinin), uremic toxins, and cytokines (e.g., tumor necrosis factor (TNF)-α, leptin, interleukin (IL)1-β) [79]. The plasma levels of several anorectic factors like cholecystokinin, neuropeptide Y, leptin, TNF-α and IL-6 are markedly increased among PD patients [80–82]. Recent research suggests that inflammatory cytokines interact with several pathways in the central nervous system to affect specific brain areas related to the appetite regulation. These exciting findings reinforce the putative links between inflammation and development of anorexia. Studies targeting inflammation or hyper-adipokinemia to improve anorexia in PD patients are warranted. This will be further discussed later in this chapter.

Underdialysis and Uremic Toxicity

Anorexia, nausea, and vomiting are traditionally signs of severe uremic intoxication. It is a common clinical experience that uremic patients who are anorectic regain appetite after the initiation of maintenance dialysis. This suggests that uremic toxins causing anorexia have been removed by dialysis. Assuming that dialyzable uremic toxins accumulate in severe renal failure and causes anorexia, it is conceivable that underdialysis may affect the appetite [83]. There are studies in HD and PD patients that report a correlation between the dose of dialysis for small solute removal (Kt/V_{urea}) and protein intake (as assessed by urea kinetics), especially in the lowest dose intervals [30, 84, 85], although there is no consensus if this relationship is a physiological relationship [86] or a mathematical artifact [87–89]. It has been argued that the relationship between Kt/V_{urea} and protein intake (urea appearance) reflects a mathematical coupling rather than a biological relationship as the two variables are to some extent dependent (both are normalized to body size and both are dependent of urea excretion in dialysate and urine) [87, 89]. However, protein intake as assessed by dietary recall also show similar relationships to Kt/V_{urea} [78] but increasing the dose of PD in prospective studies show mixed results on protein intake [90–92].

Abdominal Distension and Absorption of the Osmotic Agent

The presence of dialysate in the peritoneal cavity may suppress appetite due to interference with gastric emptying and abdominal discomfort due to low pH and high osmolarity of the solution, the increased hydrostatic pressure and, furthermore, absorption of the osmotic agent from the dialysate may also contribute to a reduced appetite in PD patients.

Upper gastrointestinal symptoms are common among PD patients [93], and a high frequency of gastroesophageal reflux [94] and retarded gastric emptying for solid foods has also been reported in patients treated with PD [95–97], especially in diabetics [97]. It is, however, not established how much of these changes that may be related to PD *per se*,

as diabetes is well known to cause delayed gastric emptying due to autonomic neuropathy, and delayed gastric emptying also has been reported in HD patients [98]. Furthermore, the presence of fluid in the peritoneal cavity did not affect intragastric or lower esophageal sphincter pressure in a study of eleven PD patients [99]. Hylander et al. [100] showed that PD patients had a significantly lower food intake than the HD patients, whereas both the PD and the HD patients had a reduced food intake and eating velocity compared to the healthy controls [100]. Moreover, no differences in food intake or eating velocity were observed among the PD patients with full compared to empty abdomen, indicating that the higher sugar load contributes to the feeling of fullness and is more important than the discomfort caused by the dialysate [100].

Balaskas and co-workers [101] reported that intraperitoneal infusion of high osmolality solutions and large filling volumes suppressed the appetite in rabbits. However, absorption of glucose and amino acids from the dialysate did not seem to have specific appetite-suppressing effect [101].

These results are in agreement with a crossover study in 16 PD patients that did not show any difference in subjective appetite and food intake during a 4-week period with one daily exchange with amino acid–based dialysis fluid compared to a control period with glucose-based dialysis fluid [102]. A experimental model was designed for the study of ingestive behavior in unstressed, free-moving, male Wistar rats with catheters channeled from the top of the scull to the oral cavity [103, 104]. This model showed that intraperitoneal injection of up to 30 mL 0.9% NaCl solution did not affect protein or carbohydrate ingestion [104]. Intraperitoneal injection of PD solutions containing 13.6, 22.7, and 38.6% of glucose induced a dose-dependent inhibition of sucrose intake but had no effect on protein intake, whereas intraperitoneal injection of amino acid solutions reduced the ingestion of both sucrose and protein in a dose-dependent manner [104]. These results indicate that the inhibition of appetite caused by solutions containing glucose or amino acids is specific to each nutritional constituent and not simply an effect of hyperosmolarity of large filling volumes. Zheng et al. found that lactate solutions may inhibit appetite more than bicarbonate solutions [105], and that the degree of appetite inhibition was higher with a higher concentration of glucose [106]. However, Davies et al. reported that calories derived from the dialysate in PD patients do not suppress appetite, but instead provide a useful and significant proportion of the total energy intake, that does not necessarily cause excessive obesity or have a negative effect on patient survival [107].

Protein and Amino Acid Losses in Dialysate

The average dialysate losses of free amino acids into the dialysate during PD are reported to vary between 1.2 and 3.4 g/24 h in different studies [39]. About 30% of the amino acids lost into the dialysate are essential amino acids. The weekly losses of amino acids into the dialysate are of the same order of magnitude as in HD patients [39].

Substantial loss of protein into dialysate is a major drawback with PD which is not present in HD. The reported average loss of protein into the dialysate varies between 5 and 15 g/24 h in different studies with large interindividual differences [39, 108–111]. Albumin is the main constituent comprising of 50–65% of the total protein loss, but several other proteins are also present in the dialysate [108–110] in amounts depending on the serum concentrations and peritoneal clearances of the different proteins. The peritoneal clearances of proteins of different molecular weight show a bimodal pattern [112–114]. The clearances of proteins up to the size of albumin is related to the ultrafiltration rate and inversely related to the molecular weight of the protein, whereas the larger proteins show a much smaller decrease in clearance with increasing molecular weight, and the clearances of large proteins are, furthermore, independent of the ultrafiltration rate [112–114].

It should be noted that protein losses indirectly may contribute to various nutritional and metabolic disturbances in patients on PD: e.g., low HDL cholesterol levels due to losses of apolipoproteins in the dialysate [115], hypercholesterolemia, increased lipoprotein(a) levels [116], altered amino acid metabolism, and metabolic bone disease due to losses of vitamin D binding protein [39]. Furthermore, the serum albumin concentration in PD patients show an inverse correlation to peritoneal albumin loss in several studies [17, 29, 32, 114, 117]. Thus, although albumin loss seems to stimulate the albumin synthesis rate [117] this may not always be enough to prevent a fall in serum albumin levels.

Peritoneal Transport Rate

As there is a close relationship between the peritoneal transport characteristics of solutes of different molecular weight up to the size of albumin [113, 118], it is not surprising that PD patients with relatively high transport rates of small solutes as assessed by the dialysate to plasma concentration ratios (D/P) during the peritoneal equilibration test (PET),

also exhibit increased protein losses and that these patients have more severe hypoalbuminemia than patients with lower D/P ratios [32, 119–123]. The patients with high transport rates have been reported to have lower nPNA and lower daily creatinine production (indicating lower muscular mass) compared to patients with lower D/P values during the PET [120, 121] and, furthermore, the morbidity has been reported to be increased among the patients with high transport rates [121, 124, 125], although this has not been seen in all studies [119, 126]. Also, Kang et al. [127] reported on a correlation between a nutritional index and peritoneal transport characteristics, but serum albumin was included in the nutritional index used in this study. In the CANUSA Study, no difference was found in nutritional status at start of treatment (except for serum albumin) between patients in different peritoneal transport groups [124]. Another study reported no differences in anthropometrics between PD patients with high versus low peritoneal transport rates [122]. Selgas et al. found no difference in nPNA between different transport groups in a prospective study, and although they reported on a higher hospitalization rate among patients with high transport rates, they found no impact of peritoneal transport rates on long-term morbidity and mortality [119]. Furthermore, Szeto et al. found no change in nutritional parameters in relation to transport status during 24 months in a prospective study of 235 continuous ambulatory peritoneal dialysis (CAPD) patients [128]. As seen from the literature, there is poor evidence that peritoneal transport characteristics will influence nutritional status (other than the influence on serum protein levels) in PD patients [128]. Possible links between high peritoneal transport status and the poor outcome seen in several studies is the risk of fluid overload in high transporters [125, 129] and we have also seen that there is a relation between high peritoneal transport rate, inflammation, and cardiovascular disease [130, 131]. It is striking that the relation between peritoneal transport rate and serum albumin [124] and some other nutritional markers was seen already at start of PD [128]. Therefore, it is likely that the relation between peritoneal transport and some nutritional parameters seen in some of the studies discussed above, in fact, are due to a relation between peritoneal transport and the malnutrition, inflammation, and atherosclerosis (MIA) syndrome [132]. High peritoneal membrane transport characteristics may merely be another feature of the MIA syndrome.

Metabolic Acidosis

It has become increasingly evident that metabolic acidosis is an important stimulus for net protein catabolism, which elicits the transcription of genes for proteolytic enzymes in muscle including the ubiquitin–proteasome pathway [133, 134]. In nondialyzed chronic uremic patients, the correction of metabolic acidosis improves nitrogen balance [135], and decreases protein degradation [136]. This latter effect seems to be mediated by the stimulation of skeletal muscle branched-chain keto acid decarboxylation, resulting in increased catabolism of the branched-chain amino acids (valine, leucine, and isoleucine), which are mainly metabolized in muscle tissue [133, 134].

PD patients with metabolic acidosis were reported to be more wasted compared with other patients using a composite nutritional score [72]. The buffer concentration in the dialysate (lactate 40 versus 35 mmol/L, bicarbonate/lactate 25/15 versus 25/10 mmol/L, bicarbonate 39 versus 34 mmol/L) needs to be individualized, and many patients will need the higher concentrations to avoid acidosis [137–140]. In PD patients using the lower buffer concentrations, acid–base status may be improved by a switch to the higher dialysate buffer concentrations, and oral bicarbonate supplementation may also be used to improve the acid–base status. Correction of acidosis (from an HCO_3 level of 19–26 mmol/L) with oral sodium bicarbonate in seven PD patients resulted in an improvement in protein turnover with decreased body protein degradation [141].

Also, improvement in the acid–base status in PD patients has been shown to result in increased body weight and plasma branched chain amino acids, and reduced muscle levels of ubiquitin mRNA [142]. Two hundred consecutive new PD patients were randomized, in a single-blind fashion, to receive a high (lactate 40 mmol/L) or low (lactate 35 mmol/L) alkali dialysate for 1 year [143]. Calcium carbonate and sodium bicarbonate were also used to correct acidosis in the high alkali dialysate group. At 1 year, the mean venous serum bicarbonate was 27.2 mmol/L in the high alkali dialysate group, and 23.0 mmol/L in the low alkali dialysate group ($p < 0.001$). It was concluded that better correction of metabolic acidosis leads to greater increases in body weight and midarm circumference, but not in triceps skinfold thickness, as well as reduced hospitalization in the first year of PD.

A randomized placebo-controlled, double-blind trial of oral sodium bicarbonate supplementation in 60 PD patients (30 in each group) with mild acidosis (plasma bicarbonate <25 mmol/L, on average 22.9 mmol/L) and a Kt/V <2.1 demonstrated that the patients randomized to oral bicarbonate (2.7 g/day) showed improved bicarbonate levels, a better nutritional status as regards SGA and nPNA, and had shorter hospitalization compared with the control group [144]. Thus, full correction of acidosis is an obvious goal for treatment in PD patients, and oral bicarbonate should be prescribed even when the blood standard bicarbonate level is only marginally decreased.

Loss of Residual Renal Function and Metabolizing Renal Tissue

The normal kidneys actively take part in the metabolism of amino acids and loss of metabolizing renal tissue may be one important pathogenic factor for the amino acid abnormalities frequently observed in uremic patients [39, 83]. Healthy kidneys are responsible, among other processes, of phenylalanine hydroxylation to tyrosine [145, 146] and glycine conversion to serine [147].

Low plasma and intracellular concentrations of tyrosine and a reduced ratio of tyrosine to phenylalanine are common in dialysis patients, while serine depletion appears to become more severe than in nondialyzed patients, since not only the plasma concentration but also the muscle concentration of serine is low [15].

It is possible that dialysis patients have less metabolizing renal tissue left compared to nondialyzed uremic patients, implying that under conditions of low protein intake or increased catabolic stress, depletion of valine, tyrosine, and serine may become limiting for protein synthesis in maintenance dialysis patients. This may partly explain why loss of the residual renal function was the factor that was most closely connected to severe PEW in a large cross-sectional PD study of nutritional status [3]. Poor residual renal function has also been shown to correlate to malnutrition in several other studies [70, 123, 148, 149] and Wang et al. reported that residual renal function has an independent and more important effect than peritoneal clearance on protein intake, energy intake, and intake of other nutrients in PD patients [150].

The residual renal function is reported to be better preserved in patients on PD than in patients treated with HD [151, 152]. PD patients often have some residual renal function several years after start of dialysis therapy [151], which may, at least in part, explain why the intracellular free amino acid pattern in muscle seem to be less abnormal in PD patients than in HD patients [7]. On the other hand, there seems to be a close relation between inflammation and more rapid decline of residual renal function in PD patients [130].

Recurrent Peritonitis and Other Infections

Uremia leads to disturbances in the immune response, with cutaneous anergy and impaired granulocyte function, thus increasing the susceptibility to infections. Peritonitis rate seems to be higher in PD patients with PEW and malnutrition indices, especially SGA, can predict the peritonitis rate in PD patients [153, 154].

In PD patients with mild peritonitis the dialysate protein losses increased by 50–100% to an average of 15 ± 3.6 g/24 h [155], remaining elevated for several weeks [6]. In addition, the spontaneous energy and protein intake has been shown to be extremely low during peritonitis [156] and, furthermore, the inflammatory response may be a strong catabolic stimulus superimposed on the enhanced protein losses. Thus, PD peritonitis was followed by a markedly negative nitrogen balance [156, 157].

Dialysis Procedure: Comparisons Between HD and PD

Compared to the HD procedure, PD appears to be a less strong catabolic stimulus, provided that the patient is free from peritonitis. One reason for this is that the blood-membrane contact during the HD procedure may give rise to an inflammatory reaction, the intensity of which depends on the membrane material that is used [158–160]. Other documented nutritional advantages of PD over HD observed include better control of acidosis, maintenance of residual renal function, lower protein turnover rate, lower catabolic effects from biocompatible membrane, and lack of fluctuating levels of small and middle size uremic toxins, which could lead to better appetite in PD patients, as previously discussed.

Despite the factors that may positively influence nutrition in PD patients there is, however, additional catabolic stress factors specific to the treatment modality (Table 21.6). There is a possibility that in PD the dialytic procedure *per se* elicits a low-grade inflammatory response stimulating protein catabolism through substances other than live bacteria present in the sterile dialysate. These substances could be microbial products (endotoxins, peptidoglycans), plastics, silicon, glucose break-down products [161], or other as-yet unknown products that elute into the peritoneal cavity. Treatment with PD also involves other catabolic factors, such as loss of appetite, insufficient removal of small solutes, dialysate loss of proteins and amino acids, and recurrent peritonitis [15, 39]. In addition, the continuous supply of glucose (100–200 g/24 h and estimated to be as much as 16–22% of the total caloric intake) and lactate from the dialysate represents a sizeable and perhaps undesirable energy load that displaces other caloric

Table 21.6 Catabolic effects of the dialytic procedure

	PD	HD
Loss of animo acids	2–4 g/day (14–28 g/week)	9–13 g/dialysis (27–39 g/week)
Loss of glucose	(uptake)	~25 g/dialysis (glucose-free dialysate)
Loss of peptides	?	2–3 g/week
Loss of protein	5–15 g/day (higher with peritonitis)	
Inflammatory stimuli	Low-grade inflammation? (particles, chemicals) Cytokine release due to peritonitis	Blood-membrane contact Cytokine release due to • complement activation • endotoxins • acetate

sources and limits protein intake while still maintaining energy intake. This indeed may induce or accentuate hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and other metabolic abnormalities [74].

Inflammation as a Cause of PEW in PD

The strong impact of inflammation on nutritional status is of importance for understanding how to best treat or prevent PEW in PD patients. As oral nutritional supplements or intradialytic supplementation have proved either only partially effective [162] or totally ineffectual [163] in the repair of nutritional status in the majority of patients, it is suggestive that other factors may be responsible for inadequate nutritional status in this group of patients. The putative associations between inflammation and malnutrition in PD patients are separately discussed in the next section within the context of the malnutrition-inflammation-atherosclerosis (MIA) syndrome.

Malnutrition-Inflammation-Atherosclerosis (MIA) Syndrome in PD

Malnutrition and Wasting: Clarification of Concepts

Malnutrition is commonly associated with decreased body weight, depleted energy (fat tissue) stores, and loss of somatic protein (low muscle mass). Moreover, it has been stated that low plasma levels of serum albumin, transferrin, prealbumin, and other visceral proteins accompany malnutrition. However, the synthetic rate of various serum proteins used as nutritional markers, such as serum albumin, prealbumin, retinol binding protein, and serum amyloid A, are vulnerable to the effects of inflammation. We found, for instance, that albumin as well as plasma amino acid concentrations are low in CKD patients with inflammation and are inversely correlated with concentrations of inflammatory markers [164]. Consequently, their use as nutritional markers in dialysis patients may be problematic. In fact, in healthy subjects subjected to semi-starvation [165], or in patients with anorexia nervosa [166], serum albumin levels decline only modestly. Heimburger et al. [1] reported that serum albumin levels did not differ significantly between well-nourished and wasted predialysis patients, whereas the presence of inflammation was associated with much lower serum albumin levels. Based on these findings we have proposed two types of malnutrition in CRF patients [34], one (Type 1,; semi-starvation) that is associated with poor nutritional intake due to anorexia and the uremic syndrome *per se,* while the other type (Type 2; wasting) is associated inflammation and co-morbidity (Table 21.7). In Type-1 malnutrition, in which inadequate nutritional intake is the predominant cause, one would expect that nutritional supplementation alone would be effective in restoring nutritional deficits. However, as mentioned above, as oral nutritional supplements or intradialytic supplementation have proven either only partially effective [162] or totally ineffectual [167] in the repair of nutritional status in the majority of patients, it is suggestive that other factors may be responsible for inadequate nutritional status in this group of patients. As inflammation may not only decrease protein synthesis but also raise resting energy expenditure and protein catabolic rate, another type of malnutrition (i.e., wasting) has been proposed, in which a consistent inflammatory response and advanced co-morbidity are the predominant causes. This inflammation-driven Type-2 malnutrition with hypercatabolism and failure to deposit nutrients caused could be the main reason for a poor nutritional status, and this condition is therefore much more

Table 21.7 Proposed features of Type-1 and Type-2 malnutrition. Note that most patients with PEW have a combination of Type-1 and Type-2

	Type-1	Type-2
Denomination	Pure malnutrition: caused by low nutritional intake	Wasting: caused by inflammation, increased catabolism, and decreased anabolism
Characteristics:		
Serum albumin	Normal/low	Low
Co-morbidity	Uncommon	Common
Presence of inflammation	No	Yes
Food intake	Low	Low/normal
Resting energy expenditure	Normal	Elevated
Oxidative stress	Increased	Markedly increased
Protein catabolism	Decreased	Increased
Reversed by dialysis and nutritional support	Yes	No

difficult to treat by pure nutritional means, unless one also treats inflammation and co-morbidities [34]. In fact, O'Keefe and Daigle [168] found that there are two different groups of malnourished dialysis patients: those consuming adequate protein and calories, presenting with hypoalbuminemia, and those suffering from a protein calorie deficit. Interestingly, in most studies on nutritional supplementation in ESRD patients, a low serum albumin level, a hallmark of inflammation, was used as an inclusion criterion. Accordingly, based on the discussion above, it is not surprising that nutritional intervention may not always result in beneficial effects on nutritional status. As cytokines have catabolic effects on protein metabolism as well as central nervous effects resulting in anorexia, an up-regulated cytokine activity may be a cause of inadequate food intake in Type-2 malnutrition. However, as proposed by Dinarello and Roubenoff [169], cytokines may perhaps play a less important role in the pathogenesis of loss of muscle mass in patients with PEW as muscle wasting increases and curtails the synthesis of cytokines, which can be viewed as a protective mechanism. Nevertheless, in the clinical setting, Type-1 and Type-2 malnutrition are in general combined and difficult to disentangle and it is likely that inflammation in most cases may act in concert with undernutrition to cause wasting.

Malnutrition, Inflammation, and Atherosclerosis Counterplay: The MIA Axis

Increased levels of C-reactive protein (CRP) [170, 171] and pro-inflammatory cytokines [164, 172] are strong predictors of wasting, and mortality, in ESRD patients. Moreover, wasting and inflammation are strongly associated with CVD [173]. Thus, it has been suggested that PEW, in part, is the consequence of chronic heart failure (CHF), and/or infection/inflammation, which triggers the development of not only malnutrition, but also atherosclerotic CVD, resulting in higher mortality rates [174]. We have proposed the presence of a syndrome consisting of malnutrition/wasting, inflammation, and atherosclerosis (MIA), which may be responsible for the majority of premature deaths in PD patients [132]. Available data [132, 170] suggested that MIA syndrome is particularly common in dialysis patients. Indeed, our group has found strong associations between malnutrition, elevated CRP levels, and the prevalence of CVD in patients starting PD [132]. Furthermore, the presence of both cardiac valve [175] and coronary artery calcification [176] is associated with the presence of inflammation in PD patients, suggesting that vascular calcification may be another feature of the MIA syndrome. It is also documented that inflammation is more common in wasted patients starting PD [177], and both malnutrition and inflammation predict cardiovascular mortality in PD patients [178]. Taken together, there seems to be a vicious circle of malnutrition/wasting, inflammation, and atherosclerosis, and it is likely that elevated levels of pro-inflammatory cytokines seem to play a central role in this scenario, having additive effects on survival [179].

Inflammatory Mechanisms Leading to PEW in PD Patients

Inflammation is a common feature in clinical conditions associated with loss of muscle mass, such as cancer, AIDS, and aging [180]. In animal studies, infusion of TNF-α, IL-1, and IL-6 led to increased muscle protein breakdown and to muscle atrophy [180]. Also, clinical studies in CKD patients have shown a link between inflammatory cytokines and

muscle wasting [181]. In fact, Kaizu et al. [182] demonstrated that muscle mass was inversely correlated to both IL-6 and CRP in HD patients, even after adjustment for age and gender. In a longitudinal study, the declining markers of muscle mass during a 1-year period in HD were also associated with higher IL-1β concentrations [183]. Moreover, patients who lost LBM after 1 year in PD had significantly elevated initial CRP levels compared with patients who gained LBM [19]. Although the mechanisms by which inflammation can lead to muscle wasting are not fully understood, enhanced protein turnover seems to play a central role. However, it is still unclear if this negative protein balance results from reduced rates of synthesis, from increased rates of breakdown, or from a combination of both. Whereas inflammation may affect the wasting process by multiple mechanisms, the adenosine triphosphate (ATP)-ubiquitin-proteasome pathway, insulin resistance, resting energy expenditure, and anorexia seem to play a major role and deserve further description. Furthermore, these interactions can be exacerbated in the context of PD therapy, as several studies have pointed out possible inflammatory burden due to glucose absorption or the observed weight gain associated to PD (Fig. 21.2).

Ubiquitin Proteasome Pathway

Metabolic acidosis is a common phenomenon in progressive CKD that may lead to stimulation of protein breakdown and subsequent muscle wasting via stimulation of the ATP-ubiquitin-proteasome pathway [184]. As TNF-α modulates, at least in part, the ATP-ubiquitin-proteasome proteolytic pathway [184] inflammation may contribute to wasting by affecting this pathway. Indeed, it has been shown that TNF-α administration to rats resulted in increased skeletal muscle proteolysis, augmentation of free and conjugated ubiquitin, and increased gene expression of ubiquitin [185]. In addition to TNF-α, other cytokines, such as IL-1 and interferon (INF)-γ were also demonstrated to up-regulate ubiquitin gene expression [185]. However, while cytokines have the potential to enforce the acceleration of muscle protein breakdown, it is largely unknown how they are transduced and converged into the hypercatabolic response and how the proteolytic pathways involved are activated.

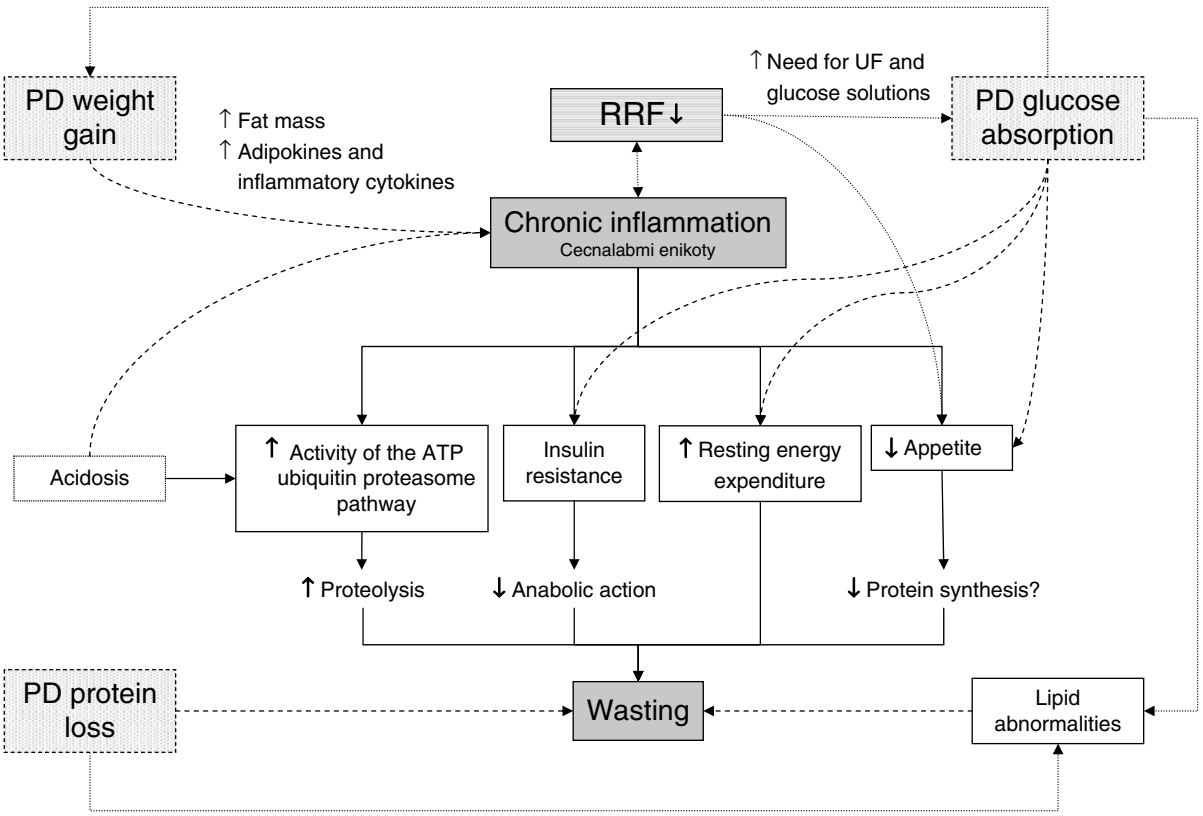

Fig. 21.2 Potential pathways linking chronic inflammation to the development of wasting in chronic kidney disease, underlying as well the processes related to PD therapy that likely influence these interactions

Insulin Resistance

Recently, several studies in non-CKD patient groups have linked inflammation to insulin resistance [186]. In fact, it has been postulated that inflammation is an integral part of the metabolic syndrome [187]. It was demonstrated that the administration of recombinant TNF-α to cultured cells or to animals impairs insulin action, and obese mice lacking functional TNF-α or TNF-receptors have improved insulin sensitivity compared with wild-type counterparts [188].

In addition, chronic administration of infliximab (a chimeric of anti TNF-α antibody) has been reported to improve insulin resistance [189]. In this respect it should also be noted that TNF-α increases lipolysis [190], which is highly correlated to insulin resistance, and that IL-6 inhibits insulin action both in vitro and in vivo muscle, liver, and adipocytes [191]. Although the exact mechanism(s) by which cytokines mediate insulin resistance are not clear, several mechanisms (such as a defect in insulin intracellular signaling pathways during inflammation, induction of lipolysis by TNF-α, and reduced production of adiponectin) are likely to contribute.

Decreased insulin sensitivity caused by a persistent inflammatory condition can predispose to loss of muscle mass by decreasing the anabolic action of insulin on the skeletal muscle. In fact, in clinical conditions where insulin resistance develops, such as in elderly subjects and in patients with type-2 diabetes mellitus, muscle wasting is often observed. By using stable isotope tracer techniques, Pupim et al. [192] showed that HD patients with type-2 diabetes had significantly increased skeletal muscle protein breakdown as compared to nondiabetic HD patients. Also, CKD stage 5 patients with diabetes mellitus had significantly accelerated loss of LBM as compared to nondiabetics during the first year of dialysis therapy [193]. Furthermore, increased energy expenditure (another factor contributing to sarcopenia) has been observed in CKD patients with diabetes mellitus in comparison to gender- and age-matched nondiabetic CKD patients [194]. Finally, as dialysis patients with hyperleptinemia have a more severe degree of insulin resistance, further studies are required to see whether leptin plays a role in insulin resistance in CKD.

Increased Resting Energy Expenditure

It should be emphasized that many of the metabolic abnormalities present during the inflammatory response, including fever, elevated oxygen consumption, enhanced lipolysis and fat utilization, increased concentration of catabolic hormones, and extensive protein catabolism, consume high quantities of energy and may account for as much as 15% of the daily energy expenditure [195]. The stimulatory effect of inflammation on energy expenditure has been demonstrated in several non-CKD inflamed patient groups, including rheumatoid arthritis, AIDS, cancer, and sepsis [196]. Recent studies have shown that inflamed CKD patients had higher resting energy expenditure [197]. Furthermore, both resting energy expenditure and inflammatory parameters decreased significantly after treatment of acute infection in CKD patients [197]. As increased resting energy expenditure has been associated with high mortality rates and worse nutritional status in dialysis patients [178], the impact of increased energy expenditure on muscle mass and body fat stores needs further evaluation.

Anorexia

The cause(s) of anorexia among PD patients are multifactorial as discussed above. Inflammatory cytokines interact with several of the pathways in the central nervous system to affect specific brain areas related to the appetite regulation and PD patients with anorexia and vomiting showed higher plasma levels of TNF-α than patients without these symptoms [82]. Moreover, the patients with worse appetite had worse nutritional index and poor clinical outcome, suggesting a link between inflammation, decreased appetite, and worsening of the nutritional status [198]. There are also data linking adipokines to inflammation and anorexia. Thus, markedly elevated leptin levels are found in advanced CKD due to impaired renal clearance, while it has been postulated that hyperleptinemia contributes to uremic anorexia [199]. Leptin is taken up into the central nervous system by a saturable transport system and binds to the long form of the leptin receptor in the arcuate nucleus of the hypothalamus. Recently, leptin signaling in the central nervous system has been shown to be an important cause of anorexia in uremic rats via signaling through the central melanocortin system [200]. In accordance, increased serum leptin levels were inversely related to inflammation and predict longitudinal changes in LBM in patients starting PD [19]. However, as others found no correlation between hyperleptinemia and decreased appetite and wasting [199], it could be speculated that in the uremic milieu there is an impaired transport of leptin across the blood–brain barrier indicating leptin resistance. As a recent study by Chen et al. [201] demonstrated that circulating CRP binds to leptin and attenuates its physiological function, further studies are needed to evaluate the impact of persistent inflammation on leptin transport across the blood-brain barrier and subsequent action in CKD as well as studies targeting inflammation or hyper-adipokinemia to improve anorexia in PD patients.

Nutritional Requirements in PD

If a macronutrient (protein, energy) or an essential nutrient (e.g., essential amino and fatty acids, vitamins, and trace minerals) are not provided in sufficient amounts, the individual will sooner or later suffer adverse reactions. Although, it may take quite some time before a nutritional deficiency is reflected in vital statistics, these subclinical deficiencies may indirectly have a negative effect by sensitizing the individual to other morbid factors, e.g., protein malnutrition may impair the immune response, resulting in an increased risk of severe infections. Thus, it is necessary (but not always sufficient) that nutritional requirements of macronutrients and essential nutrients are met to prevent the development of PEW in PD patients. In the following, we highlight some of the specific nutritional requirements in PD.

Protein Requirements

In PD patients the daily protein intake (DPI) was previously recommended to be at least 1.2 g/kg body weight/24 h (Table 21.8) [202, 203]. This recommendation was based primarily on early studies [204, 205], which were based on an analysis of relatively young active males on PD. However, these and others studies have shown that a DPI of 1.0–1.2 g/kg/day is associated with a neutral or positive nitrogen balance, with a relationship between protein intake and nutritional parameters [78, 204].

Furthermore, none of these studies show that a DPI of >1.2 g/kg/day prevents PEW or preserves nutritional status. Similar to the recommendations in healthy adults, the recommended intake of 1.2 g/kg/day was based on the assumption that this intake should be within the safe limit for 97.5% of the population (mean±2 SD). However, patients may have a stable nutritional status on a protein intake <1.2 g/kg/day. Nitrogen balance studies [78, 204] indicate that a protein intake of ≥1.0 g/kg body weight/day is enough in almost all patients, and in a nitrogen balance study of PD patients receiving an individualized diet composed to resemble the patients' spontaneously chosen energy and protein intake at home, some of the patients were in a neutral or positive nitrogen balance with a protein intake as low as 0.7 g/kg body weight/day [78]. In addition, an intake of ≥1.2 g/kg body weight/day cannot be achieved by the vast majority of PD patients but despite this they may have relatively stable nutritional status [91, 206, 207]. Therefore, we recommend a protein intake of ≥1.0 g/kg body weight/day as acceptable if the patient has no declining trend in nutritional status. However, when DPI (or nPNA in steady state) is <0.8 g/kg/day, there is a clear need to reassess the patient [208].

Most comparative studies show comparable survival in PD and HD patients in spite of a lower protein intake as calculated from urea appearance rate among the PD patients [209]. It should be noted that PD patients have a significant loss of non-urea nitrogen in dialysate [78] and the daily protein intake in PD patients may be underestimated using the commonly applied equations (which were not based on nitrogen balance studies in PD patients) [210] to

Table 21.8 Recommended nutritional intakes per day for patients treated with PD

Protein	≥1.0 g/kg body weight (= 50% of high biologic value)[a]. Higher intake is needed for wasted patients and during repletion.
Energy	= 30–35 kcal/kg (including glucose absorption from the dialysate)
Fat	30% of total energy supply (high content of unsaturated lipids)
Water and sodium	As tolerated by fluid balance
Potassium	40–80 mmol. Individualized, depending on serum levels
Calcium	Individualized, usually not <1,000 mg (supplements may be required)
Phosphorus	8–17 mg/kg (phosphate binders often are needed)
Magnesium	200–300 mg
Iron	10–15 mg (supplements often are needed)
Zinc	15 mg (supplements may be required)
Pyridoxine (B6)	10 mg
Ascorbic acid	60–100 mg
Thiamin	1–5 mg
Folic Acid	1 mg
Vitamin A, E, K	Not routinely (vitamin E may be indicated in some patients)
Vitamin D	Individual supplementation

[a]Note that previous recommendations of 1.2 g/kg/body weight/day are not sufficiently evidence based; our opinion is that a target of ≥1.0 g/kg/body weight/day is a more appropriate figure

estimate protein intake in PD patients. Several studies have shown that protein intake as measured in nitrogen balance studies [78] or estimated from dietary recall [17, 89] is markedly higher in PD patients than protein intake estimated from urea generation rate using the Randerson equation [210] in the same patients. Therefore, it is recommended to use this improved equation, which shows a higher and more correct estimate of protein intake in PD patients [211]. However, when using this formula, many PD patients still have a protein intake lower than 1.2 g/kg body weight.

Energy Intake Requirements

The energy requirements are dependent on the level of physical activity. In general, dietary energy intake for adult PD patients should be 35 kcal/kg/day, adjusted for age, in individuals not performing heavy physical exercise (Table 21.8). There are no supporting data that the energy requirements are systematically different in PD patients compared with the general population, and it is generally considered that the energy requirements are lower in older patients, and a caloric intake of 30 kcal/kg body weight/day may be recommended in patients with an age above 60 years [39, 40, 78, 208, 212]. There are no data that this calorie intake will reduce morbidity or mortality or improve the nutritional state in malnourished patients. The rationale is based on increased mortality rates in low body weight patients [213], and aggressive energy intake may correct this. In the PD patients, this recommended intake includes both diet and the energy intake derived from peritoneal glucose absorption. The glucose absorption from the dialysate may be calculated easily (if the glucose concentration in the drained 24 h dialysate is measured) by using the equation: glucose absorbed (mmol) = glucose concentration in infused dialysate (mmol/L) × infused dialysate volume (L) – glucose concentration in drained dialysate (mmol/L) × drained dialysate volume (L). In PD patients with normal peritoneal transport capacity, ≈60% of the daily dialysate glucose load is absorbed, resulting in a glucose absorption of ≈100–200 g glucose/24 h [74].

It is generally recommended that 35% of the energy should be given as fat, of which a substantial part should be unsaturated [39]. Obese patients, on the other hand, should be recommended a low energy intake and restrictions in the use of hypertonic dialysis fluid, for body weight reduction; this may also have salutary effects regarding glucose intolerance and lipid abnormalities.

Normalization of Protein and Energy Intake

The recommended protein and energy intake need to be corrected for body size. Most commonly, the patient's dry body weight is used for this normalization. However, this method does not take into account that the patient's protein and, in particular, energy requirements are lower in obese patients. Furthermore, this method is also misleading as it will yield inappropriately high nPNA values in wasted patients with a low body weight [89, 211]. Other possibilities are to normalize the patient's protein and energy requirements (and intake) to a standard body weight based on age, sex, and height from the National Health Examination Survey (NHANES) tables [214] (normal body weight), other local national data on body size, or from the Metropolitan Life Insurance Company [215] (desirable body weight). There are no systematic studies of which normalization method is most appropriate for PD patients, and, until a single uniform way of normalization has been established, it is important to be aware of the problem, and to state which method has been applied in clinical studies [209].

Vitamin and Trace Mineral Requirements

The vitamin and trace mineral requirements of PD patients have been reviewed in detail [216, 217] (Table 21.8). Inadequate dietary intake, altered metabolism in uremia, and vitamin loss into dialysate may lead to vitamin deficiencies, in particular deficiencies of water-soluble vitamins, in a few patients treated with PD [216–219]. Thiamin (vitamin B1) deficiency with encephalopathy has been described in dialysis patients [220], and may be confounded with other neurologic diseases. A common dietary intake of 0.5–1.5 mg per day can be supplemented with a daily dose of 1–5 mg of thiamin hydrochloride. Vitamin B_6 coenzymes play a vital role in several aspects of amino acid utilization and the need for vitamin B_6 is particularly critical if protein and amino acid intake is limited [217, 221, 222]. There are data suggesting that the daily requirement of pyridoxine may be higher in dialysis patients than in normal subjects and that dialysis patients should be supplemented with a minimum of 10 mg of vitamin B_6 per day [221, 223]. Folate is lost in dialysate, and, as folate levels have been reported to be reduced in serum, it is recommended to give 1 mg of folic acid

daily. High doses of folic acid (5–10 mg/day) have been shown to reduce the markedly elevated plasma homocysteine levels in uremic patients by about one-third. However, this supplementation was not fully corrected it to normal levels [224]. The question of whether these high doses of folate should be prescribed in order to lower plasma homocysteine levels and whether this will improve cardiovascular morbidity and mortality is still open, and prospective studies are needed in this area, although studies from nonrenal populations are discouraging.

Supplementation with vitamin C has also been recommended [219, 225]. However, high intake of vitamin C may aggravate hyperoxalemia in dialysis patients. Supplementation of the fat-soluble vitamins A, D, E, and K has not been recommended on a routine basis [216]. Vitamin A tends to accumulate in PD patients as well as in other patients with renal failure and supplementation should be avoided as vitamin A may have potentially harmful effects. Vitamin D and its active forms should not be prescribed as a routine but should be given on the basis of an evaluation of the bone metabolic status and taking the risks of hyperphosphatemia and hypercalcemia into consideration. Blood levels of vitamin E have been found to be normal or high in most studies in uremic patients and vitamin K deficiency has not been reported in renal failure patients [216]. However, as vitamin E (tocopherol) is a strong antioxidant compound, it may be worthwhile to consider treating selected high cardiovascular risk dialysis patients with vitamin E. A randomized controlled study of high-dose vitamin E (800 IU alpha-tocopherol/day) supplementation in high cardiovascular risk HD patients showed a significant 50% decrease in a cardiovascular composite index as compared with the placebo group [226]. However, other studies in nonrenal patient groups have not shown as good results, perhaps partly because different doses and forms of vitamin E were used.

Dietary requirements for trace elements are not well defined in PD patients. Trace element metabolism is frequently altered in chronic renal failure patients [216, 218]. High levels of trace elements have been attributed to impaired renal elimination or contamination of dialysis fluids and low levels of trace elements may occur due to inadequate dietary intake or loss of protein bound trace elements into the dialysate. Several groups have reported on decreased levels of zinc in serum, leukocytes, and muscle of PD patients [216]. Zinc deficiency has been reported to be associated with anorexia, hypogeusia, hyperprolactinemia, and impotence, which have been alleviated by zinc administration. However, these results have not been generally confirmed and the role of zinc deficiency and requirements for extra supply of zinc in the diet of PD patients remains at present controversial [216, 218], although supplementation with zinc has been suggested in patients with hypogeusia, anorexia, and muscle weakness.

Dialysis Dose

There is existing controversy about the relationship of delivered dose and nutritional status [227], as a cross-sectional correlation between Kt/V and nPNA is confounded by the fact that these two parameters are mathematically coupled. Overall, prospective studies of adequacy and nPNA or DPI have shown conflicting results. There is little direct evidence that increasing dialysis dose improves nutritional status in the short term, except from one small prospective study that suggested that nutritional parameters (nPNA and albumin) may improve with increased dialysis dose in malnourished patients without co-morbidity [92]. Another study in Asian patients showed increased protein intake in anuric patients by increasing the dose of PD from three to four daily exchanges [92, 228], but not when the dose was increased from four to five exchanges per day [228].

Furthermore, the large randomized ADEMEX study ($n = 965$) of increased dialysis dose did not show any clear improvements in nutritional parameters (nPNA, body weight, plasma albumin, prealbumin, or transferring) [91]. However,in patients who have no residual renal function or a declining residual renal function, there is a concomitant decrease in DPI. Residual renal function may therefore be an important parameter for nutritional intake in PD patients. Several categories of patients who might require additional nutritional support include severely wasted patients with complications, such as diabetic patients with gastroparesis, or hospitalized dialysis patients who often ingest even lower amounts of protein and energy [92].

Evolution of Nutritional Status During PD Therapy

Early Effects of PD Therapy on Nutritional Status

Some studies have shown that, during the first months of PD therapy, there is improvement in the nutritional status reflected as weight gain [16, 229], improvement in anthropometric parameters [4, 17, 230], and a rise in plasma proteins [4, 16], indicating altogether that there is an initial increased net anabolism. Further prospective studies of body

composition changes during the first year of PD using bioimpedance, anthropometrics [4, 17], DEXA [19, 81, 231], and the combination of total body potassium and tritium dilution [20] show that, while lean body mass seem to be rather stable, body fat mass increases considerably. Fernström reported that the body fat distribution changed with a marked increase in intraperitoneal fat (as estimated using computed tomography) [232]. In addition, part of the weight gain may be due to increased body water. However, it should be noted that these reports consisted of patients solely treated with glucose-based PD solutions without use of amino acid- or icodextrin-based solutions.

Nitrogen balance studies during the first year of PD therapy (prescribed an individualized diet composed so as to resemble the patients' spontaneously chosen diet regarding dietary protein and energy intake) show that most of these patients were in a positive nitrogen balance during the first year of PD [78]. These results are in agreement with a study of protein turnover showing that the balance between synthesis and breakdown was significantly higher in PD patients (after 3 months on PD as well as before PD start) as compared to healthy controls, indicating net anabolism among the PD patients together with normal potassium levels (which indirectly reflect a normal nutritional status) [233].

An increase in total body nitrogen (which was low at start of PD, indicating protein malnutrition) has also been reported during the first year of PD [17, 18]. In contrast, some old prospective studies of total body nitrogen indicate that a gradual deterioration in nutritional status is common after start of PD, especially in male patients, with large protein stores at the beginning of treatment [6, 234, 235]. Although contradictory results have been published concerning the changes in total body nitrogen in PD patients, they all show that PD patients in general have decreased total body nitrogen during the first year of treatment, indicating that protein malnutrition is common in these patients despite of normal anthropometric measurements [6, 17, 18, 234, 235]

Long-Term Effects of PD Therapy on Nutritional Status

Most long-term studies of nutrition in PD patients have used rather indirect measures of nutritional status. In general, protein intake [17], energy intake [236], serum albumin and total protein levels [17, 237], body weight [16, 17, 238, 239], and anthropometrics [4, 17], seem to be maintained on stable levels without further decrease in patients on long-term PD. Prospective studies of body composition using bioimpedance and anthropometrics show a tendency towards a further increase in fat mass with long-term PD treatment. However, the increase in fat mass seems to be related to the peritoneal transport type, with greater increase in patients with a more rapid small solute transport (high/high-average transporters) and thus more rapid glucose absorption [240]. Randomized trials of patients using icodextrin-based solution for the long dwell (compared to glucose solution) show an early reduction of the extracellular fluid volume and stable body weight thereafter, whereas the patients randomized to glucose-based solutions for the long dwell continued to gain body fat [241, 242].

A progressive decrease in serum albumin has been reported in patients on PD after 3 years or more [16, 239], and Davies et al. reported decreased protein intake with time on PD [236]. Furthermore, the patients with severe PEW in the international cross-sectional study of nutritional status in 224 PD patients were either older or had been on PD longer than other patients [3]. Also, as there is a high mortality rate among PD patients [16, 236, 243] and a high transfer rate of PD patients to HD [16, 236, 243] due to various complications, few patients are maintained on PD for 5 years or more. The patients that were treated with PD for longer time periods will consequently represent a positive selection of PD patients that have a more favorable clinical course, and these patients may also have a more favorable evolution of nutritional status compared to patients that die or are transferred to HD [236]. The relative stability of nutritional status in patients on long-term PD may therefore not necessarily be typical for all patients treated with PD.

Loss of Lean Body Mass During Long-Term PD Therapy

Davies et al. [236] have reported that, following an initial improvement of nutritional status, a decline may occur after about 2 years of PD treatment. Several other studies suggest that during long-term PD a gradual deterioration in nutritional status may occur with a decrease in lean body mass [20, 231, 234, 244].

The reason(s) for the tendency towards decrease in lean body mass during long-term PD are not evident but are probably multifactorial. At first, residual renal function declines with time on dialysis treatment and many patients are anuric after 2–3 years of PD. This results in decreased solute clearances, which may result in inadequate dialysis. Secondly, it is likely that the continuous loss of protein into the dialysate may contribute to a negative protein balance, although this does not seem to be major factor [128]. Furthermore, a low eating-drive has been demonstrated in PD patients despite an increased need for protein [100]. In this context, it is interesting that a high level of the anorexic

hormone serum leptin relative to the body fat mass was associated with weight loss in PD patients [19]. However, as others have found no association between the leptin concentration and recent weight change or nutritional status in ESRD patients [245, 246], more prospective studies are needed to investigate the role of hyperleptinemia in the loss of lean body mass in PD. Finally, in recent years malnutrition has been linked to inflammation [34, 132] and it has been postulated that pro-inflammatory cytokines may be an important cause of muscle wasting and hypoalbuminemia [247]. It should be noted that an increase in leptin was associated with increased CRP in our patients; However, the role of leptin compared to other inflammatory mediators for the decrease in lean body mass is presently not clear (see the earlier section on "Inflammatory Mechanisms Leading to PEW in PD Patients" for further discussion of the relation between inflammation and nutritional status).

Total Body Water in PD Patients

The estimation of total body water in PD patients is important for the assessment of nutritional status as well as for the calculation of Kt/V_{urea} as a marker of dialysis adequacy. The Watson equation [248] gives a reasonable good estimate in most PD patients, even though it has been shown to slightly overestimate total body water in obese subjects and to underestimate total body water in lean subjects [249, 250]. However, for the assessment of nutritional status, better methods for determination of total body water are needed. At present, indicator dilution methods using, e.g., tritium, deuterium, or ethanol are the gold standards for assessment of fluid status in PD patients [249, 250]. Bioelectrical impedance has been used more for this purpose, but still this method is not well validated for PD patients.

In a recent study of 82 PD patients studied at start and followed for on average 26 months (range 11–80 months), Johansson showed that there was an increase in extracellular water (calculated from the four compartment model using measured values of total body potassium and total body water from tritium dilution) with time on PD [244]. This is in agreement with the study by Enia et al. showing that PD patients had more antihypertensive treatment, higher plasma levels of atrial natriuretic factor, and higher left atrial volume and left ventricular hypertrophy compared to HD patients, indicating volume overload [251]. It has also been reported that after an initial improvement after initiation of dialysis, there is an increase in hypertension with time on PD [252, 253], which is associated with declining residual renal function [253] and may be related to fluid overload. Thus, PD patients are at risk to become volume overloaded with time on PD, in particular as residual renal function and ultrafiltration capacity declines with time [236, 253, 254]. However, most of these patients used exclusively glucose-based PD solutions and the use of icodextrin-based PD solutions for the long dwell has, in randomized trials, been shown to markedly improve fluid status with reduced total body water in general and extracellular fluid volume in particular (as assessed by deuterium dilution and multifrequency bioimpedance) [242, 255].

Increase in Fat Mass and Obesity in PD Patients

As mentioned above, weight gain and accumulation of fat tissue are seen after the start of PD [4, 17, 19, 20, 81]. However, this is not seen in all patients starting PD treatment.

Glucose is absorbed to a large extent from the dialysate and conventional PD results in an almost unique metabolic situation involving continuous 24-h absorption of glucose. It has been estimated that during conventional PD about 100–200 g of glucose are absorbed during 24 h [74] and glucose uptake from the dialysis fluid represents a significant portion of the energy intake [76, 77]. It is generally assumed that the accumulation of adipose tissue is related to the glucose absorption from the dialysate as it is more pronounced in patients with more rapid small solute transport (high/high-average transporters) [240]. However, there is no clear relation between the gain in weight and the amount absorbed and marked variations exist between patients. It is notable that especially diabetic patients [4, 19] and obese females tend to gain fat mass during PD [4, 19].

The reason(s) why only some PD patients accumulate fat mass during PD are not clear. However, as it has been shown that genetic factors may contribute to about 70% of the variations in body mass index (BMI) in nonrenal patient groups [256] it could be speculated that genetic factors also are of importance in PD patients. Obviously, there is no way to accumulate excess adipose tissue without disequilibrium between the intake and expenditure of calories. It has been found that small reductions in energy expenditure increase the risk for developing obesity [257] and that genetic factors may influence the resting metabolic rate [258, 259]. One reason for increased energy expenditure appears to entail an increased thermogenesis in adipose tissue. A key element in adipose tissue is the unique expression of mitochondrial inner-membrane proteins called uncoupling proteins (UCPs), which are transporters of free fatty

acid anions, allowing free fatty acids to function as proton carriers. While UCP3 expression has been found only in skeletal muscle, UCP2 has a wide tissue distribution and it has been speculated that UCP2 may play a role in fat tissue accumulation [260, 261]. Indeed, as it has been demonstrated that a considerable contribution of the exon 8 UCP2 polymorphism contributes to variations in body composition in PD patients this suggests that genetic predisposition may be an important factor contributing to fat tissue accumulation in these patients [262].

In nonuremic patient populations, a marked accumulation of abdominal fat tissue has been regarded as an important risk factor for cardiovascular disease. In contrast, Fleischmann et al. [263] recently showed that HD patients with a high BMI had a better survival than patients with a normal BMI suggesting that obesity actually may reduce the risk of death in dialysis patients. In this respect, it is noteworthy that it has been demonstrated that PD patients who do not accumulate fat tend to lose more lean body mass (i.e., muscle mass) during PD [262]. This finding agrees with other studies demonstrating that some patients may be at risk of losing lean body mass during long-term PD treatment [19, 20, 234, 236]. Indeed, a recent study concluded that patients with low energy stores might benefit to a larger extent from PD and that the nutritional status at the start of dialysis is an important factor to consider when a choice for the dialysis modality is made [4].

Is it Good to be Fat in PD?

In contrast to findings in the general population, a number of studies have documented that a high BMI is associated with a better outcome in the ESRD patient population [264, 265]. Thus, a recent epidemiological study of PD patients showed that a high BMI was associated with decreased mortality during the first 3 years of therapy [266]. Compared to those with normal BMI, adjusted mortality hazard ratios in the first, second, and third year were significantly elevated for the underweight patients, whereas elevated BMI constituted a survival advantage. However, BMI is not a very precise parameter of nutritional status and does not adequately reflect body composition (as BMI does not differentiate between muscle mass and fat mass). In a study of 70,028 patients who initiated dialysis in the United States from 1995 to 1999, it was demonstrated that a protective effect from a high BMI is only present in patients with a normal or high muscle mass [265]. In accordance with these findings, a recent study of 344 incident dialysis patients showed that a BMI above 25 was only associated with a better survival if the mid-arm muscle circumference was at least 90% of normal, while patients with a BMI above 25 kg/m^2 and a lower muscle mass had the worst survival [267]. Furthermore, in a recent study of 9,679 PD patients from the Australia and New Zealand Dialysis and Transplant Registry, a J-shaped relation was found between BMI and mortality, with the lowest mortality at a BMI of 20 and continuous increase in mortality and technique failure with increasing BMI above that [268]. Taken together, these results indicate that an increased fat mass in PD, like in other patients groups, may indeed have adverse metabolic consequences, including an increase in systemic inflammation, but that the effects of a decreased muscle mass are more important in determining short-term outcome.

Adipokines and PD

Recent discoveries, notably of the adipokines leptin and adiponectin, have revised the notion that adipocytes are simply a storage depot for body energy. Instead, hormones secreted by the adipocytes (adipokines) act as autogenic regulators of body fat depots, modulating gastrointestinal activities, metabolic changes, and central nervous mechanisms, and have been speculated to play a central role in the development of complications often observed in this patient group, such as insulin resistance, CVD, and sarcopenia [269]. Considering the dramatic effect that loss of renal function has on the clearance of these substances [164], and the gain in fat mass associated to PD-glucose absorption, the systemic effects of adipokines in CKD patients may be greater than in the general population (Fig. 21.2).

So far, relatively few studies have investigated the impact of adipokines on metabolic and inflammatory aspects of CKD. Leptin, the first adipokine described (1994), was shown to correlate strongly with total body fat mass and to modulate feeding behavior in rats [270]. While leptin signaling is more complex in humans, loss of renal function leads to inappropriately elevated serum concentrations of leptin [81]. In PD patients, we have shown [19] that serum leptin levels increase with initiation of PD, are inversely related to inflammation, and predict longitudinal changes in lean body mass. Furthermore, serum leptin levels appear to be an independent predictor of epoetin requirements in uremia (even after adjustment for inflammation) and there is some evidence to suggest that this pleiotropic adipokine may have hematopoietic properties [271]. Indeed, in nonrenal patients, leptin has been shown to be capable of initiating the recruitment and activation of immunocompetent cells [272], while leptin production may in turn be regulated by adipose tissue TNF-α levels [272]. Also of interest for nephrologists is the apparent ability of leptin to modulate bone modeling through central mechanisms [273], as well as the apparent ability of leptin to promote collagen formation in tissues [274], both of which may have as-yet unexplored links to vascular calcification and bone disease in uremia.

Indeed, a recent study [275] showed that leptin is able to enhance vascular calcification in vitro and in mice, suggesting a much more direct connection between this hormone and cardiovascular disease in uremia.

Adiponectin is another adipokine exclusively secreted from adipocytes found in the circulation. Low circulating levels of adiponectin are generally found in populations at enhanced risk of atherosclerotic CVD [199]. Thus, reduced adiponectin levels predispose healthy individuals to insulin resistance [199]. Although plasma adiponectin levels are generally elevated in ESRD patients [276, 277], it has been reported that PD patients with low adiponectin levels have an increased mortality rate [277], though a recent small cross-sectional study of 44 PD patients found no association between serum adiponectin levels and prevalence of clinical cardiovascular disease [278].

Resistin may serve as an example of the close links and arising classification problems between adipokines and cytokines. Although the true pathophysiological role of resistin in human disease remains unknown, it now seems clear that many different cell types secrete this peptide, with a predominance of immunocompetent cells [279]. Indeed, we and others have found that increased circulating resistin levels are not associated with insulin resistance or fat mass, but rather correlate closely with inflammatory biomarkers [64, 280].

Several mechanistic studies have enlightened us with plausible explanations of how adipocytokines might link the PEW and inflammation present in the PD population. The cause of the increased circulating pro-inflammatory cytokines during obesity is not totally understood, but it seems to a large extent to be related to a progressive infiltration of macrophages in the adipose tissue as obesity develops [281, 282]. Several mechanisms have been claimed to cause this process, including secretion of TNF-α from adipocytes [283] and increased secretion of leptin (or decreased levels of adiponectin) by the adipocytes – both of which may contribute to macrophage accumulation by stimulating transport of macrophages to the adipose tissue [283]. It should also be acknowledged that the physical damage to the endothelium, caused by the increasing lipolytic environment, can induce macrophage recruitment and a continuous production of inflammatory cytokines [283]. As visceral fat appears to produce adipokines more actively than subcutaneous adipose tissue, visceral abdominal fat tissue may be the main producer of IL-6. In accordance, in ESRD patients evaluated shortly before the start of renal replacement therapy (RRT) we found a significant association between serum IL-6 and truncal fat, but not between IL-6 and nontruncal fat [52]. It seems plausible to assume that small adipocytes in lean individuals promote metabolic homeostasis, while the enlarged adipocytes of obese individuals recruit macrophages and promote inflammation and the release of a range of factors that predispose toward insulin resistance.

Prevention and Treatment of PEW in PD

In order to prevent and treat PEW among PD patients it is important to monitor nutritional status. It is obvious that a sufficient intake of energy and protein is necessary for the maintenance of nutritional status and the prevention of malnutrition in PD patients. Furthermore, even slight acidosis should be corrected by oral supplementation with sodium bicarbonate (or altered dialysate buffer concentration). Physical exercise should be encouraged and intercurrent diseases should be actively treated. The prevention of peritonitis and other infectious complications is also crucial for the maintenance of adequate nutrition in PD patients but lies outside the scope of the present chapter. Optimal treatment of co-morbidity is an obvious goal and, in particular, if there are signs of inflammation, like increased CRP levels, it is important to seek the cause.

Targeting PD Therapy

Monitoring and Maintenance of Adequate Protein and Energy Intake

To ensure a safe supply of protein to the majority of PD patients it is recommended that PD patients should have a protein intake of at least 1.0 g/kg body weight (BW)/day, of which a large part should be of high biological value – i.e., the protein should have a high content of essential amino acids (usually animal proteins from milk, eggs and meat). It is likely that some patients may require less than this to maintain nitrogen equilibrium [78, 284]. However, it is difficult to identify such patients by simple methods. On the other hand, the patients who are initially malnourished or later develop signs of protein-energy malnutrition may require higher amounts of protein (and energy) for repleting the protein and energy stores. Some patients may benefit by eating as much as 1.4–2.1 g protein/kg/day, especially during the initial months of PD treatment [78].

The protein intake can be estimated from dietary recall or from urea kinetics (assuming that the patient is in nitrogen balance). A prospective dietary history is not always possible to obtain and is highly dependent on the

cooperation of the patient and the skill of the dietician [285], although a simplified 24-h diet recall protocol could be less labor intensive and less burdensome to the patient in assessing protein and energy intake [286]. On the other hand, the protein equivalent of nitrogen appearance rate (PNA) can easily be calculated from urea appearance rate [78]. PNA has been suggested as a more accurate term, as the true protein catabolic rate is about six times higher than PNA estimated from urea appearance rate, as most of the catabolized protein is not catabolized to urea but used for protein synthesis again [78, 287]. It is strongly advisable to monitor the estimated protein intake as assessed by urea kinetics on a regular basis for all PD patients, in order to identify patients with a suboptimal protein intake. Repeated values below 1.0 g/kg BW/day should arouse the suspicion that the protein intake is too low and the patient should be advised to increase the intake of dietary protein. However, in patients with even slight variations in body weight or in the serum urea levels (which may suggest net protein catabolism or anabolism), the estimation of protein intake based on urea kinetic modeling should be interpreted with great caution [78, 288]. In addition, the active cooperation of the patient is needed as it is crucial that the dialysate and urine collections are complete. We established an equation (based on 36 complete nitrogen balance studies in PD patients [78, 204]) that more accurately estimates dietary protein intake in PD patients from urea appearance (UA) or urea nitrogen appearance (UNA) [211]:

$$\text{PNA (g/24h)} = 15.1 + 0.195\,\text{UA (mmol/24h)} + \text{protein losses (g/24h)}$$

$$\text{PNA (g/24h)} = 15.1 + 6.95\,\text{UNA (g/24h)} + \text{protein losses (g/24h)}$$

In the absence of excessive protein losses, PNA can be calculated even more simply, without determination of protein losses in dialysate and urine:

$$\text{PNA (g/24h)} = 20.1 + 0.209\,\text{UA (mmol/24h)}$$

$$\text{PNA (g/24h)} = 20.1 + 7.50\,\text{UNA (g/24h)}$$

The addition of oral essential amino acids in tablets or to the diet may increase the biological value and the total intake of ingested protein and may improve the nutritional status [289]. Special amino acid formulas with a modified amino acid composition (high valine, addition of tyrosine and serine) have been designed to compensate for amino acid deficiencies present in uremia [290, 291]. Treatment with oral amino acid supplements in the form of tablets has been reported to result in significant improvement in the serum albumin concentration in HD patients [292].

If the dietary energy supply is considered insufficient, oral liquid or powder mixtures of glucose polymers may be used as energy supplement. For a more complete supplementation of both protein and energy, several liquid formulas containing large amounts of protein of high biological value, lipids, and carbohydrates in a small amount of fluid are available, which are suitable for the supplementary nutrition of dialysis patients (as they have a low content of phosphate, potassium, and sodium) [293]. Oral nutrition supplements could increase total protein and energy in patients with poor food intake without displacing the diet [294]. Usefulness of oral nutrition supplements has been evaluated in a number of studies, including randomized controlled trials (RCTs) that yielded inconsistent findings. These were probably due to differences in the type of supplement used, duration of use, and differences in baseline intakes and nutritional status. A randomized, open-label, controlled trial with egg white albumin-based supplement of ~30 g per day during 6 months improved nutrient intake and serum albumin [295]. Another study showed less favorable results, perhaps due to patient preference and long duration of use of the supplement in the study [296]. Therefore, when considering the use of supplements, in addition to the type and quantity used, one must also take into consideration the baseline nutritional state and intake, patient preference, acceptance, willingness to use and to purchase the supplements, tolerance and contraindications, and duration of use in the care plan.

If, despite adequate dialysis, measures to eliminate anorectic and catabolic factors, and use of food supplements, PD patients still develop severe malnutrition, it may be necessary to give enteral or parenteral nutritional supplementation with glucose and amino acids. Severely malnourished patients may have to be hospitalized temporarily for such treatment. Enteral nutrition through a thin nasogastric tube is preferable whenever possible, as it is less expensive than parenteral nutrition and does not carry the risk of catheter sepsis. Furthermore, enteral nutrition will help to preserve the gut function. In patients who need parenteral nutrition with amino acids, a mixture of essential and nonessential amino acids seems better than a solution with only essential amino acids [39]. Energy should be provided simultaneously as hypertonic glucose or a mixture of glucose and lipid emulsion. Parenteral nutrition may be needed, especially during peritonitis or sepsis [156]. Early intravenous hyperalimentation was shown to be associated with a positive nitrogen balance during peritonitis in five of seven PD patients [297].

Amino Acid-Based Dialysis Fluids

PD solutions containing amino acids may supplement in excess the daily dialysate losses of amino acids during dialysis with glucose-based solutions [298]. It has also been demonstrated that the absorption of amino acids from the dialysate during one exchange of amino acid solution resulted in amino acid absorption (on average 17.6 g/day) that was twice as large as the dialysate losses of amino acids and protein (on average 9.2 g/day) [298]. The amino acid solutions produce ultrafiltration and solute transport patterns that are similar to those with the standard glucose solutions, although the period of effective ultrafiltration, for the same concentration of the osmotic agent, is slightly shorter [299]. The treatment with intraperitoneal amino acid solution may result in a markedly positive nitrogen balance, a significant increase in net protein anabolism, a more normal fasting plasma amino acid pattern, and significant increases in serum total protein and transferrin [284]. In a large randomized study, 134 malnourished PD patients were randomized to either use one or two exchanges of an amino acid solution per day ($n = 71$) or to continue with their usual glucose-based dialysis solution for 3 months [300]. At 1 month of study, there were (by analysis of covariance) significant increases in albumin, prealbumin, transferrin, and total proteins compared to baseline values in the amino acid group. Midarm muscular circumference also increased significantly in the amino acid group. At 3 months of the study, 70% of the patients in the amino acid group had improved in two or more nutritional variables versus only 45% among the patients that were randomized to the control group, and, furthermore, there was a significant difference between the two groups in IGF-1 compared to baseline values [300]. Another randomized study showed similar positive results [301].

Dialysis Dose, Anorexia, and Nutritional Intake

In order to maintain an adequate nutritional intake, it is obvious that the patients should receive an adequate amount of dialysis, and increased dialysis dose should always be considered in patients with too low nutritional intakes. The residual renal function has been shown to be a major determinant of the total small solute clearance in PD patients [302]. As the residual renal function declines with time in most PD patients, it is important to monitor residual renal function (in addition to dialysis efficiency) and to increase the dialysis dose as residual renal function declines. However, several recent studies have demonstrated that residual renal but not peritoneal clearances are related to clinical outcome in PD patients [303, 304], and an increase in peritoneal urea and creatinine clearance by increased dialysate volume may not be enough to compensate for the loss of residual renal function, as regards mortality [304]. Therefore, anuric PD patients need special attention and careful follow-up. However, it seems that increased dialysate volume still may improve nutritional status [90, 305]. Davies et al. have reported that when dialysis volume was increased by 25% in 48 malnourished PD patients who had evidence of declining nutrition over the past 12 months [92], nutritional status stabilized, but clear signs of improvement (increased nPNA and plasma albumin) were only significant in patients without co-morbidities.

In conclusion, the prospective studies of increased dialysis dose (as assessed by Kt/V_{urea}) among PD patients tend to show a less steep relationship (or even no relationship) between Kt/V_{urea} and nPNA than the cross-sectional studies among PD patients. Furthermore, the increase in dialysate volume is often counterbalanced by a spontaneous gradual decrease in residual renal function resulting in no change of solute removal as assessed by small solute clearances [302, 306, 307]. An increased dialysis dose seem to be efficient in some PD patient groups, although it may thus not always be enough to treat and prevent malnutrition among other patient groups, in particular among patients with co-morbidity [92].

Stringent Nutrition Counseling and Exercise Performance

Nutritional counseling may be a useful tool to assist PD patients to achieve their recommended intake, and subsequently to improve their clinical outcomes [308]. Though no studies have assessed the usefulness of nutrition counseling in PD, a 12-month nutrition intervention program tailored to patient-specific barriers in 180 malnourished HD patients resulted in modest improvements in albumin levels regardless of levels of inflammatory markers [309]. These barriers included medical and social issues that required a multidisciplinary, coordinated approach to rectify problems, e.g., once acidosis is identified, the study co-coordinator worked as liaison with the nephrologist to review the dialysate bicarbonate concentration and/or oral bicarbonate prescription. Strategies such as individualized menu planning and exchange lists improved patients' knowledge about their diet and contributed to achieve the target protein levels in a randomized control study with PD patients [310]. Finally, an RCT using amino acid dialysis fluid concluded that no additional improvement in nutritional state of wasted PD patients over and above that of intensive nutritional follow-up and advice was found [311], underlining the importance of nutrition counseling in the management of PD patients.

The clinical practice guidelines [65, 312] recommend individualized and structured approaches to management by dietitians skilled in renal care. K/DOQI guidelines [65] suggest dietitian-performed nutrition assessment, which includes the development of a nutrition care plan that incorporates all aspects of the nutritional management such as assessment, diet prescription, counseling, and evaluation. These form part of the multidisciplinary treatment plan and include the patient and/or caregiver as part of the team. The care plan requires regular review and update, and may become the dialysis unit's continuous quality improvement activity.

On the other hand, exercise [313], including progressive resistance training (PRT), is known to be effective in anabolism in patients with various chronic diseases causing muscle wasting [314], which is the case in renal failure as well. RCTs engaging supervised PRT program in predialysis CKD patients on a low-protein diet [315] and in patients undergoing HD [316] have shown significant improvements in nutritional indices, body composition, and physical performance. To date, no study evaluating exercise training therapies has been conducted in PD patients, but it is feasible to state that PD patients with PEW are likely to benefit from PRT as well.

Targeting Appetite

Anorexia is a common phenomenon in dialysis patients that is associated with higher levels of pro-inflammatory cytokines, greater hospitalization rates, and poor clinical outcomes [198]. There are several different mechanisms contributing to anorexia in dialysis patients, including inadequate dialysis, delayed gastric emptying, and elevated levels of anorectic substances, like leptin and pro-inflammatory cytokines, as well as effects of the HD procedure and the intraperitoneal infusion of dialysis fluid in PD patients [317]. Although some of these causes of anorexia can be treated through measures such as an increased dialysis dose in underdialyzed patients and decreased intraperitoneal volume in PD patients with local symptoms, it is evident that these measures are not always effective. The use of appetite stimulants may be a tempting part of an integrated therapy against PEW in PD patients. Unfortunately, most appetite stimulatory drugs available are relatively ineffective and they have not been systematically tested in dialysis patients. Megestrol acetate is the most extensively studied appetite stimulant and is widely used in cancer and AIDS-patients [318]. However, megestrol acetate is associated with several side effects including hypogonadism, impotence, and increased risk of thromboembolism. Megestrol acetate has been shown to stimulate appetite in ESRD patients; however, the treatment may be risky and must be monitored closely [319]. Cannabinoids, such as dronabinol (∂-9 tetrahydrocannabinol), have been reported to increase appetite and weight gain, and this drug class has been evaluated in cancer, HIV, and Alzheimer's disease patients. A comparison of dronabinol against megesterol acetate in a group of patients with advanced cancer found that megesterol acetate had a significantly better effect on appetite and weight gain [320]. To the best of our knowledge, no studies have been performed to study the putative appetite-stimulating effects of cannaboids in ESRD patients. Several studies have demonstrated that corticosteroids increase appetite and well being in cancer patients, although a long-lasting weight gain is often not observed [321]. However, the side effects (including the stimulation of muscle proteolysis through the ubiquitin-proteasome pathway) may be serious, and therefore corticosteroids have no primary role in the treatment of malnutrition in ESRD patients. Cyproheptadine, an antihistamine with serotonin antagonist properties, has mainly been used for the treatment of cancer-induced weight loss, and in anorexia nervosa, but the effects have been questionable [322]. Furthermore, cyproheptadine has anticholinergic side effects [322]; therefore, it is probably not ideal for ESRD patients. Other possible anti-anorectic drugs, such as thalidomide (because of its anti-inflammatory effect) and melatonin (because of its effect on muscle metabolism), are presently reaching the clinical trial stage [323].

Targeting Hormones

The dramatic evolution of molecular biology and new biotechnological tools have resulted in the possibility to produce recombinant human hormones that may be utilized to treat disease. In nephrology, the use of recombinant human erythropoietin (rHu-EPO) has dramatically changed the ability to treat renal anemia, and, furthermore, the possibility to treat PEW among dialysis patients with recombinant human growth stimulating hormones seems to be a promising perspective in the future.

Correction of Anemia and Erythropoietin Treatment

Anemia is present in most ESRD patients and may be severe, especially in anephric patients and in patients who are inadequately dialyzed. Anemia leads to fatigue, diminishing exercise capacity, and physical inactivity, which may

contribute to muscle wasting and malnutrition. Correction of anemia with recombinant human erythropoietin (rHu-EPO) has been reported to improve nutritional status to a moderate degree in HD patients [324], presumably due to a secondary effect of anemia correction on physical work capacity, general well-being, and appetite, rather than a specific anabolic effect of rHu-EPO. The use of rHu-EPO for correction of renal anemia should be accompanied by an increased supply of iron to nonoverloaded patients as the hemoglobin mass increases. Therefore, the use of rHu-EPO in ESRD patients requires assessment of iron stores because iron depletion will impair the response to rHu-EPO and rHu-EPO can cause iron deficiency. The increased iron requirements should be met if possible by oral substitution with iron [325], although parenteral iron supplementation may be needed in most dialysis patients.

Anabolic Steroids

Anabolic steroids may exert a beneficial effect on the malnutrition of renal failure [326], but larger prospective studies are needed to clarify the role of treatment with anabolic steroids among these patients as well as the severity of possible adverse effects. One retrospective study of 13 PD patients showed increasing serum albumin and creatinine levels (interpreted as improved nutritional status) among nine patients who received small doses of nandrolone decanoate intramuscularly for 3 months, whereas no beneficial effect was observed among four patients who received both nandrolone decanoate and one daily exchange of a 1% amino acid solution [327]. The lack of anabolic effect among the four patients that received both nandrolone decanoate and amino acids was attributed to the low dose of nandrolone decanoate, the increased acidosis with the amino acid solution, the severity of malnutrition and the advanced age among these four patients [327].

GH and IGF-1

Recombinant human growth hormone (rhGH) administration enhances the growth velocity of children undergoing dialysis [328] and may reduce urea generation and improve the efficiency of dietary protein utilization in stable adult HD patients [329]. Furthermore, the combination of intradialytic parenteral nutrition and rhGH treatment in wasted HD patients resulted in improved nutritional parameters (increased serum albumin, transferrin, and IGF-1) as well as in a decreased intradialytic urea appearance indicating that the treatment promoted net anabolism [330]. Short-term rhGH treatment in 10 PD patients resulted in signs of anabolism including a marked increase in IGF-1 levels [331]. Furthermore, administration of rhGH resulted in a decline of plasma essential amino acids suggesting an increased utilization of essential amino acids for protein anabolism [332].

Targeting Inflammation

Given the hitherto rather poor results of energy and protein supplementation, and the fact that the cachexia of PD seems to be associated with an up-regulated pro-inflammatory cytokine system activity, new treatment strategies are needed. We believe that much could be learned from other wasted and inflamed patients groups, such as HIV, CHF, and cancer-cachexia patients, in which various anti-inflammatory treatment strategies in combination with efforts to improve nutritional intake seems to improve nutritional status and outcome. Thus, since there is now the possibility of addressing the uremic wasting syndrome on different pathophysiologic levels, we should grasp the opportunity to utilize new therapeutic modalities to try to improve the quality of life and outcome of wasted and inflamed ESRD patients.

Anti-inflammatory Nutritional Treatment Strategies

Based on epidemiological studies in both renal and nonrenal populations, it is obvious that important differences regarding the prevalence and outcome of cachexia, inflammation, and atherosclerosis exist in different parts of the world [333]. In general, the population in Southeast Asia, China, and Japan consumes a substantial amount of fish and soy, resulting in a lower fat content and a higher fiber diet than the typical Western diet. Soybeans are a unique source of the phytoestrogens genistein and daidzein (estrogen-like substances) and in the Japanese population the phytoestrogen concentration is markedly higher compared to other populations [334]. As the phytoestrogen genistein is effective in blocking inflammatory gene expression [335], dietary phytoestrogens may not only have a possible role in renal disease protection [336], but could also provide significant anti-inflammatory properties, which could be of value for both PD and HD patients. Based on these findings, prospective studies on the impact of a high-soy diet on both the prevalence of MIA and outcome in ESRD patients are warranted.

The importance of dietary fiber is underscored by a recent evaluation study demonstrating that nonrenal subjects with a high fiber consumption had a lower risk of elevated CRP [337]. The anti-inflammatory and cardioprotective effects of the omega-3 fatty acids of fish oil, mainly eicosapentaenoic acid, are well recognized [338]. In addition, Kutner et al. [339]. found that dialysis patients who reported fish consumption were 50% less likely to die during the observation period. Therefore, the potential beneficial effects of a diet with high content of dietary fibers and omega-3 fatty acids in PD patients certainly merit further investigations.

Advanced glycation end-products (AGEs), the result of the nonenzymatic reaction of reducing sugars with proteins, lipids, and nucleic acids, are usually markedly elevated in ESRD patients. It has been proposed that AGEs promote atherosclerosis through interaction with endothelial receptors [340]. Although reduced renal clearance and increased oxidative stress may be the most important causes of elevated AGEs in ESRD patients, diet may be an important source of highly reactive AGEs. As correlations have been found between one form of AGE, pentosidine, and CRP in both renal [341] and nonrenal patients [342], it has been suggested that AGEs can trigger an inflammatory response [343]. Uribarri et al. [344] have shown that dietary glycotoxins contribute to significantly elevated AGE levels in ESRD patients. Further studies are thus warranted to elucidate whether dietary restrictions of the intake of AGE may reduce both excess toxic AGE and inflammation in this patient group. Importantly, a reduction in dietary AGE content can be obtained safely without compromising the content of vital nutrients, such as dietary protein, fat, and carbohydrates [345]. It may also be possible to use drug therapy to induce the breakdown of preexisting AGEs. One example of such a drug, which is presently being evaluated in clinical trials, is ALT-711. This cross-link breaker also has beneficial effects on putative mediators of renal injury, such as prosclerotic cytokines and oxidative stress [346], that might be beneficial for ESRD patients.

Anti-inflammatory Effects of Regularly Used Drugs

Several commonly used drugs in ESRD patients, such as statins and ACE-inhibitors (ACEI), have significant anti-inflammatory effects. Statins not only inhibit cholesterol synthesis but may also have anti-inflammatory effects [347]. Indeed, two studies have demonstrated that statins, in addition to its lipid-lowering effect, also had an anti-inflammatory effect in HD patients [348, 349], but the impact on PD patients is still untested. Paradoxically, since lipoproteins isolated from normal human plasma can bind and neutralize bacterial lipopolysaccharide [350], the cholesterol-lowering effect of statins may represent a disadvantage of this treatment in wasted ESRD patients. In fact, it has been speculated that "non-lipid lowering statins" may be as effective and even more beneficial than "lipid-lowering statins" in wasted and inflamed patients [351]. This hypothesis has been challenged by the observation by Liu et al. [352], that the inverse association between total cholesterol with mortality in dialysis patients is related to the cholesterol-lowering effect of systemic inflammation and wasting. Therefore, at the present time, these novel findings support the treatment of hypercholesterolemia in this patient population. Also, the renin-angiotensin system may contribute to inflammatory processes within the vascular system. Brull et al. [353], noted that ACEI treatment was associated with a reduction in IL-6 in response to coronary artery graft surgery, and we [354] have found lower plasma levels of TNF-α in ESRD patients treated by ACEI. A recent study demonstrated that treatment with an ACEI reduced the risk of weight loss [355], supporting the hypothesis of strong relationships among wasting, the renin-angiotensin system and inflammation.

Peroxisome proliferators-activated receptors (PPAR-γ activators, e.g., glitazones) have also been shown to inhibit the activation of inflammatory response genes, and promote a deviation of the immune system away from Th1 toward Th2 cytokine production [356, 357]. As diabetes mellitus is the most common cause of ESRD and insulin resistance is present in most PD patients, this class of drugs may have beneficial effects in these patients and a randomized trial in diabetic PD patients demonstrated improved metabolic control as well as a significant reduction of CRP levels [358].

Anti-oxidants in PD

As wasting may be associated with increased oxidative stress [359] and poor nutritional intake may lead to a low nutritional intake of anti-oxidants, it could be speculated that anti-oxidative treatment strategies may be beneficial in wasted and inflamed PD patients [360]. It is of interest that vitamin E and N-acetylcysteine, have not only an anti-inflammatory potential [361, 362] and improve endothelial dysfunction [363, 364], but have also been shown to reduce cardiovascular events in dialysis patients [226, 365]. Indeed, Boaz et al. [226] demonstrated that supplementation of vitamin E (800 IU/day) reduced composite CVD endpoints and myocardial infarction in HD patients followed for 519 days and Tepel et al. [365] showed that also N-acetylcysteine (600 mg b.i.d.) reduced composite cardiovascular endpoints in a group of 134 HD-patients followed for 14.5 months. Studies in the PD population would hopefully yield similarly positive results, but larger randomized studies are needed to confirm these intriguing findings.

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Chapter 22
Calcium, Phosphate, and Renal Osteodystrophy

A. Vardhan and A.J. Hutchison

The first association between uremia and bone disease was made by Lucas and reported in *Lancet* in 1883 [1]. However, it was not until nearly 40 years later that the major clinical and radiological manifestations of the skeletal changes were accurately defined [2, 3]. In 1943, the histopathology of osteitis fibrosa and osteomalacia was described [4], and in the same year the term "renal osteodystrophy" was coined by Liu and Chu [5]. Subsequently, the abnormalities of bone mass that occur in osteopenia and osteosclerosis were also described [6]. Following the research of Stanbury and Lumb [7, 8], there began a period of rapid advance in the understanding of the processes behind altered divalent ion metabolism, and the abnormalities of parathyroid hormone and vitamin D3 production that are seen in end-stage renal disease. Despite these advances with the introduction of vitamin D3 replacement therapy, new oral phosphate binders and, most recently, calcimimetic therapy, osteodystrophy remains a common complication of end-stage renal failure, and continues to pose diagnostic and therapeutic dilemmas for clinical nephrologists.

It has become apparent that the spectrum of bone lesions seen in dialysis patients has changed over the decades. In the first two decades of dialysis, hyperparathyroid disease was usual but then became much less common with the introduction of calcium-based phosphate binders and oral vitamin D therapy [9, 10]. Furthermore, a different pattern of bone lesions is found in peritoneal dialysis (PD) and hemodialysis patients [9–12]. In a histological study of 259 chronic dialysis patients in Canada in the early 1990s, the commonest bone lesion found was high turnover hyperparathyroid disease (50%) in hemodialysis patients, and low turnover, adynamic bone (61%) in PD patients [10]. In contrast, Malluche and Monier-Faugere (Kentucky, USA) reported that in a retrospective survey of 602 patients from 1982 to 1991 the mixed lesion was the commonest diagnosis [9], regardless of mode of dialysis (56% in CAPD and 49% in hemodialysis). A more recent study of 96 hemodialysis patients demonstrated 60% had low turnover lesions [13]. The difference between these reports is noteworthy in itself, since they are large and reliable studies, but from centers thousands of miles apart. While varying diagnostic criteria may account for some of the difference, it emphasizes the fact that, in dialysis patients, histomorphometric data represent the result of pathological processes, treatment regimes, and environmental effects that have been on-going for many years.

Over the past decade, interest in osteodystrophy has exploded as the connections between calcium, phosphate, parathyroid hormone, and cardiovascular disease have emerged. Unfortunately, most of the reports to date are from retrospective analyses and are yet to be confirmed in interventional randomized, prospective studies.

Classification of Renal Osteodystrophy

In this chapter, the term *renal osteodystrophy* is used to encompass all its skeletal manifestations such as osteitis fibrosa, osteomalacia, mixed lesions, the adynamic lesion, osteoporosis, osteosclerosis, and (in children) retardation of growth. However, renal osteodystrophy also includes a variety of extraskeletal problems including myopathy, peripheral ischemic necrosis, visceral calcification, and, perhaps most importantly, vascular and valvular calcification.

Since the introduction of the undecalcified bone biopsy, significant advances have been made in the understanding of the histological changes underlying all forms of renal osteodystrophy. Renal osteodystrophy has its origins early in the course of renal failure [14, 15], so that by the time GFR has fallen to 50% of normal, at least 50% of the patients exhibit abnormal bone histology [16]. In a study of 16 patients with creatinine clearances between 20 and 59 mL/min, Baker et al. found all of them to have abnormal bone histology [17]. By the time patients start peritoneal dialysis the

A. Vardhan (✉)
Institute of Nephrology & Transplantation, Manchester Royal Infirmary, Oxford Road, Manchester MI3 9WL, United Kingdom
e-mail: anand.vardhan@cmmc.nhs.uk

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majority have an identifiable histological abnormality [18], the nature of which depends to some extent on medical management up to that time.

The classification of renal osteodystrophy is simplified by the recognition that there are essentially two groups of histological lesions – high and low turnover bone lesions plus a third intermediate category referred to as a "mixed" lesion. There may also be osteopenia or osteoporosis superimposed on these lesions, particularly in elderly female patients.

High Turnover Bone Lesions

In osteitis fibrosa cystica, the characteristic findings include a marked increase in bone resorption, osteoblastic and osteoclastic activity, and endosteal fibrosis (Fig. 22.1). In particular, the number of osteoclasts is markedly increased, and they may be larger than normal with multiple nuclei. There may be a large increase in surface resorption with dissecting cavities where the osteoclasts have tunneled through the trabecular bone. This results in deposition of fibrous tissue in the marrow spaces (peritrabecular fibrosis), and the formation of so-called "woven bone," new bone matrix that is not lamellar but disorganized in structure. Although the bone may show increased osteoid, the use of tetracycline labeling prior to biopsy demonstrates that mineralization proceeds relatively normally. Skeletal mass may diminish as the rate of resorption exceeds that of formation. The term *osteitis* implies inflammation of bone, which is not present, so that is it preferable to refer to this lesion as *severe* or *predominant hyperparathyroid bone disease*.

In mild hyperparathyroidism, elevated parathyroid hormone levels increase bone turnover but peritrabecular fibrosis is minimal or absent.

Low Turnover Bone Lesions

In osteomalacia, defective mineralization of bone, due to deficiency of 1,25-dihydroxyvitamin D3, results in a relative increase in the amount of osteoid or unmineralized bone matrix (Fig. 22.2). Osteitis fibrosa can also increase osteoid

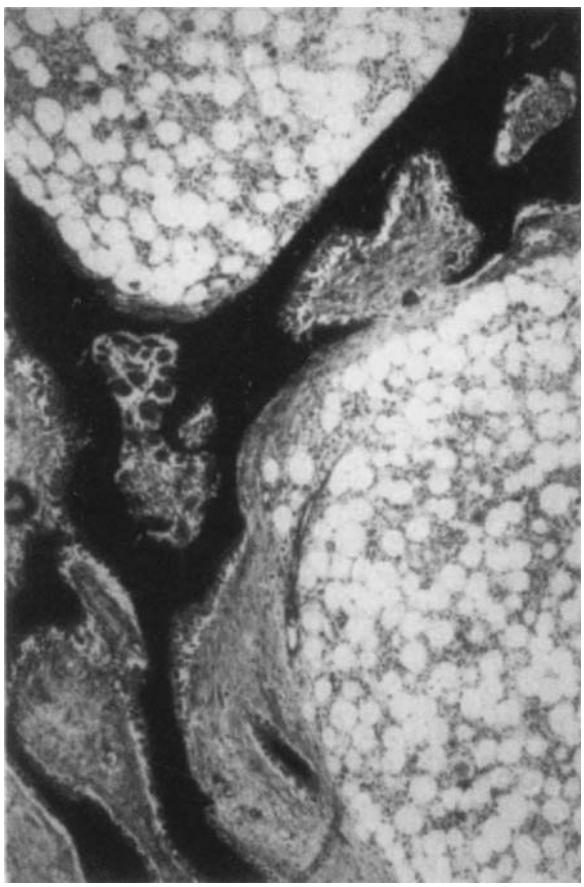

Fig. 22.1 Bone histology in severe hyperparathyroid disease. Numerous large, multinucleate osteoclasts can be seen tunnelling into mineralized trabecular bone. Osteoblasts are also numerous, and peritrabecular fibrous tissue has been deposited in the marrow cavity (toluidine blue stain; original magnification × 100)

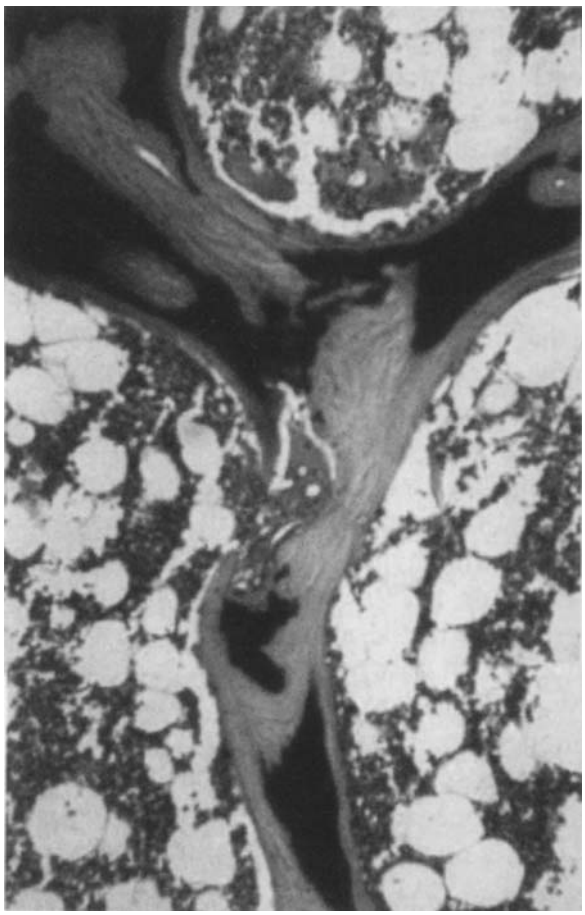

Fig. 22.2 Bone histology in osteomalacia (not aluminium-related). Broad lamellar osteoid seams surround the calcified trabecular bone. In some areas the failure of mineralization has resulted in 'islands' of calcified bone so that the mechanical strength of the trabeculum is greatly reduced (toluidine blue stain; original magnification × 100)

mass, simply as a result of increased bone turnover, but bone biopsy with dual tetracycline labeling will reliably distinguish these diseases. Use of oral aluminium for phosphate binding is decreasing, but accumulation can also lead to an osteomalacic-type osteodystrophy even in the presence of adequate 1,25-dihydroxyvitamin D3 levels [19]. In bone, the site of aluminium deposition is at the interface between mineralized bone and unmineralized osteoid. Here it appears to reduce osteoblast numbers and delay the process of mineralization, as demonstrated by diminished uptake of tetracycline into trabecular bone [20]. Studies have established an inverse relationship between bone aluminium accumulation and the rate of bone formation [21] and, even in cell-free laboratory studies, aluminium has been shown to reduce both the formation and growth of hydroxyapatite crystals [22].

Adynamic bone lesions, previously thought to be a result of aluminium accumulation in bone, are now well recognized to occur in the absence of stainable bone aluminium (Fig. 22.3), and are characterized by an abnormally low bone formation rate, a defect of bone mineralization, normal or decreased osteoid thickness, decreased osteoblastic surfaces, and normal or decreased osteoclastic surfaces [16, 23, 23–26]. This appearance was sometimes referred to as *aplastic*, a term usually reserved for structures that are congenitally absent, whereas *adynamic* more accurately conveys the inactivity of bone cells in this lesion [27]. Little is known about its etiology, and even less about its natural history, although there is evidence to suggest that it is commoner in patients with diabetes, elderly dialysis patients, and those on continuous ambulatory peritoneal dialysis (CAPD) [23–25, 28]. Overtreatment with vitamin D, and use of corticosteroids, as well as low sexual and thyroid hormone levels, are other causes that have been considered [25, 29]. Recently, a small study of PD patients implicated albumin and the malnutrition-inflammation-cachexia syndrome in the pathophysiology of the adynamic lesion [27].

Mixed Bone Lesions

In many patients, hyperparathyroidism and defective mineralization coexist with variable bone volume and rates of bone turnover. This probably reflects the fact that changes to rates of bone turnover occur much more slowly than

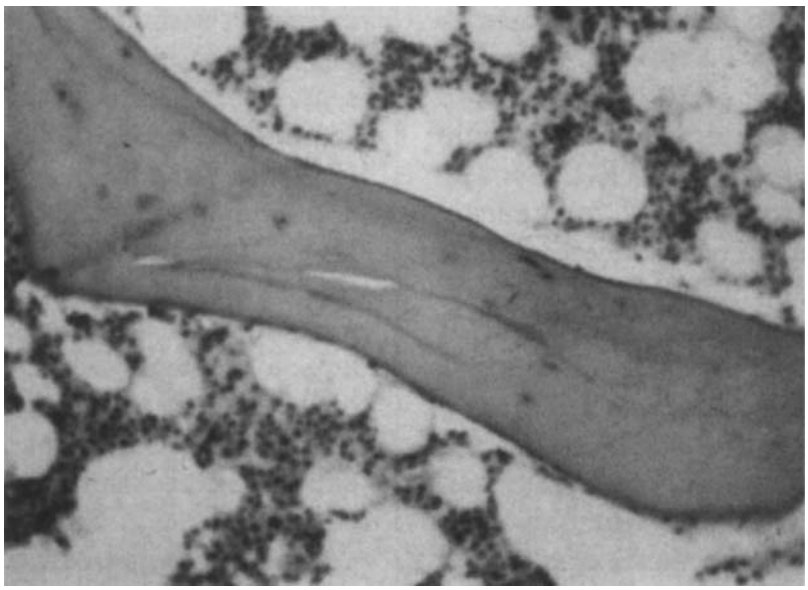

Fig. 22.3 Bone histology in the adynamic lesion. Osteoid seams are very thin or almost absent. Numbers of osteoclasts and osteoblasts are greatly reduced and unrepaired microfractures can be seen within the mineralized bone (hematoxylin and eosin stain; original magnification, × 100)

changes to biochemical parameters. These changes will also be influenced by local structural stresses and may therefore vary in space as well as time within the skeleton.

Osteoporosis

In osteoporosis, the bone mineral density is reduced, bone microarchitecture is disrupted, and the amount and variety of noncollagenous proteins in bone is altered and are therefore more at risk of fracture. Osteoporosis is defined by the World Health Organization as a bone mineral density 2.5 SD below peak bone mass in women (20-year-old sex-matched healthy person average) as measured by DEXA. Making a diagnosis in patients with chronic kidney disease (CKD) is more difficult since any type of osteodystrophy can be associated with reduced bone density [18], with no apparent correlation. Nevertheless, peritoneal dialysis patients are at greater risk of osteoporosis than the general population because of numerous risk factors found more commonly in CKD 5. These include poor nutrition, decreased physical activity, smoking and peripheral vascular disease, estrogen or androgen deficiency, low body mass index, reduced mobility, previous steroid and heparin usage, low parathyroid hormone levels, β-2-microglobulin amyloidosis, and chronic acidosis [30].

Pathogenesis of Renal Osteodystrophy

Renal osteodystrophy is recognized to be a common complication of end-stage renal failure and is believed to have its origins early in the onset of renal impairment [31]. The mechanism of its development is both multifactorial and controversial, but since normal kidneys maintain calcium, phosphate, magnesium and bicarbonate balance, synthesise 1.25- and 24,25-dihydroxyvitamin D3, act as a major target organ and excretory organ for parathyroid hormone, and also excrete aluminium, it is self-evident that renal failure will have numerous profound effects on mineral metabolism. These various factors all interact to a greater or lesser extent, but for simplicity are considered separately in the following sections.

Parathyroid Hormone and Calcium Metabolism

Bone is continually being remodeled, and in health a balance is maintained between synthesis of bone matrix (osteoid formation), its mineralization, and subsequent resorption. This balance is governed by the relative activity of osteoblasts, osteoclasts, and osteocytes. Increased secretion of parathyroid hormone (PTH) increases both the activity and numbers of these bone cells, causing an overall increase in bone turnover. Excessive production may result in deposition of fibrous tissue in the marrow spaces (osteitis fibrosa), endosteal fibrosis, and the formation of so-called

"woven bone," new bone matrix that is not lamellar but disorganized in structure. Skeletal mass may diminish as the rate of resorption exceeds that of formation. Studies from both Europe and the United States suggest that parathyroidectomy is still required in a significant number of patients. A study of 14,180 patients undergoing dialysis in Lombardy, Italy, from 1983 to 1996, reported parathyroidectomy rates of 3.3 cases per 1,000 patient-years for patients receiving renal replacement therapy for less than 5 years, and 30 cases per 1,000 patient-years for those receiving renal replacement therapy for more than 10 years [32]. In the United States, parathyroidectomy rates among prevalent hemodialysis patients declined between 1988 and 1998 but increased progressively after 1998 despite introduction of better therapies for preventing severe hyperparathyroidism [33]. However, it is generally accepted that, in the uremic patient, low/normal levels of PTH result in excessively low bone cell activity and bone turnover, or adynamic bone [9, 10, 25, 29, 34–39], and this is associated with increased rates of vascular calcification [40].

PTH is a single-chain protein of 84 amino acids, the sequence of which was established by Keutmann et al. in 1978 [41]. It is synthesized in the parathyroid chief cell via two precursors, pre-pro-PTH and pro-PTH (115 and 90 amino acids, respectively). PTH secretion occurs approximately 20 min after synthesis of the original pre-pro-PTH [42].

Significant elevations of serum parathyroid hormone have been reported in patients with only moderately abnormal glomerular filtration rates of 60–80 mL/min [17, 43, 44]. The secretion of PTH is controlled by many factors, but in renal impairment the most important stimulus is thought to be reduction in the level of serum-ionized calcium (Fig. 22.4). Factors which contribute to hypocalcemia and elevation of serum PTH are phosphate retention, defective vitamin D metabolism, skeletal resistance to the calcemic action of PTH, elevation of the "set point" at which serum calcium suppresses PTH release and impaired degradation of circulating PTH [44].

Secretion of PTH is primarily controlled by the concentration of ionized calcium in the extracellular space so that hypocalcemia stimulates, and hypercalcemia suppresses PTH release [45]. This relationship between PTH and serum calcium can be represented as a sigmoidal curve, with a basal rate of secretion persisting even during hypercalcemia [46]. In normal individuals, the basal PTH level is approximately 20–25% of the maximally stimulated PTH level and is positioned in the initial part of the steep ascent of the sigmoidal curve. Therefore, a small decrease in serum calcium produces a large increase in serum PTH secretion. Felsenfeld observed that for the same ionized calcium level serum PTH was higher during the induction of hypocalcemia than during the recovery from hypocalcemia [47]. Conversely, the PTH level was greater when hypercalcemia was induced from the nadir of hypocalcemia than when hypercalcemia was induced from basal serum calcium. Furthermore, the set point of calcium was greater during the induction of hypocalcemia than during the recovery from hypocalcemia. This differential response of PTH to the direction of change of serum calcium is known as "hysteresis," and there is evidence that the PTH–calcium curves may differ in different forms of renal osteodystrophy or after a specific form of therapy such as desferrioxamine or calcitriol [47–49].

As well as suppressing PTH secretion, hypercalcemia is also known to decrease parathyroid cell cyclic adenosine monophosphate (cAMP) but it is not clear whether this is the means by which PTH is controlled or whether it is a secondary phenomenon [50].

Hyperplastic parathyroid glands are less sensitive to ionized calcium levels than are normal glands, suggesting that one cause of elevated PTH in chronic renal failure may be a shift in the "set point" for calcium-regulated PTH secretion, in addition to the increase in parathyroid mass. The set point is defined as a calcium ion concentration necessary to suppress the secretion of PTH by 50%. Furthermore the degree of responsiveness across the calcium-sensitive range is altered so that hyperparathyroidism is a product of the increase in tissue mass (because the nonsuppressible, basal secretion is increased) and the lack of suppression by calcium in the normocalcemic range.

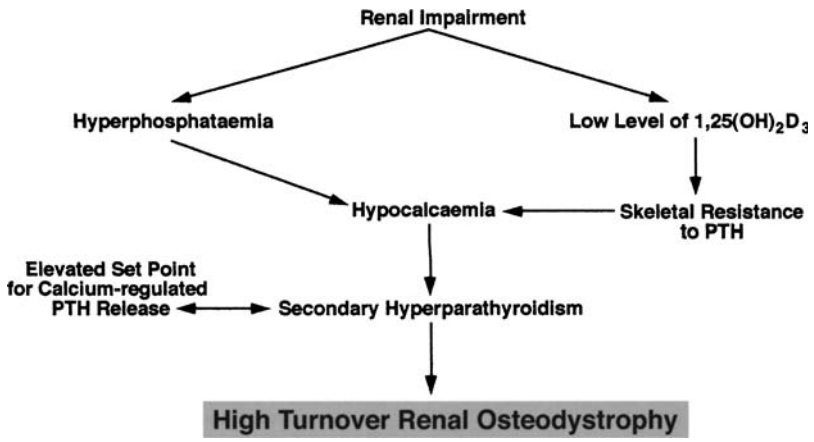

Fig. 22.4 Factors contributing to the production of excess parathyroid hormone in dialysis patients

Thus normal concentrations of ionized calcium may not be sufficient to suppress hyperplastic parathyroid glands, and serum levels have to be increased to the upper limits of normal to control the release of PTH in patients with secondary hyperparathyroidism [46]. However, there is evidence that once the parathyroid gland size exceeds a certain limit, the nonsuppressible basal secretion alone becomes sufficient to increase serum parathyroid hormone to hyperparathyroid levels [51]. When this occurs parathyroidectomy was previously the only remaining option, but with the introduction of cinacalcet many patients may now avoid this procedure.

Firm evidence now exists that parathyroid cells possess specific nuclear receptors for 1,25-dihydroxyvitamin D3 [51–53]. When given intravenously to a group of 20 hemodialysis patients calcitriol produced a marked suppression ($70.1 \pm 3.2\%$) of PTH levels without a significant change in serum calcium, confirming that it is an important regulator of PTH secretion at least in states of calcitriol depletion [53]. Substantial degradation of calcitriol occurs in the intestine so that oral vitamin D increases intestinal calcium absorption but the delivery of calcitriol to peripheral target organs is limited [54, 55]. This could explain the greater effect of intravenous, compared to oral, calcitriol. PTH secretion is also affected by ionized magnesium, however, only severe hypomagnesemia seems to have any clinical relevance in that it has been shown to inhibit PTH secretion [56].

In addition to the abnormalities of secretion that occur in chronic renal failure, the process of degradation is incomplete. Normally, intact PTH is degraded by the liver and kidneys, resulting in the production of amino (N)- and carboxy (C)-terminal fragments. The fragments are further metabolized by the kidney, so that in the absence of renal function they will accumulate. C-terminal fragments are detectable up to 2 weeks after parathyroidectomy in chronic renal failure, yet decrease by 80% within 24 h of a successful renal transplant. So-called "second-generation" PTH assays, called "intact" PTH assays, have been developed since 1987. They use two different antibodies, the first, directed against the C-terminal region of PTH, and the second directed against the N-terminal region. These "sandwich" assays were the first radioimmunometric assays, and were thought to measure only the full-length 1–84 PTH, however, they also measure large PTH fragments (namely 7–84 PTH). These N-terminal truncated PTH fragments inhibit the action of PTH by blocking its binding to its normal receptor. They may also bind to a specific C-terminal PTH receptor and may have biological functions in the skin, bone, hematopoietic system, and placenta [57]. The third generation of PTH assays have been developed since 2000 and use the same sandwich and radioimmunometric techniques, with the first antibody directed against amino acids 39–84, but the second antibody has been restricted and directed against the first six N-terminal residues of 1–84 PTH. They have been demonstrated to be most sensitive, and more specific, when measuring bioactive intact 1–84 PTH. It is now clear that different assays can give significantly different results as demonstrated by a study of 15 different methods [58]. In terms of correlation with bone histology, most experience has been gained with sandwich assays specific to the whole, or intact, 1–84 PTH molecule. These appear to correlate well with the biological effects of PTH on bone in chronic renal failure [18, 59], and whether "third-generation" assays have any advantages remains to be seen [60].

Vitamin D Metabolism

The similarity between the bone disease caused by simple vitamin D deficiency and that which occurs in chronic renal failure has been recognized for many years, both at clinical [1] and histological levels [4]. It was also known that renal failure was associated with impaired intestinal absorption of calcium [5]. In renal failure both the bone lesions and the defect in calcium absorption were shown to be correctable by oral calciferol, but the amount required to have an effect is much larger than in simple deficiency states. The disease is "vitamin D resistant." Vitamin D3 (calciferol) circulates in the blood bound to vitamin D-binding protein, after having been synthesized in the skin or absorbed from the diet. In the liver it is metabolized by the enzyme vitamin-D-25-hydroxylase to form 25-hydroxyvitamin D (calcidiol, 25-OH-D). In most patients with chronic renal failure, 25-OH-D levels are normal if they eat a balanced diet and their skin is not completely covered from the sun.

In the kidney 25-OH–D is further metabolized by a mitochondrial cytochrome P–450 oxidase, 25-OH–D-1α-hydroxylase, to form 1,25-dihydroxyvitamin D3 (calcitriol), the biologically active form of vitamin D. Various studies have indicated that the proximal convoluted tubules (PCT) are the principal site of $1,25(OH)_2D_3$ production [61]. In 1973, Mawer et a1. showed that calcitriol could not be detected in the serum of patients with chronic renal failure, after injection of radioactive cholecalciferol, and suggested that it was the inability to form this metabolite that was the cause of the vitamin D resistance[62]. This is now known to be the case, and is a result of reduced renal 1α-hydroxylase activity caused by loss of renal mass, hyperphosphatemia and possibly by uremic toxins [63]. In addition to renal production of 1,25-OH–D3, humans can, in certain pathological states, produce it extrarenally. In sarcoidosis cultured alveolar macrophages and lymph node homogenates can convert 25-OH–D to 1,25-OH–D3 and a similar process

probably accounts for the hypercalcemia and hypercalciuria sometimes seen in other granulomatous diseases such as tuberculosis, silicosis, berylliosis, and fungal diseases. In CAPD patients who have had one or more episodes of peritonitis cultured peritoneal macrophages are also able to convert 25-OH–D3 to 1,25-OH–D3 [64].

Once synthesized in the kidney, 1,25-OH–D3 is transported by vitamin D-binding protein to its target cells. It enters the cell by a mechanism that is poorly understood and is then transported to the nucleus. Here it interacts with its nuclear receptor, phosphorylating it to bring about interaction with chromatin and transcription of specific genes. In the small intestine this results in expression of the gene coding for calbindin, the calcium-binding protein. The activity of other proteins is also affected, with the net result that calcium and phosphate absorption from the intestine is stimulated. The effect of 1,25-OH–D3 on bone is to increase removal of calcium. A small decrease in serum ionized calcium stimulates PTH production which in turn stimulates the kidney to produce 1,25-OH–D3, 1,25-OH–D3 in conjunction with PTH increases osteoclastic activity and release of calcium, returning the ionized calcium level to normal.

1,25-OH–D3 has been conclusively shown to suppress PTH secretion in dialysis patients when administered orally or intravenously [53, 65–71]. It undoubtedly also has important immunoregulatory functions and is able to decrease the rate of proliferation of certain tumour cells, such as the HL-60 (human promyelocytic) cell, and even transform them into mature macrophages. 1,25-OH–D3 can also inhibit the proliferation of cultured human keratinocytes, an ability that has important clinical implications in that it has been shown to dramatically improve psoriasis in 75% of a group of patients given up to 2 μg/day [72]. It has recently been suggested that vitamin D deficiency may be an important factor in the pathogenesis of hypertension and insulin resistance in end-stage renal failure [73].

Phosphate Metabolism

In the past, overactivity of the parathyroid glands in renal failure was explained by the trade-off hypothesis of Bricker [74, 75]. He postulated that as renal failure progresses there is a tendency for serum phosphate levels to rise and ionized calcium levels to fall, resulting in a compensatory rise in PTH. The increase in PTH reduces tubular reabsorption of phosphate in the remaining nephrons and increases serum calcium. Thus serum values of phosphate and calcium may be kept within, or near, the normal range at the expense of rising PTH levels and its resultant effects on the skeleton. However, more recent work has cast doubt on this, with the observations that hyperparathyroidism can develop even in the presence of a high serum calcium [75], and that hyperphosphatemia stimulates PTH secretion independent of serum calcium concentration [76–78]. However, increased phosphate excretion results in decreased activity of 25-OH–D-1α-hydroxylase, and consequently decreased production of 1,25-dihydroxyvitamin D3 [72]. This in turn stimulates increased synthesis and secretion of PTH in an attempt to stimulate renal production of 1,25-dihydroxyvitamin D3. As renal failure progresses the compensatory effect of PTH on 1,25-dihydroxyvitamin D3 deficiency is overcome and an absolute deficiency develops [16]. This further stimulates PTH levels and decreases gastrointestinal calcium absorption [79]. With further progression of renal failure, to a glomerular filtration rate of around 10 mL/min, phosphate excretion can no longer be increased and hyperphosphatemia occurs, exacerbating the hypocalcemia. At this stage, hypocalcemia further stimulates PTH secretion, although doubt remains as to its role in the earlier stages of renal failure. In addition hyperphosphatemia is associated with extraskeletal calcification in soft tissues and, perhaps more worryingly, in blood vessels.

Magnesium Metabolism

Although magnesium metabolism is affected by decreasing renal function, the clinical relevance of this is unknown. In normal subjects magnesium is absorbed from the small intestine and excreted in the urine, so that elevated serum levels are seen in renal failure [80]. In vitro, magnesium is an inhibitor of crystallization and may increase bone levels of pyrophosphate – another inhibitor of mineralization [81]. In uremia, bone magnesium is correlated with serum magnesium, and serum pyrophosphate is increased [82]. Hence, it is theoretically possible that elevated serum magnesium could play a role in the development of osteomalacia, but there is no evidence in the literature that this is the case.

Moderate hypomagnesemia can contribute to elevation of serum PTH [83], whereas severe hypomagnesemia has been shown to inhibit PTH secretion [56].

Aluminium and Osteodystrophy

In 1978, Ward et al. made the association between aluminium and bone disease in dialysis patients [19]. Since then the importance attached to reducing exposure to aluminium has increased, but aluminium hydroxide is still in use as a "rescue therapy" in cases of severe hyperphosphatemia.

A normal human daily intake of aluminium ranges from 2 to 20 mg but gastrointestinal uptake is estimated to be only 0.5–1% of this. Normal urinary aluminium excretion varies between 20 and 50 mg/day but was shown to increase to 200–400 mg/day when normal individuals were given aluminium hydroxide in amounts commonly given to dialysis patients [84]. In end-stage renal failure the loss of urinary excretion plus exposure to aluminium in dialysate solutions, phosphate binders, and volume replacement fluids can result in the total body content rising by a factor of up to 20. Serum levels are a poor guide to total body load, since it is strongly protein-bound and largely deposited quickly in tissues such as bone, liver and spleen.

Aluminium accumulates at the interface between mineralized bone and unmineralized osteoid, where it delays the process of mineralization. Aluminium also accumulates in parathyroid glands and suppresses their secretion of PTH. In patients with aluminium-related bone disease and renal failure, PTH levels are commonly lower than would be expected and may be suppressed to normal levels, giving some degree of protection from hyperparathyroid bone disease [85], but possibly resulting in development of the adynamic bone lesion [59] and other toxic effects.

It is likely that aluminium-related bone disease will gradually disappear as fewer physicians use aluminium-based phosphate binders, and exposure from other sources is sought out and reduced to minimal levels.

Acid-Base Balance

The role of acidosis in the pathogenesis of renal osteodystrophy is unclear. However, acidosis is involved in both calcium balance and PTH release. Acidotic azotemic patients show increased losses of urinary and faecal calcium which can be reduced by alkali treatment, resulting in restoration of a neutral calcium balance [86]. In a study of 54 uremic patients, infusion of sodium bicarbonate produced a rise in arterialized capillary blood pH and a proportional fall of around 20% in serum PTH [87, 88]. No significant change in serum ionized calcium was observed during the study. The clinical significance of these findings remains to be elucidated but it seems likely that, as with changes in magnesium metabolism, the effects are of much less importance than those associated with PTH and vitamin D.

Calcitonin

Calcitonin is a 32-amino acid single-chain peptide, and the major stimulus for its secretion is hypercalcemia. Circulating calcitonin has a short half-life (around 10 min) and depends on renal function for degradation and excretion, so that high circulating levels are found in patients with renal failure [89–91]. Its role in normal human subjects is debated, since neither the absence of this hormone (as in completely thyroidectomized patients) nor its thousand-fold excess (as in patients with thyroid medullary carcinoma) is generally associated with any abnormality of calcium homeostasis or skeletal integrity [92]. However, there is around 40% structural homology between PTH and calcitonin receptors, the latter being found in bone, kidney, central nervous system, testis, placenta and on some tumour cells.

Clinical and Radiological Features of Renal Osteodystrophy

Clinical features of the altered mineral and skeletal metabolism that occurs in renal failure may be considered under two broad headings: extraskeletal and skeletal manifestations (Table 22.1).

Extraskeletal Manifestations

Extraskeletal manifestations are a result of deposition of phosphate and calcium in soft tissues. Calcium deposition in the skin may contribute to the pruritus that in severe cases can be quite disabling for dialysis patients, preventing

Table 22.1 Clinical and radiological features of renal osteodystrophy

Clinical manifestations
Skeletal
Bone tenderness
Bone pain
Joint pains
Spontaneous fracture
Growth retardation
Extraskeletal
Renal "red eye"
Pruritus
Myopathy
Tumoral calcification
Peripheral ischemic necrosis
Radiological manifestations
Hyperparathyroidism
Erosion of tips of terminal phalanges, radial aspects of middle phalanges, distal ends of clavicles
"Pepper-pot" skull
Thinning of cortex in tubular bones
Osteopenic vertebral bodies with sclerotic upper and lower surfaces, results in "rugger-jersey spine" appearance
Visceral/vascular calcification
Osteomalacia
Looser's zones (most often in pubic bones or femur), otherwise no specific features in milder cases
Adynamic lesion
No specific features, but associated with increased risk of vascular calcification

sleep and resulting in widespread excoriations with skin sepsis [93]. Calcification in the conjunctiva is another common problem leading to the intensely painful "red eye," with flecks of calcium often clearly visible on examination.

Perhaps the most important extraskeletal manifestation is calcification of the vascular tree that frequently becomes visible on plain X-rays. Most commonly the calcification is localized to the medial layer of small and medium-sized arteries (Monckeberg's sclerosis) [40, 94–98]. However, the abdominal aorta, femoral and digital arteries are often clearly outlined on films taken for skeletal survey, but the same process is undoubtedly occurring in the mesenteric, cerebral and coronary vasculature, resulting in considerable morbidity and mortality in dialysis and transplant patients [36, 99]. In severe cases, vascular calcification in the iliac and femoral vessels may render a patient untransplantable because anastomosis of the vessels becomes impossible. Furthermore the risk of preoperative myocardial infarction is greatly increased, and heart failure, controlled by strict attention to fluid balance while on dialysis, may be unmasked by renal transplantation.

Although hyperphosphatemia can cause an increase in the calcium–phosphate product, to a point where its solubility product is exceeded and precipitation may occur, analysis of vascular tissue has shown that calcification is not simply a passive process. Rather, under the right conditions, vascular cells can express bone cell surface markers and lay down hydroxyapatite, suggesting a much more active and regulated process. Recent studies have shown that arterial calcification is an active process that is regulated by a variety of genes and proteins [100]. Arterial calcification appears to be a process similar to bone formation implicating a variety of proteins involved in bone and mineral metabolism detected in atherosclerotic plaques and/or medial calcifications Since elevations of phosphate, calcium, and calcium–phosphate product have been associated with mortality and morbidity, it is now widely believed that vascular calcification could be the link.

A study of the calcium–phosphate product in a large number of hemodialysis patients demonstrated that the relative risk of death for those with a serum phosphate level greater than 6.5 mg/dL was 1.27 relative to those with a lower level [101]. The increased risk was not reduced by statistical adjustment for coexisting medical conditions, delivered dose of dialysis, PTH level, nutritional parameters or markers of noncompliance. The calcium–phosphate product showed a mortality trend similar to phosphate alone, with those patients having products greater than 72 mg^2/dL^2 showing a relative mortality risk of 1.34 compared to those with products less than 52 mg^2/dL^2. Similar findings have been reported from other studies of dialysis patients [102] as well as those with earlier CKD [103]. There seems little doubt that tight control of serum phosphate is vitally important for any dialysis patient, although it must be remembered that these studies are retrospective and not interventional.

Skeletal Manifestations

Skeletal signs and symptoms of renal osteodystrophy include bone pain, bone tenderness, spontaneous fractures, retardation of growth, and joint disease. With the exception of adolescents with tubulo-interstitial pathology, symptoms are unusual in patients with end-stage renal disease, unless the decline in renal function has been particularly slow. However, those with tubulo-interstitial disease and adolescent patients are more prone to overt bone disease. The prevalence of symptoms among dialysis patients varies greatly from unit to unit, which may reflect differences in reporting or true differences due to a dialysis-induced cause such as aluminium intake [104, 105]. Both osteomalacia and osteitis fibrosa may be associated with bone pain, tenderness, fatigue, and proximal muscle weakness. In addition, lower back and lower limb pain contribute to the reduced exercise ability that is common in dialysis patients. This in turn worsens muscle weakness and loss of skeletal mass. Periosteal new bone growth and osteosclerosis are usually asymptomatic but may often be seen on skeletal radiography.

Radiological Features

Regular radiological assessment using plain radiographs – the traditional annual "skeletal survey" – is now rarely carried out in order to monitor renal osteodystrophy since radiological signs of hyperparathyroid disease detected by such radiographs are relatively late features.

The earliest radiological feature of hyperparathyroidism is subperiosteal erosion occurring at the tufts of the terminal phalanges, the radial aspect of the middle phalanges and the distal ends of the clavicles. In a study of 30 end-stage renal failure patients, performed immediately prior to commencing dialysis, erosion of the terminal phalanges was only seen in five of the eight patients who had severe hyperparathyroid disease on bone biopsy and serum PTH values [18]. However, plain radiographs did not identify patients with mild hyperparathyroid disease, and the majority of patients were judged to have essentially normal skeletal surveys. These findings are in agreement with those of Owen et al., who compared plain skeletal radiology with bone histology in 82 patients with renal failure, and found no correlation between radiological and histological indices [106] Malluche and Faugere agree that information obtained from skeletal X-rays is limited and often misleading, and that most radiological signs considered to be pathognomonic of severe osteitis fibrosa can be found in any of the three histological types of renal osteodystrophy [16]. In addition, a skeletal survey provides a relatively high dose of ionizing radiation for such inconclusive information.

Low turnover adynamic bone may have no specific radiological features [36], and the introduction of oral vitamin D metabolites has largely abolished osteomalacia so that it is rarely found, even in histological studies [107].

In recent years, other radiological techniques have been developed for examining bone in a more quantitative fashion, including skeletal scintigraphy, measurement of bone density and mineral content by single or dual photon densitometry, plus single and dual energy quantitative computed tomography (QCT) scan [108, 109]. These techniques are discussed later in the chapter.

Renal Osteodystrophy and PD

The introduction of CAPD in the 1970s provided new opportunities for the investigation and management of renal osteodystrophy. However, reports of its management in CAPD remain confusing, with some showing improvement [55, 104, 110] and others showing deterioration [111–113].

The different pattern of bone lesions seen in PD and hemodialysis is now well described [9–12, 114]. There are several differences between the dialysis modalities which may affect mineral metabolism [11]. PD is associated with far greater losses of middle- and large-molecular-weight protein fractions, thereby removing more transferrin-bound aluminium, as well as 25-hydroxyvitamin D3. With PD, weekly phosphate removal is greater than hemodialysis, and it provides a steady-state biochemical profile unlike the "saw-tooth" pattern of hemodialysis. Furthermore, the high calcium concentration in standard peritoneal dialysis fluids of the past may have significantly suppressed PTH levels, contributing to the higher incidence of low-turnover bone disease seen in PD. In contrast, a hemodialysis patient may experience episodes of relative hypocalcemia two or three times each week, which may well stimulate PTH production.

Calcium and Phosphate Balance in PD

In end-stage renal disease serum phosphate levels begin to rise and ionized calcium levels begin to fall once the GFR is less than 20 mL/min. These abnormalities can be at least partially corrected by the administration of oral calcium carbonate, although some concern exists about its use in CKD 5. However, ionized calcium levels may still be low (0.9–1.1 mmol/L) when patients start PD, even though total serum calcium levels are normal [115]. Serum levels usually rise once PD has begun, despite the majority of patients now using dialysis fluids with a calcium concentration of 1.25 mmol/L. Gastrointestinal absorption and peritoneal flux of calcium during dialysis are the two major determinants of overall calcium mass balance in peritoneal dialysis patients.

Gastrointestinal Absorption

The gastrointestinal absorption of calcium has been studied by several groups and is known to be dependent on many factors including the degree of uremia, serum phosphate level, PTH level, 1,25-dihydroxyvitamin D3 level, and total calcium intake. In uremic subjects, Recker and Saville [116] found that calcium absorption ranged from 5 to 59%, while Clarkson and colleagues [117] and Ramirez et al. [118] reported figures of 8% and 28%, respectively. In a study of CAPD patients in our own unit, calcium absorption rate was subnormal in 18 of 19 subjects, although significant variation existed between patients. Percentage absorption ranged from 3.2 to 23.9%, results not dissimilar from those in uremics [119]. Blumenkrantz examined absorption of dietary calcium in CAPD patients over the range 500–2,500 mg/day [120] and suggested that it can be represented by the empirical relationship $Y = 0.42X - 277$ (where $Y =$ amount absorbed, $X =$ intake in mg/day). Therefore if the intake is around 730 mg/day, approximately 30 mg of calcium is absorbed by the patient.

If calcium salts are to be used as first-line therapy for hyperphosphatemia then oral intake and gastrointestinal absorption will be necessarily high. Once a patient is established on dialysis, control of hyperphosphatemia is very important, not only to minimize further stimulation of PTH secretion, but also to keep the calcium–phosphate product within the normal range. Failure to do this can result in rapid progression of vascular and soft-tissue calcification. The PD patient's high-protein diet (recommended minimum protein intake 1.2 g/kg/day) provides an obligatory phosphate intake of up to 1,200 mg daily [120, 121]. Although peritoneal dialysis controls the hyperphosphatemia of end-stage renal disease more effectively than does hemodialysis [113, 122, 123], it removes only 310–320 mg/day [120, 124] – rather less than one-third of the amount required to bring phosphate levels into the normal range. Therefore, if a neutral phosphate balance is to be achieved, the gastrointestinal elimination of phosphorus needs to be around 700 mg/day [125]. Since 40–80% of dietary phosphorus is absorbed by patients with renal failure [123], the fraction of phosphate absorbed must be reduced, and hence gastrointestinal elimination increased, by oral phosphate-binding agents.

The Role of Calcium Salts in Renal Osteodystrophy

Established phosphate binders, available for clinical use, include aluminium hydroxide and carbonate, calcium carbonate and acetate, magnesium carbonate, keto-analogues of amino acids, sevelamer hydrochloride, and lanthanum carbonate (Table 22.2). Each of these binders has advantages and disadvantages, but only four are in widespread use – calcium carbonate, calcium acetate, sevelamer hydrochloride, and lanthanum carbonate. Calcium carbonate and acetate remain in regular use in many countries as first-line phosphate binders in PD patients, where maintenance of optimal serum calcium and phosphate levels is central to the treatment of hyperparathyroidism. However, concern has arisen that calcium overload may contribute to adynamic bone and vascular calcification [94, 97]. Therefore, the U.S. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines suggest limiting the dose to a maximum of 1.5 g elemental calcium per day [126]. Calcium ketoglutarate is also in use, particularly in certain European countries [127].

Table 22.2 Available compounds for use as phosphate binders in dialysis patients

Calcium-based	Others
Calcium carbonate	Aluminium hydroxide/carbonate
Calcium acetate	Magnesium hydroxide/carbonate
Calcium gluconate	Sevelamer hydrochloride
Calcium alginate	Lanthanum carbonate
Calcium-ketovalin	

When CAPD was first introduced aluminium gels were the standard phosphate binders, and a high calcium concentration in the dialysis fluid (1.75 mmol/L–3.5 mEq/L) was therefore beneficial, rapidly bringing serum calcium levels into the normal range. As the dangers of aluminium accumulation became apparent [85, 128], aluminium-containing phosphate binders were replaced by calcium salts as first-line therapy for hyperphosphatemia in most renal units. Unfortunately calcium salts frequently result in hypercalcemia when given in sufficiently large oral doses to control serum phosphate [129–135], so that aluminium-containing phosphate binders continued to be used. It has been suggested that, when used in low doses, with careful monitoring of serum aluminium, these binders are safe [85]. However, although only about 1% of the oral dose of aluminium is absorbed [136], even on modest doses this represents between 5 and 10 mg of elemental aluminium daily. Since PD removes only 40–50 mg daily [137] it is evident that tissue accumulation is inevitable and significant. Reduction of dialysis fluid calcium concentration was advocated as a means of extending the use of calcium salts and preventing hypercalcemia and was studied both in hemodialysis [138, 139] and peritoneal dialysis patients [140–146].

The demonstration of an association between mortality and high/normal calcium levels by United States Renal Data System (USRDS) and Dialysis Outcomes and Practice Patterns Study (DOPPS) data [101, 102, 147] has persuaded many physicians that utilizing high/normal serum calcium levels to suppress PTH is no longer tenable. However, no prospective randomized trials have been undertaken so far to validate current guidelines. In order to maintain serum calcium below 2.37 mmol/L while controlling hyperphosphatemia use of the more expensive non-calcium-containing phosphate binders is required. This is impossible in many countries around the world on grounds of cost, and is even causing concern the United States [148–150].

Control of serum phosphate is not only important in terms of its effect on PTH, but also for prevention, and sometimes treatment, of extraskeletal calcification. This potentially lethal aspect of renal osteodystrophy is a particular hazard in patients who have persistent hypercalcemia and hyperphosphatemia. It was traditional to prescribe aluminium-containing binders for such patients on the grounds that the aluminium absorbed is likely to be less harmful than allowing the process of vascular calcification to continue unchecked. Utilization of noncalcemic phosphate binders is now a more appropriate (and expensive) approach.

Noncalcemic Phosphate Binders

A more efficient dialysis fluid is an attractive way of improving phosphate clearance, and this was tried in the early 1980s in an experimental rat model [151]. Polyethylenimine was utilized as an osmotic agent, and demonstrated measurable binding to phosphate. Unfortunately it was toxic to the rats and produced gross morphological changes in the visceral mesothelium and associated organs. A variety of other oral phosphate-binding agents have been tested and some are in clinical use [152]. However, none has completely abolished the problem of hyperphosphatemia because of problems with efficacy, potency or palatability.

Two noncalcemic compounds now generally available are poly[allylamine hydrochloride] (RenaGel, Geltex Pharmaceuticals, Waltham, Mass., USA) and lanthanum carbonate (Fosrenol, Shire Pharmaceuticals, Andover, UK). Poly[allylamine hydrochloride] is a nonabsorbable calcium- and aluminium-free compound that is as effective as calcium carbonate [153]. It also has a beneficial effect on the patients' lipid profile with a reduction in serum total and LDL cholesterol.

Lanthanum was first reported as a potential oral phosphate binder by Graff and Burnel [154]. Phosphate binding was estimated by the reduction of urinary excretion and increase in faecal excretion, and lanthanum citrate was found to be as effective as aluminium chloride, with less (but not zero) systemic absorption. Human studies have confirmed its phosphate binding properties in vivo [155–159] and it has been studied for up to 3 and 6 years, and has been commercially available since 2005. Although concerns exist in some quarters about its long-term safety, no clinical data has emerged to justify this [160]. The renewed interest in control of serum phosphate has reinvigorated the search for other more effective binders and several are in various stages of development [161].

Peritoneal Flux and Reduced Calcium Dialysis Fluid

During an exchange of 2 L of 1.36% glucose, 1.75 mmol/L calcium PD solution there is a net influx of calcium to the patient, although the amount varies from one study to the next (84 ± 18 mg/day [120], 300 mg/day [162]). The transfer of calcium is also influenced by ultrafiltration rate and volume [163], so that a 1.36% glucose solution results in a 10 mg calcium uptake by the patient but the greater ultrafiltration from a 3.86% solution leads to a loss of 20 mg. This gives a net daily absorption of 10 mg if one hypertonic bag is used per day. In another study, Kwong et al. [164] found an uptake of 29 mg per 1.36% exchange and a loss of 6 mg per 3.86% exchange, suggesting a larger net gain of around 80 mg daily. However, a lower PD fluid calcium concentration of 1.5 mmol/L causes the balance to become negative with a loss of 50 ±

36 mg/day [105]. These findings suggest that patients using dialysis solutions containing 1.75 mmol/L of calcium are in a significantly positive calcium balance even before considering the additional gut absorption from oral calcium carbonate and vitamin D therapy.

The theoretical work by Martis et al. [125] formed the basis for the commercial production of a peritoneal dialysis fluid with a calcium concentration of 1.25 mmol/L, in an attempt to decrease the incidence of hypercalcemia in CAPD patients taking oral calcium salt phosphate binders. Clinical studies have now confirmed this theoretical work [145, 165] and it is now the commonest concentration in general use. Although dialysis fluids with other concentrations of calcium can be obtained (0, 0.60, 1.00, 1.45 mmol/L), 1.25 mmol/L would appear to be the logical choice for a standard PD fluid because it is so close to normal serum ionized calcium levels. This results in a homeostatic effect, with calcium being lost into the peritoneum when serum levels are above 1.25 mmol/L, but being absorbed from the peritoneum during times of relative hypocalcemia. All other proposed calcium concentrations are outside the normal range of serum ionized calcium and therefore cannot exert this homeostatic effect.

Convective effects of ultrafiltration increase the removal of calcium from the peritoneum so that patients using one or more 3.86% glucose exchanges per day will have a significantly greater negative peritoneal calcium balance than patients using only 1.36% exchanges [166]. While in theory this could result in some degree of hypocalcemia, in practice it rarely occurs, as calcium absorption from oral phosphate binders is usually sufficient to compensate.

A 2-year prospective biochemical, radiological, and histological study of 1.25 mmol/L calcium PD fluid showed it to be safe in compliant, well-monitored patients [141, 144]. It allowed administration of larger doses of calcium carbonate (now considered less desirable) and achievement of good control of serum phosphate and calcium–phosphate product. Parathyroid hormone levels were suppressed in the majority of patients, and bone histology and density did not deteriorate.

Cunningham et al. [146] used 1.25 mmol/L calcium dialysis fluid to enable the use of calcium carbonate plus alphacalcidol in a group of CAPD patients. In 17 CAPD patients taking oral calcium carbonate, reductions in dialysis fluid calcium concentration to 1.45 mmol/L or 1.00 mmol/L enabled most of the patients to also take oral alphacalcidol. Parathyroid hormone, serum aluminium, and alkaline phosphatase levels were all decreased during the 11 months of the study, with the authors concluding that a dialysate calcium concentration of 1.75 mmol/L is too high for the majority of calcium carbonate–treated patients, and that substantial reductions of the dialysate calcium concentration are required. Other workers have used 1.0 mmol/L calcium fluid in PD patients, again with similar results [39, 167]. Utilization of solutions with calcium concentrations of 1.00 mmol/L and below put the patient into a permanent negative calcium balance, so that very close attention must be given to PTH levels and compliance with oral calcium and vitamin D therapy, but this approach has been reported to increase PTH levels and bone turnover in patients with adynamic bone [168].

Serum Magnesium in PD

Magnesium levels are consistently elevated in PD patients managed with standard dialysate containing 0.75 mmol/L of magnesium [140]. No toxicity has been reported at these levels, indeed hypermagnesemia may have a suppressive effect on PTH release and retard the development of arterial calcification in PD patients [169]. Hypermagnesemia may therefore be beneficial, but it has also been shown that normalization of serum magnesium is associated with an improvement in bone histology in hemodialysis patients [170]. Reducing the magnesium content to 0.25 mmol/L normalizes serum magnesium levels in CAPD patients [122, 165]. Parsons et al. [171, 172] have described the use of a low-calcium/zero magnesium PD fluid with a combination of calcium carbonate and magnesium carbonate in liquid form as the phosphate binder. Using this approach, mean serum phosphate levels of 1.4–1.5 mmol/L were obtained without causing hypermagnesemia, although hypomagnesemia was seen in two of 32 patients. Zero magnesium fluids have also been studied by Shah et al. [173] and offer the advantage of permitting larger doses of magnesium salt phosphate binders, but there are two disadvantages. First, patients may experience gastrointestinal upset, since magnesium salts have a laxative effect [174], and secondly monitoring of compliance and serum magnesium levels becomes obligatory, as hypomagnesemia has been associated with cardiac rhythm disturbances [175–177] and electrocardiographic abnormalities [178, 179].

Acid–Base Balance and 40 mmol/L Lactate PD Fluid

There is considerable evidence that as renal mechanisms for acid excretion fail, bone mineral stores become an important source of buffer [180, 181]. Acetazolamide produces a metabolic acidosis in normal subjects by inhibiting carbonic

anhydrase in the proximal tubular epithelium, resulting in a bicarbonate diuresis. In virtually anuric hemodialysis patients it might therefore be expected to have little effect, but in fact produces a severe metabolic acidosis [182], suggesting that it is interfering with extrarenal buffering. Carbonic anhydrase is present in osteoclasts [183], and may be activated by PTH to promote bone resorption by release of H^+ ions [184]. The availability of bone buffers and bicarbonate would therefore depend on the activity of PTH, and could be inhibited by acetazolamide. It can therefore be seen that during a time of prolonged metabolic acidosis, such as exists in many PD patients using PD fluid with only 35 mmol/L lactate [185], buffering by bone would be linked to bone resorption and increased PTH levels.

The use of PD fluids containing 40 mmol/L lactate, or newer so-called biocompatible fluids containing only bicarbonate, or bicarbonate plus lactate, correct the mild acidosis experienced by most PD patients using the older lower lactate concentration [186]. Optimal correction of acidosis has been shown to change the progression of osteodystrophy in hemodialysis patients by Lefebvre et al., who, over 18 months, prospectively studied two groups of patients, dialyzed against either standard dialysis fluid (32–24 mmol/L), or against fluid supplemented with 7–15 mmol/L of bicarbonate to achieve a predialysis plasma bicarbonate of 24 mmol/L. The supplemented group had a decreased rate of progression of secondary hyperparathyroidism in patients with high bone turnover, and stimulated bone turnover in those with low bone formation rates [187].

Parathyroid Hormone in PD

Although the prevalence of symptomatic bone disease has decreased in recent years, the 1989 EDTA Registry report showed that around 40% of all patients dialyzed for up to 15 years still required parathyroidectomy [188]. This partly reflects the poor understanding of the pathogenesis of secondary hyperparathyroidism that existed in the 1970s and 1980s, and partly the difficulty of monitoring vitamin D and PTH levels. However, only slightly better rates have been reported more recently from the Lombardy registry in Italy, where it was noted that PD patients had a higher likelihood of parathyroidectomy than HD patients [32]. In the multicenter DOPPS study, the adjusted rate of parathyroidectomy varied four-fold across the DOPPS countries, and was significantly associated with baseline concentrations of phosphorus, calcium, calcium-phosphorus product, PTH, and dialysate calcium concentration [102].

PD has been shown to clear significant amounts of PTH from the serum. Using a C-terminal assay Delmez et al. [163] found a clearance rate of 1.5 mL/min or $13.6 \pm 3.2\%$ of the estimated total extracellular iPTH. Despite this, there is no clearcut consensus on the effect of PD on PTH levels, although the weight of evidence is in favor of a steady decline with time [104, 110, 189, 190]. However, other reports show no change [163], an increase in the levels [111] or a variable response [112]. The reason for these differences probably lies in the widely varying practices between centres with regard to the use of phosphate binders, vitamin D3 treatment and also the different radioimmunoassays used for measurement of iPTH and its fragments.

Until the 1990s, CAPD tended to be seen as a prescription in itself, with a standard set of guidelines that were suitable for every patient. As a result, the majority were treated with four 2-L exchanges, a phosphate binder, vitamin supplements and a small oral dose of 1,25-dihydroxyvitamin D3. PTH levels were rarely measured, and the dosage of calcitriol was changed only if hypercalcemia occurred or evidence of osteitis fibrosa appeared on plain radiology of the hands.

Maintenance of a high serum ionized calcium (1.2–1.3 mmol/L) and strict control of serum phosphate, from the time of first starting dialysis, has been shown to decrease PTH levels in CAPD patients without the addition of vitamin D3 therapy [142, 143]. However, the increased incidence of adynamic bone, its association with vascular calcification and studies of bone turnover rate, have resulted in a plethora of guidelines suggesting that the appropriate target range for PTH is somewhere between 2 and $5 \times$ ULN (upper limit of normal) [126]. Although these opinion-based guidelines seem sensible given the current state of our knowledge, they have never been tested in a randomized controlled, outcome trial, and it is not known whether targets for PD patients should be different.

In a large and long-term study of PTH and all-cause mortality in 345 HD and 277 PD patients, over 14 years, survival after adjustment for age, race, gender, months on dialysis at enrollment, diabetic status, and nutritional markers were significantly better for patients with enrollment PTH greater than 200 pg/mL than for patients with PTH 65 to 199 pg/mL and patients with PTH less than 65 pg/mL. For PD patients, age, diabetes, and months on PD at enrollment were inversely associated with PTH, whereas black race, albumin, creatinine, and phosphate were associated positively [191]. However, in a very similar size study of 251 PD patients, Oreopolous's group found no such association [192] emphasizing the difficulty of interpreting observational, retrospective chart studies.

Vitamin D in PD

Vitamin D metabolism is well known to be abnormal in uremia, with very low levels of 1,25-dihydroxyvitamin D3 [62]. However, there are additional factors affecting vitamin D levels relating to the PD itself. Levels of 1,25-dihydroxyvitamin D3 are known to be very low, and sometimes undetectable, at the start of PD if prior treatment has not been given [18]. 25-Hydroxyvitamin D3 levels are usually within the normal range at the start of CAPD but begin to decline thereafter [104, 124]. This is not unexpected since peritoneal dialysis effluent contains significant amounts of vitamin D binding protein, an α_2-globulin of molecular weight 59 kDa, which binds all three vitamin D metabolites (1,25-dihydroxyvitamin D3, 25-hydroxyvitamin D3, and 24,25-hydroxyvitamin D3). Losses of 1,25-dihydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 have been shown to average approximately 6–8% of the plasma pool per day [193]. Thus, PD patients may require 2–3 times the maintenance doses used in hemodialysis patients if it is thought necessary to bring serum levels of 1,25-dihydroxyvitamin D3 into the normal range, These doses frequently produce the problem of hypercalcemia.

In England a seasonal variation in 25-hydroxy-vitamin D3 levels was found by Cassidy et al. [194], and in sunnier climates patients may be able to maintain 25-hydroxyvitamin D3 levels within the normal range throughout the year. Whether 24,25-dihydroxyvitamin D3 plays an important role in bone mineralization remains to be proved, but Dunstan et al. [195] have shown that the combination of 1,25-dihydroxyvitamin D3 and 24,25-dihydiroxy-vitamin D3 given orally did not appear to confer any additional benefit compared with 1,25-dihydrox-yvitamin D3 alone. This result is challenged by the work of Chaimovitz, Gal-Moscovitzer, and others, who suggest that 24,25-dihydroxyvitamin D3 plays a role in the regulation of PTH levels [196–199], and when given in conjunction with 1,25-dihydroxyvitamin D3 suppressed osteoclastic parameters without causing hypercalcemia.

The Role of Vitamin D Analogue Therapy in PD

Vitamin D therapy in PD has traditionally been used for the treatment of elevated PTH levels (greater than 5–6 $\times$ ULN) in one of two ways. If serum calcium levels are low, then a daily oral dose of calcitriol or 1-alphacalcidol will raise serum calcium and thereby suppress PTH secretion. Alternatively if serum calcium is already towards the top end of the normal range then twice weekly, "pulse therapy" will produce larger peak serum vitamin D levels, which, in theory, should also suppress PTH secretion, but with less stimulation of gastrointestinal calcium uptake. Small-scale studies have provided some evidence for this approach [67, 70, 71, 200, 201].

Oral Pulse Calcitriol Therapy

The idea of pulse therapy was initially investigated in hemodialysis patients, where thrice-weekly intravenous pulses of 1,25-(OH)2D3 were administered at the end of a hemodialysis session [53]. This regime resulted in marked suppression of iPTH levels with a mean decrement of around 70%, although Slatopolsky surmised that this was largely as a result of the rise in serum ionized calcium that occurred during the study. Furthermore, this study also demonstrated that when equal doses of intravenous or oral calcitriol were given, the serum concentration of calcitriol was 6–8 times higher with the intravenous preparation, resulting in a greater delivery to nonintestinal target tissues and allowing greater expression of its biological effect on the parathyroid glands. However, even this degree of suppression was insufficient to restore iPTH to satisfactory levels, because of the large nonsuppressible basal secretion rate of hypertrophied glands. Interestingly, it has also been shown that administering calcitriol at night reduces both the incidence and severity of hypercalcemia in hemodialysis patients [202].

Korkor demonstrated that the parathyroid glands from patients with chronic renal failure contained only one-third as many calcitriol receptors as are found in parathyroid adenomas [203], and in animal studies it is known that uremia results in a two- to four-fold decrease in receptor numbers as compared to normal values [204, 205]. Thus it is likely that reduced receptor numbers in the parathyroid glands of uremic patients render them less responsive to the inhibitory effects of calcitriol, so that suppression requires high peak serum levels.

Since the initial work of Slatopolsky several other workers have confirmed that both pulse intravenous 1,25-dihydroxyvitamin D3 and α-calcidol are effective in reducing serum PTH levels in hemodialysis patients [65, 66, 70], although all found difficulty in distinguishing direct effects on parathyroid secretion from indirect effects mediated by raising serum calcium. Subsequent studies in CAPD patients have tended to confirm this work, but some controversy still exists over the ideal regime of administration [206–208]. It is, however, clear that 1,25-dihydroxyvitamin D3 does have a direct suppressive effect on parathyroid cells by influencing transcription of the parathyroid gene [52, 205, 209].

With current concern about vascular calcification and calcium loading, oral pulse therapy would appear to be the most appropriate method of administration for PD patients, but outcome studies are once again lacking, and cinacalcet may have obviated the need to study this further. However, vitamin D manufacturers are "fighting back" with retrospective, observational data to suggest that perhaps vitamin D therapy confers a small survival benefit in HD patients [210], and its immunological effects may yet turn out to be important to dialysis patients.

Intraperitoneal Vitamin D Therapy

Delmez et al. demonstrated that calcitriol could also be given intraperitoneally in CAPD patients where again it produced a rise in serum ionized calcium levels and a significant fall in serum PTH [55]. However, continued control of serum phosphate is also required, since hyperphosphatemia will significantly blunt the effect of calcitriol therapy [211]. It has been shown that 22-oxa-calcitriol can be given effectively by the intraperitoneal route, but adherence to PD vinyl bags varies and may result in uncertain serum levels [212, 213]. However, the risk of introducing infection while injecting vitamin D, and the fact that such a route has additional practical difficulties in automated PD has prevented this technique from gaining general acceptance.

Calcitriol Analogues

In rats with normal renal function 22-oxa-calcitriol has been shown to have very little calcemic activity [214], yet it suppresses PTH mRNA levels equally as effectively as 1,25-(OH)2D3 [215]. A similar effect is reported in dogs with over 12 months of renal failure, where administration of a single intravenous dose of 5 mg of 22-oxa-calcitriol decreased PTH by 80% over 24 h without any change in serum calcium or phosphate levels [215]. However, Drueke and co-workers found similar degrees of hypercalcemia in rats with chronic renal failure treated with either 1,25-(OH)2D3 or 22-oxa-calcitriol [216], and this observation has been confirmed in other studies of hyperparathyroid hemodialysis patients, where PTH suppression was associated with a rise in serum calcium [217–219]. Other analogues, such as 2b-3-hydroxypropoxy calcitriol, EB 1089, and KH 1060, are under investigation as immunosuppressive agents, as well as for their effects on divalent ion metabolism [220].

Although prospective comparisons against calcitriol are very limited, current evidence suggests that new active vitamin D analogues, such as 19-nor-paracalcitol and doxercalciferol, adequately control PTH levels with minimal changes in serum calcium and phosphate during treatment with calcium-containing phosphate binders. In the past, the development of adynamic bone occurred in a substantial proportion of dialyzed patients treated with calcitriol therapy and calcium containing binders. Therefore, the long-term skeletal response to the new active vitamin D sterols remains to be established and whether patients will develop adynamic bone is not known at the present time. Furthermore, the impact of the addition of calcium-free phosphate binders on the control of secondary hyperparathyroidism in conjunction with the new active vitamin D analogues remains to be studied. A retrospective, observational study has suggested a small improvement in survival with intravenous paricalcitol but such data cannot be regarded as scientifically robust at this time [210]. Whether the cost of these new analogues can be justified by improved patient outcomes remains to be proven.

Calcimimetics

Compounds that act as calcium receptor agonists are called calcimimetics because they mimic or potentiate the effects of extracellular calcium on parathyroid cell function. By targeting the calcium sensing receptor, cinacalcet provides a new means of regulating PTH secretion by amplifying the receptor's sensitivity to extracellular calcium and reducing PTH concentrations [221]. The discovery of such compounds with potent and selective activity enables a pharmacological approach to regulating plasma levels of PTH.

Results from clinical trials examining single and multiple doses up to 180 mg once daily suggest that treatment with cinacalcet not only reduces plasma PTH concentrations but also leads to a concomitant decrease of serum calcium and phosphate in patients with secondary hyperparathyroidism receiving hemodialysis [222–225]. It reduces PTH to within K/DOQI targets in 44–56% of patients with a greater number (~60%) achieving at least a 30% reduction in serum PTH from baseline [226]. Analyses of combined data from randomized, blinded, placebo-controlled, 6- to 12-month studies of cinacalcet versus standard care for secondary HPT showed statistically significant and clinically meaningful reductions in the risks of parathyroidectomy, fracture, and cardiovascular hospitalization. Although the individual clinical studies were designed to assess changes in biochemical parameters and not a priori clinical end points, the prospective and interventional nature of the combined data lends credibility to the clinical relevance of biochemical control in secondary HPT and suggests that therapy with cinacalcet may lead to beneficial effects on clinical outcomes [227]. Long-term treatment has been shown to effectively sustain reductions in PTH for up to 3 years [228]. Cinacalcet's efficacy appears to be similar in both hemodialysis and peritoneal dialysis patients [229].

Side effects reported in a trial of cinacalcet [230] compared to placebo include nausea (32 versus 19%) and vomiting (30 versus 16%). The frequency of nausea was unrelated to dose, but vomiting occurred more frequently at higher doses. Hypocalcemia (<1.90 mmol/L) occurred significantly more frequently in cinacalcet-treated than placebo-treated patients (5 versus 1%). In the titration phase of this study more cinacalcet-treated patients than placebo-treated patients withdrew (15 versus 7%), and just less than another 5% of patients later withdrew from treatment as a result of these adverse effects.

Renal Osteodystrophy in Diabetic PD Patients

A number of reports over the past 12 years have suggested that insulin-dependent diabetes mellitus is associated with lower serum levels of PTH [114, 231, 232], and decreased responsiveness to acute hypocalcemia [233]. Therefore, it has been suggested that diabetic patients may be more prone to low-turnover bone disease, and relatively protected from severe hyperparathyroidism. However, until recently it has been difficult to separate the effects of diabetes from those of aluminium accumulation, but Pei et al. [114] have now shown that diabetes mellitus is an important risk factor for both aluminium-related bone disease and the adynamic bone lesion. These authors also noted that diabetes appears to enhance the risk of developing aluminium bone disease, possibly by increasing gastrointestinal absorption and bone surface accumulation of aluminium. This finding adds further impetus to the drive to eliminate use of aluminium-based phosphate binders wherever possible.

The Idiopathic Adynamic Bone Lesion in PD

The spectrum of bone disease has changed over the past 15 years with the emergence of the adynamic bone lesion, now present in 20–60% of dialysis patients according to various histological studies [9, 23, 25, 35, 36, 234, 235], and the welcome decline in the usage of aluminium-containing phosphate binders. The association of adynamic bone with low PTH levels has resulted in a reassessment of attempts to suppress serum PTH to "normal" levels in both predialysis and dialysis patients [34, 35] and acknowledgement that blanket prescription of continuous low-dose oral calcitriol therapy for all dialysis patients is unwise [236].

This lesion occurs more commonly in patients aged over 50 years at start of dialysis (Table 22.3), in those with a longer duration of predialysis renal failure [36], in diabetic patients [114], and in PD patients compared to HD patients [28]. In a longitudinal histological study of bone disease in CAPD [142], five of eight patients who completed a full 2 years of follow-up were found to have developed the adynamic lesion (Fig. 22.5). None of the patients reported symptoms attributable to the lesion, and it has no characteristic radiological findings. Bone mineral density did not decline over the 2 years, but even longer follow-up may be required for signs and symptoms to appear. It is associated with normal or suppressed levels of parathyroid hormone [9, 28, 36, 237, 238], and high or high normal levels of ionized calcium. Sherrard et al. noted that the adynamic bone lesion was the commonest histological diagnosis in their study of 267 dialysis patients [10], and that it occurred more frequently in PD (61%) than in hemodialysis patients (36%). They suggest that this may be due to the more sustained and higher calcium levels associated with PD, which may result in more effective suppression of PTH than the intermittent calcium load of hemodialysis.

Perhaps the most significant feature of the adynamic bone lesion is its association with vascular calcification, which may be related to the higher serum calcium levels found in patients with this lesion. This is a worrying association

Table 22.3 Associations of the idiopathic a dynamic bone lesion

Clinical
Age >50 years
Diabetes mellitus
Commoner in PD than hemodialysis patients
Biochemical
Low/normal parathyroid hormone
High/normal ionized calcium
Low/normal bone alkaline phosphatase and other markers of bone turnover
Radiological
Increased incidence of vascular calcification

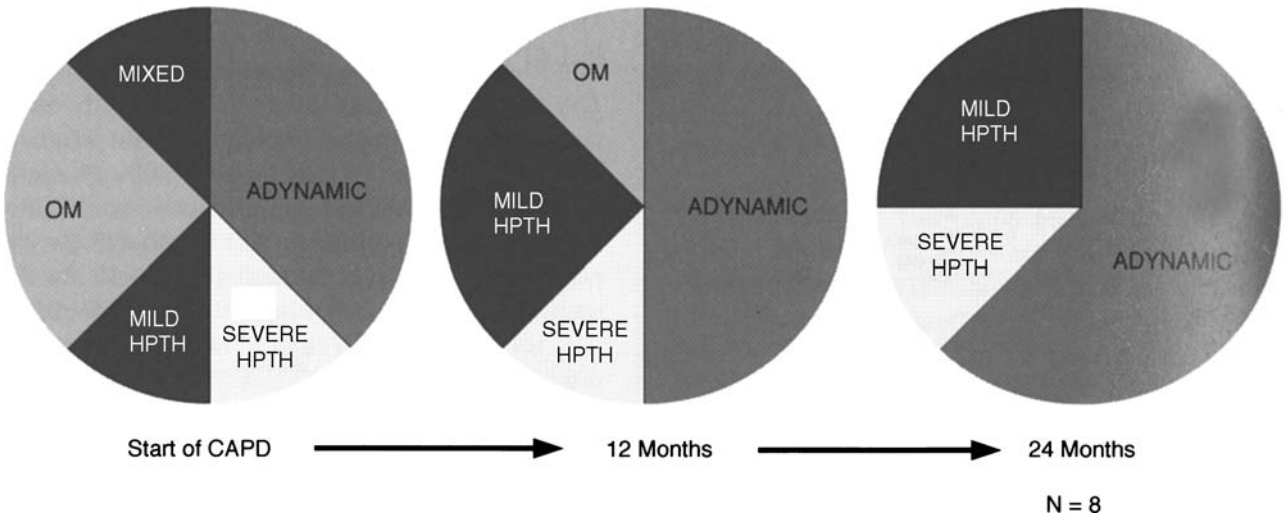

Fig. 22.5 Changes in bone histology in eight patients over 24 months of continuous ambulatory peritoneal dialysis. OM, Osteomalacia; HPTH, hyperparathyroidism

since many of these patients will be hoping for renal transplantation, which may become impossible when vascular calcification is severe. Evidence has accumulated pointing to the active and regulated nature of the calcification process. Elevated phosphate and calcium, common in patients with adynamic bone, may stimulate sodium-dependent phosphate co-transport involving osteoblast-like changes in cellular gene expression. Arterial calcification is responsible for stiffening of the arteries with increased left-ventricular afterload and abnormal coronary perfusion as the principal clinical consequences [239]. It also seems likely that adynamic bone would be significantly more prone to the osteoporotic effects of high-dose steroid immunosuppression, as well as avascular necrosis of the femoral head [240]. Treatment of osteoporosis remains uncertain, since the long-term effects of bisphosphonates in CKH are unknown [241–243].

Under normal circumstances the skeleton provides a large buffering capacity for both serum calcium and phosphate. If the bone is adynamic its buffering ability may be significantly reduced, and serum levels are therefore much more easily influenced by dietary intake or absorption from the dialysis fluid. Under these conditions there is a greater

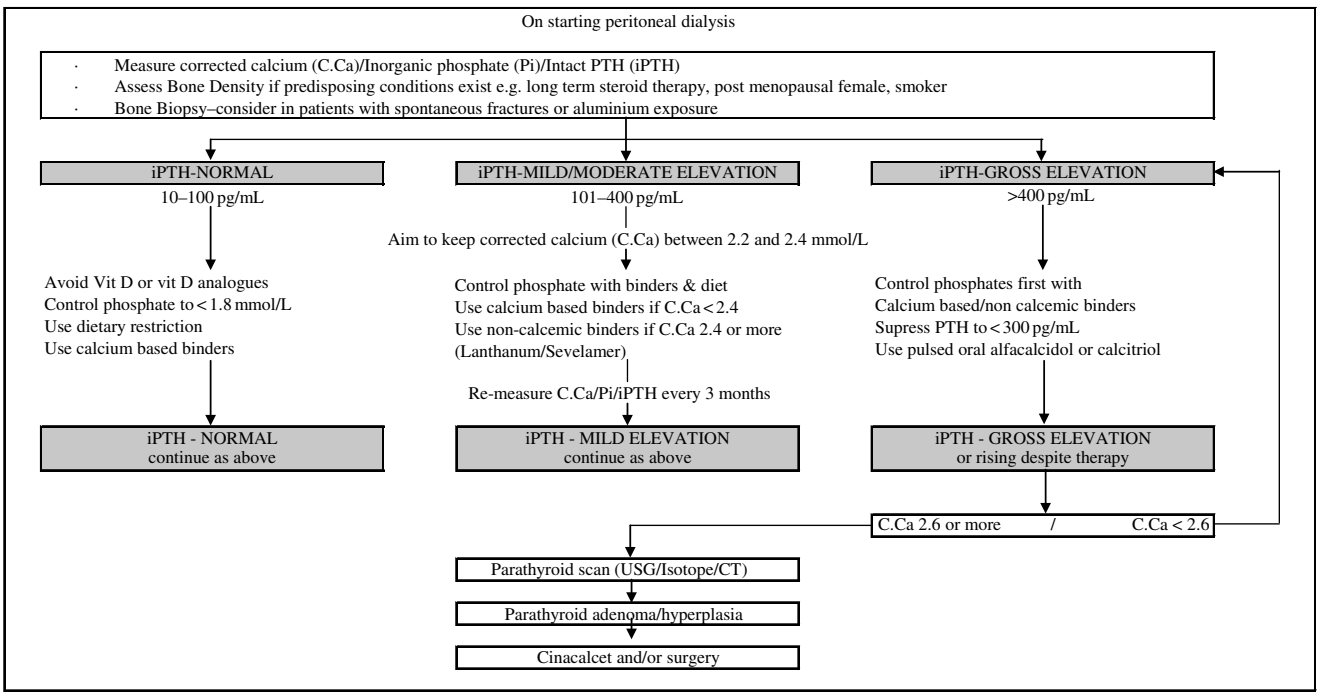

Fig. 22.6 Clinical algorithm for the monitoring and management of renal osteodystrophy in PD patients

likelihood of the calcium–phosphate product being exceeded, and the process of metastatic calcification beginning. If this is the case then it would be very important to allow PTH levels to rise slightly and stimulate bone turnover, while maintaining strict control of serum phosphate. In this way one would also hope to induce resorption of vascular calcium deposits [168]. It is evident that the use of calcitriol, a powerful modulator of calcium and PTH, should be tailored to the individual patient's clinical situation, not merely prescribed in an unthinking fashion as a "vitamin supplement." Tailoring of any therapy requires the clinician to gather certain data in order to determine appropriate management. In this case one needs to examine the patient's serum calcium, phosphate, and parathyroid hormone levels, in conjunction with bone histology data in certain cases. On the basis of these findings one can plan individual treatment along the lines of the clinical algorithm shown in Fig. 22.6.

Recommendations for Management of Osteodystrophy in PD

Techniques for monitoring renal osteodystrophy in PD patients are still evolving. In the past, different units have approached the problem in widely differing ways, with some only monitoring serum calcium, phosphate and alkaline phosphatase plus annual skeletal surveys, and others performing much more detailed (and expensive) investigations, sometimes including bone biopsy. If we consider the available techniques under three broad headings – biochemical, radiological and histological – certain recommendations can be made, given the present state of understanding (Table 22.4).

Biochemical Monitoring

In dialysis patients, changes in serum calcium and phosphate do not reflect disease processes within the skeleton as they may do in patients with normal renal function. They are primarily influenced by the patient's diet and oral intake of phosphate binders plus the amount of dialysis that patient is receiving. A rise in serum alkaline phosphatase is more indicative of increased bone turnover, but is seen only in advanced hyperparathyroidism and levels are influenced by liver and intestinal production. A rising level is generally associated with histologically severe osteitis fibrosa. The bone isoenzyme of alkaline phosphatase is a more sensitive indicator and low levels are associated with a greater likelihood of adynamic bone histology [36]. Measurement of serum osteocalcin is possible, providing a marker of osteoblast activity, but the very short half-life of the molecule means that unless the serum is spun and frozen within 20 min any subsequent assay is likely to be invalid. For this reason it seems unlikely to be helpful in clinical practice, and in any case reports show a close correlation with intact PTH levels in dialysis patients [244]. Another marker of hyperparathyroid bone disease, tartrate-resistant acid phosphatase (TRAP), has recently been reported to be a sensitive indicator of high- and low-turnover bone states [245–247]. This enzyme is produced by actively resorbing osteoclasts, and can be measured in serum by immunoassay or colorimetrically. Experience with this marker is limited at present [247].

The most widely available, and generally useful, marker at present, is intact PTH, which should be measured every 3 or 4 months in all PD patients. Regular measurement of total alkaline phosphatase is unnecessary, although it will continue to be performed as part of the "liver screen."

Table 22.4 Recommendations for the management of renal osteodystrophy in adult PD patients (see also Fig. 22.6)

1. Restrict dietary phosphate, as far as possible within the confines of a 1.2 g/kg/day protein diet.
2. Use 1.25 mmol/L (2.5 mEq/L) calcium dialysis fluid to minimize hypercalcemia. Individual patients may require higher or lower concentrations depending on serum ionized calcium (or total corrected calcium) and phosphate levels.
3. If serum phosphate >1.8 mmol/L and calcium <2.30 mmol/L start calcium carbonate/acetate given twice daily with main meals. Dose titrated to serum calcium and phosphate levels. Educate patients to distribute dose according to phosphate intake.
3. If serum phosphate >1.8 mmol/L and calcium >2.30 mmol/L start lanthanum carbonate or sevelamer hydrochloride given twice daily with main meals. Dose titrated to serum phosphate levels. Educate patients to distribute dose according to phosphate intake.
4. Measure serum parathyroid hormone every 3 months (see Fig. 22.6) and use pulse oral vitamin D3 therapy if necessary. Replace 25-hydroxyvitamin D3 if serum levels are low.
5. Introduce cinacalcet if PTH continues to rise.
6. Measure serum magnesium and aluminium every 6 months, unless patient is taking oral aluminium (then measure every 3 months).

Radiological Monitoring

Routine, full skeletal surveys are unnecessary, and have largely been replaced by regular monitoring of serum PTH with plain X-rays of the hands plus a single lateral view of the lumbar spine [106, 248, 249]. This greatly reduces the dose of radiation previously received by PD patients without detriment to patient care. Ideally, some measurement of skeletal bone density should be made at the time of starting dialysis in all patients, so that those with subnormal bone density can be identified and special efforts made to improve the situation. Whether this measurement is best performed by QCT, SPA, DPA or DEXA scan would depend on local facilities, finance, and expertise.

Skeletal scintigraphy may be performed using technetium labeled 99m-methylene diphosphonate, but correlation of scan results with bone histology is poor, although increased uptake has been demonstrated in severe hyperparathyroid bone disease [250–252], and it has been demonstrated to be a method of monitoring response to treatment [253, 254].

Single-photon absorptiometry (SPA): A highly collimated beam of photons is used with 125I as a source. However, the single-energy beam requires a constant thickness of soft tissue around the bone to produce reliable results, and it cannot distinguish between trabecular and cortical bone. Studies have found that mineral content tends to be lower than normal in patients with renal failure [18, 255–257], but it does not allow differentiation between different types of osteodystrophy.

Dual photon absorptiometry (DPA): DPA utilizes an isotope with two energies (153 Gd), thereby overcoming the requirement of SPA for a constant thickness of soft tissue around the bone. It can therefore be used to measure bone mineral density in any skeletal site, but normal scan results have been seen in hemodialysis patients with histologically proven osteodystrophy [249].

Quantitative computed tomography (QCT): the principle of this technique is the same as for standard CT scanning, and a calibration phantom placed under the patient is used to relate bone mineral density to Hounsfield units. True bone density is measured in g/cm^3 and it is less affected by artefacts such as soft tissue calcification. However, it delivers a relatively high radiation dose.

In our own experience, bone density measurements are, if anything, less helpful than plain radiographs, since there is no correlation with histological diagnosis. Although end-stage renal failure patients were found to have reduced bone density, compared to age- and sex-matched normal values, the majority of patients had both QCT and SPA results within 2 SD of normal. Piraino et al. used QCT to measure bone mineral density in a group of 31 patients who had been on dialysis (19 peritoneal dialysis, 10 hemodialysis) for a mean of 5.3 years [258]. It is now known that the type of dialysis influences bone histology [11], therefore it may be misleading to consider peritoneal dialysis and hemodialysis patients together. However, as in our study, Piraino et al. found that serum PTH was a better indicator of the type of bone disease present than was QCT-determined bone density, and concluded that the usefulness of this technique in patients with renal failure is limited.

Dual-energy X-ray absorptiometry (DEXA): this has become the most widely used method of quantifying bone mineral density in renal osteodystrophy and osteoporosis. It has several theoretical advantages over the other techniques, including low radiation dose, greater precision and rapidity of scanning. Despite this, measurements can be distorted by several artefacts such as osteophytes, calcification of the aorta or other soft tissues, and previous vertebral collapse. In 25 dialysis patients no correlation was found between QCT and DEXA measurements of vertebral bone mineral density [259]. Results can be difficult to interpret because low density can be associated with almost any type of osteodystrophy [18, 36, 260–262].

While single bone density measurements may be unhelpful, sequential studies might be more helpful, especially if one has initially established the histological diagnosis by biopsy. Decreasing bone density in a patient known to previously have osteitis fibrosa would suggest deterioration, especially if associated with a high iPTH.

Transiliac Bone Biopsy

Bone biopsy with tetracycline labeling is undoubtedly the only reliable method of diagnosing the type and severity of renal osteodystrophy. This is rarely performed in clinical practice because of patients' and doctors' perceptions of its painfulness and invasiveness. In our experience it is no more painful than Jamshidi marrow biopsies, which are routinely performed in many clinical situations if the blood film suggests it is necessary.

Local expertise permitting, PD patients could undergo a tetracycline-labeled bone biopsy at the time of starting dialysis, to establish the exact histology of their bone plus the degree of aluminium accumulation. In many cases this could be performed under general anesthetic by the surgeon as the Tenckhoff catheter is inserted. Thereafter, one can probably surmise what is happening to the histology on the basis of regular PTH measurements once the initial histology is known. However, few centers have the expertise to either perform a biopsy or to interpret them histologically.

Most countries have created guidelines for management of bone and mineral metabolism, or else they follow European Best Practice or K/DOQI. However, all these guidelines have similar underlying principles. They all depend first on maximal restriction of dietary phosphate, within the limitations of a diet providing 1.2 g protein/kg body weight per day, and usually on the routine use of PD fluid with a calcium concentration of 1.25 mmol/L, magnesium of 0.25 mmol/L, and lactate of 40 mmol/L or bicarbonate buffer. Appropriate phosphate binders should be given in doses adequate to maintain serum phosphate below 1.8 mmol/L and aluminium-containing binders should be avoided. If hypercalcemia occurs, calcium carbonate could be partially or completely replaced by lanthanum carbonate [157] or sevelamer hydrochloride [153]. Serum ionized calcium and iPTH should be measured every 3 months to provide a guide for treatment with oral calcitriol. If iPTH is less than 300 pg/mL (or 5 × ULN) then vitamin D3 is not required. If iPTH exceeds 300 pg/mL then attention should be paid to maintenance of a mid-range serum calcium level and tighter dietary control of phosphate where possible. Calcitriol should be given as intermittent-pulse doses [71], and iPTH remeasured after 3 months. If the level remains significantly elevated, or is rising, then introduction of cinacalcet may be appropriate if it is financially affordable. If PTH continues to rise appropriate scans should be ordered to search for a parathyroid adenoma with a view to possible parathyroidectomy (provided the patient does not have significant aluminium deposition).

Serum magnesium levels should be measured once every 6 months, especially in those patients whose dietary intake may be low, to check for hypomagnesemia. Plasma aluminium levels should also be monitored every 6 months depending on local circumstances, although some units now reserve this only for patients taking aluminium-based phosphate binders. It must be remembered that aluminium uptake can be significantly enhanced by citrate ingestion and oral vitamin D3.

Utilization of any carefully thought out guidelines should enable reasonable control of divalent ion metabolism, and prevention or amelioration of osteodystrophy in the majority of PD patients. However, while the targets for calcium, phosphate, calcium-phosphate product, and PTH are more easily achieved in PD patients than HD [263], some may be mutually exclusive. Further advances will hinge on a greater understanding of the vitamin D/parathyroid axis in renal failure, along with the development of safe, noncalcemic analogues of vitamin D3 plus more efficient phosphate binders and calcimimetics, and most importantly prospective, randomized, controlled, interventional studies to examine patient outcomes.

Summary

Disorders of calcium, magnesium, phosphate, vitamin D3, and parathyroid hormone can combine to produce a variety of skeletal and extraskeletal pathologies in PD patients. The recognition that osteodystrophy is linked to vascular disease and patient mortality has reinvigorated research into the underlying mechanisms and the creation of new pharmaceutical agents.

New noncalcemic phosphate binders have now entered clinical use, and further increase the options available to clinicians. Calcimimetic agents are also available and provide an effective means of controlling PTH independently of serum calcium levels. Vitamin D analogues are currently perhaps of least certain value in PD, especially since they are largely only available for intravenous use. However, new pharmaceuticals come with significant expense, to the point that many patients, even in wealthy countries, will never be able to receive them, and at present their effect on patient outcome remains unknown. It is imperative that both pharma and academia combine to demonstrate these agents' benefit, or lack of benefit, in order not to waste large amounts of money which might be better invested in the dialysis process itself.

The judicious use of a variety of biochemical and radiological investigations, plus bone histomorphometry where appropriate, can provide a rational basis for the monitoring and management of divalent ion metabolism and renal osteodystrophy in PD patients. Sadly, most guidelines can at present only be based on opinion, and therefore we must heed the words of the K/DOQI authors: *Since the majority of the recommendations made in this set of guidelines are based on opinion, it is imperative that evaluation of their clinical outcomes be made a component of their implementation. In addition, the paucity of evidence based information in this field requires that a more integrated approach to research efforts be planned and conducted to provide answers to the many issues that remain to be elucidated* [126].

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Chapter 23
Cardiovascular Disease and Inflammation

P. Stenvinkel and E. Ritz

Epidemiology of Cardiovascular Disease in Chronic Kidney Disease

Patients with chronic kidney disease (CKD) have a markedly reduced lifespan. Cardiovascular disease (CVD), including stroke, acute myocardial infarction (AMI), sudden death, peripheral vascular disease (PVD), and congestive heart failure (CHF), accounts for premature death in more than 50% of dialysis patients from North America and Europe [1]. As premature CVD accounts for the majority of all-cause mortality, CKD should, like diabetes mellitus (DM), be considered a "high risk" group for CVD [2] and vascular disease should be treated with the same maximum armatorium of drugs and with active interventions, such as coronary artery by-pass graft (CABG), as would be indicated in the high-risk segments of the nonrenal population. This includes the use of antiplatelet agents, angiotensin-converting-enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARBs), β-blockers, nitroglycerine, and statins.

Subtle kidney dysfunction predisposes to increased cardiovascular risk [3] and the highest risk for premature death due to cardiovascular complications is observed in CKD patients receiving renal replacement therapy (RRT) (Fig. 23.1). Thus, to reduce the heavy burden of CVD in dialysis, patient screening for cardiovascular risk factors and intervention should start already at early stages of CKD, particularly since the efficacy of this approach has been well documented [4]. Even though accelerated atherosclerosis seems to be an important cause of the high cardiovascular mortality in dialysis patients, the CVD pattern is atypical and a number of additional factors, such as vascular calcification, left ventricular hypertrophy (LVH), cardiac fibrosis, sympathetic overactivity, inflammation, oxidative stress, and anemia, contribute to the high cardiovascular mortality rate. The data of the USRDS registry show that cardiac arrest/arrhythmia is the major cause of cardiovascular death in this patient population. This is presumably accounted for by additional factors, such as imbalance between cholinergic tone and sympathetic overactivity, cardiac fibrosis, electrolyte disturbances, etc. Although dialysis technology has improved markedly over the last 20 years, dialysis patients still die at a rate of about 10–20% per year – a survival worse than that documented in patients with metastatic cancer disease. The prospective HEMO [5] and ADEMEX [6] trials found that further increasing the dialysis does not lower mortality. It is therefore imperative that, in order to improve the poor survival, nephrologists identify the factors accounting for the discrepancy between the cardiovascular and chronological age [7].

If the diagnosis of CVD is based on clinical signs and symptoms, the true prevalence and incidence of atherosclerosis and its sequelae will always be underestimated. There are many examples of problems in defining the exact cause of death in CKD patients, such as in sudden cardiac death and cardiac failure. Moreover, it is often difficult to ascribe death to a single cause because many CKD patients die with a complex clinical picture of CVD, protein-energy wasting (PEW), and infectious complications [8]. Reports from various U.S. dialysis registries are inconsistent regarding the effect of hemodialysis (HD) and peritoneal dialysis (PD) on outcome. Based on a review of publications and additional analyses of U.S. Medicare, a recent review by Vonesh et al. [9] concluded that patient survival was similar for HD and PD patients when differences in case-mix were adjusted for (Fig. 23.2). However, important differences in survival between HD and PD seem to exist when evaluating selected subgroups of patients. Among aged patients with diabetes mellitus (DM), PD was associated with worse survival in the United States, but not in Canada and Denmark [9]. There are striking differences in cardiovascular mortality in dialysis patients when comparing patients from different parts of the world, even after adjustment for standard risk factors and dose of dialysis. In general, Hispanic, Asian, and black dialysis patients have a better survival than Caucasian dialysis patients. A recent study of more than 600,000 dialysis patients from 26 countries showed that a substantial proportion of the variability in mortality rates observed in dialysis

P. Stenvinkel (✉)
Division of Renal Medicine K56, Karolinska University Hospital at Huddinge, 141 86, Stockholm, Sweden
e-mail: peter.stenvinkel@ki.se

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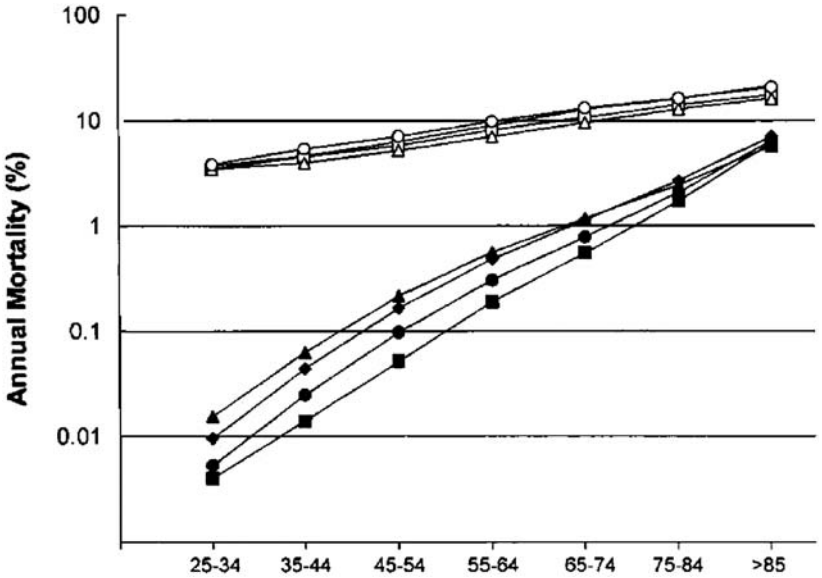
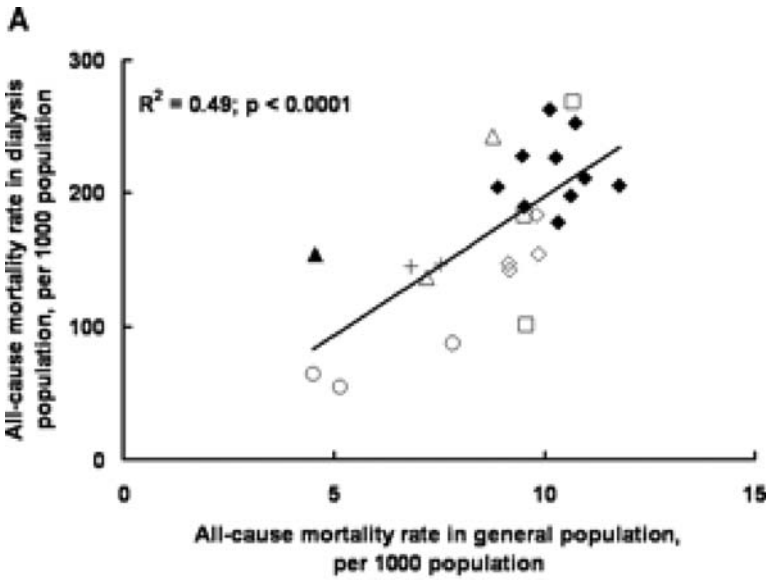


Fig. 23.1 Cardiovascular mortality in CKD. Cardiovascular mortality defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema in the general population (GP) compared to end-stage renal disease (ESRD) treated by dialysis. Data stratified by age, race, and gender. Age categories are shown on the horizontal line. Adapted with permission [1]



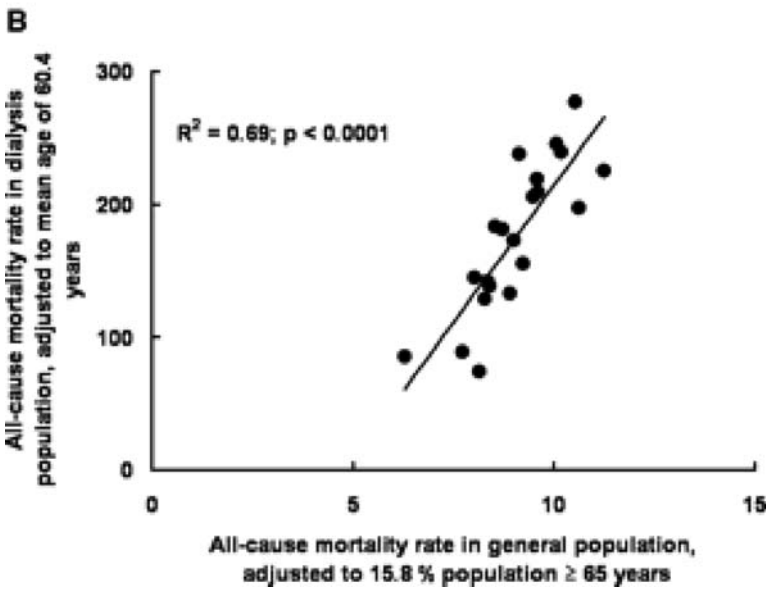


Fig. 23.2 Population-averaged survival curves comparing hemodialysis and peritoneal dialysis survival based on an overall proportional hazards regression model for U.S. Medicare patients 1995–2000. Adapted with permission [9]

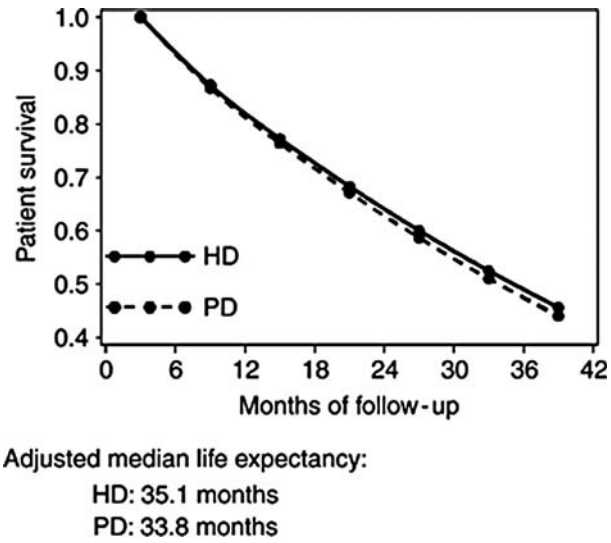


Fig. 23.3 Relationship between atherosclerotic cardiovascular disease (ASCVD) mortality rates per 1,000 population between the general population (GP) and the dialysis population (DP) among 23 countries identified by region. Adapted with permission [10]

patients was attributable to the variability in background atherosclerotic CVD (Fig. 23.3). Thus, genetic and/or environmental differences seem to account for a major part of the observed differences in CVD mortality among dialysis patients around the world [10].

Reverse Epidemiology

Seemingly paradoxical observations have been made in various patients groups (especially geriatric populations) with chronic debilitating diseases (such as CKD and CHF) where the relation between traditional established risk factors, such as hypercholesterolemia, hypertension (HT), obesity, and outcome was opposite to what is found in the general population. This phenomenon has been referred to as "reverse epidemiology" [11]. CKD may be one of the clinical situations in which the presence of this phenomenon is most pervasive [11]. In dialysis patients associations between clinical and laboratory values, demographics, and mortality, including cardiovascular death, are different and, in some cases, even in the opposite direction of those derived from the general population [11]. Thus, whereas traditional risk factors, such as DM and smoking, were strongly associated with CVD in HD patients, neither serum total cholesterol nor systolic blood pressure were associated with coronary artery disease (CAD) [12]. In fact, an analysis of a group of more than 12,000 prevalent HD patients showed that serum cholesterol was inversely associated with poor survival [13]. Subsequently, it was demonstrated that the inverse association of total cholesterol level with mortality in dialysis patients is likely due to the cholesterol-lowering effect of systemic inflammation and/or protein/energy wasting (PEW), rather than a protective effect of high cholesterol concentrations [14]. It should be emphasized that the presence of "inverse epidemiology" may not necessarily imply that the principles of vascular pathophysiology are different in CKD patients, but rather indicate that other superimposed factors, such as PEW and inflammation, are more important risk factors for premature death in this specific patient group.

Risk Factors for Cardiovascular Disease

Traditional (Framingham) Risk Factors

By accepting older and sicker patients for dialysis treatment, the burden of vascular disease in the renal patient population has increased dramatically. Thus, the prevalence of both traditional and nontraditional cardiovascular risk factors that normally increases with age, such as HT, hyperhomocysteinemia, dyslipidemia, oxidative stress, and inflammation, is excessive in dialysis patients. Traditional and novel risk factors usually coexist; their relative importance is unknown and difficult to disentangle.

Age, Gender, and Smoking

As CVD is generally a disease of middle-aged and older patients, the majority of patients starting RRT are already in the age where CVD is common. According to data from the United States, the average patient who started dialysis was older than 60 years. The adjusted risk of death increased by 3% for every additional year of age. Retrospective data from USRDS showed that advanced age was one of the most powerful predictors of cardiac death in dialysis patients [15]. Also, male gender, another traditional risk factor for CVD, is associated with worse outcome also in CKD patients. It has been reported that, in all age groups, the incidence of AMI is nearly 2.5 times more frequent in male than in female CKD patients. However, female patients have an increased risk of CVD as well, because of menopause due to age and/or disease: about 70% of women on HD are menopausal before or after starting RRT and the incidence of AMI is 3–5 times higher in female CKD patients than in the general female population at all age groups. As in the general population, smoking is associated with vascular disease in CKD patients as well. Data from the HEMO study showed that 52% of 936 patients either smoked cigarettes at the time of entry to the study or had a history of smoking. It is clearly imperative to motivate the CKD patient to stop smoking at any stage of CKD [16], since smoking adversely impacts on cardiovascular prognosis as well as on progression of renal failure.

Diabetes Mellitus

The USRDS registry has shown that the annual number of diabetic patients admitted to dialysis treatment more than doubled between 1995 and 2000 [16] and DM has become the single most important cause of end-stage renal disease (ESRD). But, recent observations in the United States show that the past continuous increase of incident diabetic patients has petered out. Unfortunately, survival of diabetic patients on dialysis continues to be poor and considerably worse than the survival observed of dialysis patients with other underlying renal diseases. The major causes of death in diabetic patients are cardiovascular complications. Clearly, as most cardiovascular complications accumulate before diabetic patients enter dialysis programs, there is definitely a need for improved care of the diabetic patient at the predialysis stage. The presence of DM is associated with a 65% increase in the odds of having CAD and a 3.6-fold increase in PVD, and with a 34% increased risk of death after AMI, respectively, when compared to nondiabetic ESRD patients [12]. The most dramatic increase of risk concerns left ventricular (LV) dilatation (13.7-fold) and systolic dysfunction (26.7-fold) [17]. The reasons why diabetic patients have such a high risk for vascular disease is probably multifactorial. Compared to nondiabetic patients, diabetic patients starting dialysis exhibit a risk factor profile that would predispose them to CVD, including dyslipidemia, HT, increased oxidative stress, PEW, and inflammation (particularly from diabetic foot problems). Diabetic foot problems were one of the most powerful predictors of death in the 4D study (Die Deutsche Diabetes Dialyse Studie). Observational data document the role of glycemic control on survival even in diabetic patients on dialysis [18]. Guidelines from the American Heart Association and the American Diabetes Association recommend in diabetic CKD patients optimal glycemic control, lowering BP values to target levels, and lipid monitoring [19]. Eye examination and foot care to prevent diabetic foot ulcers are specific problems in the diabetic dialysis population. Otherwise, treatments of HT, CAD, and other cardiovascular conditions must be at least as thorough and appropriate in this particular high-risk group as in the general CKD population.

Hypertension

Hypertension is a recognized traditional risk factor for vascular disease. It plays a role in atherogenesis by contributing to an early step in the atherogenic process, i.e., endothelial dysfunction. Hypertension is also a key risk factor for the development of stroke, LVH, and LV dysfunction. Hypertension is highly prevalent in the dialysis population with estimates of up to 75–85% of patients [18]. Isolated systolic HT with increased pulse pressure is by far the most prevalent blood pressure (BP) anomaly in dialysis patients: the high pulse pressure results from sclerosis of the media (arterial stiffening) and premature return of the reflected pulse wave from the periphery, increasing LV afterload and thus contributing to progressive LV dysfunction and CHF. In dialysis patients, decreased BP may develop as a consequence of progressive or severe LV dysfunction with the attendant high risk of CV death. These patients develop hypotension even though LV dysfunction had initially been caused by arterial hypertension and/or increased pulse pressure. These considerations explain the conflicting findings on the relationship between blood pressure and mortality in dialysis patients. The usual finding is a U-shaped curve with high risks at low as well as high blood pressure. Isolated systolic HT and increased pulse pressure probably indicate the high BP-related long-term risk scenario in CKD patients, while low mean and diastolic BP predict early mortality.

Treatment of arterial HT is not optimal in many CKD patients. Long-term observations show, however, that survival is best in dialysis patients with BP values in the low normal range [18, 20]. BP targets should be oriented at the WHO criteria and should even be in the low-normal range in CKD patients with diabetic nephropathy. Hypotensive episodes (orthostatic hypotension, hypotension during ultrafiltration) must be avoided, however, since they increase the risk of CV death [20]. Twenty-four-hour BP measurements should be used in a screening approach to identify non-dippers. Many CKD patients have even a paradoxical nighttime increase in blood pressure, which is missed by daytime blood pressure measurements. One cornerstone of treatment is volume control, i.e., finding the optimal "dry weight" of the patient and preventing salt overload by dietary salt restriction. Due to their parallel cardioprotective effects, ACE-I, ARBs, and β-blockers are first-line drugs to treat HT in CKD patients. Extracellular volume overload, one of the most potent contributors to HT and thus LV pathology, is mostly a consequence of sodium retention. Therefore, sodium restriction and diuretics are important to blunt fluid retention and efforts should be made to preserve residual diuresis. In this regard, PD may be a more favorable treatment option. In HD, long and, in problematic cases, more frequent sessions, allow safe and mostly asymptomatic fluid removal. The most impressive results were achieved in Tassin, France – 8 h of dialysis three times a week combined with a low-salt diet led to proportion of >90% normotensive patients without administration of antihypertensive drugs [21]. Disappointingly, a recent randomized study of 200 CKD patients in the late stages 4–5 showed that a multiple risk factor intervention program (focused on BP, dyslipidemia, hyperhomocysteinemia, hyperphosphatemia, and anemia) did not improve vascular structure and function [22].

Plasma brain natriuretic peptide (BNP) and cardiac troponins (TnT, TnI) are relevant prognostic risk markers in the evaluation of heart disease in CKD patients. Whereas BNP (a peptide hormone that is released by ventricular myocytes) reflects cardiac filling pressures, troponins indicate myocardial ischemia. It should be emphasized that false-positive moderate elevations of BNP and troponins are often observed in patients with impaired renal function. In prospective cohort studies from Hong Kong, both TnT [23] and NT-pro-BNP [24] were shown to be important risk predictors of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic PD patients.

Dyslipidemia

In the general population, hypercholesterolemia is a well-established risk factor for cardiovascular morbidity and mortality. In the CKD population, this relation is less clear, since some of the major cardiovascular abnormalities in this group of patients, such as cardiomyopathy, may be less dependent on dyslipidemia than on other factors. Paradoxically, low, rather than high, serum cholesterol levels predict poor outcome in HD patients [13]. However, this phenomenon could be attributed to PEW and inflammation, since after adjusting for CRP levels, high cholesterol predicted risk in the noninflamed dialysis patients [14]. Progressive loss of renal function leads to changes in the composition of blood lipids that are associated with vascular disease [25]. Dyslipidemia is a common feature in PD patients who exhibit a more atherogenic profile than patients treated by HD with higher total and LDL-cholesterol, apolipoprotein-B, and triglyceride levels and reduced HDL-cholesterol levels [26]. Although the etiology of this constellation is not fully understood, glucose loading and protein loss across the peritoneum are likely contributors. Lipoprotein-(a) [Lp(a)] levels are also markedly elevated in PD patients [27]. Elevated Lp(a) levels have been reported to be associated with increased CVD mortality both in HD and PD patients [28]. Because statins reduce the incidence of cardiovascular events both in the general population and in type II diabetics, this class of drugs has traditionally been considered safe and efficient in treating dyslipidemia in PD [29]. However, the benefit of statins in dialysis patients has been recently questioned by the 4D study [30] where atorvastatin had surprisingly no significant effect on cardiovascular death, nonfatal myocardial infarction, and stroke in HD patients. Other prospective randomized studies, such as AURORA (2,700 dialysis patients) and SHARP (9,000 CKD 3–5 patients) are ongoing, but will not provide results before 2008/09. To the best of our knowledge, there are no ongoing prospective studies that examine the long-term effects of statins on cardiovascular outcome in PD patients. A reduction of the glucose exposure associated with conventional PD fluids, achieved by substitution with icodextrin- or amino acid–based solutions, may be yet another treatment option to improve dyslipidemia in PD patients.

Insulin Resistance

Insulin resistance, which is often part of a metabolic syndrome that includes dyslipidemia, HT, inflammation, oxidative stress, endothelial dysfunction, and sympathetic overactivity, is a common and early phenomenon in the CKD patient [31]. Although it has been demonstrated that insulin is a predictor of cardiovascular mortality independent of body mass index (BMI), HT, and dyslipidemia, [32], whether and to what extent insulin resistance, contributes independently to the adverse CV outcome of CKD and ESRD patients is currently unclear. Even though correction of acidosis and hyperparathyroidism may improve insulin resistance, there is so far no clear evidence that this improves

cardiovascular outcome. There is increasing evidence in the literature showing that insulin resistance can be modulated with the use of RAS blockade and thiazolidinediones [33]. It has been postulated that glucose loading in PD patients may worsen insulin sensitivity. Thus, glucose sparing prescription strategies may be of importance to alleviate the systemic consequences of continuous glucose loading in PD. However, reports are controversial: while continuous cycling PD patients showed increased insulin resistance as compared to HD [34], chronic ambulatory PD therapy normalized insulin resistance similar to HD therapy [35]. The use of icodextrin solutions for the long dwell could be a promising solution to this issue, as these solutions have been reported to reduce increase insulin sensitivity [36] as well as having beneficial effects on plasma levels of adipocytokines [37]. Although lifestyle changes, including exercise and balanced diets, are recommended, their protective effect on cardiovascular morbidity and mortality in CKD has not yet been proven. Whereas increased BMI has repeatedly been found to be associated with improved outcomes in North American HD patients, the association between increased BMI and survival has been less consistent in PD patients, [38]. It should also be noted that a recent study based on the NECOSAD cohort showed that the association between BMI and mortality in a European HD population is similar to that of the general population [39]. The reasons(s) for the apparent paradox between BMI and outcome may be that dialysis patients have such a short expected survival that they do not die of the potential adverse effects of overnutrition [38]. Clearly, as loss of fat mass is associated with increased risk of death in dialysis patients [40], PEW must be avoided at all stages of CKD.

Nontraditional and/or Uremia-Specific Risk Factors

Oxidative Stress

Oxygen radicals are continuously generated in the metabolism, but oxidative stress (an imbalance with too much free radicals and/or to little antioxidants) plays a role in the pathogenesis of many common complications of PD, such as CVD, PEW, and anemia [41], as well as functional and structural changes in the membrane [42]. Patients with CKD are subjected to enhanced oxidative stress, as a result of both reduced antioxidant systems (vitamin C and selenium deficiency, reduced intracellular levels of vitamin E, reduced glutathione activity) and increased pro-oxidant activity associated with advanced age, co-morbidities (such as DM), inflammation, reduced renal function *per se*, and bio-incompatibility of dialysis solutions and membranes [41]. One study showed that oxidative stress appears to increase as CKD progresses and found significant correlation with level of kidney function [43]. Evidence in the literature support the concept that increased oxidative stress is associated with an increased risk of cardiovascular events in CKD patients [41]. In addition to increased generation of pro-oxidants, CKD patients may also be subjected to increased loss and/or decreased intake of anti-oxidants as a result of poor appetite. It has been demonstrated that patients with signs of PEW and a low S-albumin concentration have a significantly diminished plasma antioxidant capacity due to the diminished availability of thiol groups [41]. It seems plausible that increased inflammation and hypoalbuminemia will have a synergistic effect on the cardiovascular risk, because inflammation results in increased production of oxidants by leukocytes and hypoalbuminemia results in reduced scavenging capacity for these oxidants [41]. An important role of oxidative stress in mediating CVD in CKD is suggested by two recent placebo-controlled interventional studies showing that vitamin E [44] and acetylcysteine [45], two well-established antioxidative treatment strategies, decreased the number of cardiovascular events in HD patients. As both studies were rather small, larger adequately powered randomized trials with antioxidative treatment strategies are warranted both in HD and PD patient populations.

Endothelial Dysfunction

The endothelium is a functional barrier between the vessel wall and the blood stream that plays an important role in the control of fibrinolysis, coagulation, vascular tone, immune response, and growth. Like in other disorders characterized by a high burden of vascular disease, endothelial dysfunction is a prominent feature of CKD. Although this has not been extensively studied, there are reasons to believe that endothelial dysfunction is a prominent feature in PD patients. In a study by Mittermayer et al. [46], baseline forearm blood flow was lower and the L-NMMA response smaller in 37 PD patients compared to healthy controls. Asymmetric dimethylarginine (ADMA) was related to basal, but not acetylcholine-stimulated, NO-bioactivity [46]. The reason(s) for endothelial dysfunction in dialysis patients are multiple and include inflammation, retention of ADMA, hyperglycemia, hyperhomocysteinemia, oxidative stress, dyslipidemia, and HT. The importance of endothelial dysfunction in the vascular health of CKD patients is underscored by the fact that surrogate markers of endothelial dysfunction, such as adhesion molecules [47] and ADMA [48], are independent predictors of death in dialysis patients. ADMA is especially interesting because it interferes with

several hormonal systems [48] and predicts cardiovascular events [49]. A study in HD patients reports that treatment with a calcium channel blocker (amlodipine) and ARB (valsartan) caused a significant 40% reduction in plasma ADMA levels [50]. Similar studies have not yet been performed in PD patients.

Recent evidence suggests that detached circulating endothelial cells (CEC) serve as a potential marker of endothelial damage in both nonrenal and renal patients. The prognostic value of an increased number of CEC in HD patients was recently demonstrated [51]. Normally, in response to ischemic insult and cytokine stimulation, endothelial progenitor cells (EPC) are mobilized from the bone marrow to act as "repair" cells in response to the injury. In the first reported study of EPCs, an association between history of CVD and EPCs, but not between endothelial function and EPCs, was reported in 38 PD patients [52].

Anemia

Anemia, a major factor associated with LVH and LV dilatation in dialysis patients, is further discussed in Chapter 26.

Cardiovascular Calcification

Vascular calcification (more detailed discussion in Chapter 25), which affects arterial media, atherosclerotic plaques, the myocardium, and the heart valves, is a common feature of CKD [53] that is strongly predictive of CVD and mortality in dialysis patients [54]. Vascular calcification can be visualized by conventional x-ray techniques (qualitatively, semi-quantitatively) and by multislice spiral or electron beam computer tomography (EBCT). By ultrasound techniques, valvular and large artery calcification can be estimated, and pulse wave velocity measurements provide a functional estimate of the severity of media sclerosis. Cardiac valve calcifications are more frequent in "inflamed" PD patients than in "noninflamed" patients, and confer a 6-fold higher risk of CV death [55]. Increased calcification in PD patients has been associated with increased inflammation [56], low fetuin-A levels [57], and the use of calcium-based phosphate binders [19]. The "Treat-to-goal" study, in which 200 HD-patients were randomized to receive either calcium-containing phosphate binders or the calcium-free binder sevelamer [58], showed that, whereas calcium-containing phosphate binders were associated with progression of coronary and aortic calcification over the period of 1 year, sevelamer treatment was associated with cessation of progressive calcification. In a recent randomized trial, 127 incident HD patients treatment with sevelamer was associated with a significant survival benefit as compared to the use of calcium-containing phosphate binders [59]. Clearly, these interesting data will need confirmation in larger patient cohorts also including PD-patients.

Autonomic Dysfunction and Sleep Apnea

Raised sympathetic activity has been proposed to be a significant cardiovascular risk factor in CKD patients as it raises arterial pressure, triggers arterial damage, and is a major player in the development of LVH. In a cohort of 228 patients undergoing regular HD, sympathetic nerve overactivity, at least as indirectly evaluated by plasma concentrations of norepinephrine, was associated with mortality and cardiovascular outcomes [60]. In HD patients, the beta-blocker carvedilol caused impressive lowering of mortality [21]. The cholinergic (i.e., vagus nerve controlled) system is another part of autonomic nervous activity that needs consideration. As the cholinergic anti-inflammatory pathway is a neural mechanism that inhibits local cytokine release, studies are needed to evaluate the putative association between autonomic dysfunction and persistent inflammation and innate immune responses in the context of uremia [61].

The sleep apnea syndrome is a frequent complication in dialysis patients with a reported prevalence of 21–47% [62], a prevalence at least 10–12 times higher than in the general population. Zoccali et al. [63] demonstrated that nocturnal hypoxemia ($SaO_2 < 95\%$) is associated with a 5 times higher risk of cardiovascular events. Consequently, nocturnal hypoxemia must be considered an important cardiovascular risk factor in dialysis patients and studies evaluating the effect of nasal continuous positive airway pressure (CPAP) treatment are needed, since, in an observational study, this reduced long-term CV outcome in nonrenal patients [64]. A study from Hong Kong suggested that, compared to conventional chronic ambulatory PD, nocturnal cycler-assisted PD has a therapeutic edge as a result of better fluid clearance during sleep [65].

Advanced Glycation End-Products (AGEs)

As pentosidine, carboxymethyllysine (CML), and other AGEs formed by glycosylation and oxidation accumulate in the uremic milieu, it has been speculated that AGE and carbonyl stress contribute to long-term complications in CKD,

such as accelerated atherosclerosis, dialysis membrane dysfunction, and dialysis-related amyloidosis. However, neither elevated plasma pentosidine [66] nor CML [67] levels have been found to predict mortality in dialysis patients. Since the ingestion of such "glycotoxins" in the diet may contribute to elevated AGE levels in dialysis patients, it has been speculated that low dietary intake and PEW may explain, at least in part, the observed paradoxical relation between AGEs and outcome, although this could not be confirmed by measurements [68]. Heat sterilization of glucose-based PD fluids readily produces glucose degradation products (GDPs) and GDPs accelerate the formation of AGEs in the peritoneal cavity. Therefore, further studies are needed to evaluate whether the high levels of glucose, GDPs, and lactate buffer present in PD solutions may contribute to alterations in peritoneal cell function, peritoneal damage, and CVD as has been suggested by experimental studies [69].

Hyperhomocysteinemia

When CKD patients reach the stage when RRT is initiated, $>90\%$ have signs of elevated (>10–15 μmol/L) total homocysteine (tHcys) levels [70]. Although experimental evidence shows that tHcys causes endothelial dysfunction, reduces the bioavailability of NO and enhances smooth muscle cell proliferation [71], the results of clinical studies in CKD have been notoriously inconsistent [69]. Whereas some cross-sectional studies reported higher levels of tHcys in dialysis patients with CVD, others found no difference, or even paradoxically low tHcy levels, in those with CVD [70]. A number of reasons that may explain why tHcys does not show up as a significant risk factor in many of these studies [70]. As tHcys exist mainly in a protein-bound form, there is a strong positive correlation between tHcys and S-albumin. Clinical states characterized by hypoalbuminemia, such as PEW and inflammation, might explain the apparent reverse association between tHcy and clinical outcome, It has been suggested that a mutation within the C677T methylenetetrahydrofolate reductase (MTHFR) gene, which is associated with elevated tHcys levels, may contribute to excessive cardiovascular risk. However, a prospective multicenter study of 417 HD and 44 PD patients did not support the hypothesis that MTHFR C677T polymorphism is a vascular risk factor in the dialysis population [72]. At least three large controlled randomized trials in the general population (VISP, HOPE, and NORVIT), as well as two smaller studies in CKD patients [73, 74], have recently shown no benefit of folic acid supplementation on events of vascular complications or outcome. Although high intake of folic acid and vitamins B_6 and B_{12} in PD patients has been shown to normalize homocysteine levels in PD patients [75], no randomized trials with hard outcomes have yet been reported in this patient population. Taken together, there is today no reason for prophylactic supplementation of folic acid in dialysis patients. Data from ongoing prospective randomized trials in renal cohorts (FAVORIT and HOST) are therefore much anticipated.

Genetic/Epigenetic Factors

Genetic factors may affect the prevalence and magnitude of complications in CKD patients, which in turn may affect the risk of vascular complications and outcome in the dialysis population. For instance, a single nucleotide polymorphism in the IL-6 gene was associated with higher plasma IL-6 level and co-morbidity score in HD patients [76]. Studies in PD patients are needed to evaluate the impact of genetic alterations in various cytokine genes on membrane characteristics as well as on the clinical phenotype. Not many studies evaluating the impact of genetic polymorphisms on clinical phenotype and/or peritoneal membrane characteristics in PD patients have been published. However, one study showed that a functionally relevant polymorphism of IL-6 may have a considerable effect on the basal peritoneal permeability [77]. Also, genetic polymorphisms within the vascular endothelial growth factor (VEGF) gene were shown to be associated differences of peritoneal transport and survival in a group of 135 PD patients [78]. In a small study of 86 Chinese PD patients, a polymorphism within the endothelial NO synthase (eNOS) gene was shown to be associated with basal peritoneal permeability [79]. Moreover, the ACE polymorphism may determine recombinant human erythropoietin responsiveness in PD patients [80]. As the numbers of included patients in these studies were low, confirmatory studies in large populations are needed to provide the PD community with a more precise approach to identify "high-risk" patients.

A novel approach in atherosclerosis research focuses on the role of epigenetics, which refers to changes in gene expression that are not coded in the DNA sequence itself, but result in post-translational modifications in DNA proteins. Of interest, epigenetic modifications persist in subsequent cell generations. Changes in genomic DNA methylation are crucial in diseases such as aging, mental health, cancer, and arteriosclerosis [81]. As inflammatory mediators, such as IL-6, have been shown to promote methylation changes [82] and are associated with DNA hypermethylation in CKD patients [83], further studies are needed to determine whether epigenetic DNA alterations

contribute to accelerated atherosclerosis in CKD. Since epigenetic DNA modifications are potentially reversible, there is a possibility for the development of targeted epigenetic therapies.

Inflammation in Chronic Kidney Disease

Inflammation Is a Common Feature in Chronic Kidney Disease that Predicts Outcome

In accordance with results in the general population [84] numerous studies in CKD patients have shown that elevated CRP predicts both all-cause and cardiovascular mortality in HD [85–87] as well as in PD [88–90] patients. Data from the Modification of Diet in Renal Disease (MDRD) study [91] showed that both high CRP and low S-albumin are independent risk factors for all-cause mortality in CKD stages 3 and 4 as well. Inflammation is a common feature of CKD and starts early in the process of declining renal function. In a survey of 663 CKD 5 patients from Sweden, Germany, and Italy more than two-thirds of the patients had CRP >3.4 mg/L [92]. Recent data from the United States shows that out of 1.761 HD patients, 39% had CRP levels ranging between 15 and 30 mg/L and 29% even had a CRP level ≥30 mg/L [93]. Large cohort studies comparing the prevalence of inflammation in HD and PD patients have, to the best of our knowledge, not yet been conducted. Studies in PD patients show that elevated CRP is an independent predictor of nonfatal myocardial infarction [94] and increased incidence of CVD [89]. PD individuals in the top CRP quartile had a cardiovascular risk about 5 times higher than those in the lower quartile [89]. A direct association was shown between elevated neutrophil count at start of PD and overall and cardiac mortality [95]. Also, other inflammatory markers, such as IL-6 [96–98] and fibrinogen [99] predict mortality in dialysis patients. The evaluation of a large cohort of U.S. dialysis patients demonstrated that septicemia was associated with increased cardiovascular death risk [100]. This observation supports the role of inflammation as a cause of vascular disease. Although the dialysis procedure per se may promote an inflammatory response, available data suggest that persistent inflammation (and its partner in crime: oxidative stress) starts early in the process of a failing kidney function [101]. The Chronic Renal Impairment in Birmingham (CRIB) study [102] demonstrated that kidney disease is associated with inflammation even in patients with moderate CKD. Other studies show that elevation of inflammatory biomarkers is a common phenomenon in elderly patients with mild–moderate CKD as evaluated with serum creatinine [103–105].

Multiple Causes of Inflammation in Chronic Kidney Disease

Both dialysis-related and dialysis-unrelated factors may contribute to the high prevalence of inflammation in CKD patients (Fig. 23.4). Not surprisingly, intercurrent clinical events are the most important factor predicting elevated

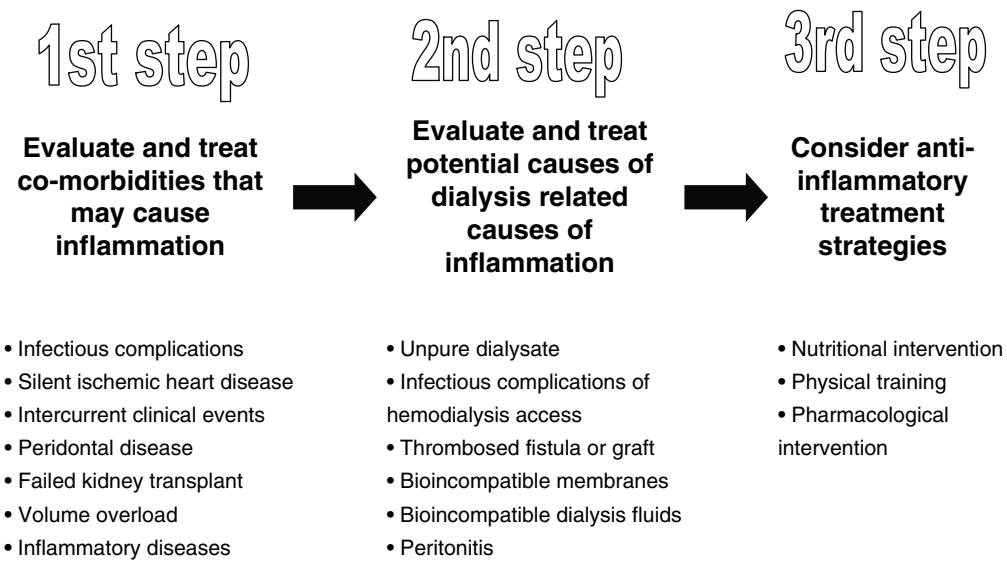


Fig. 23.4 How to handle the dialysis patients with persistent inflammation

CRP alterations in CKD [106]. It is also evident that persistent infections with *Chlamydia pneumoniae* and *Helicobacter pylori* [107–109] as well as periodontitis [110] contribute to inflammation. Obesity is another factor that may contribute to a state of subclinical inflammation in dialysis patients and in one study visceral fat mass was significantly associated with circulating IL-6 levels in patients starting RRT [111]. As a reduction of kidney function *per se* may be associated with an inflammatory response and differences in residual renal function may also contribute to "uremic inflammation" [112]. Volume overload and/or CHF are common complications in dialysis patients that also may be linked to inflammation [113]. According to the "intestinal leak" hypothesis, it is thought that edema renders the intestinal mucosa permeable to bacterial endotoxin as shown in heart failure patients [114]. One study demonstrated strong interrelations between inflammation, residual renal function and cardiac hypertrophy in PD patients [115]. Failed kidney transplants may be yet another reason of inflammation in dialysis patients [116]. In addition, some specific components of the HD procedure may contribute to inflammation, such as clotted access grafts [117], contact of blood with artificial dialysis membranes [118], and catheter infections [119]. It has also been suggested that diminished up-regulation of anti-inflammatory factors, such as IL-10, in response to HD treatment could contribute to persistent inflammation in some patients [120]. It should be noted that the dialysis procedure might also include some specific anti-inflammatory properties. It has been observed that 12 months of PD were associated with unchanged median CRP; in contrast, 12 months of HD were associated with declining CRP levels [121]. Further studies evaluating the potential anti-inflammatory effects of repeated heparinization during HD are needed to exclude heparin as the explanation for this difference in CRP.

PD patients are also subjected to some specific causes of inflammation associated with the dialysis procedure. Conventional bioincompatible glucose-based PD solutions contribute to systemic inflammation via GDPs generated during heat sterilization, which may induce peritoneal inflammation and the formation of AGEs [122]. Additionally, glucose-based solutions lead to a substantial uptake of glucose [123], which may cause oxidative stress [124], a potent cause of inflammation. Whereas it is obvious that acute bacterial peritonitis will lead to a transient high-level inflammation, it should also be recognized that persistent unresolving peritonitis, such as from *Pseudomonas* species, *Staphylococcus aureus,* and fungal causes, may contribute to low-grade, chronic inflammation in PD patients. Patients who have peritonitis produce high levels of IL-1, IL-6, TNF-α, IL-12, and IL-4 in PD effluent and plasma [125]. Volume overload may, via bacterial or endotoxin translocation in patients with severe gut edema, lead to immunoactivation and increased inflammatory cytokine production [126]. Finally, as high-transporter PD patients usually are more inflamed than low-transporters, peritoneal transport status may also be associated with inflammation [127].

In Sweden, about 25% of incident and prevalent dialysis patients have what would be considered to be normal (or even low) CRP levels ($<$2 mg/L). Indeed, dialysis treatment and/or other clinical inflammatory events cannot alone account for the large inter- and intraindividual variability in the prevalence of inflammation. As there is evidence of substantial heritability (35–40%) for CRP levels [128], individual factors significantly influence the levels of inflammatory markers in dialysis patients [129]. Several candidate genes may affect the prevalence of inflammation in ESRD. The rapid development in the field of genetics has opened up entirely new possibilities to understand the impact of genotype on disease development and progress. The identification of genetic variations in genes related to inflammation and PEW might be an interesting approach to identify dialysis patients at high risk who may benefit from more aggressive treatment. Moreover, since the association between uremic cardiovascular risk factors, such as inflammation, may be confounded or affected by reverse epidemiology [11], genotype-association studies would be preferred as the association with CVD should be unbiased and nonconfounded. For this purpose, large integrative studies on genotype-phenotype associations and impact on clinical outcome should be performed. So far, most of the investigators have focused on single nucleotide polymorphisms within the CRP, IL-6, TNF-α, and IL-10 genes. Hopefully, prognostic or predictive multigene DNA assays will in the future provide the nephrological community with this more powerful approach to identify "high-risk" CKD patients at an early stage of the disease so that accurate individual treatment strategies can be implemented [130].

Do Inflammatory Biomarkers Promote Vascular Disease?

Although the concept that inflammation plays a central role in the pathophysiology of atherosclerosis and CVD has gathered momentum [131], we do not know yet whether an elevation of CRP promotes vascular injury or is just a reflection of its existence. While CRP initially was felt to be only a marker of inflammation, some believe that CRP is also a direct mediator of vascular disease [132]. Inflammatory stimuli that cause release of proatherogenic cytokines also stimulate hepatic CRP production. Therefore, some investigators argued that the association between vascular damage and CRP is indirect and that inflammatory mediators other than CRP, such as IL-6, are the main culprits

[133]. Indeed, the association may well be indirect, since elevated CRP is also associated with other cardiovascular risk factors, such as oxidative stress, insulin resistance, and vascular calcification [133]. On the other hand, *in vitro* data have emerged, showing that CRP has direct pro-inflammatory and prothrombotic effects [134], and thereby contributes to ischemic tissue damage in both the brain and heart of adult rats [135], inhibits EPC differentiation and function [136] and up-regulates angiotensin type-1 receptors [137]. In addition, in contrast to humans, CRP administration was associated with increased mortality and infarct size in rats undergoing coronary artery ligation. No deaths and an infarct size not different from that of vehicle-treated rats was observed in rats pretreated with a specific small-molecule inhibitor of CRP, 1,6-bis(phosphocholine)-hexane [138]. However, despite the numerous reports of potential proatherogenic properties of CRP *in vitro*, the evidence that CRP promotes atherosclerosis *in vivo* is controversial. As the observed epidemiological association between CRP and health outcomes might be affected by reverse causation or confounding, the Mendelian randomization approach (i.e., study of the association between a disease and a specific gene polymorphism) [139] has been used to obtain insight into the true nature of the vascular disease/CRP association. In one study a common CRP polymorphism was associated with significant differences in CRP concentrations, but was not associated with the CRP genotype and coronary events [140]. By the same approach, other studies demonstrated no evidence that CRP is causal in the pathology of neither the metabolic syndrome [141] or HT [142]. Accordingly, in a recent study of 504 white and 244 African-American incident dialysis patients, one CRP haplotype predicted lower CRP, but no association was found between CRP haplotypes and incident CVD [143]. Taken together, although conflicting, current data suggest that elevated CRP is not causally linked to CVD and that other inflammatory biomarkers may be the real culprits. Given the strong associations between circulating IL-6 levels and cardiovascular outcome in dialysis patients [96–98], this pro-inflammatory cytokine has been suggested to have proatherogenic properties [133]. Indeed, comparative studies of different inflammatory biomarkers show that IL-6 is the strongest predictor of future cardiovascular morbidity and mortality. Moreover, in a prospective trial of patients starting dialysis treatment, elevated IL-6 was associated with more rapid progression of carotid intima media arteriosclerosis [107]. A common variant in the promoter region of the IL-6 gene was associated with a higher risk of CVD in 775 incident dialysis patients [144]. Taken together, the data available in the literature suggest that IL-6 has direct proatherogenic effects [133].

Inflammation in CKD – Can It Be Treated?

Although inflammation is a common feature in ESRD that predicts all-cause and cardiovascular mortality, we do not know yet whether inflammation is just a reflection of vascular disease or actually a promoter of accelerated atherogenesis. However, as anti-inflammatory treatment strategies, such as statins, ACE-I, and aspirin, have beneficial effects on cardiovascular mortality in the general population, it would be of interest to evaluate various nutritional and pharmacological anti-inflammatory treatment strategies also in this high-risk patient population [145]. To the best of our knowledge, no large randomized studies have yet evaluated whether the use of more biocompatible PD solutions, such as icodextrin, lead to less inflammation. One small study in PD patients showed that systemic CRP decreased when heparin was given intraperitoneally [146], but larger prospective trials evaluating this putative anti-inflammatory agent are needed. In Fig. 23.5, some putative nutritional and pharmacological treatment strategies are listed. Until data from randomized trials are available, careful search for infectious processes and correction of volume status can be recommended.

Conclusion

Dialysis patients have an exceptionally high mortality rate, much of which results from CVD. Although traditional risk factors, such as HT, DM, dyslipidemia, and smoking, are highly prevalent among dialysis patients, they cannot by themselves fully explain the unacceptable high rate of cardiovascular complications in this population. Much recent interest has focused on various nontraditional and or uremia-specific risk factors, such as inflammation, volume overload, oxidative stress, hyperhomocysteinemia, autonomic dysfunction, and vascular calcification. Current data show that the prevalence and magnitude of these risk factors are increased even at an early stage of declining renal function. Therefore, risk assessment and intervention should be initiated even in early stages of CKD.

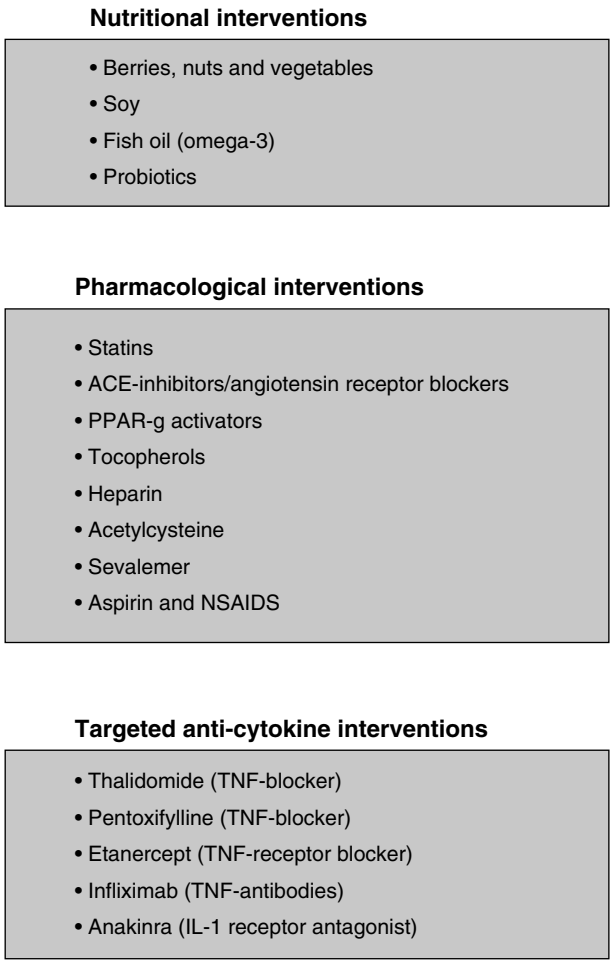


Fig. 23.5 Potential nutritional and pharmacological treatment strategies using persistent noninfectious inflammation and oxidative stress as a target

Abbreviations

ACE-I	Angiotensin convertine enzyme inhibitor
ADMA	Asymmetric dimethylarginine
AGEs	Advanced glycation end-products
AMI	Acute myocardial infarction
ARBs	Angiotensin receptor blockers
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
CABG	Coronary artery by-pass graft
CAD	Coronary artery disease
CEC	Circulating endothelial cells
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CVD	Cardiovascular disease
CHF	Congestive heart failure
GDPs	Glucose degradation products
CKD	Chronic kidney disease
CML	Carboxymethyllysine
DM	Diabetes mellitus
EBCT	Electron beam computer tomography

EPC	Endothelial progenitor cells
ESRD	End-stage renal disease
Hcys	Homocysteine
HD	Hemodialysis
HDL	High-density lipoprotein
HT	Hypertension
IL	Interleukin
Lp(a)	Lipoprotein(a)
LV	Left ventricular
LVH;	Left ventricular hypertrophy
MTHFR	Methylenetetrahydrofolate reductase
NMMA	N(G)-monomethyl-L-arginine
NO	Nitric oxide
NSAID	Non steroidal anti-inflammatory drugs
PD	Peritoneal dialysis
PEW	Protein energy wasting
PVD	Peripheral vascular disease
RAS	Renin angiotensin system
RRT	Renal replacement therapy
TNF	Tumor necrosis factor
TnT	Troponin T
USRDS	United States Renal Data System
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

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Chapter 24
Vascular Calcification in Chronic Kidney Disease

M. I. Yilmaz, K. Matsubara, P. Stenvinkel, B. Lindholm, and R. Mehrotra

Vascular calcification (VC) of medium-sized muscular and large elastic arteries and arterioles is an important complication of uremia, which is closely linked to, and can therefore serve as a marker of, atherosclerosis as well as of arteriosclerosis. There are two forms of VC depending on whether it occurs in the intima or media of blood vessels. *Intimal calcification* occurs in *atherosclerotic lesions* [1, 2], and as atherosclerotic plaques mature they typically develop associated calcification [3]. *Medial calcification*, which is characterized by mineralization of the elastic lamina of large and medium-sized arteries, is responsible for the pipe-stem appearances once known as Monckeberg's medial calcinosis or sclerosis. Medial calcification is associated with vascular stiffening and *arteriosclerosis*, and is especially common in elderly patients and those with diabetes mellitus (DM) and end-stage renal disease (ESRD) [4, 5]. The distinction between atherosclerosis and arteriosclerosis is not always clear, and a mixture of intimal and medial calcification is often present in affected vessels in patients with ESRD [6]. Whereas VC may contribute to atherosclerotic lesions in humans, its main impact on the overall mortality in ESRD patients is probably by decreasing the elasticity of the vessels [7, 8]. As will be shown in this review, the vascular calcification process has great similarity with a process of vascular *ossification*. However, in this review we will keep the term *vascular calcification* as it is still the most commonly used expression. VC can potentially be influenced by various nutritional, pharmacological, and dialytic therapies, but it is not known whether peritoneal dialysis (PD) as such significantly alters the risk for developing VC or if the consequences of VC in PD patients differ from patients undergoing other forms of dialysis.

Clinical Consequences of VC

Although we know today that VC can lead to devastating organ dysfunction depending on its extent and the organ affected, the calcification of blood vessels commonly seen with DM, ESRD, aging, and atherosclerosis was earlier considered to be a rather benign finding [1]. In the general population, *coronary artery calcification* (CAC) occurs almost exclusively in the intima of the blood vessels as an integral component of atherosclerosis. The CAC burden has a modest correlation with obstructive coronary artery disease (CAD) but a strong relationship with total plaque burden [9]. The CAC score increases with age, and Blacks and Hispanics appear to have a lower CAC burden than Caucasians [10], suggesting a genetic impact on the calcification process (see below). In almost every population studied, the CAC score predicts outcome. CAC is very common in dialysis patients and is also present in young adults and adolescents with chronic kidney disease (CKD) [11–14]. Whereas it is well established that the process of VC begins very early in CKD patients [15], the severity of calcification increases with increasing dialysis vintage in prevalent ESRD patients in whom 80% may have detectable CAC [14, 16]. VC in the media of large arteries leads to increased stiffening and decreased compliance of these vessels, and therefore CAC is associated with widened pulse pressure and increased pulse wave velocity as well as with left ventricular hypertrophy (LVH) in ESRD patients [17, 18]. Not surprisingly, the presence and/or severity of arterial medial VC is consistently associated with increased risk for death among ESRD patients [19, 20]. Thus, because VC itself may contribute to initiation or progression of CVD over and above its link to atherosclerosis, it has a profound influence on cardiovascular function and health in ESRD patients.

M.I. Yilmaz (✉)
Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden
e-mail: mahmutiyilmaz@yahoo.com

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Cardiovascular Events and VC

Cardiovascular events are significantly increased in CKD patients and the annual mortality rate due to CVD is approximately 10- to 20-fold higher in ESRD patients than in the general population [21, 22]. During the past decade, the patient population with ESRD has more than doubled and CKD is thought to be a major contributor to development of CVD [23]. CVD is the major cause of death in ESRD patients, accounting for 50% of all deaths [24]. The increased risk of mortality among these patients may to a large extent be explained by their predisposition to VC. Thus, the extent and/or severity of vascular VC in ESRD patients is associated with increased risk for death [25–27].

As VC leads to vascular stiffness, and vascular stiffness is associated with LVH, CAD, and cardiac events, the relationship between VC, CVD, and mortality is important. Increased cardiovascular mortality in ESRD patients can thus be predicted by the presence of large vessel disease, due to its links with increased myocardial oxygen demand, subendocardial ischemia, and vascular afterload, with a propensity to develop LVH [13, 28]. Furthermore, increased pulse pressure and pulse wave velocity in the elastic arteries of the femoral, aortic, and carotid arteries is associated with increased mortality in dialysis patients [29, 30].

As will be discussed in greater detail below, hyperphosphatemia, vitamin D deficiency, and secondary hyperparathyroidism are predictable consequences of the progressive decrease in GFR among patients with CKD [15]. Disordered mineral metabolism (hyperphosphatemia, hypercalcemia, and hyperparathyroidism) is now considered to be an independent and unique risk factor for CVD among individuals with ESRD [31] as these abnormalities are important in the pathogenesis of the accelerated VC, and are significantly linked to all-cause and CVD mortality in patients with ESRD [32, 33], as well as to arterial medial calcification, a strong prognostic marker of CVD [1, 34].

Epidemiologic studies suggest that even mildly elevated serum phosphate concentrations confer an increased risk for nonfatal cardiovascular events, cardiovascular mortality, and all-cause mortality [31, 35]. An association between hyperphosphatemia and all-cause mortality has been reported also among patients undergoing PD [36].

How to Detect and Assess VC

Several techniques can be used to detect VC (Table 24.1). Post-mortem VC can of course be investigated in great detail by histology in autopsy specimens [37–39]. As none of the other available tools (see below) can reliably distinguish for example intimal from medial calcification, the "gold standard" method for detailed investigations therefore remains histological examination of arterial specimens.

Among the many methods that have been used to make the ante-mortem detection of VC, and to grade its severity and monitor progression, the simplest technique is plain X-rays, which can be used to detect pipe-stem calcification of the internal elastic lamina and tunica media. Most of the X-ray studies show that VC in large and small vessels can indeed be detected in nondialyzed, hemodialysis (HD), PD, and renal transplant patients [40, 41]. Although, the X-ray technique is not highly sensitive, and not a very precise tool for quantification of VC, it can still be used to grade the severity of VC (see below).

Computed tomographic (CT) methods are probably the most sensitive clinical tests to detect VC, and also allow *quantification* of the extent and severity of VC. The best documented among these tests, electron beam computed tomography (EBCT), uses an electron gun to generate X-rays, thus permitting very rapid scanning times [9]. The total calcification burden in ESRD patients, ascertained either using ultrasonography by the number of calcified blood vessels, or using EBCT scan by the total CAC score, is associated with mortality [25, 27, 42]. Measurement of coronary calcium scores by EBCT has been validated by numerous studies, and EBCT is also thought to be the most sensitive, noninvasive method of detecting coronary heart disease and tracking progression of disease and efficacy of therapy [43, 44]. Since EBCT uses prospective ECG gating during image acquisition, the exposure to ionized radiation is relatively low. *Multislice/helical CT scanning* is a relatively new technology that has improved spatial resolution and retrospective ECG gating, and is less influenced by pulse rate than EBCT [45]. Given the limited availability of these resource-intensive CT imaging methods, the use of a composite score derived from plain radiography, pulse pressure, and echocardiography has been advocated for routine clinical practice [46]. However, the sensitivity, specificity, and predictive value of such a composite score need to be further studied. In a recent study, Bellasi et al. [47] compared the results obtained with simple noninvasive techniques with those obtained using EBCT for CAC in hemodialysis patients, and showed that simple measures of cardiovascular calcification, in particular *abdominal aorta calcification* on plain X-ray films of the lumbar aorta, and, to a lesser extent, the presence of *valvular calcification* as assessed by

Table 24.1 Methods used or proposed to assess vascular calcification in ESRD patients

Method of diagnosis	Value and limitations
Histology – *Radial artery* (during fistula surgery) – *Inferior epigastric artery* (during transplant surgery)	Highly sensitive and specific but not suitable for clinical practice or population-based studies [33, 146]
Radiology – *Plain X-ray* – *Ultrasonography*	Low sensitivity, semi-quantitative, distinction of intimal and medial calcification not validated; calcification detected by plain radiography and ultrasonography predicts adverse outcome in ESRD [25, 40, 41]. A lateral X-ray of the lumbar abdominal aorta may provide relatively accurate measurements of VC [47]
Echocardiography	The presence of valvular calcification is a good predictor of coronary artery calcium measured by computed tomography [47]
Physiological tests – *Pulse pressure* – *Pulse wave velocity*	*Pulse pressure* is not a good measure of coronary artery calcium [47]. Strong association between p*ulse wave velocity* (PWV) and abdominal aorta calcification on plain X-ray (and a borderline association with thoracic aorta and coronary artery calcification) [147]
Cardiovascular Calcification Index – *Plain radiography* – *Echocardiography* – *Pulse pressure*	This index combines plain radiography, echocardiography, and pulse pressure; no data to define cut-offs for pulse pressure; sensitivity, specificity, and predictive value unknown [46]
Computed Tomography – *Electron-beam computed tomography (EBCT)* – *Multirow spiral computed tomography (MSCT)* – *Spiral computed tomography (CT)*	Quantitative, highly sensitive and specific, utility limited by inter-scan variability; EBCT scores predict outcome in ESRD; MSCT – high radiation exposure; spiral CT – possible lower sensitivity [27, 42–45]. These techniques, and especially EBCT, are not generally available, and high costs may limit their utility

Source: Modified after Kalpakian MA, Mehrotra R [148]

echocardiography showed a good correlation with EBCT. This shows that these relatively simple and inexpensive imaging tests may prove very useful for screening of cardiovascular calcification and identify patients at higher risk for cardiovascular events, which should stimulate clinical research focusing on VC.

Mechanisms of Vascular Calcification

There are several clinical, biochemical, immunological, and genetic factors that may influence the development of VC in ESRD patients (Fig. 24.1). VC is an active process that involves trans-differentiation of vascular cells into an osteoblastic phenotype with subsequent deposition of hydroxyapatite – a mineral found in bone [4]. VC may include both chondrogenic and osteogenic differentiation, and these processes may differ between mice (primarily chondrogenic with cartilage formation) and humans (primarily osteogenic with bone tissue formation). Whereas the disordered bone and mineral metabolism in ESRD is probably the most important factor in the pathogenesis of VC, numerous other factors including genetic predisposition are also important. In particular, co-morbidities (in particular diabetes mellitus and CVD) and inflammation are strongly related to VC. As blood vessels normally express inhibitors of mineralization, such as matrix GLA protein (MGP) and pyrophosphate, conditions (such as inflammation) that lead to lack of these molecules ("loss of inhibition") may promote the development of VC. Several key regulators of bone formation and bone structural proteins, including bone morphogenetic protein-2 (BMP-2), osteopontin, matrix vesicles, MGP, osteoprotegerin, fetuin-A ,and Cbfa-1 are expressed in atherosclerotic plaques, and some of these are thought to be strongly associated with genetic predisposition (see below).

Bone and Mineral Disorders and VC

Renal osteodystrophy and extraskeletal calcifications, such as VC, are, from a clinical point of view, the principal complications associated with the disordered bone and mineral metabolism in uremia. Recent studies have consistently shown that disordered mineral metabolism is an independent risk factor for CVD [36, 48, 49]. Before exploring the relationship between the disordered mineral metabolism and VC in ESRD, two important points need to be made.

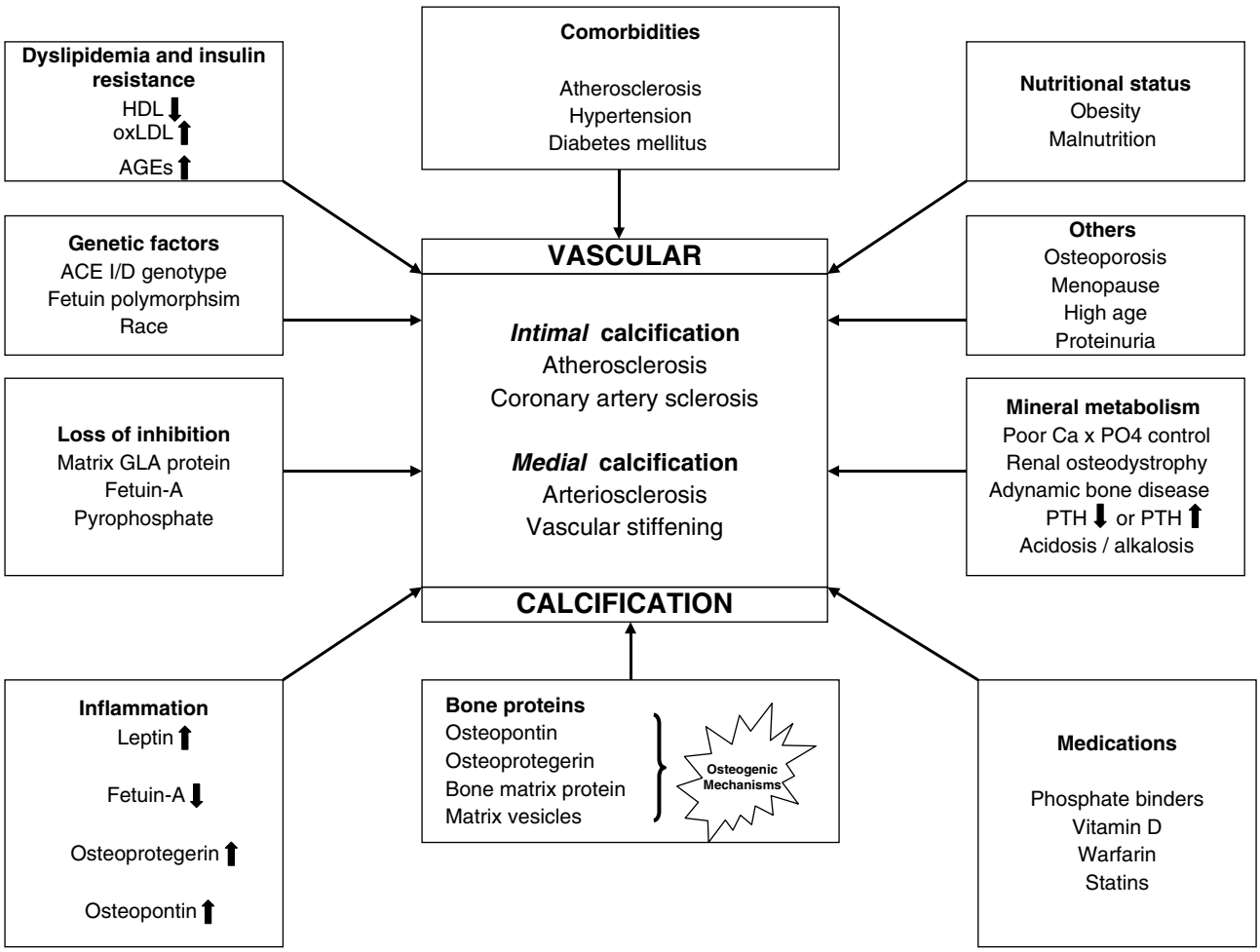

Fig. 24.1 Potential causes of vascular calcification in ESRD

First, because ESRD is characterized not only by medial but also by intimal calcification, the calcification burden ascertained noninvasively (EBCT) represents a composite of intimal and medial calcification [6]. Second, the process of VC is multifactorial and disordered mineral metabolism is not the exclusive, and perhaps not even the predominant cause of the increased calcification burden seen in ESRD patients.

Whereas the serum levels of markers of disordered mineral metabolism were previously viewed largely as surrogates for bone turnover and its impact on bone health, the serum levels of calcium, phosphate, and serum parathyroid hormone (PTH) are now seen as more directly associated with cardiovascular risk. Thus, in vitro studies have shown a pathogenetic role of calcium, phosphate, and other components of the uremic plasma in inducing the active process of VC [50–52]. Several cross-sectional clinical studies have shown an association between hypercalcemia, hyperphosphatemia, and (either high or low) PTH levels with severity of VC among ESRD patients [14, 53]. As there is a relationship between hyperphosphatemia and VC, hyperphosphatemia is associated with a progressive increase in the risk for mortality and is now generally thought to be a critical factor in the pathogenesis of the accelerated VC in ESRD patients [33, 53, 54].

Elevated serum levels of calcium and phosphate directly affect the cell-mediated regulation of VC. Some investigators have made use of vascular smooth muscle cell (VSMC) culture systems. Both intimal and medial calcifications are active, cell-mediated processes that involve the trans-differentiation of vascular cells to osteoblastic phenotype. The molecular marker often used to detect this trans-differentiation is Osf2/Core binding factor alpha 1 (Cbfa-1), a binding protein for osteoblast-specific cis-acting element, Osf2. By binding to and regulating the expression of specific genes, Osf2/Cbfa-1 plays a key role in the differentiation of mesenchymal cells to osteoblasts. Adding phosphorus or phosphate donors to culture media of VSMC, in concentrations seen in ESRD patients, induces the expression of Osf2/Cbfa1 and mineralization [50, 52]. Calcium-induced mineralization is dependent on the function of a sodium-dependent phosphate co-transporter. Thus, it appears that phosphate enters the VSMC through Pit-1, a type III

sodium-phosphate co-transporter, induces trans-differentiation to an osteoblastic phenotype and eventually leads to mineralization through increased expression and secretion of matrix vesicle and apoptotic bodies. Similarly, high calcium concentrations may also induce mineralization, and high calcium and phosphate concentrations act synergistically, and not only additively [1, 52].

Primary hyperparathyroidism has been increasingly recognized as a risk factor for CVD (through VC, LVH, and hypertension) [3, 55, 56]. Secondary hyperparathyroidism also has a strong association with cardiovascular pathology, and PTH is now seen as a uremic toxin [57]. Disordered bone and mineral metabolism associated with CKD leads to secondary hyperparathyroidism by several mechanisms: phosphate retention (trade-off hypothesis), decreased circulating levels of 1,25 dihydroxy vitamin D and vitamin D resistance associated with uremia, skeletal resistance to the calcemic action of PTH, and reduced number of calcium sensing receptors [15]. Some authors have suggested that mineralization defects seen in early stages of CKD may be manifestations of hyperparathyroidism [58]. The spectrum of renal osteodystrophy seen in patients with CKD is probably primarily a direct result of vitamin D deficiency and/or resistance, hyperparathyroidism, skeletal resistance to PTH, and metabolic acidosis; and the disordered calcium and phosphate metabolism are likely to exert their effects through one or more of these mechanisms [15]. As 25 hydroxy vitamin D and vitamin D binding proteins are lost in the urine of individuals with proteinuric renal diseases, the severity of vitamin D insufficiency is dependent on the magnitude of proteinuria [15, 59, 60].

Cell culture studies indicate that PTH-related peptide inhibits calcification, and treatment of calcification-prone mice with human PTH significantly attenuates valvular calcification [61, 62]. Consistent with these observations, an inverse relationship between serum PTH (and bone turnover) and extent of VC has recently been reported in humans [26]. These result suggest that oversuppression of PTH may also contribute to VC. This is an important observation of great clinical relevance for peritoneal dialysis patients in whom *adynamic bone disease* is a common problem [63, 64].

Bone Proteins, Inhibitors of VC, and Other Factors

Whereas VC is found in the majority of advanced atherosclerotic lesions, some inherited diseases are characterized by isolated medial calcification of arteries [7, 65]. Although calcification is most common in atherosclerotic lesions, atherosclerosis and VC appear to be separate genetic entities, as demonstrated by mouse studies [66, 67]. Moreover, VC may exist in the absence of atherosclerosis and, thus, the VC aspect of atherosclerosis can and should be separately studied [7]. For example, mice deficient in osteoprotegerin or MGP display arterial calcification, which occurs in the absence of atherosclerosis [68, 69]. Genetic polymorphisms have also been linked with VC in clinical studies. The relationship between coronary artery plaque calcification and angiotensin–converting enzyme (ACE) DD genotype was recently shown by intravascular ultrasound in a human study [70]. This finding suggests that ACE I/D gene polymorphism may be related to the development or progression of atherosclerotic plaque calcification.

Selective deletion of genes that are important for VC have been studied in several animal knockout (KO) models, but the role of genetic factors on VC, particularly medial calcification, in humans is less clear as many studies may be underpowered to detect such associations.

Matrix GLA Protein

Matrix GLA protein (MGP), first identified as a bone matrix protein, is a gamma-carboxylated mineral-binding extracellular matrix (ECM) protein. MGP is found in the normal artery wall, its expression increases with increasing extracellular calcium concentrations, and it is also increased in atherosclerotic plaques [4, 71, 72]. MGP expression is restricted to vascular smooth muscle cells (VSMC) and chondrocytes in mice. As shown by MGP-KO mouse experiments, MGP directly inhibits mineralization in arteries and cartilage [69]. MGP also inhibits mesenchymal cell differentiation to the osteogenic lineage by sequestering the potent osteogenic and chondrogenic differentiation factor, BMP-2 (see below). The effect of MGP and BMP-2 depends on the degree of MGP gamma-carboxylation and the ratio of the levels of these two molecules. These findings suggest that lack of function of MGP rather than its amount may be the factor that increases risk of calcification [4, 73, 74]. The local increase of MGP expression during VC may limit the extent of calcification because MGP can bind to BMP-2 [13, 75]. The gamma-carboxylation of MGP is a vitamin K-dependent enzyme and in the case of deficiency of functional vitamin K, VC may be enhanced owing to decreased availability of functional of MGP. An association between VC and lower vitamin K intake was demonstrated in postmenopausal women [4, 76]. Moreover, as warfarin interferes with the availability of bioactive vitamin K, it may therefore interfere with MGP function. Deficiencies of several local and circulating inhibitors of calcification have been explored in recent studies of ESRD patients. Clinical studies suggest that ESRD may be associated with a

relative deficiency of MGP and animal studies indicate that administration of bone morphogenic protein-7 (BMP-7; see below) may attenuate VC [77, 78]. All these observations suggest that MGP participates in a regulatory system to control and limit mineralization and is potentially important in patients with CKD.

Bone Morphogenic Proteins

Bone morphogenic proteins induce the formation of bone and cartilage. BMP-2 belongs to the transforming growth factor (TGF) beta superfamily of proteins. BMP-2 is a potent osteoinductive factor in mesenchymal stem cells and marrow stromal cells and the expression of BMP-2 has been detected in human calcified arteries [13, 73, 79]. BMP-2 is also a powerful inducer of differentiation of pluripotent mesenchymal cells to osteoblastic lineage and bone formation. A clinical study demonstrated that BMP-2 levels in pooled uremic serum are two times higher than in normal human serum and also that BMP-2 production increase during calcification with uremic serum [80]. Bone morphogenetic protein 7 (BMP-7) is an essential renal morphogen that maintains renal tubular differentiation in the adult and is down regulated in renal failure. In an animal study, Davies et al. [77] showed that BMP-7 is an effective treatment of VC in the murine model of atherosclerosis and renal failure, a finding that may have important implications for the development of future therapies for this condition in humans both with and without uremia.

Core Binding Factor α-1 (Cbfa-1)

Core binding factor α-1 (Cbfa-1) is one of the transcriptional factors that regulate osteoblastic differentiation and bone formation. Cbfa-1 has been identified as an essential factor for osteoblastic differentiation, and bone disappears in Cbfa-1-KO mice [81, 82]. The osteoblast is a cell of mesenchymal origin that, once terminally differentiated, produces most of the proteins present in the bone ECM and therefore controls the mineralization of this ECM. Cbfa-1 is thought to be the switch that turns this mesenchymal cell into an osteoblast, as mice deficient in Cbfa-1 fail to mineralize bone [13, 81]. Studies on the importance of Cfba-1 in the VC of CKD and non-CKD atherosclerosis suggest that Cfba-1 is a key regulatory factor in the VC observed in dialysis patients and that expression of Cfba1 may lead to dedifferentiation of VSMC into osteoblast-like cells [51, 83].

Osteopontin

Osteopontin is a single-chain polypeptide with a molecular weight of approximately 32,600 Da. Osteopontin is an extracellular structural protein and an organic component of bone, which functions as an important calcification inhibitor. Synthesis of osteopontin is stimulated by calcitriol. Osteopontin directly inhibits calcification of cultured bovine aortic smooth muscle cells and inhibits aortic valve calcification in vivo [4, 84, 85]. Mice with a genetic deficiency of MGP and osteopontin have accelerated aortic calcification compared with mice deficient in MGP alone, consistent with the concept that osteopontin inhibits mineralization [4, 86]. In HD patients, osteopontin plasma levels were significantly *higher* compared to healthy volunteers and positively correlated with aortic calcification index [87]. This may suggest that the elevated osteopontin levels are a counter-regulatory response to the increased calcification burden and may serve to limit the extent of VC.

Osteoprotegerin

Osteoprotegerin, also known as osteoclastogenesis inhibitory factor (OCIF), is a cytokine and a member of the tumor necrosis factor (TNF) receptor superfamily. Osteoprotegerin (OPG) has been demonstrated to be a potent inhibitor of bone resorption in vivo. It acts as a decoy receptor, binding and inactivating OPG Ligand (OPGL), which is an essential factor required for osteoclast differentiation. Transgenic overexpression of OPG in mice produces an osteopetrotic phenotype due to the inhibition of growth-related bone resorption [78]. Disruption of the OPG gene produces osteoporosis marked by excessive bone resorption indicating the importance of this molecule in normal bone physiology. Osteoprotegerin, a receptor activator of nuclear factor kappa B (RANK) homolog, works by binding to the RANK-ligand (RANKL) on osteoblast/stromal cells, thus blocking the RANK-RANKL interaction between osteoblast/stromal cells and osteoclast precursors.

Emerging evidence indicates that OPG is not merely a protective factor for bone, but may, in fact, act as a protective factor for the vascular system [88]. One recent study demonstrated RANKL and OPG immunoreactivity in the not diseased vessel wall and in early atherosclerotic lesions in human tissues, whereas in advanced calcified lesions, only RANKL was detected in the extracellular matrix surrounding calcium deposits [79]. In the rat model, warfarin-induced vascular calcification was prevented with OPG treatment [89]. Whereas OPG prevents arterial calcification in

mice its function in human arteries is for now unknown. Human studies have shown a paradoxically positive association between serum osteoprotegerin levels and CAC [78]. It is possible that this reflects a counter-regulatory response to the increased calcification burden.

Fetuin-A

Synthesized in the liver, circulating fetuin-A (in humans also known as alpha 2 Heremans Schmid glycoprotein, AHSG) is a negative acute phase reactant and a potent inhibitor of precipitation of calcium and phosphate [90]. Cell culture studies have demonstrated that fetuin-A is internalized in matrix vesicles released from trans-differentiated VSMC and, thus, may inhibit the active, cell-mediated process of VC [91].

As discussed above, VC is not a passive process resulting simply from supersaturation of minerals in blood [13], and therefore not only factors such as hyperphosphatemia and hypercalcemia, but also mediators such as osteopontin, Cbfa-1, and calcification inhibitors, including fetuin-A, play a critical role [92]. Several investigators have studied the role of fetuin-A in CKD. In a cross-sectional study, Ketteler et al. [90] showed that chronic HD patients had lower levels of fetuin-A than healthy controls. They observed that fetuin-A deficiency was associated with inflammation as well as with increased mortality. In parallel, Stenvinkel et al. [93] reported that a low fetuin-A level was associated with malnutrition, inflammation, and cardiovascular mortality as well as with a polymorphism in the gene encoding fetuin-A in ESRD patients starting dialysis. Another study showed that low circulating levels of fetuin-A were correlated to valvular calcification, atherosclerosis, malnutrition, and inflammation, and predicted mortality and cardiovascular events in PD patients [94]. Thus, it is now well established that fetuin-A deficiency in patients with ESRD is associated with increased risk for death [78, 90]. It is not known whether fetuin-A levels differ between PD and HD patients.

However, even though a cross-sectional study demonstrated an inverse association between CAC score and fetuin-A levels in ESRD patients, a longitudinal study was unable to demonstrate its ability to predict progression of CAC [78, 95]. An increase in aortic stiffness, as reflected by an increase in pulse wave velocity (PWV) or aortic augmentation index (AI), is an important predictor of cardiovascular mortality in dialysis patients [29]. In a cross-sectional study in patients with HD and PD with a low level of inflammatory activity, Hermans et al. [96] demonstrated that fetuin-A could *not* be identified as an independent predictor of aortic stiffness as measured with PWV and AI. Furthermore, nondialyzed diabetics with CKD have high rather than low fetuin-A levels, and serum levels are directly (and not inversely) related to the calcification burden [97]. As observed for osteopontin and OPG (see above), it is possible that this may reflect a counter-regulatory response. Additional studies are needed to further refine our understanding of the role played by fetuin-A deficiency and that of other inhibitors in the high calcification burden seen among dialysis patients.

Leptin

Leptin is a 16 kDa protein hormone that plays a key role in regulating energy intake and energy expenditure, including the regulation of appetite and metabolism. Leptin receptors have been identified on aortic vascular smooth muscle cells and have been shown in vitro to promote VC of bovine vascular cells [98]. The differentiation of marrow osteoprogenitor cells is regulated by leptin. These results suggest that leptin regulates the osteoblastic differentiation and calcification of vascular cells and that the artery wall may be an important peripheral tissue target of leptin action.

Oxidized Lipids

Vascular calcification shares several features with skeletal bone formation at the cellular and molecular levels, and osteoporosis is associated with both atherosclerosis and VC [99, 100]. Osteoporotic postmenopausal women are at significantly greater risk for CVD than age-matched controls [101]. Oxidized low-density lipoprotein (LDL) may be one of several pathogenetic mediators that lead to osteoporosis and VC. Thus, patients with lower bone density and osteoporosis may also have higher lipid levels, more severe coronary atherosclerosis, and have a greater risk of stroke death [102]. Lipids have been shown to accumulate in bones of mice and around bone vessels in patients with osteoporosis [103]. Oxidized lipids that induce atherosclerosis also induce mineralization and differentiation of the osteoblastic cells in the artery wall [104]. Consistent with this finding, hyperlipidemia is associated with VC in mice [105]. Lipid oxidation products that promote atherogenesis also inhibit osteoblast differentiation, but they also promote mineral formation by vascular cells [100]. HDL may also play an important role in regulating VC associated with atherosclerotic lesions [106]. HDL is susceptible to oxidation, and oxidized HDL has proinflammatory characteristics [107]. In one in vitro study, human HDL was found to inhibit the spontaneous osteogenic differentiation and mineralization of calcifying vascular cells (CVCs) [106]. These results suggest that

HDL may regulate the calcification of vascular cells and osteoblastic differentiation. Thus, it is possible that the uremic dyslipoproteinemia, which is further impaired in patients undergoing PD, may have a significant impact on the processes leading to VC.

Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs) are initiated by the reaction of reducing sugars with free amino groups of proteins or amino acids [108]. Accumulation of AGEs such as pentosidine in tissues contributes to normal aging processes [109], and is accelerated by enhanced production (e.g., diabetes mellitus) and also by decreased renal removal (e.g., end-stage renal disease) of glycoxidation products and AGE precursors [110]. Accumulation of AGEs in arteriosclerotic lesions has been suggested to play an important role in the development and progression of arteriosclerosis [111], and is correlated with aorta calcification index in HD patients [111]. In a recent study, Taki et al. [112] showed that pentosidine was positively correlated and independently associated with CAC in HD patients. These results suggest that AGEs may play an important role in the pathogenesis of VC.

Matrix Vesicles and Apoptosis

Matrix vesicles are thought to initiate calcification in forming bone and mineralizing cartilage [113]. Matrix vesicle-like structures have been found in calcified arteries and heart valves [114, 115]. These structures are derived from VSMCs from advanced carotid atherosclerotic plaques [116]. The link between cell death and VC has been recognized in some pathological studies [117, 118]. One study provided evidence that apoptosis precedes VSMC calcification and that apoptotic bodies derived from VSMCs may act as nucleating structures for calcium crystal formation [119].

Treatment of Vascular Calcification

The association between *hyperphosphatemia* and cardiovascular risk has been fairly well established by multiple observational studies, which demonstrate that there is a significant excess mortality over what is age-expected in CKD patients. Hyperphosphatemia stands out as a very significant risk for CVD, and this is not simply because of a decrease in excretion or a failure of excretion; there is also a significant component coming from excess bone resorption. Hyperphosphatemia has been shown to contribute not only to VC but also to LVH, and perhaps to cardiomyopathy. Thus, not only a cardiovascular surrogate (vascular calcification), but also a "hard" cardiac endpoint (cardiac hypertrophy) has been linked to hyperphosphatemia. However, it needs to be remembered that these data only point to an association – there is no unequivocal evidence that reducing serum phosphate levels or otherwise optimizing the management of the disordered bone and mineral metabolism in CKD either slows or reverses VC or even reduces the risk for death or cardiovascular events. Nevertheless, optimizing the management of disordered mineral metabolism, particularly hyperphosphatemia, remains a desirable goal in the care of patients with CKD.

Dietary phosphorus restriction, oral administration of phosphate binders, and dialysis are all relatively effective means by which one may control hyperphosphatemia. Thus, it may be possible to reduce plasma phosphate levels by better dialysis techniques, and by better patient education about diet (and soda drinks, which contain excessive amounts of phosphorous) and phosphate binders. However there is a balance of risk between achieving good phosphate control versus avoiding excess calcium loading. Phosphate binders are the centerpiece of treatment, and the reason for that is that dietary intake cannot really be limited because limitation of intake decreases protein intake. However, in PD patients the possibility to use dialysis fluid with amino acids instead of glucose as osmotic agent allows provision of 25–30% of the daily protein requirement without the delivered phosphate load attendant with oral complex protein may be potentially significant [120].

Sevelamer

As elevated serum calcium and phosphate concentrations are strongly correlated with VC and CVD mortality in ESRD, there is an increased focus on the use of *non-calcium phosphate binders*. One such binder is sevelamer, which has direct actions on the skeleton, and its mechanism of decreasing serum phosphate is more than just decreasing absorption. According to a recent study, sevelamer hydrochloride is well tolerated, controls serum phosphate levels

in CAPD patients as well as calcium- and aluminum-containing binders, and improves the lipid profile in these patients as well [121]. According to results of a recent study in mice, sevelamer may have important actions in decreasing diabetic and uremic vasculopathy and perhaps also be capable of increasing bone formation rates [122]. There is increasing evidence of multiple pleiotropic effects of sevelamer in humans. Nonetheless, a controversy has raged regarding the benefit of sevelamer hydrochloride over calcium-based phosphate binders. Based upon the direct association between VC and daily intake of elemental calcium in cross-sectional studies [11], two randomized controlled clinical trials have been completed among HD patients [123, 124]. Both the trials reported that treatment with non-calcium-based phosphate binder, sevelamer hydrochloride, was associated with significantly slower rate of progression of VC when compared to calcium-based binders. Thus, decreasing Ca and P burdens appear to be beneficial in blocking VC. Use of calcium-based binders is more likely to result in hypercalcemia or oversuppression of PTH – two factors that, as discussed earlier, are likely to worsen VC. It is unclear, however, whether the calcium load from calcium-based binders accelerates VC in the absence of hypercalcemia and/or oversuppression of PTH. Indeed, in one of the two trials there was no demonstrable association between rate of increase in CAC scores and the daily intake of elemental calcium [123]. Furthermore, detractors of the calcium-loading hypothesis suggest that the cholesterol lowering effects of sevelamer, rather than calcium loading from calcium-based binders, may have contributed to the differences thus far reported. A positive association between sevelamer treatment and survival as compared to the use of calcium-containing phosphate binders was recently shown by Block et al. [125]. However, the recently concluded Dialysis Clinical Outcomes Revisited (DCOR) study failed to demonstrate a survival benefit of sevelamer hydrochloride over calcium-based binders, in patients undergoing HD, and therefore this controversy is likely to continue [126]. Further research on the mechanism of action of sevelamer on VC is needed.

Lanthanum Carbonate

Lanthanum carbonate (LC) is another new non-aluminium- and non-calcium-based phosphate binder. Interestingly, an in vitro study showed that it may have anticalcification/antiatherosclerotic properties [127]. Clinical studies have indicated that this compound is well tolerated and effectively reduces serum phosphorus levels [128–130]. There is a need to undertake studies to explore whether the use of lanthanum carbonate attenuates the rate of progression of VC in humans.

Vitamin D

Among ESRD patients, the combination of high phosphate and calcium, and either a high or a low PTH, appears to be associated with the highest risk for mortality compared to normal calcium, normal phosphate, and *high* PTH, which seem to be associated with the lowest mortality [3, 131]. Given the central role of vitamin D and its analogs in the management of secondary hyperparathyroidism, it is important to know the potential role of these agents in the genesis or progression of VC. However, the data regarding vitamin D therapy and VC is rather sparse, although a recent study suggested that there may be differences between vitamin D analogs with regards to their ability to induce VC in animals [132]. There is an inverse relationship between VC and bone density in ESRD [133]. It could be speculated that pathologically low bone remodeling (*adynamic bone disease*) associated with active vitamin D treatment and low parathyroid hormone (PTH) levels may predispose to ectopic calcification of vessels, valves, and heart. This may be of particular importance for PD patients in whom a too effective treatment of hyperparathyroidism may lead to low PTH levels and to adynamic bone disease.

Antihypertensive Drugs

Apart from their effects on blood pressure, antihypertensive agents can influence the development of VC. Nifedipine, a calcium channel blocker, was found to slow progression of CAC in hypertensive patients compared to treatment with diuretics [134]. Furthermore, animal studies have demonstrated that treatment with an endothelin (ET-1) receptor antagonist or angiotensin II blocker, irbesartan, may prevent the increase in pulse pressure as well as VC [135, 136].

Statins

Several clinical studies have reported that hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) may inhibit VC and one of the most interesting pleiotropic effects of statins is thought to be the inhibition of VC. Thus, results from clinical trials suggest an association of statin use with slowed progression of calcific aortic stenosis [137, 138] and CAC [139]. Statins also inhibited calcification of atherosclerotic plaques in experimental hyperlipidemic animals [140]. In one recent study it was shown that statins inhibit phosphate-induced calcification in human aortic smooth muscle cells by preventing apoptosis via restoration of the growth arrest-specific gene 6 (Gas6). The regulation of Gas6 by statins occurs at the post-transcriptional level. Thus, there is ample evidence of a preventive role of statins in VC, which could potentially be of value for the treatment of cardiovascular disease [141].

Role of PD and HD

There are few studies comparing the specific impact of PD or HD as such on VC. However, in one study PD was associated with a lower calcification burden as compared with matched HD patients [142]. There are several factors associated with both dialytic modalities that could play a role for VC. One such factor is that the treatment of the disordered bone and mineral metabolism may be easier with PD than with HD because of the possibility to use dialysis fluid with a lower and more physiological concentration of calcium and the better maintenance of residual renal function in PD versus HD. This may also contribute to an improved steady state control of calcium, magnesium, and phosphate in PD patients. This in turn may allow usage of higher doses of calcium-containing phosphate binders, which could result in better control of phosphate levels without the risk for hypercalcemia. The possibility that PD may allow a better control of serum calcium and phosphate levels may facilitate a more effective suppression of high PTH levels, and this could also be the consequence of a more intensive use of vitamin D. On the other hand, too successful a control of calcium and phosphate and suppression of PTH may increase the likelihood of *adynamic bone disease,* which is thought to be risk factor the development of VC, because excess calcium (which can not be taken up by the adynamic bone) is instead deposited in soft extraskeletal soft tissues such as the vasculature [143].

Another factor in PD that potentially could influence VC is the more efficient control of acidosis in PD as compared to HD, which in some patients may lead to *alkalosis*. Alkalosis has been suggested to contribute to VC by facilitating precipitation of calcium but it is unclear if this really has an impact in ESRD patients. Thus, although alkalosis theoretically could play a role in extraskeletal calcification, there are many other systemic and general factors that potentially predispose to soft tissue calcification in uremic patients, and it is therefore difficult to prove that alkalosis indeed plays a role [144]. Interestingly, there are reports about extraskeletal calcification, particularly extensive peritoneal calcification in PD patients [145], but this could be more related with severe peritoneal fibrosis or sclerosing peritonitis.

Summary

The present review shows that VC is a common problem and is highly correlated with CVD mortality and morbidity in patients with HD and PD. It is therefore important to develop effective therapeutic strategies that may prevent and potentially reverse VC. Several mechanisms, including abnormal mineral metabolism, may contribute to the development of VC in dialysis patients. As PD is an effective therapy as regards continuous control of small solutes such as calcium, it should offer some advantages compared with HD. However, further studies are needed to clarify whether the mode of dialysis therapy plays a role for VC, and how the many specific factors other than the disordered bone and mineral metabolism (Fig. 24.1) that may contribute to VC are influenced by dialysis.

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Chapter 25
Anemia in PD Patients

A. Rastogi, I.C. Macdougall, and A.R. Nissenson

Epidemiology

The prevalence of anemia and the use of erythropoiesis stimulating agents (ESAs) and parenteral iron in peritoneal dialysis patients have consistently been less than that seen in hemodialysis patients [1]. Most relevant data in this area is available from the United States and the USRDS and CMS ESRD Clinical Performance Measures project (CMS CPM project). Trends reported by the USRDS through calendar year 2004 show lower mean hemoglobin, lower EPO doses, and less use of parenteral iron therapy in peritoneal, compared to hemodialysis patients [1]. These facts are reflected in the economic data, only available through 2002. From 1998 through 2002, the annual Medicare payments for ESAs per patient on hemodialysis rose from $4,389 to $6,159, while for patients on peritoneal dialysis the Medicare payments were only $1,839 in $1998 and $3,074 in 2002. Similarly, Medicare payments in 1998 and 2002 for parenteral iron, for hemodialysis and peritoneal dialysis patients respectively, were $772 rising to $1,067 compared to $84 rising to $140 [2].

Although one might conclude from this data that peritoneal dialysis patients *require* less ESAs and iron for appropriate anemia management, this is not necessarily the case. The most recent report of the CMS CPM project (data collected the last quarter of 2004 and first quarter of 2005) shows that despite a similar mean hemoglobin for adult hemodialysis and peritoneal dialysis patients, fewer peritoneal dialysis patients are receiving ESAs (88% versus 95%) or parenteral iron (28% versus 69%). Reflecting the latter, fewer peritoneal dialysis patients are achieving the minimal target iron goals of ferritin >100 ng/mL or Tsat $>20\%$ compared to hemodialysis patients [3, 4]. It should be noted that pediatric patients on peritoneal dialysis, although more likely to receive an ESA than adult peritoneal dialysis patients, have a lower mean hemoglobin, and a greater likelihood of absolute iron deficiency based on ferritin and Tsat values [3]. On the other hand, nephrologists have responded to these data and there has been a steady increase in mean hemoglobin in both the pediatric and adult peritoneal dialysis groups, as shown in Figs. 25.1 and 25.2.

Causes of Anemia in PD Patients

The anemia seen in patients with kidney disease is usually normocytic, normochromic, and is multifactorial in origin with decreased EPO production the proximate and most important cause. In addition, inefficient erythropoiesis because of underlying inflammation and circulating uremic inhibitors of EPO action, decreased RBC survival, iron deficiency, blood loss from frequent blood draws and during dialysis (in hemodialysis patients), and ongoing mild gastrointestinal bleeding all contribute as well. Inflammation also adversely impacts iron metabolism as discussed later. Rarely, bone marrow fibrosis associated with severe secondary hyperparathyroidism also contributes to anemia.

Erythropoietin (EPO) Physiology

The kidney is particularly well suited to be the body's oxygen sensor as it can differentiate between changes in blood flow from changes in oxygenation. It senses and regulates both oxygen tension and extracellular fluid volume. Erythropoietin (EPO) is the key regulator of erythropoiesis. The kidney is the major site of erythropoietin production

A. Rastogi (✉)
Department of Medicine, Division of Nephrology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
e-mail: ARastogi@mednet.ucla.edu

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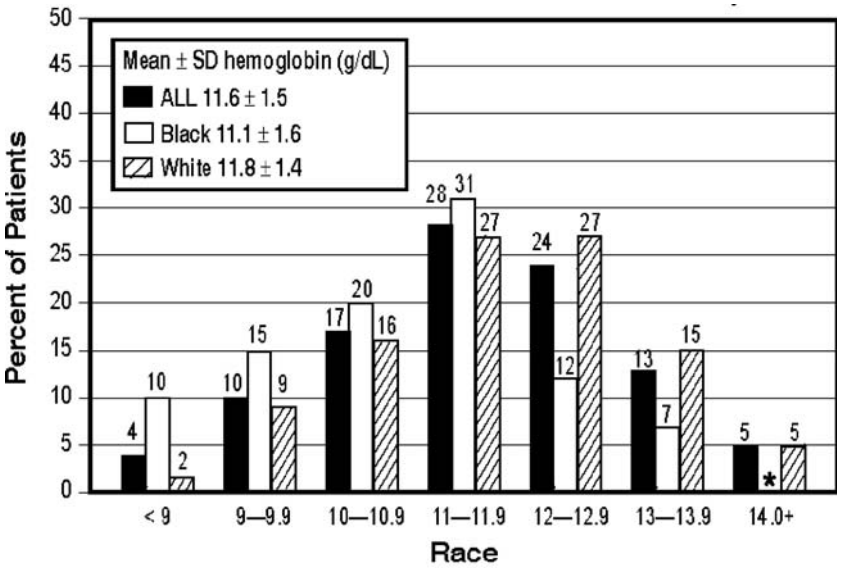
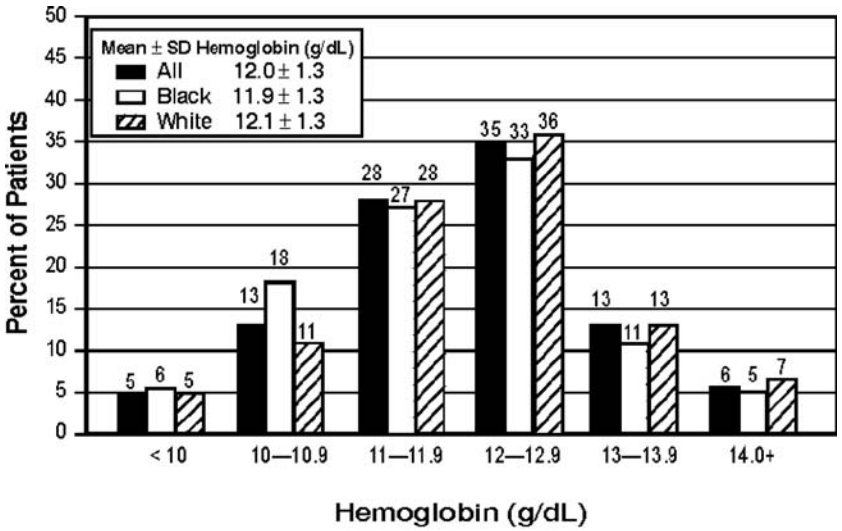


* Value suppressed because n < 11.
Note: To convert hemoglobin conventional units of g/dL to SI units (g/L), multiply by 10.

Fig. 25.1 Distribution of mean hemoglobin values (g/dL) for all pediatric (aged < 18 years) peritoneal dialysis patients, by race, October 2004 – March 2005. 2005 ESRD CPM Project



Note: To convert hemoglobin conventional units of g/dL to SI units (g/L), multiply by 10.

Fig. 25.2 Distribution of mean hemoglobin values for adult peritoneal dialysis patients in the U.S., by race, October 2004–March 2005. 2005 ESRD CPM Project

in the adult human, with the liver making a small contribution (the liver is the major site in the fetus) (Fig. 25.3). Within the kidney, peritubular interstitial fibroblasts (also known as the type I interstitial cell) are the predominant site of erythropoietin synthesis.

EPO belongs to a cytokine superfamily that includes growth hormone, prolactin, interleukins 2 through 7, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage (GM)–CSF, M-CSF, and others [5]. EPO

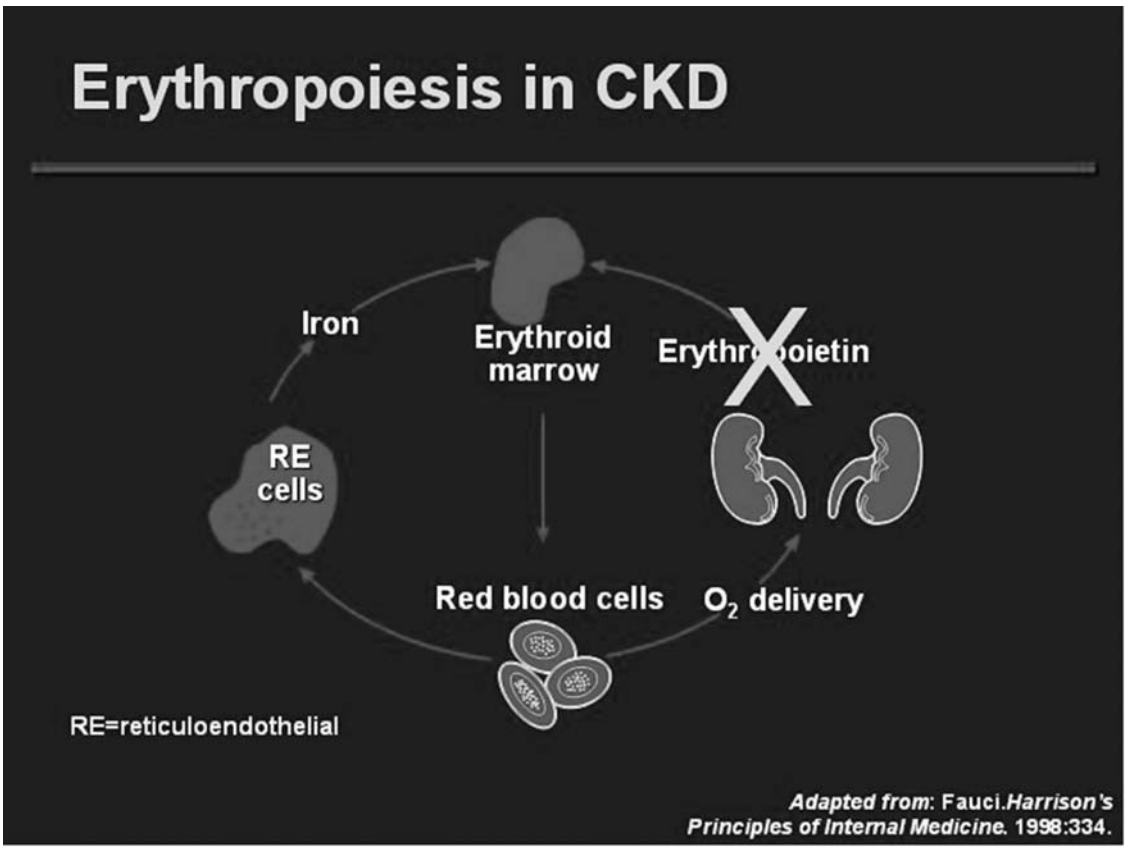


Fig. 25.3 Erythropoiesis in kidney disease

is an acidic glycoprotein with a molecular weight of 30.4 kDa. The peptide core of EPO is made of 165 amino acids with two bisulfide bridges. Carbohydrates comprise about 40% of the molecule in the form of N- and O-linked glycans [6, 7]. The glycans affect the pharmacokinetic profile of EPO significantly. Both the endogenous circulating EPO and the recombinant form have several glycosylated isoforms [8]. The N-glycans are required for the in vivo biological activity of EPO with the terminal sialic acid residues being of special significance [9, 10]. Asialo EPO is rapidly removed from the circulation by the galactose receptors on the hepatic cells [11]. At the same time, addition of N-glycans to recombinant EPO by site directed mutagenesis prolongs the in vivo life of the molecule [12, 13]. It is of interest that the affinity of EPO analogues for EpoR decreases with increasing glycosylation [14].

EPO Gene

Plasma EPO in adults is produced primarily in the kidney, and to a lesser extent in the liver. The expression of EPO mRNA and protein is regulated primarily at the transcriptional level. Hypoxia is the major stimulus for EPO production and is the best understood among other stimuli. The discovery of hypoxia inducible factor (HIF) by Semenza et al. provided further insight into the oxygen sensing mechanism. HIF is a heterodimer composed of α and β subunits. In the presence of oxygen, HIF is inactivated by post-translational hydroxylation of specific amino acid residues within its α subunits. Prolyl hydroxylation promotes interaction with the von Hippel–Lindau protein (pVHL) E3 ubiquitin ligase complex and proteolytic inactivation by proteasomal degradation, while asparaginyl hydroxylation blocks coactivator recruitment. These hydroxylation steps are catalyzed by a set of non-heme Fe(II)- and 2-oxoglutarate–dependent dioxygenases prolyl-4-hydroxylase (HIF-PHD) whose absolute requirement for molecular oxygen confers sensitivity to hypoxia. Only in hypoxic cells can HIF survive, allowing nuclear translocation, ß dimer assembly, and induction (or repression) of gene expression [15–17] (Fig. 25.4).

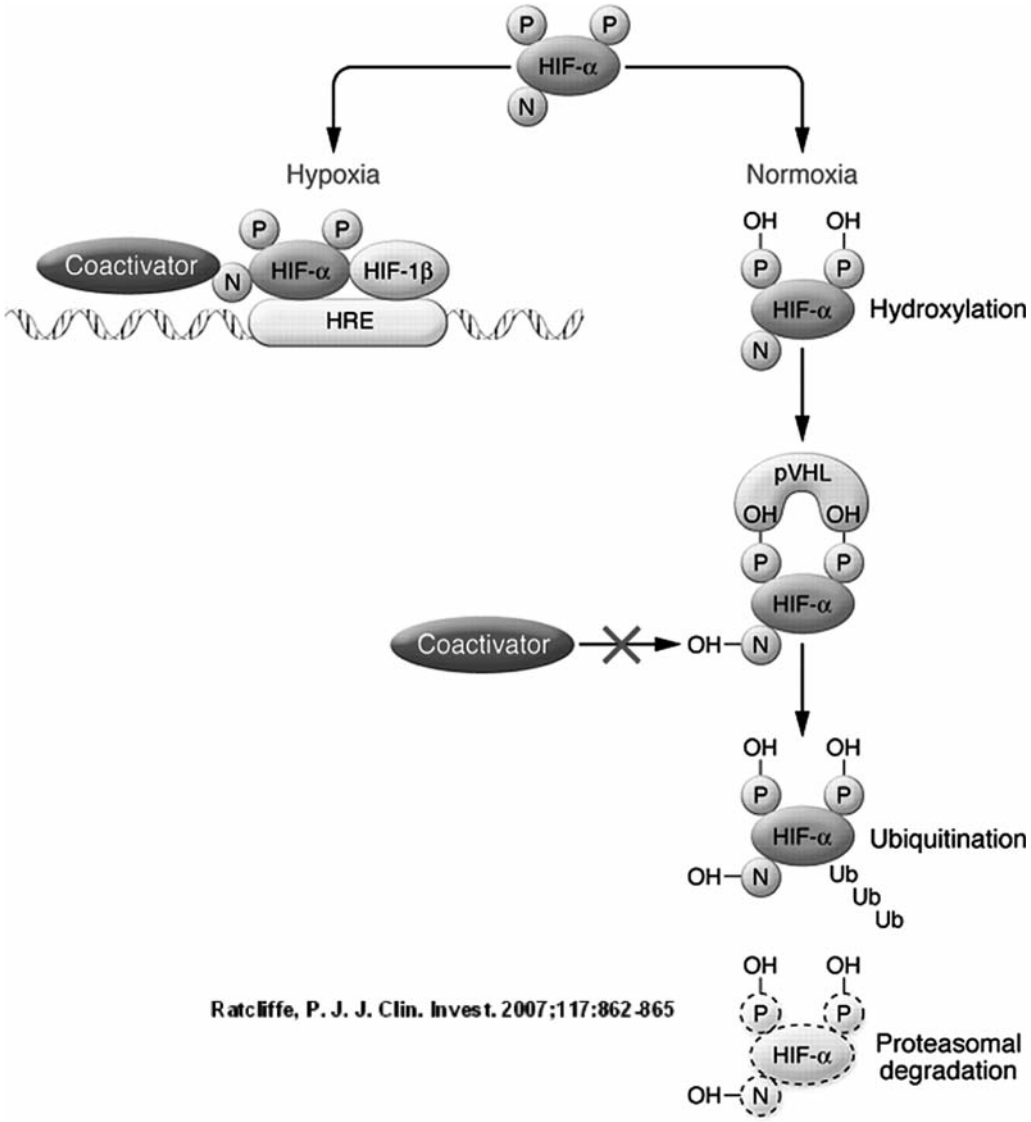


Fig. 25.4 HIF activity under hypoxic and normoxic conditions. In normoxia, hydroxylation at 2 proline residues promotes HIF-α association with pVHL and HIF-α destruction via the ubiquitin/proteasome pathway, while hydroxylation of an asparagine residue blocks association with coactivators. In hypoxia, these processes are suppressed, allowing HIF-α subunits (both HIF-1α and HIF-2α) to escape proteolysis, dimerize with HIF-1β, recruit coactivators, and activate transcription via HREs. N, asparagine; P, proline; OH, hydroxyl group; Ub, ubiquitin.

EPO-R and EPO/EPO-R Interaction and Signal Cascade

EPO-R is a membranous receptor that belongs to the cytokine class I receptor superfamily [18, 19]. It has an extracellular N domain, a single hydrophobic transmembrane segment, and a cytosolic domain. Extensive studies including site directed mutagenesis and X-ray diffraction analysis have shown that EPO has two domains located primarily on Helix C and D, that are required for binding to the EPO receptor (EPO-R) [20–24](Fig. 25.5). X-ray structural analysis of the unliganded EPO-R also shows it to exist as a homodimer. The binding of EPO to the receptor causes conformational changes that bring the two arms of the dimeric receptor close for Janus Kinase 2 (JAK2) to phosphorylate the dimeric partner and set up the signal transduction cascade (Fig. 25.6). As a consequence of this, several tyrosine residues of the EPO-R are phosphorylated and provide a docking site for signaling proteins containing SRC homology 2 (SH2) domains. Phosphatidyl inositol 3 kinase (PI-3 K)/Akt, STAT5, MAP kinase, and protein kinase C are different pathways through which EPO carries out its biological actions. Hematopoietic cell phosphatase (HCP) terminates the effects of EPO by catalyzing JAK2 dephosphorylation. Following dephosphorylation, the

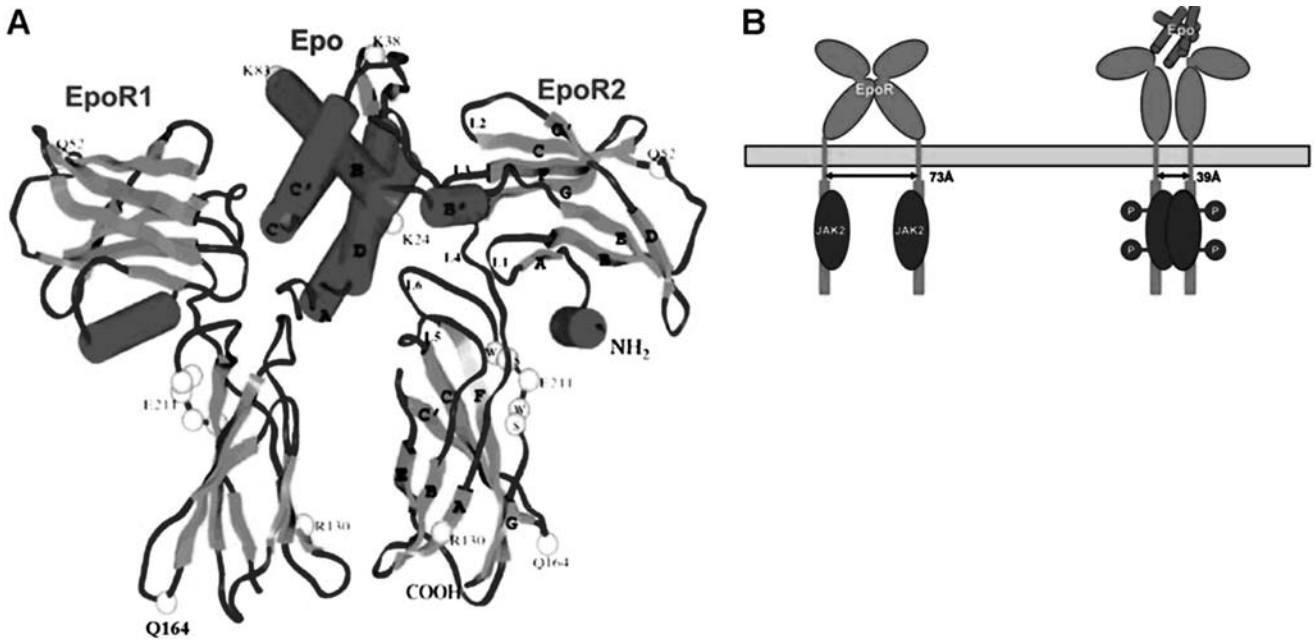


Fig. 25.5 Binding of EPO to its homodimeric receptor and initiation of signal transduction. (**a**) Crystal structure of the complex of EPO with 2 extracellular domains of EPO-R). Red cylinders denote α-helices and green ribbons denote β-sheets. For detailed information on interacting sites in the complex see [136]. (**b**) Schematic representation of the conformational change imposed on the dimeric EPO receptor (Epo-R) upon binding to Epo. The close proximity off the cytosolic domains of the dimeric Epo-R enables autophosphorylation of JAK2 and the initiation of signal transduction. Modified from [137]

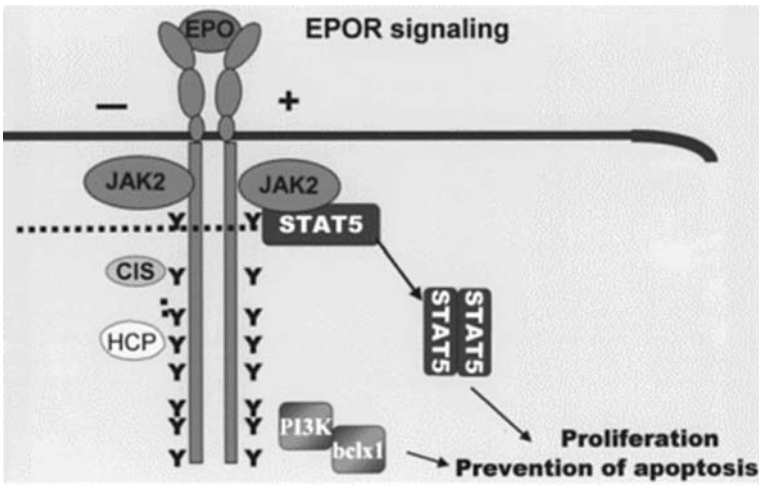


Fig. 25.6 Simplified Scheme of EPO signaling, involving autophosphorylation of JAK2, phosphorylation of EPO receptor, homodimerization of STAT5, activation of PI-3 K, phosphorylation of SHC to form a complex with GRB, SOS and Ras, and the sequential activation of the serine kinase RAF, MEK, and MAPK. This signal cascade results in inhibition of apoptosis and promotion of proliferation and differentiation of erythrocytic progenitors. The EPO/EPO-R complex is internalized and degraded. EPO action is also terminated by HCP which catalyzes the dephosphorylation of JAK2 [25]

EPO/EPO-R complex is internalized. Sixty percent 60% of the internalized EPO is resecreted with the other 40% being degraded intracellularly [25].

Erythropoiesis and EPO

Erythrocytic progenitor cells in the bone marrow are the principal targets of EPO (Fig. 25.7). When the concentration of EPO is low, a majority of the progenitor cells undergo apoptosis with only a small percentage undergoing differentiation and proliferation. The major mechanism by which EPO promotes erythropoiesis is by preventing apoptosis [26]. Burst forming unit-erythroid (BFU-E) is the earliest EPO responsive progenitor. BFU-E gives rise to several colony forming units–erythroid (CFU-E). CFU-E have the highest density of EPO-R on their surface, hence are the most responsive and

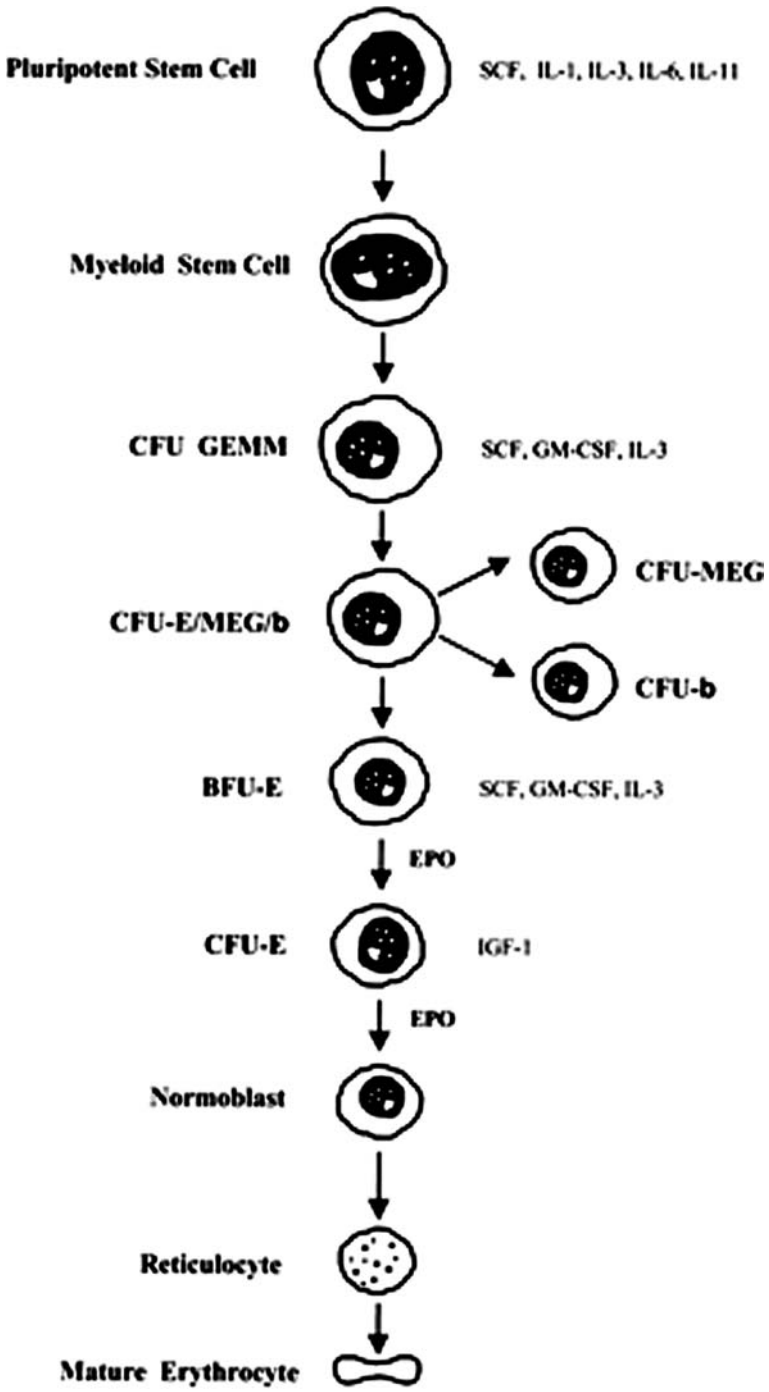


Fig. 25.7 The growth factors that influence erythropoiesis from the pluripotent stem cell to the mature erythrocyte

sensitive to EPO. GATA-1 is an important transcription factor in erythropoiesis and the balance between it and caspase activity largely determines the rate of differentiation and proliferation of erythrocytic progenitors [27–29]. GATA-1 inhibits apoptosis by inducing anti-apoptotic protein bcl-xl [30].

Altered Iron Metabolism in CKD Patients

Iron metabolism in humans has no excretory pathway. Hence, iron homeostasis depends upon regulation of absorption of iron that occurs in the duodenum. There is also recycling of iron from senescent red blood cells. Hepatocytes

and macrophages of the reticuloendothelial system are the major sites of iron storage in humans. Transferrin delivers iron from the gut and also from storage sites to the sites of erythropoiesis.

Iron homeostasis is altered in patients with kidney disease. Transferrin levels are low impairing the transport of iron. In addition, the release of iron from storage sites is also impaired. Finally, there is impaired iron absorption from the GI tract.

The abnormalities of iron metabolism seen in patients with chronic kidney disease are similar to those seen in patients with chronic inflammatory states. These include low serum iron and transferrin saturation and impaired release of iron from storage sites. Chronic kidney disease is now known to be a state of chronic inflammation. It is not surprising, therefore, that CKD shares many similarities with other inflammatory states including elevated circulating levels of inflammatory cytokines such as IL-6 that has been associated with poor response to ESA treatment.

The exact molecular mechanisms for the perturbed iron metabolism seen in states of inflammation and kidney disease have yet to be elucidated. However, there are several newly discovered molecules that have increased our understanding of iron homeostasis [31–33]. Hepcidin, a 25 amino acid peptide that is secreted by the liver is one of them. Hepcidin is a key regulator of systemic iron homeostasis and affects iron metabolism in a number of ways, including inhibiting intestinal iron absorption and iron recycling by the reticuloendothelial system, and preventing iron mobilization from hepatic stores. Hepcidin is an important mediator of the anemia of inflammation and its role in patients with kidney disease is under intense study. Hepcidin regulates iron efflux from enterocytes, hepatocytes, and reticuloendothelial cells by causing internalization and eventual degradation of ferroportin, a membrane-based iron exporter present on most cells. Hence, hepcidin serves as a regulator of both iron absorption and distribution. It is upregulated in response to increased body iron levels or in the presence of inflammation and is downregulated in response to hypoxia, anemia, and oxidative stress. An increase in hepcidin expression during infection or inflammation results in a decrease in iron availability through sequestration of iron by reticuloendothelial cells and decreased intestinal iron absorption. Hepcidin has recently been shown to directly bind to iron, which can be another potential mechanism by which it sequesters iron intracellularly.

It is very important, therefore, to make sure that adequate iron stores are maintained for erythropoiesis in CKD patients. As the iron demand by the proliferating erythroid precursors frequently exceeds iron stores once ESA treatment is started, iron supplementation is almost invariably required to maintain efficient erythropoiesis. The most recent KDOQI recommendations in this regard are shown in Table 25.1.

Table 25.1 Key differences between current guidelines (KDOQI Anemia 2006) and previous guidelines (KDOQI 2000 and EBPG 2004)

Topic	KDOQI 2000 Anemia guideline	EBPG 2004 Anaemia guideline	KDOQI 2006 Anemia guideline	Reason KDOQI 2006 differs from prior guidelines
Definition of Anemia by Hb	<12.0 g/dL in males and postmenopausal females < 11.0 g/dL in premenopausal females and prepubertal patients	<12.0 g/dL males <11.0 g/dL females	<13.5 g/dL males <12.0 g/dL females	KDOQI 2006 uses more recent NHANES data set, defines anemia as any Hb below the 5th percentile for the adult, gender-specific population. Among males, no adjustment is made for age >70 years, to exclude the possibility that pathological conditions contribute to lower Hb values. Among females, the 5th percentile determination is made only among individuals without evidence of iron deficiency, as defined by TSAT <16% or ferritin <25 ng/mL
Target Hb	11–12 g/dL	>11.0 g/dL target >12.0 in CVD not recommended Hb>14.0 g/dL not desirable	≥11 g/dL, caution when intentionally maintaining Hb >13 g/dL	Current guideline reflects QOL benefits at Hb maintained ≥11.0 g/dL, risks when intentionally maintaining Hb >13.0, and recognition that Hb will often exceed 13 g/dL unintentionally, without evidence of increased risk, in patients with Hb intent to treat ≥11.0 g/dL

Table 25.1 (continued)

Topic	KDOQI 2000 Anemia guideline	EBPG 2004 Anaemia guideline	KDOQI 2006 Anemia guideline	Reason KDOQI 2006 differs from prior guidelines
Target Iron Status	TSAT (%) lower limit: 20 upper limit: 50	TSAT (%) lower limit: 20 target: 30–50	TSAT (%) lower limit: ≥20	TSAT: Current guideline reflects unchanged lower bound for iron therapy: upper limit of TSAT not specified
	Ferritin (ng/mL) lower limit: 100	Ferritin (ng/mL) lower limit: 100 target: 200–500	Ferritin (ng/mL) lower limit: 200 HD-CKD 100 non-HD-CKD > 500 not routinely recommended	Ferritin: Current guideline distinguishes HD- from non-HD-CKD on basis of available evidence. Lower limit sets objective of iron therapy. There is insufficient evidence to assess harm and benefit in maintaining ferritin > 500 ng/mL. In HD-CKD, 200 ng/mL reflects evidence for substantial efficacy of IV iron at ferritin < 200 ng/mL
Adjuvants				
L-Camitine	Not recommended	Not recommended for general use	Not routinely recommended	Current guideline based on low-quality evidence which shows lack of efficacy
Ascorbate			Not routinely recommended	Current guideline reflects combination of safety concerns and low quality evidence of efficacy
Androgens		Selective use	Not recommended	Current guideline reflects serious safety concerns. Evidence for efficacy is low quality

Diagnosis of Anemia of CKD in PD Patients

The anemia seen in patients with renal disease is morphologically normocytic, normochromic. EPO levels and corrected reticulocyte count are inappropriately low in these patients reflecting the hypoproliferative bone marrow. Bone marrow examination is usually normal to hypoproliferative and is not routinely indicated to make a diagnosis of CKD-related anemia. In addition, EPO levels should not be measured in order to diagnose anemia of CKD, as they are difficult, if not impossible to interpret.

The diagnosis of anemia of CKD is a diagnosis of exclusion. All the nonrenal causes of anemia should be excluded in a patient with decreased GFR and anemia. The work-up of patients should include red blood cell indices, absolute reticulocyte count, iron panel including serum iron, total iron binding capacity, percentage transferrin saturation and serum ferritin, white blood cell count and differential, platelet count, and testing for blood in stool. The hemoglobin content in reticulocytes can also be assessed. B12 and folate levels in the blood should also be measured.

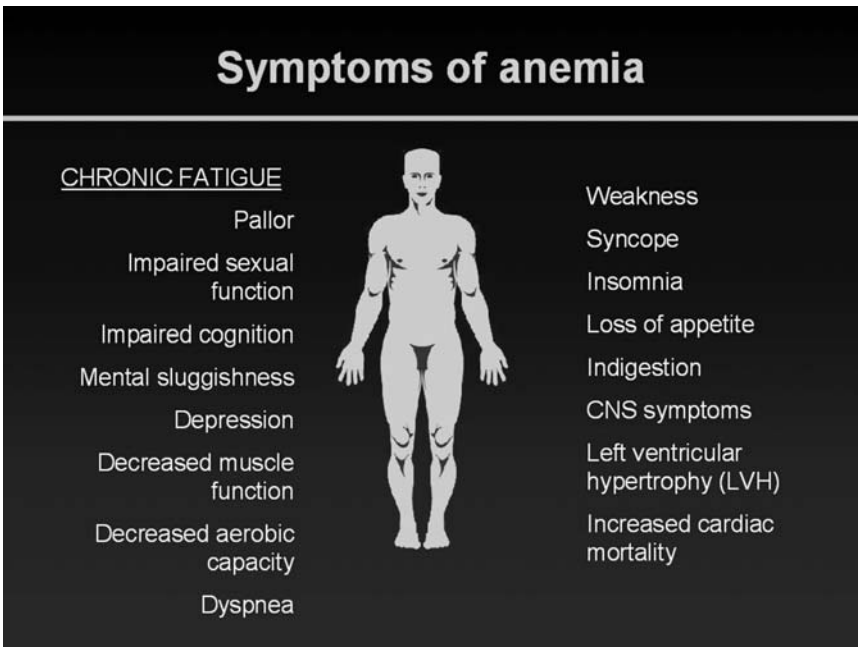
Iron deficiency is a major cause of anemia in CKD patients prior to starting dialysis, and is the most common cause of initial or acquired hypo-responsiveness to ESAs. K/DOQI recommends iron status testing prior to staring ESAs, every month during initial ESA treatment, and at least every three months during stable ESA treatment. The target iron status labs are as shown in Table 25.1.

Clinical Manifestations of Anemia

Symptoms

Patients with chronic anemia develop a constellation of symptoms, not all of which may be present in any one individual. A detailed list of such symptoms is shown in Table 25.2, and the nature of these symptoms will depend on

Table 25.2 Symptoms of anemia



the severity of the anemia, along with various compensatory mechanisms such as increased cardiac output, shift of the oxygen dissociation curve, increase in 2, 3 diphosphoglycerate levels, among other factors. Initially, the patient may be aware of having less energy than previously, with a reduced ability to perform physical activities, such as climbing stairs or walking uphill. These symptoms may manifest themselves at a hemoglobin concentration of around 9–10 g/dL, but there is considerable interindividual variability regarding the threshold hemoglobin level at which these symptoms occur. Once the hemoglobin concentration falls to levels of around 6 g/dL, the patient will often become aware of quite profound fatigue, lethargy, inability to perform even moderate exercise satisfactorily, and breathlessness on exertion. Again, if the onset of the anemia is insidious and slowly progressive, as occurs in patients with concomitant hemoglobinopathies such as sickle cell disease, the previously mentioned compensatory mechanisms may limit the severity of this symptomatology.

Many of the symptoms resulting from the anemia associated with chronic kidney disease were previously attributed to uremia, and it is only since effective therapies became available for correcting this anemia that it has become apparent that many of the symptoms a CKD patient might complain of are in fact due to their anemia and not their uremia.

Clinical Signs

Most patients with a mild anemia (hemoglobin around 9–10 g/dL), may exhibit few clinical signs of this condition, although mild pallor may be present. At lower hemoglobin concentrations of around 5–6 g/dL, the clinical signs become much more obvious, and include a sinus tachycardia, bounding peripheral pulses, increased pulse pressure, forceful cardiac impulse, mid-systolic flow murmur, and evidence of peripheral vasodilatation. Most of these clinical signs arise from the compensatory changes in heart function, causing increased cardiac output as a result of both increased stroke volume and heart rate. Peripheral vascular resistance falls as a result of the vasodilatation, and over time eccentric hypertrophy of the left ventricular muscle develops.

Consequences of Anemia Treatment

The advent of agents able to stimulate erythropoiesis in the late 1980s allowed nephrologists to study the effects of inducing a sustained correction of anemia with maintenance of higher hemoglobin levels, in a way that intermittent and repeated blood transfusions could not. It became apparent fairly early on that there were positive effects on

cardiorespiratory function [34], exercise capacity [34, 35], and quality of life [36]. Reports of additional benefits, such as improved brain and cognitive function [37, 38] and bleeding diathesis [39], soon followed, and it became apparent that the sustained correction of anemia caused improvement in quite a number of physiological systems.

Effects on the Cardiovascular System

As mentioned above, patients with chronic anemia develop various adaptive cardiovascular mechanisms to compensate for the reduced oxygen-carrying capacity of the blood as a result of the low hemoglobin concentration. These include an increase in cardiac output and hypoxia-induced peripheral vasodilatation. The latter condition, with the decreased viscosity of anemic blood, reduces peripheral vascular resistance. In the longer term, the chronic increase in cardiac output leads to a compensatory increase in left ventricular mass that, along with hypertension, contributes to the high prevalence of left ventricular hypertrophy in CKD patients [40, 41]. These changes in cardiac geometry, often a combination of left ventricular hypertrophy and dilatation, in turn, lead to the high cardiac morbidity and mortality in the CKD population. Exercise capacity is also correspondingly reduced [35], partly due to these cardiac abnormalities, and partly due to negative effects of anemia on skeletal muscle function. This can be assessed both by measures of functional capacity and assessments of respiratory physiology, including the maximum oxygen consumption, anaerobic threshold, and the diffusion capacity of the lungs. Many of those effects were previously shown to be reversed following correction of anemia by red cell transfusion [42] and renal transplantation [43], and later by recombinant human erythropoietin [34]. Although many of these older studies were uncontrolled, it is pertinent to note that the striking changes in cardiorespiratory function were achieved by quite large increments in hemoglobin concentration; thus, the mean baseline hemoglobin in the study by Macdougall and colleagues [34] was 6.3 g/dL, increasing to a mean of around 11–12 g/dL. The more recent randomized controlled trials examining correction of renal anemia [44–47] have much smaller increments and involve treating anemia at a much earlier stage in the progression of the disease. The actual differences in hemoglobin concentrations before and after treatment, or between treatment groups, are in the range of only 2–3 g/dL. This fact becomes highly relevant when discussing changes in cardiac geometry before and after correction of anemia. Thus, while many older studies have universally shown improvements in left ventricular mass following recombinant human erythropoietin therapy [34, 48], the pretreatment hemoglobin values are considerably lower than the corresponding values for the more recent negative randomized controlled trials examining left ventricular geometry [45, 46]. Most of the studies examining changes in cardiovascular function following correction of anemia are in hemodialysis patients, but there is no reason to suggest that similar effects are not seen in the peritoneal dialysis population, and indeed the more limited literature on anemia correction in PD patients is consistent with this.

The hemodynamic changes following correction of anemia were first described by Neff et al. [42] and later by Duke and Abelmann [49] long before erythropoietin therapy became available. Both these groups of workers showed that the high cardiac output of anemia was reversed, along with an increase in systemic vascular resistance. The reduction in cardiac output occurs as a result of a fall in both stroke volume and heart rate. These hemodynamic changes have also been shown to occur following correction of renal anemia with erythropoietin therapy [50]. Indeed, one of the side-effects associated with epoetin is hypertension, which in the earliest clinical trials could be severe, and associated with seizures and/or encephalopathy [51]. Several mechanisms have been proposed to explain the pathogenesis of epoetin-associated hypertension, but one of these is an imbalance between the increased systemic vascular resistance and the reduced cardiac output following correction of the anemia. Thus, it may be that in some patients the increase in peripheral vascular resistance was proportionally more marked than the reduction in cardiac output. The increase in whole blood viscosity associated with correction of anemia may also contribute to an enhanced systemic vascular resistance [52].

As evidence began to accumulate on the positive effects of erythropoietin therapy on the cardiovascular system, a number of randomized controlled trials were initiated to examine whether this treatment could impact on cardiovascular morbidity and mortality in CKD patients [44–47]. Quite a few such clinical trials have now been published, but the two largest were in hemodialysis and predialysis stage 3–4 CKD patients [44, 47]. Both of these studies employed two treatment arms with different target hemoglobin concentrations, and both studies did not show improved cardiovascular outcomes at the higher target hemoglobin level. Indeed, and more concerningly, there was a possible increased risk of harm at the higher target hemoglobin level. The Scandinavian multicenter study [53] did include peritoneal dialysis patients, but this study was underpowered for mortality, and did not examine other possible cardiac end-points. The CREATE study [46], which was published in the same issue of *New England Journal of Medicine* as the CHOIR study [47], was conducted in predialysis stage 3–4 CKD patients and showed no difference in cardiovascular

event rate between earlier and more complete correction of anemia versus later and less aggressive treatment of anemia. However, the event rate was lower than predicted, again causing this study to be underpowered for the primary end-point.

The vast majority of anemia correction studies have been conducted in hemodialysis patients. Those that have examined the effect of erythropoietin in peritoneal dialysis patients are usually small and uncontrolled, but the effects seen are generally similar to those reported in the hemodialysis population. There is some evidence that the hemodynamic changes following correction of anemia with erythropoietin may be less marked in the PD population compared to HD patients. Fernandez et al. [54] compared hemodynamic parameters in a group of 25 hemodialysis patients and compared results with a second group of 27 peritoneal dialysis patients. In both groups, there was a decrease in cardiac output and an increase in peripheral vascular resistance, although the changes were more marked in the hemodialysis group.

Noncardiovascular Effects of Anemia Correction

There are many studies documenting a wide variety of secondary effects associated with erythropoietin therapy. Studies on the coagulation and hemostatic pathways, prompted by the early observation of possible increased vascular access thrombosis with erythropoietin in hemodialysis subjects, have documented a reduction in bleeding time, along with changes in platelet function, both aggregation and adhesion to endothelium [55]. The standard coagulation tests are unaffected by erythropoietin, as are measurements of the coagulation factors. However, a prothrombotic state may develop due to increased blood viscosity [52], reductions in protein C and protein S levels [56], and increases in thrombin-antithrombin III levels [57], factor VIII-related activities [58], and plasminogen activator inhibitor-I production.

The hematocrit is the major determinant of whole blood viscosity [52], and thus an erythropoietin-induced increase in red cell mass inevitably causes an increase in blood viscosity. Furthermore, the relationship between hematocrit and blood viscosity is exponential, such that a linear increase in the former results in a disproportionate increase in the latter [52]. Detailed rheological studies have indicated that the increase in blood viscosity occurs solely as a result of the larger quantity of circulating red cells, without any change in plasma viscosity or the rheology of the red cells themselves in terms of their deformability or aggregability [56].

Objective assessments of quality-of-life parameters [36, 59] and of brain and cognitive function [37, 38] have also shown improvements following erythropoietin therapy. Patients report subjective improvement in memory, concentration, and other higher cerebral functions. Electrophysiological studies have shown an increase in amplitude of the P3 component of the brain event-related potential [37], and higher scores in various neuropsychological tests have been recorded. These findings suggested that anemia may be an important factor in the etiology of uremic brain dysfunction.

Impaired sexual function is common in dialysis patients; in females, this is manifest by anovulation, amenorrhoea, and infertility, while in males, erectile dysfunction, reduced libido, oligospermia, and gynecomastia are often present. Erythropoietin therapy has been shown to improve libido, potency, and sexual performance in males [60, 61], and a return of regular menstruation and even pregnancy [62] have been reported in female dialysis patients. These effects may be partly mediated by changes in prolactin or testosterone levels, since reductions in the former and increases in the latter have been found following erythropoietin treatment. Other diverse endocrine effects that have been reported in association with erythropoietin include suppressive effects on the renin-angiotensin system, the pituitary-adrenal access, growth hormone levels, glucagon, gastrin, follicle stimulating hormone, and luteinizing hormone, while there are reported increases in plasma insulin, parathyroid hormone, and atrial natriuretic peptide [63].

Anemia correction also appears to have effects on the immune system. Levels of circulating cytotoxic antibodies progressively decline in patients receiving erythropoietin therapy [64], and this effect is only partly due to the avoidance of blood transfusion. There is an increase in immunoglobulin production and proliferation of B cells, and an enhanced seroconversion response to hepatitis B vaccination [65]. Phagocytic function in neutrophils is also increased [66]. Uremic pruritus is lessened following commencement of erythropoietin therapy, possibly due to a reduction in plasma histamine concentrations [67]. The nutritional status of patients treated with erythropoietin has also been shown to improve.

Specifically in peritoneal dialysis patients, Lubrich-Birkner et al. [68] examined the effects of erythropoietin therapy on dialysis efficiency, and more specifically ultrafiltration, in a group of 14 PD patients. Ultrafiltration improved from 0.70 ± 0.22 to 1.03 ± 0.47 mL/min following a 4-h dwell time with 1.5% glucose dialysate solution ($p < 0.03$). The authors postulated that this increase in peritoneal ultrafiltration might be due to enhanced mesenteric perfusion resulting from improved cardiac function following correction of renal anemia.

Management of Anemia in Patients on PD

Available Practice Guidelines

Following the introduction of erythropoietin therapy, along with an increased realization of the importance of iron management in CKD patients, a number of clinical practice guidelines have been developed both nationally and internationally (Fig. 25.8). Along with guidance on how to manage patients showing a suboptimal response to ESA therapy, the use of adjuvant treatments, and the management of complications such as pure red cell aplasia, these guidelines mainly focused on the use of ESA and iron therapy. Probably the most contentious issue to be discussed in these documents, however, was the appropriate target hemoglobin range that nephrologists should aim for. Thus, while ESA therapy could allow CKD patients to achieve completely normal hemoglobin concentrations, similar to the general population, there has been a concern from the very beginning that this may not be appropriate or cost-effective in CKD patients, and may even be harmful. Discussions about target hemoglobin concentration have gone full circle over the last decade or so, with the original DOQI Guidelines in the United States suggesting a target hemoglobin concentration of 11–12 g/dL. In 1999, the first edition of the European Best Practice Guidelines for the Management of Anemia in Chronic Renal Failure was published, with an open-ended target hemoglobin concentration of > 11 g/dL. In the same year, the Canadian Society of Nephrology published a recommended target hemoglobin range of 11–12 g/dL, in line with the earlier DOQI Guidelines. The Australians produced the "Caring for Australians with Renal Insufficiency" (CARI) Guidelines in 2000, suggesting different hemoglobin target ranges for patients with and without cardiovascular disease (11–12 g/dL for the former and 12–14 g/dL for the latter). The US K/DOQI Guidelines were revised in 2001 [69], but the target hemoglobin range remained at 11–12 g/dL. Both the Australians in 2003 and the Europeans in 2004 [70] revised their anemia management guidelines, with only minor alterations to their previous versions as regards target hemoglobin. The National Institute for Clinical Excellence (NICE) in the U.K. published their CKD Anemia Management Guidelines in 2006 [71], and this included a recommended target hemoglobin range of between 10.5 and 12.5 g/dL. In the same year, the U.S. K/DOQI Guidelines were again revised [72], with a more relaxed hemoglobin target range from previously (above 11 g/dL, with caution maintaining a hemoglobin target > 13 g/dL). The publication of the aforementioned CHOIR [47] and CREATE [46] studies provided an impetus for an unscheduled reconvening of the K/DOQI Anemia Work Group, and this resulted in a retightening of the hemoglobin

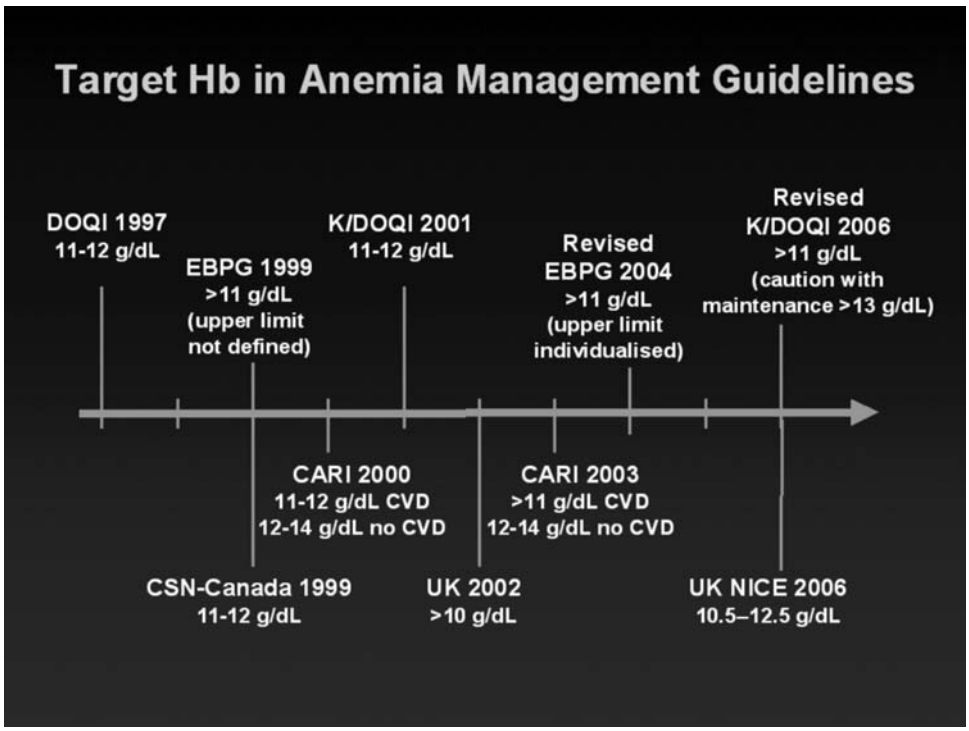


Fig. 25.8 Target hemoglobin in anemia management guidelines

target back to 11–12 g/dL (Clinical Practice Recommendation), with strong advice not to target hemoglobin concentrations > 13 g/dL (Clinical Practice Guideline) [73].

It should be noted, however, that the vast majority of evidence supporting these guidelines comes from the hemodialysis, and more recently the predialysis CKD populations, and there is a paucity of good quality scientific evidence generated from the PD population. Whether these guidelines can be extrapolated to this latter population is a matter of debate, with some authors suggesting that this is indeed appropriate, and others suggesting that the modality of dialysis is one of the factors influencing the choice of target hemoglobin concentration for an individual patient [74]. Part of the rationale for the latter suggestion comes from the realization that fluid shifts are much more constant in the PD population, in contrast to hemodialysis patients in whom the hemoglobin concentration postdialysis may be transiently 2–3 g/dL higher due to hemoconcentration across the dialysis session.

EPO and Other Erythropoiesis-Stimulating Agents

The advent of recombinant human erythropoietin therapy in the late 1980s is without doubt one of the greatest advances in nephrological practice in modern times. The rationale for its use was obvious, given that anemic CKD patients had inappropriately low levels of EPO production in relation to their hemoglobin concentration [75]. The breakthrough that allowed this advance came in 1977 with the successful isolation and purification of human erythropoietin from the urine of patients with aplastic anemia by Miyake et al. [76]. This led to the isolation and cloning of the erythropoietin gene in 1983 [77], which in turn allowed the large-scale synthesis of recombinant human erythropoietin in sufficient quantities to be used in clinical practice. The early clinical trials in hemodialysis patients used intravenous erythropoietin administered thrice weekly [78, 79]. Subsequently, the subcutaneous route of administration was investigated and found to be a practical alternative [80], and this route has become the standard of care for PD patients, predialysis CKD patients, and some hemodialysis populations. In the late-1980s, the intraperitoneal route was investigated as a potential means of administering erythropoietin to patients on peritoneal dialysis. The peak concentrations of erythropoietin were, however, only 2–5% of those obtained with the same intravenous dose, and the bioavailability of intraperitoneally administered epoetin was disappointingly low at 3–8% [81].

The half-life of intravenous epoetin is fairly short, at around 6–8 h [82], and this has implications for the frequency of injections. Thus, if the intravenous route is used (HD patients only), epoetin should be given 2–3 times weekly. The half-life of subcutaneous epoetin is much longer at around 20–24 h. Thus, although many studies have investigated the use of subcutaneous epoetin given 2–3 times weekly, there are also reports of dosing up to once a week, or even once every two weeks in PD patients [83].

Following the introduction of epoetin therapy, approximately 90–95% of patients will respond with an improvement in their anemia. A significant increase in reticulocyte count is usually evident within a few days of commencing therapy, and an increase in hemoglobin concentration is seen by 2–3 weeks. The increase is dose-dependent, and most physicians will aim for an increment of around 1 g/dL per month in order to minimize the risk of adverse effects. Along with the rise in hemoglobin concentration, there is also an increase in red cell count, but no significant changes in the white cell or platelet counts are usually seen. The serum ferritin and/or transferrin saturation will usually decline following the introduction of erythropoietin, since large quantities of iron are used up in the manufacture of new red cells.

Clinical trials of epoetin have compared different routes of administration (e.g., intravenous versus subcutaneous), while others have examined different frequencies of administration. A large randomized controlled study by Kaufman et al. [84], showed that the dose requirements with subcutaneous administration were approximately 30% lower than with intravenous administration. This was confirmed in a large meta-analysis [85]. Although a series of studies have investigated reducing the injection frequency of subcutaneous epoetin, with at least two randomized studies showing dose equivalents of once versus three times weekly dosing [86, 87], it is generally recognized that reducing the injection frequency of this short-acting ESA may result in an increased risk of a dosing penalty, i.e., higher dosages may be required to obtain the same effect as that obtained by more frequent administration.

These results have led to the development of second- and third-generation erythropoietic agents. The first of these was initially called Novel Erythropoiesis Stimulating Protein (NESP), and subsequently called darbepoetin alfa. This agent was created by inserting an extra two N-linked glycosylation chains into the erythropoietin molecule in order to accommodate a greater number of sialic acid residues [13]. It was previously established that the circulating half-life of erythropoietin was dependent on the number of sialic acid residues; isoforms with the largest number of sialic acid residues had the longest half-life [88]. A pharmacokinetic study in 10 peritoneal dialysis patients confirmed this hypothesis, when the mean half-life of darbepoetin alfa administered intravenously was 25.3 h versus 8.5 h for epoetin alfa [89]. The subcutaneous half-life of darbepoetin alfa in this study was around 48 h, although

subsequent pharmacokinetic studies have shown that this may be around 70 h if the frequency of blood sampling is increased [90]. These pharmacokinetic parameters translate into less frequent dosing, and the Phase II and Phase III trials of darbepoetin alfa examined administering this drug once-weekly, or once-every-alternate-week [91, 92]. This frequency of dosing for darbepoetin alfa can correct anemia and maintain hemoglobin concentrations as effectively as 2–3 times weekly epoetin administration. Furthermore, in contrast to that previously described for epoetin, there is no difference in dose requirements for darbepoetin alfa between intravenous and subcutaneous administration [91]. Less frequent dosing schedules of darbepoetin alfa have also been investigated [93], but the scientific quality of all the studies is poor due to their non-randomized uncontrolled design. Thus, at the present time, it remains unclear what proportion of patients can be maintained on once-monthly dosing with darbepoetin alfa, and at what dose penalty, if present.

Other agents have been developed with a view to once-monthly administration. The first of these is Continuous Erythropoietin Receptor Activator (CERA), which is a pegylated form of epoetin beta [94]. To create this molecule, which is approximately twice the size of epoetin at around 60 kDa, a large methoxypolyethyleneglycol polymer chain was integrated via amide bonds between the N-terminal amino group of alanine and the amino groups of lysine (Lys^{45} or Lys^{52}) by means of a succinimidyl butanoic acid linker. This new agent has an even longer circulating half-life of around 130 days for both intravenous and subcutaneous administration, and this has been shown both for healthy subjects and for peritoneal dialysis patients [95]. C.E.R.A. has been investigated using twice-monthly administration in the correction phase of therapy [96], and once-monthly dosing in the maintenance phase of treatment [97]. Details of the receptor binding kinetics and metabolic fate of CERA are emerging, and it is clear that both darbepoetin alfa and CERA have lower affinities for the erythropoietin receptor than either endogenous or recombinant EPO. One hypothesis currently being investigated is that CERA, partly due to its large molecular size, does not undergo internalization at the erythropoietin receptor, and may therefore be available to activate other vacant EPO receptors on the cell surface.

Hematide is also being investigated as a once-monthly erythropoietic agent [98]. This molecule is a synthetic peptide-based ESA, which again employs a pegylation chain to prolong its half-life, and its amino acid structure bears no resemblance to that of erythropoietin. Nevertheless, it shares the same functional and biological characteristics of the protein hormone, being able to activate the EPO receptor and invoke the same intracellular signalling cascade involving JAK2 and STAT-5 pathway [99]. Hematide stimulates red cell production and is now in Phase III of its clinical trial programme. The Phase II data showed that it was able to correct anemia and maintain hemoglobin concentrations with once-monthly dosing in both dialysis and nondialysis patients, with a similar safety profile to that of the existing ESAs. In addition to once-monthly dosing, there are a number of other potential advantages, including those of manufacture (synthetic peptide chemistry rather than recombinant DNA technology involving a cell line), stability at room temperature, and reduced immunogenicity. Since anti-Hematide antibodies do not cross-react with endogenous or recombinant EPO, patients should not develop pure red cell aplasia (see below).

Another class of ESAs is also in clinical development, namely the HIF stabilizers [100, 101]. HIF (hypoxia-inducible factor) is a transcription factor that upregulates EPO gene expression, and this is normally inactivated due to prolyl hydroxylation. Inhibitors of this latter enzymatic pathway have been manufactured, and these are orally active. Phase II clinical trials in CKD patients have shown that the HIF stabilizers can increase the hemoglobin concentration when administered thrice-weekly [101]. Two concerns with this class of agent have arisen, however. Firstly, it is still unclear whether these agents could upregulate erythropoiesis genes including EPO, without significantly affecting other HIF-sensitive genes, such as vascular endothelial growth factor (VEGF). At least 100 other HIF-sensitive genes have been identified to date. Secondly, the death of a female patient from fulminant hepatic necrosis in one of the phase II studies of FG-2216, the first HIF stabilizer, has seriously jeopardized the further development of these agents at the present time.

Many other strategies or approaches to stimulating erythropoiesis are under development or becoming available [98]. These include the emergence of biosimilar EPOs in Europe now that the erythropoietin patent has expired, other EPOs such as epoetin delta (which is manufactured by gene activation technology in a human fibrosarcoma cell line), EPO gene therapy, and different delivery systems for erythropoietin, e.g., inhalation by aerosol. It is too early to predict what impact some of these innovative approaches will have in the management of CKD anemia.

Iron Therapy

Patients with chronic kidney disease are usually in negative iron balance, due to a combination of various factors including poor dietary intake, anorexia, and increased blood loss from the dialysis procedure, repeated blood

sampling, and occult gastrointestinal losses. The latter is exacerbated by the known platelet dysfunction associated with uremia, heparin during dialysis, and aspirin therapy. As a result, CKD patients are commonly iron-deficient, and this may be worsened following the introduction of ESA therapy due to the high requirements for iron caused by new red cell production.

As a result, many CKD patients require iron supplementation, particularly if they are concomitantly receiving ESA therapy [102]. Iron supplementation may be given orally, intramuscularly, or intravenously. The intramuscular route is generally not recommended because of the risk of precipitating intramuscular bleeding, along with concerns about unpredictable bioavailability. Oral iron is simple and cheap to administer, but absorption from the gastrointestinal tract is impaired in uremia due to the action of hepcidin. There is also a high incidence of side-effects associated with oral iron therapy, including nausea, abdominal discomfort, constipation, and diarrhea. Ferrous sulfate is probably the most widely used oral iron salt, and this may be an option for some patients not receiving regular hemodialysis.

Many patients, including almost all patients on hemodialysis, however, require intravenous iron supplementation. There are several iron compounds available worldwide for intravenous use, including iron dextran, iron sucrose, iron gluconate, and iron polymaltose. Intravenous iron may be given as a bolus injection, or as an infusion.

Several randomized controlled trials showed that the efficacy of IV iron is superior to that of oral iron in both hemodialysis [103, 104] and peritoneal dialysis [105] patients. The latter was a prospective crossover trial comparing intermittent intravenous and continuous oral iron supplementation in a group of PD patients, with a 12-month follow-up. Hemoglobin concentrations increased significantly during the intravenous phase compared with each of the oral phases ($p < 0.05$), and similar patterns were seen for both transferrin saturation and ferritin results. Intravenous iron supplementation was associated with a much lower incidence of gastrointestinal disturbances (11% versus 46%, $p < 0.05$), and the authors concluded that administering IV iron every two months in PD patients was better tolerated and resulted in superior hemoglobins and body iron stores compared with daily oral iron therapy [105].

As with the ESAs, there are a number of alternative strategies under development for supplementing iron. These include oral iron products with potentially better absorption from the gut, along with alternative IV iron preparations, such as ferumoxytol, for which a dose of 510 mg can be administered over 17 sec, and ferric carboxymaltose (Ferinject), for which a dose of 1000mg may be administered over 15 minutes.

Other Adjuvant Therapy

Several studies have investigated the potential benefits of administering other adjuvant agents to erythropoietin therapy. Most of the studies are uncontrolled, and/or in fairly small numbers of patients, and thus the evidence in relation to this issue is not particularly strong. Indeed, the revised K/DOQI Guidelines Work Group in 2006 [72] concluded that the evidence for most of these adjuvant agents was not strong enough to recommend their routine use in patients receiving ESA therapy. Nevertheless, there may be isolated instances when one or more of them are appropriate.

Folic Acid Supplementation

Routine folate supplementation is not usually necessary in patients receiving ESA therapy, although some CKD patients, particularly those receiving hemodialysis, are prone to develop folate deficiency as a result of folate losses during dialysis, poor dietary intake due to anorexia, and the occasional use of drugs that interfere with folate metabolism. ESA therapy may also increase folic acid requirements, and may therefore precipitate a folate deficiency. Pronai et al. [106] reported some resistance to epoetin in hemodialysis patients due to folate deficiency, and a clue in this study was the presence of a raised MCV. These patients responded to folic acid supplementation at a dose of 10 mg/day, despite having normal plasma levels of folic acid. Generally, measurements of red cell folate are preferable to serum folate in terms of sensitivity and specificity.

Vitamin B12

Vitamin B12 is another small molecular weight substance that can be lost during dialysis. Nevertheless, B12 deficiency is even less common than folate deficiency, although there is one report in the literature of epoetin resistance due to B12 deficiency which was corrected by giving B12 supplementation [107]. As a result of this case, the authors then screened the remainder of their dialysis population receiving epoetin, and in none of the 30 patients tested was a B12 deficiency found. Thus, although it is important to consider this as a cause of epoetin resistance, particularly if there is an unexplained macrocytosis, there is no indication for routine B12 supplementation in patients on ESA therapy.

Vitamin B6

Vitamin B6 has a role in heme synthesis and in the incorporation of iron into heme. It is less important as a co-factor in erythropoiesis. Vitamin B6 deficiency may occur in dialysis patients as a result of poor dietary intake, impaired metabolism of the active form (pyridoxyl-5-pyrophosphate), losses in the urine (particularly when frusemide is given), and losses in the dialysate. As with iron and folate, it is likely that vitamin B6 requirements will be increased in patients receiving ESA therapy, and this may therefore precipitate a B6-deficient state. Mydlik et al. [108] reported resistance to epoetin due to B6 deficiency, which was corrected by giving B6 supplementation. This may be given at a dose of 100–150 mg/week, and it is also important to realize that a deficiency of vitamin B6 can occur in the red cells despite normal plasma levels of this vitamin as described by Mydlik et al. [108].

Ascorbic Acid

A number of dialysis patients are known to develop vitamin C deficiency, and some authors have advocated routine supplementation in this patient group. Nevertheless, epoetin resistance due to vitamin C deficiency has not been a problem, and the main interest with this vitamin is whether it could have a potential role in treating functional iron deficiency in patients with iron overload. This was first suggested by Gastaldello et al. [109], who treated four hemodialysis patients, all of whom were receiving epoetin and who had a functional iron deficiency despite the presence of iron overload. Administration of IV ascorbic acid improved the response to epoetin dramatically, and the effect was lost when the vitamin C was withdrawn. The response, however, was regained with further administration of vitamin C. These observations were put to the test in a randomized controlled prospective study from Taiwan. Tarng et al. [110] recruited 50 hemodialysis patients with functional iron deficiency on epoetin despite high serum ferritin levels, and randomized them to two protocols, each with a control group. The first protocol consisted of intravenous iron sucrose, 100 mg across each dialysis, for a total of five treatments. The second protocol involved administering IV ascorbic acid 100 mg across dialysis thrice weekly for a total of eight weeks. The patients given intravenous iron showed no response, but those given IV ascorbic acid showed a significant rise in hematocrit, and a reduction in epoetin dose requirements [110]. The serum ferritin levels in these patients showed a progressive fall, the transferrin saturation levels rose, and there was a decrease in the levels of zinc protoporphyrin. The suggested explanation for this effect was mobilization of iron from tissue stores, or increased iron utilization in the erythron.

Vitamin D

Secondary hyperparathyroidism may exacerbate the anemia associated with CKD. Various explanations for this have been suggested, including a direct effect of PTH on erythroid progenitor cell growth, and the development of bone marrow fibrosis. Treatment of hyperparathyroidism by high-dose vitamin D has been shown to improve renal anemia, even in patients not receiving epoetin. Furthermore, high dose 1-alfacalcidol has been shown to augment the response to epoetin, allowing reductions in dosage requirements. Albitar et al. [111] treated 12 hemodialysis patients with high-dose pulsed IV alfacalcidol, and observed an increase in mean hemoglobin from 8.7 ± 1.2 g/dL at baseline to 10.3 ± 0.98 g/dL at three months. Similarly, Goicoechea et al. [112] treated 28 hemodialysis patients with 2 μg of calcitriol intravenously after each dialysis. After 12 months of treatment, 19 patients had shown a significant response, with an increase in mean hemoglobin from 10.6 ± 1.5 g/dL to 12.2 ± 1.5 g/dL ($P < 0.001$). The increase in hematocrit in this study correlated with the decrease in PTH levels, and it was therefore impossible to dissociate a direct effect of vitamin D from the suppression of hyperparathyroidism.

L-Carnitine

Carnitine is a highly water-soluble low molecular weight quaternary ammonium compound that may be lost during dialysis. Its main physiological role is felt to be in skeletal and cardiac muscle metabolism, but it has also been found to have a role in stabilizing the red cell membrane. Thus, carnitine deficiency may induce a shortened red cell survival. Kooistra et al. [113] showed that the response to epoetin correlated with blood carnitine levels, with carnitine-deficient patients requiring the highest doses of epoetin. Labonia [114] treated two groups of patients, one with L-carnitine supplementation for six months, and the other with placebo. No change in epoetin dose requirements was seen in the placebo group, but the patients given L-carnitine had a 38% reduction in epoetin dose compared to baseline ($p < 0.02$).

Androgens

Even before epoetin therapy was available, androgens were used in some patients to enhance erythropoiesis. Unfortunately they were successful in mild cases of anemia only, and it is thought that this may be mediated via an enhanced sensitivity of erythroid progenitor cells to erythropoietin. Several studies have examined androgen supplementation in patients receiving hemodialysis or peritoneal dialysis along with epoetin therapy. Ballal et al. [115] treated 15 adult male hemodialysis patients with epoetin 2,000 units thrice weekly with or without the addition of 100 mg nandrolone decanoate intramuscularly each week. After 12 weeks of therapy, the hematocrit had increased significantly in the group receiving epoetin alone, but there was a much more marked response in the group receiving combination therapy ($p < 0.001$). Similar benefits were seen in a study by Gaughan et al. [116] in 11 male and 8 female patients on dialysis. Two controlled studies have shown discrepant results. In an earlier study, Burns et al. found no difference in response to intravenous epoetin with the addition of intramuscular nandrolone decanoate over a 16-week period, but in another randomized controlled trial in peritoneal dialysis patients [117] nandrolone potentiated the response to epoetin in addition to improving the nutritional status of the patients in the study. There are two concerns about using androgen adjuvant therapy. The first is the high incidence of side-effects, including virilization, hirsutism, voice changes, acne, cholestasis, and hepatic damage. There is also a concern that androgens may increase the risk of prostatic carcinoma. Several nations with limited financial resources have shown some interest in the potential role of androgens in augmenting the response to epoetin.

Other Cytokines/Growth Factors

Although erythropoietin is the major regulator of red cell production, a number of other cytokines and growth factors are known to be involved in this process. Insulin-like growth factor-1 has been shown to stimulate erythropoiesis, and a study in 5/6 nephrectomized mice showed that IGF-1 may augment the response to epoetin therapy [118]. Similarly, a study of interleukin-3 administration to 5/6 nephrectomized rabbits showed some potentiation of the response to epoetin.

ESA Resistance

Patients showing a suboptimal response to ESA therapy should be investigated for an underlying cause. The common causes of hyporesponsiveness are listed in Table 25.3, and a suggested algorithm for investigating this problem is outlined in Fig. 25.9. Thus, the most common causes of a poor response to ESA therapy are iron deficiency, infection/inflammation, and underdialysis [119, 120]. Less common, but still important causes of resistance to therapy, include other hematinic deficiencies such as B12 or folate, bleeding, hemolysis, primary marrow disorders (such as myelodysplastic syndrome), and hemoglobinopathies. Antibody-mediated pure red cell aplasia, although sensationally

Table 25.3 Causes of a poor response to ESA therapy

Causes of a poor response to ESA therapy	
Major	*Minor*
Iron deficiency	Blood loss
Infection / inflammation	Hyperparathyroidism
Underdialysis	Aluminium toxicity
	B_{12} / folate deficiency
	Haemolysis
	Marrow disorders, *e.g. MDS*
	Haemoglobinopathies
	ACE inhibitors
	Carnitine deficiency
	Obesity *(SC EPO)*
	Anti-EPO antibodies (PRCA)

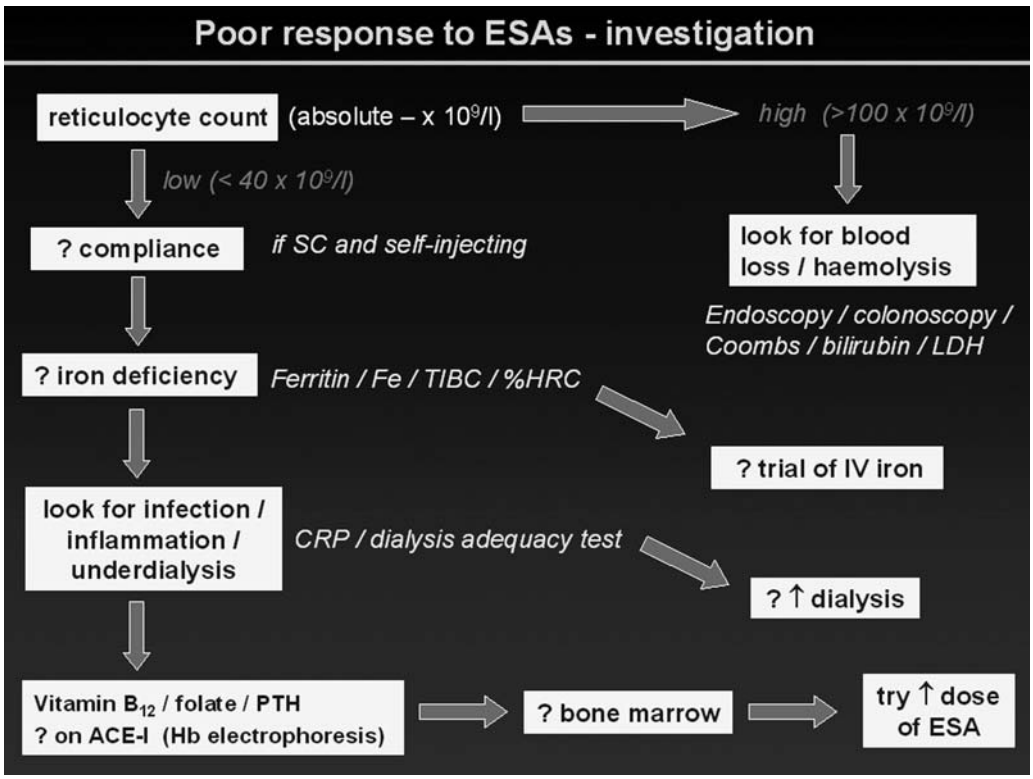


Fig. 25.9 Poor response to ESAs – investigation

highlighted in the literature over the last few years [121], is astonishingly rare, and should be considered only after other more common causes have been excluded.

A useful screening test in any patient showing a less than optimal response to ESA therapy is the absolute reticulocyte count [122]. Although this is not an exact science, patients receiving conventional doses of ESAs generally run reticulocyte counts between 50 and 100×10^9/L. Patients with low reticulocyte counts (e.g., $< 40 \times 10^9$/L) should firstly be evaluated for compliance. At least two studies have highlighted this as a significant problem in peritoneal dialysis patients who are self-injecting their epoetin [123, 124]. Measurement of erythropoietin levels may expose any patient who denies this as a problem. Iron status should then be examined and, if there is any possibility of iron deficiency, then a trial of intravenous iron may be useful. Investigation for underlying causes of infection/inflammation may be indicated if the CRP level is high, and underdialysis should also be considered. Measurement of vitamin B12 or folate levels may be useful in excluding these less common hematinic deficiencies, and examination of the PTH level may exclude severe hyperparathyroidism. Some patients on ACE inhibitors appear to develop some resistance to ESA therapy; this is an individual effect that is not usually seen on a population basis. Hemoglobin electrophoresis may be useful to exclude hemoglobinopathies in certain ethnic groups. If there is still doubt about the response to therapy, then a bone marrow test may be useful, and this may reveal such causes as myelodysplastic syndrome. If all else fails, then it may be appropriate to try escalating the dose of ESA therapy.

If the reticulocyte count is high, particularly if this is above 200×10^9/L, then blood loss or hemolysis are the only possible causes of this. Upper gastrointestinal endoscopy or colonoscopy may be appropriate for examination of bleeding, while a hemolysis screen may include a Coombs' test, bilirubin level, LDH level, and haptoglobins.

Complications of ESA Therapy

ESA therapy is remarkably well tolerated, with a low incidence of adverse effects. Around 20–30% of patients may develop a worsening of their hypertension, but this is usually easily managed by fluid removal on dialysis or increasing the antihypertensive medication. Seizures and/or encephalopathy that were reported shortly after epoetin therapy was introduced [51] are now very rarely seen. Vascular access thrombosis has been associated with the use of epoetin therapy [44], and may be a problem, particularly at high hemoglobin concentrations. There has also been concern

about enhanced thrombogenicity in cancer patients receiving erythropoietin. An increase in composite cardiovascular events was reported in the CHOIR study of predialysis stage 3–4 CKD patients targeting a hemoglobin concentration of 13.5 g/dL compared with a hemoglobin of 11.3 g/dL [47], although this study has been subject to a number of criticisms [125]. Nevertheless, this study, along with the U.S. Normal Hematocrit Study [44] and the Lancet meta-analysis [126] have together accumulated enough evidence to recommend that CKD patients should not target a hemoglobin concentration above 13 g/dL, as recently described in the US KDOQI Anemia Guideline Work Group update (KDOQI Anemia Guidelines 2007 update). Other adverse effects of ESA therapy are much less common, and include hyperkalemia, clotting of the dialysis lines, skin irritation and rash, "flu-like" symptoms following the first few injections, and antibody-mediated pure red cell aplasia [121]. This latter complication is due to the development of antierythropoietin antibodies, which not only neutralize the therapeutic erythropoietin but also the patient's own endogenous erythropoietin, thus causing complete cessation of erythropoiesis in the bone marrow, and rendering the patient transfusion-dependent. The reticulocyte count is extremely low (usually $< 10 \times 10^9$/L), and a bone marrow examination shows very low or absent red cell precursors (usually <5% erythroblasts), but normal white cell and platelet maturation. The white cell and platelet counts are usually normal, although there may be a mild thrombocytopenia. Antibodies against human erythropoietin can be detected by radioimmune precipitation assay or ELISA, and are found to be neutralizing on a bioassay [121].

Complications of Iron Therapy

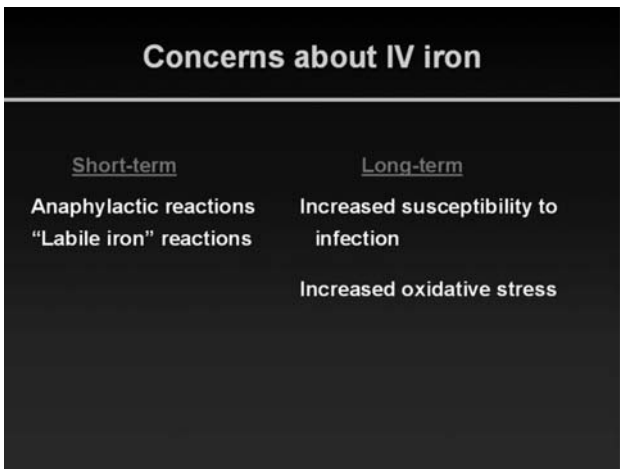
As previously mentioned, oral iron supplementation is generally free of major adverse effects, but side-effects are common, and are usually related to the gastrointestinal tract. Thus, nausea, abdominal discomfort, constipation, and diarrhea have all been reported.

Regarding intravenous iron, there have been some concerns raised about the safety of all IV iron preparations [127], and these can be considered under short-lived acute reactions and potential long-term detrimental effects (Table 25.4).

The administration of IV iron is usually not associated with any immediate adverse effects. Some patients will, however, experience an acute reaction either during or immediately following the administration of iron. Typical reactions are characterized by sudden-onset hypotension, breathlessness, abdominal or back pain, and flushing.

Anaphylaxis may occur with iron dextran, probably mediated via preformed dextran antibodies. The cause of the milder anaphylactoid reactions, which are a characteristic of all IV iron preparations is, however, not clear, but it seems apparent that the latter reactions are generally encountered when too much iron is administered too rapidly. Many patients not receiving dextran-containing IV iron can be rechallenged with a lower dose administered more slowly. The incidence of severe anaphylactic reactions to iron dextran has been estimated to be around 0.7% of patients treated with this preparation, and, although this catastrophic reaction is rare, hospitalization and death may occur. It seems apparent that the non-dextran iron preparations (iron sucrose and iron gluconate) have a lower risk for severe life-threatening reactions than iron dextran. It is, however, very difficult to define the relative rates of reactions with the different iron preparations, and there have been no well-designed, adequately powered comparative studies examining this issue, most of the evidence coming from retrospective analyses of clinical databases.

Table 25.4 Concerns about IV Iron



Another safety concern with IV iron supplementation is related to the risk of infection. Since iron is an important growth factor for bacteria and other infectious micro-organisms, supplemental iron can exacerbate bacterial proliferation. In animal studies, administration of iron has been shown to promote infection. Furthermore, iron supplementation may inhibit important defence mechanisms, such as polymorphonuclear leukocyte function [128]. In short, intravenous iron can potentially enhance bacterial proliferation while reducing the body's ability to fight infection. The supportive evidence for this, however, originates from in vitro studies, while a large multicenter prospective European study did not find any relationship between serum ferritin or iron treatment and risk for infection [129]. Nevertheless, despite the absence of definitive clinical data, it seems prudent to avoid IV iron administration in the setting of acute bacterial infection.

There has been much discussion and debate about the potential of IV iron therapy to induce or exacerbate oxidative tissue injury [130, 131]. Although it is recognized that iron may indeed cause oxidative changes in DNA, protein, or lipids, this should only occur in direct contact between iron and the tissues, and not in iron safely bound in biological complexes such as ferritin, transferrin, and hemosiderin, or when tightly bound in a carbohydrate shell, as occurs with the parenteral iron preparations. Following injection of intravenous iron, however, there may be some release of iron into the circulation, and this free iron may cause a significant increase in oxidative stress. Again, in in vitro studies, Zager et al. [132] found that iron dextran, iron sucrose, and iron gluconate all led to some degree of lipid peroxidation, and, more recently, Leehey et al. [133] found evidence of increased oxidative stress following administration of iron gluconate to CKD patients. These and other studies, therefore, suggest that there is probably some release of free iron into the circulation following injection of IV iron, and that some degree of oxidative stress occurs. What is not clear is whether this oxidative stress leads to any harmful clinical effects, either tissue injury or worse outcomes. CKD patients are exposed to frequent events causing oxidative stress, including the process of dialysis itself. Indeed, in a randomized controlled study, Scheiber-Mojdehkar et al. [134] compared the levels of lipid peroxidation in a group of hemodialysis patients who received and who did not receive intravenous iron across a hemodialysis session. There was a transient increase in peroxide generation in both groups of patients, but the addition of IV iron did not enhance this. With regard to mortality, Feldman et al. [135] examined the incidence of all cause mortality in a large cohort study involving 33,566 hemodialysis patients from Fresenius dialysis centers, using a multivariate model to account for the timing of intravenous iron. There was absolutely no hint of any relationship between the cumulative 6-month iron dose and the probability of mortality in this study. In summary, although nephrologists should be cautious about the potential effects of IV iron in increasing oxidative stress, it is not clear just how much additional oxidative stress is generated by administration of intravenous iron, and whether this has any adverse implications.

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Chapter 26
Chronic Peritoneal Dialysis in the Elderly

E. Grapsa and D.G. Oreopoulos

Commonly, an individual is designated as elderly at 65 years. During the last century, the number of people living beyond age 65 has increased and this will continue increasing. In 1900, only 4% of the Western world's population was over 65 years of age, but now this fraction is 12% and rising [1]. By the year 2040, 21% of the population in the United States will be over 65, and by the year 2050, one in 20 people in the United States will be older than 85 [2, 3]. This progressive increase in the elderly worldwide and the success of dialysis have produced a dramatic increase in the numbers of elderly dialysis patients, described as the "epidemic of aging in RRT" (renal replacement therapy) [4, 5]. Thus, in the United States in the last four years, the United States Renal Data System (USRDS) has noted a continued growth in the number of treated patients but a slowing of the incident rates. More than 100,000 new patients began therapy for end-stage renal disease (ESRD) in 2003 and the median age of the incident population has reached 64.8 years. In 2003, 26,000 people age 75 or greater began ESRD therapy in the United States, and at the end of the year close to 70,000 people of this age group were counted among the prevalent population. Patients aged 75–79 account for 47–50% of both the incident and prevalent populations; one in three elderly ESRD patients is 80–84 years old, and 17–19% are 85 or older [6]. In Canada, in 1989, 35% of ESRD patients were over the age of 65 compared to 25% in 1981 [7]. According to the Canadian Institute for Health Information (CIHI), the most rapidly growing age group is that of patients 75 years and older, with an annual growth rate between 1981 and 1997 of 16.3% [8]. In 1990, in a U.K. dialysis center that provides the sole nephrological service for a population of 1.2 million people, those over 65 constituted more than 25% of all new patients accepted for dialysis [9]. In England in 2000, 28% ($n = 4103$) of dialysis patients were over 65 and 10% ($n = 1465$) were 75 years of age or over [10]. In 1977, only 9% of patients starting renal replacement therapy were older than 65 years; in 1980, 11%; in 1983, 30%; and by 1992 this population had increased to nearly 37% [11, 12]. Thus, elderly patients, who previously were excluded from dialysis, now are the fastest-growing segment of the dialysis population [12, 13]. Similar results have been reported by Jager et al. from six national registries (Austria, Finland, Belgium, The Netherlands, Norway, and Scotland). The percentage of older people among the incident ESRD patients rose from 22% in 1985 to 48% in 1999 and from 14 to 29% among prevalent patient (ERA-EDTA Registry). Overall, the incidence of the 65–74 group increased threefold and the prevalence fourfold over the period 1985–1999, while those in the 75+ age group increased 11- and 12–fold, respectively (ERA-EDTA Registry) [5].

In most countries hemodialysis is the principal form of therapy in the elderly with ESRD [14, 15]. Chronic peritoneal dialysis, while used extensively in Canada, the U.K., and some other countries, has been systematically neglected in others such as the United States. The incident rates of peritoneal dialysis in Australia between 1999 and 2003 fell from 33 to 27% in the group aged 65–74 and increased from 13 to 17% in the group aged 75–84 [16]. As a mode of treatment in the elderly with ESRD [14, 15, 17, 18], renal transplantation and home hemodialysis remain limited and controversial.

Criteria for Dialysis Modality Selection

A dialysis modality for elderly patients can be selected only after a comprehensive evaluation. The choice will be influenced by what is available and by the biases – therapeutic and financial – of the individual nephrologist. When both dialytic modalities are equally available the decision between home peritoneal dialysis (PD) versus in-center hemodialysis (HD) is influenced by many factors, including patients' preference, social considerations such as living conditions and family support, and medical considerations [19–21]. In addition, a number of physiological changes

E. Grapsa (✉)
Alexandra Hospital, Renal Unit, Athens, Greece
e-mail: egrapsa@teledomenet.gr

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associated with aging may influence the choice in these patients [22]. Common in this population [23] are such co-morbid conditions as diminished cardiovascular reserve (clinical or subclinical), and impaired baroreceptor function, all of which may contribute to poor compensatory response to fluid removal with dialysis [24]. The incidence of dangerous arrhythmias is higher in dialysis patients older than 50 years of age [25]. Bleeding diathesis, which is common in the elderly, partly explains the increased transfusion rate in these patients before erythropoietin (EPO) and IV iron were widely used. Thus, elderly patients received a mean of 6.9 ± 0.2 units of blood per year compared with 3.4 ± 0.6 units per year for younger controls ($p < 0.02$) [26].

Vascular disease is also common in the elderly but the literature contains conflicting reports concerning the success and morbidity of the arteriovenous fistula [27, 28] in these patients. The incidence of co-morbid chronic illness increases with advancing age. Thus, 70% of individuals older than 65 have one chronic illness and 30% of these have three or more comorbid conditions [29]. Constipation and chronic diverticulosis, which may complicate the clinical course of older ESRD patients, may be accelerated by the constipating effects of some of their multiple medications [30, 31].

Of the systemic diseases that lead to ESRD in the elderly, hypertension and diabetes taken together account for 40–65% [32, 33].

The selection of dialysis may also be influenced by metabolic characteristics such as chronic bone loss from osteoporosis, a high rate of malnutrition, a tendency to carbohydrate intolerance [13], and alterations in metabolism produced by a variety of drugs. Also, poor tissue turgor and impaired wound healing in the elderly may lead one to select hemodialysis. It must be emphasized that peritoneal dialysis permits home treatment that many elderly people desire. PD can be performed successfully at home even in elderly individuals of advanced age if they have family support or access to a network of medical and social support such as homecare services [34]. Similarly, peritoneal dialysis is also suitable for elderly living in nursing homes [19, 35–40].

Advantages of Peritoneal Dialysis in the Elderly

Chronic PD has a particular place in the management of elderly ESRD patients and is now used worldwide in their treatment. Various authors have recognized the medical and/or social advantages of PD for the elderly [19, 35–40]. Co-morbid diseases such as hypertension, ischemic heart disease, and diabetes are more common in these patients [39]. PD achieves better control of hypertension with fewer antihypertensive medications [41, 42], better fluid balance with minimal hemodynamic stress, and better blood glucose control through intraperitoneal insulin therapy [43]. The anemia of chronic renal failure is often less severe in patients on PD due to lower blood losses, removal of inhibitors of erythropoiesis, and reduced hemolysis. These considerations are important for the elderly with ischemic heart disease and also lead to lower EPO requirements to maintain hemoglobin (Hb) levels at the desired levels [44–46].

ESRD patients may develop cardiac arrhythmias due to such factors as coronary atherosclerosis and advancing age. PD does not seem to provoke or aggravate arrhythmias even in elderly or cardiac patients [47, 48]. Furthermore, this modality does not require a vascular access [49].

Some additional medical advantages of PD for the elderly are better maintenance of residual renal function and a more efficient removal of β_2-microglobulin and middle molecules such as parathyroid hormone [48–53].

Although most older people living in the community are cognitively intact and fully independent in their daily activities, a substantial number report major limitations in activity due to chronic disease. Peritoneal dialysis allows the

Table 26.1 Advantages of peritoneal dialysis in the elderly

Good control of hypertension
Requires few antihypertensive medications
Good fluid balance
Minimal hemodynamic stress
Efficacy of intraperitoneal insulin therapy in diabetics
Good control of anemia; requires less erythropoietin
Good control of cardiac arrhythmias
No need for vascular access
Maintenance of residual renal function for longer periods than hemodialysis
Removal of β_2-microglobulin and other middle molecules such as parathyroid hormone
Home dialysis in a familial environment
Low hospitalization rates

elderly person to be dialyzed at home. Those who live a long distance from a dialysis center, or those who live in a nursing home, also will do better on peritoneal dialysis [36]. Performed by trained home nurses, PD and especially automatic peritoneal dialysis (APD) with the use of a night cycler provides the elderly patient with a convenient, comfortable and safe means of home dialysis in a familiar environment without reliance on family members. Thus, because of all these advantages and its low reported rate of hospitalizations and peritoneal dialysis–related complications, we consider PD to be a successful alternative to center dialysis. Table 26.1 summarizes the advantages of peritoneal dialysis in the elderly.

Disadvantages of Peritoneal Dialysis in the Elderly

ESRD is a severe illness; its treatment requires a change in the lifestyles of both the patient and his/her family, especially in the elderly. Inability to perform self-dialysis, due to dementia, mental impairment, blindness, hemiplegia, and other physical handicaps, is an important relative contraindication of PD when family or social support is inadequate [35, 54]. Some relative contraindications in the elderly are similar to those in young ESRD patients, such as extensive diverticulosis, polycystic kidney disease with very large kidney, low-back pain, peripheral vascular disease, and morbid obesity; any of these might force discontinuation of PD, once started; their impact may be minimized and the patient may continue his/her PD treatment at home by continuous cyclic peritoneal dialysis (CCPD) performed mainly at night [55, 56].

Reduced peritoneal surface area due to adhesions from previous extensive abdominal operations, chronic ostomies, recurrent pancreatitis, and recent aortic prosthesis are major contraindications of PD [57]. PD may exacerbate rather than improve the condition of malnourished patients [58, 59]. One may consider the use of the presternal catheter in patients with tomas, especially in patients who want to be treated at home [60].

Patients on PD who have chronic hypotension, due to poor salt and fluid intake and increased ultrafiltration, may develop ischemic vascular syndromes, particularly of the lower extremities [61].

Nutrition and Adequacy of Dialysis in the Elderly on Peritoneal Dialysis

The impact of malnutrition increases significantly with age. Nutritional deficiencies are due to a combination of social, economic, psychological, and biochemical factors that keep older people from acquiring and assimilating an adequate and balanced diet [62]. Because renal failure impairs the mechanisms that conserve lean body mass, malnutrition is also a common complication of uremia. Potential reasons for this association are an inadequate diet due to anorexia and the excessive catabolism stimulated by uremia [63] and inflammation [64]. Protein calorie malnutrition is frequent among patients treated with HD or PD [65, 66]. Finally, during PD the loss of proteins and amino acids into dialysis fluid, which is accelerated during peritonitis, may increase the likelihood of malnutrition, especially in the presence of an inadequate protein intake [67].

In a multinational/multicenter study, Young et al. observed that the incidence of malnutrition was related to the patient's age, nutritional status at the start of PD, the length of time on PD, and the residual renal function (RRF) [68]. In another study of 937 patients with a mean age of 54 ± 13 years, severe malnutrition, according to a composite nutritional index (CNI), was present in 19% PD patients; there was no correlation between indices of adequacy and serum albumin or CNI [69]. Ross and Rutsky found malnutrition in 20% of elderly and 2% of young PD patients [22], and Tzamaloukas et al. found that nutrition indices are worse in older than in younger PD patients with the same small solute clearances [70]. Older patients reach similar PD parameters (i.e., adequacy and laboratory data) compared to the younger ones while they show higher total fat mass (TFM) (as percentage of total body weight), and stable RRF. Furthermore, elderly patients show a faster deterioration of indices of both inflammation and atherosclerosis and therefore are not able to improve their nutritional parameters with dietetic interventions [71]. Serum albumin correlates negatively with age, the presence of diabetes mellitus, female gender, and peritoneal permeability expressed by D/P creatinine [72]. Cianciaruso et al. reported that calorie malnutrition is also common among regular dialysis patients and that it is more prevalent in the elderly (51% versus 35% in the young); however, they found no difference in incidence of malnutrition between the two dialysis modalities, viz hemodialysis and PD [59]. In a recent study, Ishizaki et al. assessed the nutrition status of elderly patients on PD by subjective global assessment (SGA), creatinine generation rate, serum albumin, and ratio of extracellular fluid to total body water (ECF/TBW) and found that good nutrition status and good clinical outcomes depend on adequate solute removal and sufficient UF [73]. Shimomura et al. reported that the key factor for the poor outcome of dialysis in elderly patients is low dietary protein intake; they

found that a large proportion of elderly PD patients were assigned to the "poor" group, according to a clinical score using serum albumin, hematocrite (Ht), lean body weight (LBW), and serum cholesterol level. Compared with the "fairly well-to-do" and "intermediate" groups, the "poor" group did not show definite differences in the urea kinetic parameters but they had the lowest values of blood urea nitrogen (BUN) and normalized protein catabolic rate (nPCR) (g/kg/day) [74]. These authors also suggested that protein and nutrient supplements can improve the abnormal biochemical and physical nutritional parameters of the elderly. After administration of nutrients they found that the values of Kt/V urea increased simultaneously with increases in nPCR; they also observed a significant positive correlation between Kt/V urea and nPCR in elderly patients [75]. Nolph et al., who reported similar results, found that the relationship between normalized protein catabolic rate (nPCR) and weekly urea clearance, normalized to total body water (i.e., Kt/V), and serum albumin levels, are similar for older and younger PD patients. These authors concluded that poor protein intake in the elderly should not be attributed to advanced age if weekly urea clearances are low. Poor food intake, with mean values equaling only 18% of the recommended daily intake for calories and 34% for protein, have been reported by Boudville et al. among 13 PD patients (age 58.4 ± 13.7 years old). Oral nutritional supplements before a meal seems to increase caloric and protein intake compared with the placebo [76]. Increases in protein intake in response to increases in urea clearances are similar in older and younger PD patients [77]. Mooraki et al. [78] reported similar weekly Kt/V, weekly creatinine clearance (WCC), nPCR, serum albumin levels, and weekly EPO requirements in elderly and in young PD patients.

Cancarini et al. found that nPCR decreased significantly as the patient's age increased ($p = 0.007$) but this decrease was not correlated with time on PD, gender, or serum albumin. Serum albumin did not change as age increased. These authors concluded that long-term PD does not necessarily impair nutritional status, and suggested that the oldest patients can maintain adequate serum albumin concentration with lower protein intake than can younger ones [79]. Abdo et al., who studied adequacy of dialysis and nutritional status of CCPD and CAPD patients, also found a statistically significant inverse correlation between age and nPCR. Kt/V was also lower as age advanced, although this did not reach statistical significance [80]. Russell et al. reported a high incidence of malnutrition among PD patients (59%), as evidenced by anthropometric data. Using subjective global assessment, 49% of peritoneal dialysis patients had scores that indicated some degree of malnutrition; of the malnourished patients, 86% were mild to moderately malnourished, and 14% were severely malnourished (all of the latter were more than 70 years of age). These authors suggest that the first stage of dietetic intervention is determination of the degree of malnutrition; then one will establish dietary requirements accordingly [81].

Quality of Life

Age-Related Quality of Life (ERQoL)

Quality of life is the result of many influences on the individual's personal and social environment. According to the World Health Organization (WHO) quality of life "is the personal perception of an individual of situation in life, within the cultural context and values in which he lives and in relation to his objectives, expectations, values and interests" [82]. It is interesting that, while decline in physical functioning is evident in the elderly, mental health scores show little change [83]. An important component of QoL is depression. More than 10% of elderly persons living in the community show significant symptoms of depression [84]. In most instances, such syndromes are related to physical disability or other life stresses [22]. In another study of older dialysis patients (>70 years) who were depressed, almost half of the depressed patients were also cognitively impaired [85].

Comparison of Quality of Life Between Elderly and Young Dialysis Patients

The quality of life in older people is particularly associated with lack of symptoms, and independent patients on PD tend to have less dialysis-related symptoms and better quality of life than their HD counterparts [86]. The quality of life of older dialysis patients depends on the group to which they are compared. When they are compared with older people without ESRD, elderly dialysis patients report not only significantly greater functional impairment but also significantly more emotional distress, more negative psychological effects, and lower life satisfaction levels [87]. When they were compared with younger people on dialysis (PD or HD), Stout et al. [88] found (on several scales of assessment) that those less than 60 years of age appeared less satisfied with life. In contrast, the elderly group, with and without risk factors, perceived life to be less stressful than did younger patients. These investigators concluded that the elderly had a

good perceived quality of life even when risk factors had been added. The lifestyle of elderly patients on peritoneal dialysis (marital status, family relationships, working ability, sleep, tiredness, appetite, hobbies, sports, friendships, sexual activity, mood, travel, self-management, and happiness) seems to be similar to that of younger patients according to Trbojevic et al. [89]. On the contrary, using the Karnofsky and Campbell Happiness scale, Moody et al. found that patients on dialysis, older than 75 years of age, were less active and less outgoing; however, these older patients perceived their health to be quite good and they took life more positively than did younger dialysis patients. These very old subjects were neither particularly happy nor unhappy [90]. Rebollo et al. using the SF-36 Health Survey, scored and standardized for age and sex, studied patients 65 years and older and compared them with the scores of those younger than 65. They reported that the loss of health-related quality of life (HRQoL) of patients on RRT aged 65 and over was lower than in the younger patients [91]. Octogenarians seem to have similar social functioning and mental health but poorer physical health compared to younger dialysis counterparts [92, 93]. Kadambi et al., concluded that, despite the higher mortality rate and technique failure in the elderly compared to the young patients, the peritonitis rates and most quality of life measures are not different than for younger patients [94]. De Vecchi reported that 29 of 39 elderly patients on CAPD (74%) and 30 of 53 younger patients (57%) considered their lifestyle "acceptable" after 1 year of dialysis. Thirty-four of 39 elderly patients (87%) and 32 of 53 (60%) of the younger patients ($p < 0.02$) rated their physical and social state as better than or comparable to that which they had enjoyed before the onset of terminal uremia [95].

In another study, Muthny and Koch [96] reported that 30% of the hemodialysis patients (age 14–85 years old) were not satisfied with their life in general compared to 17% in the CAPD group (age 22–77 years) and 5% in the transplanted groups (age 17–72 years). On average, elderly patients reported more marked complaints, less general life satisfaction and higher satisfaction with partnership and family life [96]. McDonald et al. reported that the elderly tolerated home dialysis well and were able to maintain their independence with a good quality of life [97]. However, Diaz-Buxo et al. [98] found lower scores among elderly patients in all modalities compared to young patients but those on PD and home HD had a higher score than those on center hemodialysis. Recently, Barendse et al., using the Renal Treatment Satisfaction Questionnaire (RTSQ), reported that although there were no significant differences in total RTSQ scores between the HD and PD treatment groups (mean age 52.8 ± 14.3 years) there was a nonsignificant trend for PD-treated patients to be more satisfied overall; PD-treated patients were significantly more satisfied with regards to discomfort or pain associated with their treatment and more likely to recommend their treatment to others with chronic kidney disease (CKD) [99]. As indicated by Karnofsky score, McKevitt et al. reported a high degree of disability among those over 60 years of age on dialysis. Only 32% of patients scored 70 or over and 33% of patients had mild to severe intellectual impairment on the Pfeiffer Short Portable Mental Status Questionnaire, while 62% demonstrated depressive symptoms on the Beck Depression Inventory [100].

Quality of Life and Family Support

Physical function of PD patients is significantly more impaired in elderly patients with co-morbidity, especially if they have been on PD for long periods [101].

The study of Carey et al. [102] shows the important role of family support among PD elderly patients. These authors found that among PD elderly patients with mild- and high-functioning families, only 9 and 5%, respectively, had been transferred to hemodialysis for psychosocial reasons at 1 year and 21 and 16% at 2 years. On the contrary, in low-functioning families, 67% of elderly PD patients had transferred to hemodialysis by 1 year [98]. Older patients who lost their spouses, and had no adequate family support, grieve for prolonged periods – an experience that predisposes them to a major depression. However, despite the presence of such problems, Ross and Rutsky reported low frequency of depression in elderly dialysis PD patients [22].

Complications in Elderly Patients on Peritoneal Dialysis

Catheter-Related Complications

Among PD patients many complications are related to the catheter, such as early or late pericatheter leak, exit-site infections, cuff extrusion, or herniation at the peritoneal tunnel [103]. Holley et al. found no differences in age with regards to the rate of catheter complications among 411 PD patients, with and without tunnel infections [104]. Others have reported similar tunnel infection rates in young and elderly PD patients [22, 95]. Gentile et al. reported a lower

incidence of complications among the elderly (17%) than among younger patients (21%) [14]. Lupo et al. found that catheter failure was more frequent in younger patients < 40 years old (24%) mainly due to exit-site tunnel infections, while in patients older than 60 years this incidence did not exceed 16% [105]. In another study that compared 103 elderly PD patients with those 18–40 years old, Holley et al. [106] found a lower tunnel-infection rate in the elderly (0.15 versus 0.25 episode per patient-year) compared to the younger group. Similarly, Nissenson et al. [107] found that only 9% of the elderly PD patients required catheter replacement compared to 20% of younger patients; 7% of the elderly had tunnel infection versus 13% of the younger. Contrary to these findings, Tzamaloukas et al. [108] analyzed 120 episodes of peritonitis and found that the variables associated with catheter removal were: advanced age, prolonged duration of peritonitis and coexisting exit-site and tunnel infection.

Hernias

Frequently PD patients develop one or more of several types of hernias such as umbilical, inguinal, incisional (at the site of a previous laparotomy), at catheter insertion, and in the epigastric area [14, 22, 105, 109]. Recently, Garcia-Urena et al. reported that 73% of hernias in patients on PD 67 ± 8.5 years old occur before starting dialysis [110]. Poor tissue turgor is a frequent accompaniment of ageing and conceivably could contribute to an increased incidence of hernia in elderly PD patients. Despite this, several authors have reported a similar frequency of hernia development between younger and elderly PD patients (7.8% versus 9.9%) [14, 22, 105, 111].

Constipation

Constipation is common in any age group of PD patients but may be even more frequent in the elderly. Chronic constipation is associated with an increased risk of bowel perforation in patients with ESRD. Sometimes, bowel perforation is associated with the presence of multiple diverticuli. Lower gastrointestinal bleeding due to diverticulitis leads to fecal peritonitis and may necessitate partial colectomy and cessation of peritoneal dialysis. However, the rate of lower gastrointestinal bleeding seems to be similar in young and elderly PD patients [22].

Lipid Abnormalities

This is common among patients on PD [112–114]. Maiorca et al. reported that, in both women and men, blood cholesterol was significantly higher in elderly patients on PD compared to those on HD. However, they found no significant differences in triglyceride levels between the patients on these two modalities [115]. Panarello et al. [114] reached similar conclusions. Drug therapy of hyperlipidemia with statins seems to be safe in patients on HD and PD with similar median percentage changes for all ages [116, 117]. However the recent 4D study (Die Deutsche Diabetes Dialyse Studie) [118] has cast some doubt about the benefit of treating lipid abnormalities in diabetic ESRD patients.

Peritonitis

The incidence of peritonitis in elderly patients on PD varies among centers from 0.42 to 2.8 episodes per patient-year, depending on the connection system used [38, 95, 105, 107, 119–125] and whether the patients themselves are able to do the exchanges [115]. In a survey of PD in Japan, Kawaguchi found a lower incidence of peritonitis in that country compared to other countries [126]. A multicenter analysis conducted by Imada et al. in Japan demonstrated a peritonitis rate of one episode per 53.4 patient-months (0.22 year). The data were derived from 1428 patients who were treated in 25 dialysis units; each unit managed over 40 PD patients between November 1994 and September 1996 [127]. Dimkovic et al. reported that in peritoneal dialysis patients 80 years and older, peritonitis rate was 1/28.6 patient months, exit-site infection rate was 1/75.1 patient-months and responded well to treatment. However, the incidence of peritonitis was higher among institutionalized debilitated patients (1/5.3 patient-months) [128]. Peritonitis is the main reason for hospitalization of patients on PD [14, 38, 105, 107, 109–121, 129–138].

Several authors [14, 45, 103, 106, 107, 115, 135] have reported no difference in the incidence of peritonitis between young and elderly patients. Among 3,188 patients on various connection systems followed under the USRDS, Port et al. [125] found a significantly higher relative risk (RR) for peritonitis among younger and black patients. Similarly,

Nebel and Finke [133] reported better results in the elderly, but others [22, 95, 124, 125] have found worse results. The distribution of organisms responsible for peritonitis and the therapeutic approach were similar between elderly and young patients [107, 139]. With respect to the bacteria responsible for these infections in all PD patients in Japan, Imada et al. [127] found that the distribution was similar to those from series reported elsewhere in the world [119]; these included *Staphylococcus aureus* (25.5%), *Staphylococcus* sp. (17.8%), and *Staphylococcus epidermidis* (12.5%). Contrary to these observations in 10 PD patients aged 68 years or older, Joglar and Saade [137] found a high incidence of fungal peritonitis (33.3%). As a cause of drop-out among 231 young and elderly CAPD patients, Piccoli et al. [138] found the contribution of peritonitis was similar (21% versus 20%). As a cause of death, peritonitis was more common among patients older than 65 years (2.3%) and among those older than 75 (3.2%), than among those younger than 65 years (1.4%). It is worth mentioning that among 27 patients with encapsulating peritoneal sclerosis in PD, only 3 (11%) were elderly [139].

Morbidity of Elderly Patients on Peritoneal Dialysis

An important element in the morbidity of dialysis patients is hospitalization; such confinement impairs the patient's quality of life and increases the costs of dialysis therapy. Cardiovascular disease, infections – pneumonia and peritonitis, diabetic complications, fluid overload, and gastrointestinal disease – are some of the causes for hospitalization [115, 140, 141]. Admission rates for cardiovascular procedures, particularly stents and angioplasty, tend to increase over time; this is also true for the small percentage of admissions associated with valvular procedures [142]. Admissions for peritonitis have fallen by 38%. For cardiovascular procedures, rates have fallen by 17% for hemodialysis patients but have increased by 12 and 31% in the peritoneal dialysis and transplant populations respectively. And for heart catheterizations admission rates have grown 41 and 12% in hemodialysis and peritoneal dialysis patients, respectively, but have fallen by 22% for those with transplant. The elderly, who have a variety of co-morbid conditions, may require additional hospitalization [142]. According to the USRDS 1998 annual data, the mean numbers of admissions in the older and younger age group are 1.4 and 1.5, respectively. Members of both age groups spent 30 or more days in hospital. In both dialysis modalities, admission rates increased with age. Overall, hospitalization rates among PD patients were slightly higher than for hemodialysis patients in each age group until the age of 65; after this age, PD patients had a lower hospitalization rate. This finding is consistent with trends reported in 1996 and 1997 USRDS reports. In 1996, it was reported that hospitalization rates for PD patients had been falling steadily while those for hemodialysis patients were relatively stable [143]. According to the (2005) USRDS report, hospital admission rates in the elderly are highest in the first 6 months after initiation of dialysis, then fall to almost half the next 6 months. Over the next 48 months, rates remain quite steady in patients with a primary diagnosis of diabetes at 2.2–2.3 admissions/patient/year at risk; rates for those with hypertension or glomerulonephritis remain between 1.9–2.0 and 1.65–1.75, respectively. At 6 months, after day 90 of ESRD, adjusted hospital admission rates for peritoneal dialysis patients are 24% lower than those for hemodialysis patients. As time on dialysis increases, admission rates tend to become similar. As in the non-ESRD population, age is strongly associated with increasing prevalence of dementia among hemodialysis patients. In 2003, incident dementia rates among blacks grew from 1.4% in those age 44–65 to10.3% in patients age 85 and older; among whites the rates were 1.2 and 6.4%, respectively. Dementia rates in peritoneal dialysis patients are much lower than in hemodialysis patients and very low in transplant patients [142].

Many investigators have reported a greater number of hospitalization days per year for the elderly patients (~22 versus 17 days/patient-year) [95, 103, 143–145] compared to younger patients. Among the elderly who cannot do their own dialysis exchanges, the difference becomes greater (44 days/patient-year). However, Wadhwa et al. [146] found lower hospitalization rates and shorter durations of stay (one admission/6 patient-months) among elderly disabled PD patients with home nurses, than among those without such assistance (one admission/4 patient-months). The incidence of hospitalization in patients older than 80 years, was 1/14.7 patient-months and the patients spent 7.5 days in hospital/patient-year [128].

Anderson [119] reported a hospitalization rate of 22.4 days/patient-year among PD patients (age 31–88) ($x \pm \mathrm{SD} = 62.7 \pm 12.8$) living in a nursing home. Gangrenous stump infections and peritonitis accounted for 14 and 10% of admissions, respectively. These complications, along with delirium, hyperglycemia, acute cardiovascular accident events, volume depletion, volume overload, and pneumonia, accounted for 62% of admissions.

After a multicenter study, Malberti et al. reported that the average number of hospital admissions in 1983 was 2,369 for a total of 31,433 hospital days (9.21 days/patient-year); this number increased to 4,295 in 1992 for a total of 49,793 hospital days (9.92 days/patient-year). For each patient, the mean hospitalization days/year is directly proportional to

age at entry, namely 4.6 days/year in those aged 15–24 years, 10.2 in those aged 25–44, 19.8 in those aged 45–65, 31.7 in those aged 65–74, and 34.3 in those over 75 years old. There was no significant difference in the hospitalization rate between males and females. The hospitalization rate of elderly patients on peritoneal dialysis did not differ from that of patients on hemodialysis [145]. Recently, Selgas et al. reviewed eight papers that compared the two dialysis modalities and reported also that the hospitalization rate of elderly people treated by PD is similar to that of those treated by HD [147].

Mortality of Elderly Patients on Peritoneal Dialysis

The risk of death in ESRD patients increases with age and with coexisting diseases [146, 148–152]. Several studies have reported that age, the presence of diabetes, and cardiovascular disease are associated with a shorter survival rate [12, 19, 95, 105, 119, 153–156]. Early (within 90 days) mortality among elderly patients on dialysis increased significantly from 15% for those aged 65–75, to 20% for those aged 79–84, and 30% for those older than 84 years [157]. Most of these deaths were related to comorbid conditions.

The 5-year survival was 15% lower for patients older than 65 years than it was for younger ones in Europe (EDTA Registry 1995) [12]. Two years survival of 47% and 3 years of 39% have been reported by Dimkovic et al. for 31 non institutionalized patients and 7 institutionalized patients older than 80 years on PD. These authors also reported a 91.5% death-censored technique survival at 12 months and 81.4% at 30 months [128]. Munshi et al. found that 1-year survival among elderly people on dialysis (PD and HD) was 53.5% for those $=75$ years old (56 patients), 72.6% for those 65–74 years old (201 patients), and 90.6% for those younger than 65 years (379 patients); the corresponding 5-year survival for these groups of patients was 2.4%, 18.8%, and 61.4%. Among the elderly, 46% had two co-morbid factors at the onset, 26% developed multiple complications while on dialysis, and spent 20% of their time in hospital. Withdrawal from dialysis remained the most common cause of death in this group of individuals at 38% followed by cardiovascular causes (24%) and infectious (22%) [158].

Mignon et al. [19] found 2- and 4-year survival rates of 47 and 25%, respectively, in the elderly. These authors excluded from this analysis those who died before the 90th day of treatment. Salomone et al. [159] reported an increase in 2-year survival for the elderly between the years 1981–1985 and 1986–1992 (54.6% versus 59%, p 0.05). In a review of their experiences over a 10-year period, Lupo et al. [105] found that the elderly over 70 years old on PD had a survival rate of 80% at 12 months, 60% at 24 months, and 40% at 48 months. Age was an independent relative risk of death, independent of cardiovascular disease, diabetes, and neoplasm.

Malberti et al. [145] reported that elderly patients undergoing dialysis (HD or PD) during the period 1983–1992 had a 64% 2-year survival rate, 39% at 4 years, and 13% at 8 years.

In elderly patients the absence of systemic diseases leads to a better Kaplan–Meier cumulative 2-year survival: 75.8% versus 62.5% among those with systemic disease [145]. At the start of RRT, the presence of one or more co-morbid risk factors is associated with a lower cumulative survival rate [155]. Survival decreases as age increases. Thus, the 5-year survival of patients over the age of 65 is 20%, compared to 85% for those aged 15–44 years [155]. Survival of diabetic patients is also influenced by age; elderly diabetic female patients on peritoneal dialysis have a higher mortality rate than younger patients and the death in these patients was attributed mainly to vascular causes [160]. Diabetics over 65 years have a 5-year survival rate of only 10%, compared with 58% for diabetics aged 15–44 years. Compared to those on HD, patients on PD had a 12% lower hazard ratio (0.80) or a 12% increase in survival compared to those on hemodialysis (hazard ratio 1.0), while those in the intermittent peritoneal dialysis group had a 97% increase in hazard ratio (1.97) [155]. Winkelmayer et al. reported a 16% higher mortality rate among elderly patients on peritoneal dialysis in comparison with those on hemodialysis, particularly among those with diabetes, during the first 90 days of RRT a similar mortality between day 91–180 and a higher rate thereafter [161].

Churchill et al. reported a higher 18-month survival for those $=$ 65 years of age in Canada (82%) compared to those in the United States (61.1%) [162]. On the contrary, DeVecchi found that patient survival was significantly worse in the elderly on PD compared to young patients – 12 month 80% versus 90%, 24 month 70% versus 80%, 36 month 46% versus 75%, 60 month 20% versus 60% [95].

The USRDS 1998 annual data reported an overall improvement in survival of dialysis patients. Thus, between 1985 and 1995 [163], first-year death rates for the 65–74-year age group decreased from 40.4 to 30.3 per 100 patient-years of risk. According to the 2005 USRDS report, the cause-specific mortality (starting 90 days after initiation of therapy) shows that across categories of age, gender, and race, mortality rates tend to be high at 6 months and fall, often quite dramatically, over the next 6 months, and then rise steadily during the following 4 years. By age, overall mortality

between months 6 and 12 falls nearly 21% for age 75 and older. Cardiovascular disease, infection, and withdrawal are the most common causes of death [142].

Death rates for dialysis patients 65 years and over are almost twice as high as for those 44–64 years old. Nondiabetic hemodialysis and peritoneal dialysis patients have similar death rates for all cardiac causes. Cardiac arrest accounts for the deaths of 20% of nondiabetic patients on hemodialysis versus 19% of those nondiabetic peritoneal dialysis patients. A larger proportion of diabetic hemodialysis patients (24%) die of cardiac arrest than diabetic peritoneal dialysis patients (20%). A higher percentage of peritoneal dialysis patients, both nondiabetics and diabetics, die of infections (20%) than do hemodialysis patients (16%). A larger proportion of nondiabetic patients on hemodialysis (7%) die of malignancy than do those on peritoneal dialysis (4%) [163].

Cardiac causes – cardiac arrest, acute myocardial infarction, and other cardiac diseases – account for almost one-half of the reported deaths of dialysis patients in all age groups.

Infection accounts for almost one-quarter of all deaths in the 20–44 age group, but only 17 and 14% of deaths in the 45–64 age group and >65-year-old age group, respectively. Of the infection category, more than 75% have septicemia, about 6% have cerebrovascular disease in each age group of all patients, while 1 to 4% of deaths in dialysis patients is attributed to malignancy [164].

One out of every five dialysis patients withdraws from dialysis before death; the overall withdrawal rate was 39 per 1,000 dialysis patients/year. Patients aged 65 years and older have a much higher rate of withdrawal than do younger patients. Almost one-quarter of all dialysis patients aged 65 years and older withdrew from dialysis before death [164].

Comparisons of Hemodialysis and Peritoneal Dialysis in Elderly Patients

Hemodialysis and peritoneal dialysis have been regarded as equivalent replacement therapies for elderly ESRD patients. The outcomes of these two modalities have been compared using mortality rates, hospitalization days, technique survival, complications, biochemical status, clinical status, and life satisfaction [109, 115, 120, 165, 166]. While most of these studies showed no difference in mortality between PD and HD [9, 132, 138, 154, 167], some have described better results for PD than for HD in elderly patients [115, 136, 168]. Age and co-morbid conditions seem to have a statistically significant impact on patient survival but the type of dialysis does not [136]. According to recent studies, mortality rates between HD and PD seems to be similar for the first two years but thereafter the relative risk of death increases for the peritoneal dialysis elderly patients [161, 169]. Elderly diabetic patients on PD appear to have a higher relative risk of death than diabetic patients on HD in the United States, although the comparisons of other cohorts show no difference [168]. Iqbal et al. reported that elderly diabetic patients on PD have better control of blood pressure and maintain residual renal function longer than do similar patients on HD for the first 2 years; mortality in their two groups was comparable [170]. In Canada the survival – at least for the first 2 years – is better in PD than HD for all age groups [155]. In a comparative study from 81 dialysis units in 19 U.S. states with 1,041 dialysis patients (274 on PD and 767 patients on HD), the risk for death for all age groups did not differ between patients undergoing peritoneal dialysis and those undergoing hemodialysis during the first year, but the risk became significantly higher among those undergoing peritoneal dialysis in the second year (RH 2.34). However, after stratification, the survival rate was not different between the two modalities [171]. Twenty-five percent of patients undergoing peritoneal dialysis and 5% of hemodialysis patients switched type of dialysis.

In their 10-year study (1983–1993), Marcelli et al. reported that survival of 895 diabetic patients was similar between the two modalities. In a multivariate analysis that took into account all possible confounding factors – sex, age, pretreatment risk factors such as severe heart disease, severe vascular disease, cirrhosis of the liver, cachexia, and other risk factors such as the presence of malignancy – these authors showed that age, type of diabetes, pretreatment presence of severe vascular disease, and cachexia were independent factors significantly related to survival [172]. However, the modality of dialysis was not an independent significant variable. Among those patients without any baseline risk factors, the mean life expectancy was about 4 years for those 45–64 years of age, 2.2 years for those 65–74 years of age, and 1.8 years for patients older than 75 years [172].

Gentil et al. have reported that elderly diabetics on center hemodialysis have a higher probability of changing to PD, whereas those on PD showed a trend to remain on this treatment [154].

Analysis of the USRDS 1997 report showed that, among younger (<55 years) diabetic patients, mortality rates tended to be higher on hemodialysis than on PD, while the opposite was true among older patients [173].

According to the 1998 USRDS report, even though the average age and proportion of diabetics among new patients has increased steadily each year, death rates during the 5 years on the two dialysis modalities not only did not increase, but instead declined by 12% during 1988–1998 [163].

After reviewing data from the Canadian Organ Replacement Register, Fenton et al. reported that the combined PD group has a 12% decrease in hazard ratio (0.88) or a 12% increase in survival compared to HD – a group hazard ratio 1.0 [155].

In a 10-year follow-up, Maiorca et al. [174, 175] found no difference between the survival of PD and hemodialysis patients; the survival curves were very close for the adults and the differences were nonsignificant for the elderly. Those over 75 years of age had a better survival on PD in the first year of treatment. "Drop-outs" from dialysis, which were higher on PD, decreased with age; patient retention on PD was worse than on hemodialysis for all patients except for the elderly, for whom it was similar. Technique failure was significantly higher on PD and was inversely related to age [175]. Comparison of clinical outcomes in elderly ≥ 67 years old on HD and PD patients, by Collins et al., showed that the elderly on PD had outcomes that were significantly worse than their HD counterparts, even after adjusting basic patient demographics, the co-morbidity index, severity of disease with hospital days, and glomerular filtration rate (GFR) at the time of start of dialysis [176]. In light of conflicting evidence of differential effects of dialysis modality on survival, patients' experience becomes a more important consideration in choosing between hemodialysis and peritoneal dialysis according to Rubin et al. They report that patient satisfaction among 736 patients, who recently started dialysis at 37 dialysis centers, participating in the Choices for Healthy Outcomes in Caring for End-stage Renal Disease (CHOICE) study, is higher on PD patients than those on HD (85% versus 56%) and significantly more likely to give excellent ratings for each specific aspect of care rated (69% excellent versus 30%, respectively) [177]. Kadambi et al. concluded that, despite the higher mortality rate and technique failure in the elderly compared to the young patients, most quality of life measures are not different than for younger patients [94].

Access Methods in Elderly on Hemodialysis and Peritoneal Dialysis

In 122 patients, Kim et al. found that the cumulative survival rate of all peritoneal catheters was significantly longer than the arteriovenous fistula (AVF) survival rate in 172 HD patients: 84% versus 74% at 1 year, 73% versus 61% at 2 years, and 63% versus 48% at 3 years ($p = 0.029$). They saw no differences in peritoneal catheter survival according to gender, age, or diabetes. Compared with AVF, peritoneal catheters survived for a significantly longer period in the male elderly population ($p = 0.0092$) and in diabetic patients ($p = 0.0022$) [178].

Elderly HD patients required more access procedures than did those on PD [45], but more elderly PD patients were transferred to HD [9, 144, 167].

Hospitalization Rates in Elderly on Hemodialysis and Peritoneal Dialysis

The hospitalization rate (days per year) was similar in elderly patients on HD and on PD (31 for HD and 30 for PD) [45]. Benevent et al. [120] reported that elderly PD patients had fewer days in hospital per month of treatment (4.74 ± 0.53 days) but more admissions (2.29 per year) than those on HD (6 ± 2.72 days per month, 1.48 admissions per year).

Malberti found that hospitalization rate was related to age, sex, and presence of systemic nephropathies or malignancy, but not to treatment modality [145].

The USRDS 1998 annual report also recorded a lower hospitalization rate for the PD elderly patients [143]. Peritonitis was the primary cause of hospitalization (31%) in this group; other causes were cardiovascular diseases (22%), neurological symptoms (11%), and technique-related complications other than peritonitis (9%). In the HD group, the main cause of hospitalization was cardiovascular diseases (26%), while other causes were thrombosis of vascular access (15%), technique-related difficulties other than vascular access (12%), and neurological complications (8%) [143].

Habach et al. (found the admission rate per patient-year at risk for peritoneal dialysis patients was 14% higher than the rate for HD patients (RR 1.4, $p < 0.001$), after adjusting for race, gender, age, and cause of ESRD. Admission rate per patient-year was 1.8 HD versus 2.03 PD and hospital days 13.79 HD versus 25.35 PD for patients up to 65 years of age. Similarly, Brunori et al. reported fewer hospital days per patient year for 51 patients on HD > 65 years (17.6 days/patient-year), and 24.0 days/patient-year for 109 patients on PD > 65 years old. The number of admissions per patient-year was 1.8 for HD and 1.7 for PD patients > 65 years old [165].

Among 2,319 older dialysis patients in Georgia and South Carolina between 1982 and 1986 [149], cardiovascular complications (23%) and access-related complications (18.5%) were the most common causes of hospitalization.

Biochemical and Clinical (QoL) Status in Elderly on Hemodialysis and Peritoneal Dialysis

The overall incidence of hypertension in a Japanese series was similar in the two groups (HD and PD) [126] but was higher in the HD elderly [45]; arrhythmias were more frequent in the elderly on HD than among those on PD [113]. The incidence of malnutrition was similar in the two groups [113, 129]. There were no significant differences in levels of blood urea nitrogen, serum creatinine, calcium, or phosphorus [45]. Cholesterol levels were lower and serum albumin levels higher in elderly HD patients [45, 113, 114].

Elderly patients on PD are said to have a better quality of life (QOL) than those on HD [115], but others reported that this feature is similar in the two groups [179]. Diaz-Buxo reported higher QoL scores in elderly patients on PD and home HD, than those on center HD [98]. Finally, Harris et al., in their 12-month prospective study (174 patients) from four hospital-based renal units in London, reported that the elderly, 70 years or older, on PD and HD had similar QoL [180].

Access of the Elderly to Dialysis

Many elderly patients, who are suitable for renal replacement treatment, are not referred for a nephrological opinion and so are denied dialysis [181]. This policy may be responsible in large part for the great difference in the numbers of new patients who present for dialysis in various countries.

Thus, in the U.K. [182], of 16 hypothetical patients (most of them elderly) who were described in brief vignettes, non-nephrologist consultants and general practitioners, on average, considered 6.9 and 7.4 patients, respectively, as unsuitable for dialysis. This figure was significantly higher than the 4.7 patients considered unsuitable by nephrologists.

In the United States, Sekkarie and Moss [183] did a prospective study of 76 primary care physicians and 22 nephrologists and found that the former withheld dialysis from 22% of ESRD patients, compared with only 7% withheld by nephrologists. In deciding not to refer a patient for dialysis, 25% of these primary-care physicians did not consult a nephrologist and 60% cited age as a reason not to refer. (It should be noted that the Institute of Medicine Committee for the study of the Medicare ESRD program explicitly rejected age as a criterion for patient acceptance.)

Nonreferral for dialysis also occurs in Ontario, Canada. Among the physicians who responded to the questionnaire circulated by Mendelssohn et al. [184], 14% of family physicians and 45% of internists indicated that in the previous 3 years they recalled not referring patients for dialysis, who died subsequently with ESRD. These physicians based their decisions on the wishes of a competent patient (94%), short life-expectancy (88%), poor quality of life (87%), and age (64%).

Among physicians, both increasing age and co-morbidity were associated with a greater stated choice of non-referral. Other factors affecting the referral pattern were distance from the dialysis center and overcrowding of the nearest dialysis center. Age increased the nonreferral pattern in all these categories.

Low referral by primary care physicians may be based on inadequate knowledge of the indications for and prognosis of modern dialysis, which then may be imparted unchallenged to the potential patient [185].

In the United States, the expanding role of the primary care physician and the diminishing role of the specialist, a pattern promoted by managed care, will undoubtedly change the practice of medicine in general, and dialysis in particular [183].

In the Canadian study mentioned above, 67% of the physicians believed that health care is rationed in Ontario. We want to stress that the government of Ontario has no explicit policy to ration dialysis among its citizens who require this treatment. Thus, physicians seem to be responding to the government's indirect measures by conducting a form of rationing, something the government, or in the United States, the managed-care organizations, will avoid doing overtly.

In the United States, the health-care providers who compete to obtain the "business" of the various managed-care agencies (business here represented by the illness of patients) have to make a profit by minimizing expenditures in various aspects of their operations. This they achieve mainly by keeping hospitalization rates low and by keeping to a minimum referrals to specialists. This approach falls most heavily on those patients, like the elderly, who require frequent hospitalization and often have multisystem disease, which requires the care of specialists. Nevertheless, the managed-care industry will not acknowledge this approach as policy (hidden rationing) – hence managed-care organizations and their physicians join in a kind of conspiracy against the elderly and all those who may require expensive care.

The existence of this conspiracy is reflected in the vocabulary used. Thus, we talk about managed "care" when in essence we mean managed expenditures. The patients are consumers and the money spent on them represents lost income, and those who are ravaged by disease or old age are considered as financial burdens. Furthermore, we believe that, as has been set out in a 1998 article in *Lancet* [185], with the legalization of assisted suicide and subsequent euthanasia, the elderly with ESRD will be coerced covertly into believing that it is "the right thing to do" and be encouraged to choose "death with dignity" rather than submit to the "indignities of this wretched treatment." Eventually, primary care physicians will fall in line with this "conspiracy" and will do their part: they will stop referring these patients to the nephrologist, as they have started doing already [183].

Another more sinister way of encouraging/enticing primary care physicians to maintain the earnings of the managed-care corporation is the policy of incentives. The more the physician saves the agency, the greater his/her bonus at the end of the year. This policy is sinister because it takes advantage of the greed latent in all of us, and eventually it will undermine the patient/doctor relationship.

What Should We Do?

We will repeat here some of the recommendations Hall and Berenson made to those physicians who want to preserve their patients' trust and be their advocates in a managed-care environment [186]:

(a) Maintain high scientific standards by practicing evidence-based medicine.
(b) Be impartial, i.e., use the same clinical criteria for all patients even when they have different degrees of insurance protection.
(c) Do not enter into any incentive arrangement that is not common use elsewhere, especially one that you would be embarrassed to describe to your patients.

At the same time insurance companies should be encouraged and, if necessary, required by legislation, to describe to prospective clients their incentive policies. Governments should ban and make illegal "gag" clauses that prevent physicians from protesting or revealing what they believe is unethical in these managed-care plans.

Finally when, because of forces beyond our control, we cannot offer a treatment to a new patient, we should tell such patients the unpleasant truth that they are deprived of care because of economic policies of the government or the managed-care organization.

In conclusion, nonreferral of elderly for dialysis does occur in North America and we expect that, in the near future, the elderly will have even greater difficulty in gaining access to life-supporting chronic treatment.

We believe that, in their professional goals, nephrologists should include education of primary care physicians and geriatricians about what dialysis (HD and PD) does and what the dialysis team can offer in terms of life prolongation and quality of life on dialysis.

With a few exceptions, such as the demented patients or the patient who has a life-expectancy of less than 2 or 3 months and the patient who requires restraint before he/she can be dialyzed, all other ESRD patients, after they have been fully informed, should be allowed to decide for themselves whether they want to be dialyzed.

Finally, we believe that physicians (all of us, nephrologists, geriatricians, and primary care physicians) should focus and refocus continuously on our primary goal, that is, on being our patients' advocates. Whenever there is a conflict between our patients' interests and our own, or those of the organization that employs us, the interests of the patients always take precedence.

Dialysis Withdrawal

In the United States, there has been a recent increase in deaths due to withdrawal from dialysis; the percentage of such deaths increased from 9.7% in 1988 to 17.6% in 1996 [187] to 22% in 2002 [142]. Almost all reports confirm that deaths due to dialysis withdrawal are much more frequent among the elderly than among younger patients [188, 189]. Chronic failure to thrive (an outdated term previously used in geriatrics to describe symptoms of dementia, functional decline, and or depression) is the most common reason given for withdrawal (42.9%) followed by the nonspecific "acute medical complications" and "other." The mean age of those who withdrew or used hospice care, among 115, 239 deceased patients, in the USRDS 2001–2002 report, was about 74 years [142]. With the anticipated increase in the number of elderly patients on dialysis, nephrologists are encountering the issue of withdrawal with increasing frequency [190]. Data from the U.K. indicate that, in the very old (≥ 75 years), withdrawal from dialysis remained

the most common cause of death (38%), followed by cardiovascular causes (24%) and infections (22%) [158]. Also, in Canada, withdrawal from dialysis is high (30% of all deaths) among the very old people [128]. Discontinuation of dialysis in a French cohort of 1,436 patients was also high (20,4%) and was the most common cause of death. These patients had a significantly higher rate of dementia (17.5% versus 6.4%), poor general conditions (55% versus 15%) and were dependent for daily activities compared to patients who died from other cause, but they were not different in age, sex, duration of treatment, and dialysis technique. The decision to stop dialysis was made most often by a physician (77.5%) [191]. In another French study, Clement et al. reports that although the main reasons for refusing dialysis in the elderly, were cognitive disorders, severe dementia, and irreversible neurological conditions, none of these factors where actually *found to be in and of themselves decisive*. Refusing or discontinuing dialysis is an accepted practice of the nephrologists in one region of France [192].

Patients who die following withdrawal from dialysis may be divided into two main categories: a) those with decision-making capacity and b) those without decision-making capacity. Sekkarie's prospective study [183] showed that 37% of those who died after withdrawal from dialysis lacked decision-making capacity.

When he/she is capable of making the decisions to withdraw, the patient decides that the quality of life on dialysis is not acceptable and eventually the nephrologist has to comply with the patient's wishes. Here, the patient's right to autonomy overrides all other ethical principles.

On the other hand, the patient who has lost his/her decision-making capacities poses more difficult ethical and legal problems. An important factor in the management of this group is the presence (or not) of an advance directive and/or the designation of a surrogate decision maker.

Despite all efforts to encourage them to sign advance directives, only 20% of patients in the United States have completed an advance directive [193]. A survey in Pittsburgh showed that many patients were unwilling to sign an advance directive; 50% of these said they feared that, by signing a living will, they might influence the subsequent conduct of their physicians [193]. This lack of trust is particularly prominent among black patients who receive their care from a predominantly white medical profession [186]. Why this lack of trust? What aspects of our practice or behavior convince our patients that we will not act in their best interests when they are no longer able to decide for themselves [194].

What should we do for the 20% of patients who, in their advance directives, indicate that they want dialysis to be continued if they lose their decision-making capacity, or for the patients without advance directive whose families request the continuation of dialysis? We believe that, when we encourage a patient to give an advance directive, we enter into a contract that commits us to respect and follow their wishes, whatever is decided. However, it seems that, although we are prepared to follow such wishes if patients ask for discontinuation of treatment, we do not know what to do, and become uncomfortable when they ask for continuation of treatment. If patient autonomy is the primary ethical principle behind such decisions, one should continue dialyzing these patients even if the health-care team believes such treatment is futile. However, in increasing numbers, nephrologists are acknowledging that they find it difficult to follow through when an advance directive clashes with their own beliefs [195]. For example, if they believe that continuing to offer medical care to a patient in a persistent vegetative state (PVS) is futile and offends their moral integrity [196].

We believe that resolving such ethical dilemmas requires patience, understanding, and compassion. In North America, societal attitudes and principles seem to be changing from a model that gives primacy to the principle of patient autonomy, to a community-based model that values societal objectives and the common good above the wishes of the individual, as eloquently described by Callahan in his book *Setting Limits* [196–199]. Arnold Eiser believes that, under these new circumstances, the community shall (should) have the capacity to set, develop, and administer guidelines concerning such problem areas of decision making [196]. The communitarian perspective holds that the community has an interest in assisting the profession of medicine to maintain its integrity and will not compel it to provide nonbeneficial futile medical care [196]. An additional benefit of such a policy is that it saves money; for example, the cost of care for those who have completed an advance directive to discontinue treatment is less than one-third the cost of those without such a directive [200].

We disagree with this approach and believe that under these circumstances advance directives would lose their force and meaning.

The main risk in adopting the communitarian approach is that some individuals, who believe that they should continue being dialyzed for religious reasons (such as Orthodox Jews and some Catholics) may conclude that they are being discriminated against; but worse [201, 202], this approach may be used predominantly for economic reasons. In conclusion, we believe that the expected dramatic increase in the numbers of elderly who suffer from ESRD in the next decade will bring into play economic pressures that will make death due to withdrawal from dialysis an increasingly common event [203, 204].

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Chapter 27
Long-Term Peritoneal Dialysis Patients

Changes in Membrane Structure and Function

O. Devuyst, R. van Westrhenen, and N. Topley

Peritoneal dialysis (PD) has now been utilized for more than 25 years as a first-line therapy for the treatment of end-stage renal failure. It is now accepted that patient survival on PD is similar to hemodialysis when comparable analyses are made [1, 2]. As we have gathered new knowledge over the past decade, however, about the potential complications associated with long-term therapy, such as structural and functional alterations to the peritoneal membrane and end-stage sclerosing syndromes such as encapsulating peritoneal sclerosis (EPS), there remain legitimate concerns as to whether this mode of therapy can provide adequate treatment for end-stage renal disease in the longer term [3]. Despite advances in treatment guidelines there still remains in PD a considerable dropout rate in the early years of therapy, due mainly to infective episodes and membrane dysfunction [4].

There has been a considerable increase during the past few years in our understanding of the physiology of peritoneal transport, and the basic pathophysiology of the peritoneal membrane during PD [5–8] and those factors that impact on it during the therapy (Fig. 27.1). This understanding has gone hand-in-hand with (and to some extent driven by) the development and utilization of a new generation of "biocompatible" dialysis solutions whose design has been based on rational improvements in their physiological nature [9–13]. The sum of this research and developmental endeavour has been a much greater understanding about the pathophysiology of the dialysis process and both its local (in the peritoneum) and systemic consequences as well as a clearer view of how inflammatory processes that are driven by infective events or by exposure to dialysis solutions impact on the peritoneum during its life as a dialyzing organ (Fig. 27.1). Central in these findings have been significant advances based on improved basic science knowledge (and its application from other organ systems) and careful clinical observation of the precise histopathological changes in the structure of this membrane that occur as a result of uremia and how these are modulated by periods of PD therapy [14–17]. During this same period, information on what was initially referred to as peritoneal host defense, but is now understood in the context of the wider peritoneal inflammatory response, has developed into a significant understanding of how the interplay between the resident cells of the peritoneal membrane (the mesothelium, peritoneal fibroblasts, and resident leukocyte populations) and infiltrating leukocytes (of all phenotypes; polymorphonuclear neutrophilic leukocytes [PMN], monocyte/macrophages, and T cells) contribute to a complex series of tightly controlled processes, mediated by different classes of secreted cytokines, inflammatory mediators, surface and soluble receptors, and distinct intracellular signalling cascades (Fig. 27.2). These serve and are designed to orchestrate responses to infectious stimuli and effect acute and resolving peritoneal inflammation [18–22]. We have also developed our understanding of what occurs when these processes become dysregulated resulting in the genesis of a more "chronic inflammatory scenario" and to define the relationship between this dysregulated inflammation, tissue damage, and membrane dysfunction. Equally, it has become clear that we are dealing with a process complicated by the interaction of several factors that result in the "net inflammatory state" in PD patients. These include uremia, the cellular and secreted components of inflammation (cytokines and growth factors), the dialysis solution components, and the cellular targets of their action (Fig. 27.2). In the context of the peritoneal membrane this is, in effect, all the cells in the peritoneal membrane and functional structures, compact zone and the vascular bed (and adipocytes) [23] that are impacted upon.

Another key development in recent years has been the identification of the potential importance of the plasticity of cellular phenotype (epithelial to mesenchymal transition; EMT) as a key process whereby resident cells, under the influence of inflammation and/or dialysis solution exposure, contribute to detrimental alterations in peritoneal membrane structure and function [24–28].

O. Devuyst (✉)
Division of Nephrology, Université Catholiqué de Louvain Medical School, Brussels, Belgium
e-mail: olivier.devuyst@uclouvain.be

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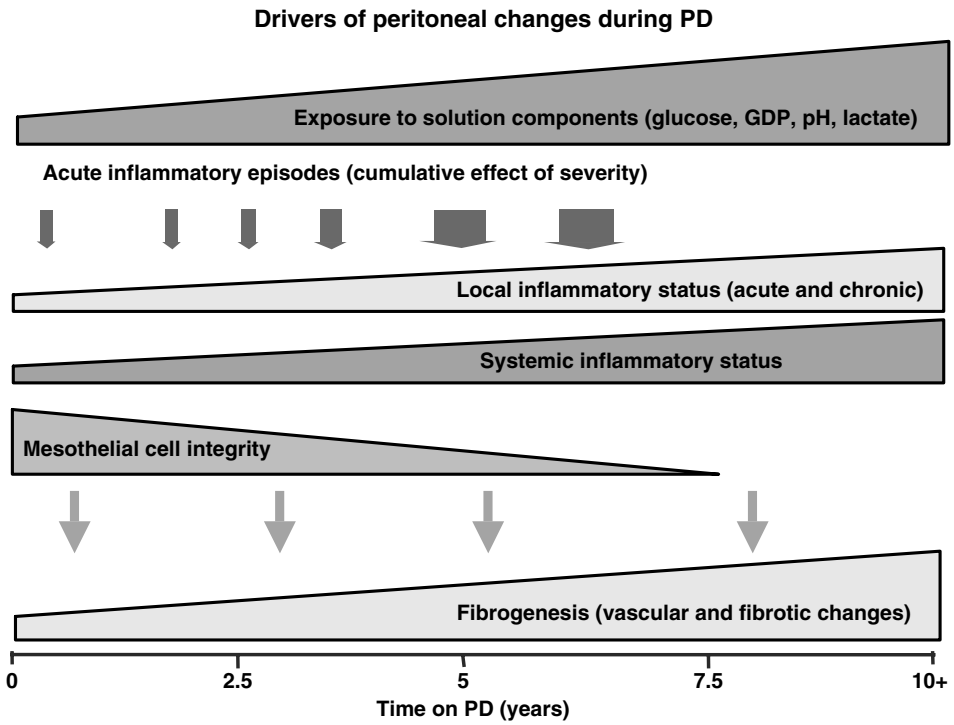


Fig. 27.1 Factors responsible for driving alterations to peritoneal structure and function

The aim of this chapter is to provide an updated overview of current understanding of peritoneal membrane structure and function, and how this is altered by PD therapy with its associated inflammatory changes, chemical insults, and intermittent infective episodes. This will range from a review of the pathophysiological changes induced by PD therapy to an exploration of the (intrinsic and extrinsic) mechanisms that drive peritoneal membrane structural and functional changes. The review will be based on the available published evidence and will utilize data from clinical

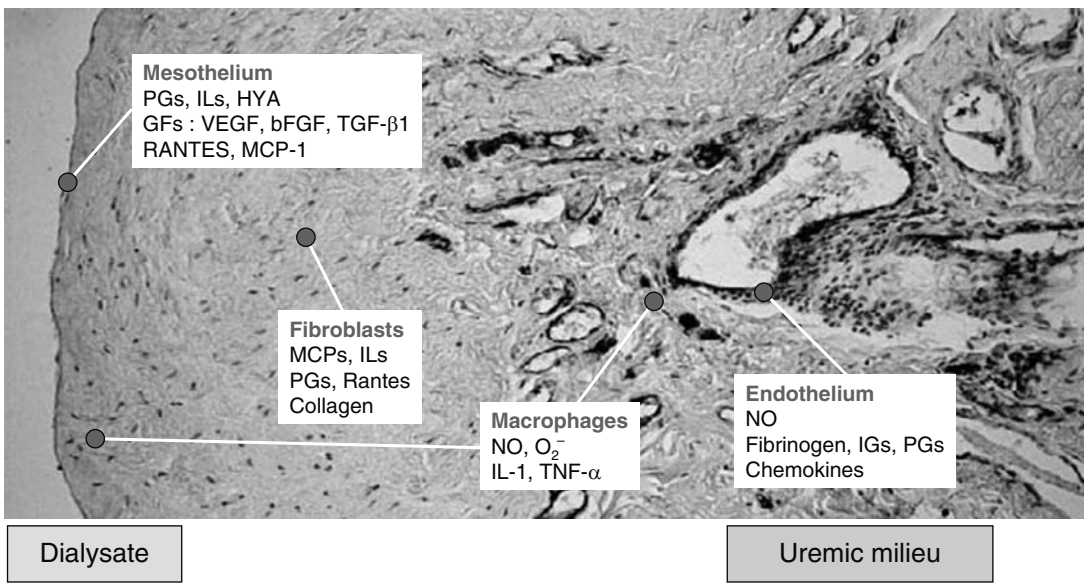


Fig. 27.2 Cellular interactions and inflammatory response in the peritoneal membrane exposed to peritoneal dialysis. The major mediators released by each cellular component of the peritoneal membrane are indicated: GFs, growth factors; HYA, hyaluronan; IGs, immunoglobulins; ILs, interleukins; MCPs, monocyte chemoattractant proteins; NO, nitric oxide; O_2^-, superoxide anion; PGs, prostaglandins. The release of these mediators is influenced by exposure to the dialysate and the uremic milieu

observational studies, longitudinal characterization of changes in PD patients, as well as recent in vitro findings and data from animal models of inflammation and dialysis solution exposure. We will attempt to describe the molecular mechanisms that are involved in driving membrane structural and functional changes.

Peritoneal Structural Changes over Time

Central in the development of theories about how the process of PD induces changes to the peritoneum have been those studies that have sought to characterize the histopathological changes that occur in the peritoneal membrane both from standpoint of changes driven by uremia *per se* but most importantly those that are a feature of the process of the PD therapy. Observations on structural alterations in the peritoneal membrane in PD patients date back to the early observations made by Dobbie and DiPaolo [29–37], which were the forerunners of more contemporary studies by Honda and eventually the peritoneal biopsy registry [15–17, 38, 39]. These have provided the basis for our increased understanding of what is actually occurring in the peritoneum during PD and has begun to indicate those factors that might be responsible (or at least associated with) the observed structural alterations (Fig. 27.3).

Peritoneal Biopsy Data

Early observations on peritoneal membrane alterations were made in samples taken at catheter replacement or removal or at autopsy. The sum of these observations suggested alterations in the mesothelium (denudation, loss of microvilli), interstitium (various degrees of "fibrosis"), and alterations in the vascular bed [40–44]. These early studies showed clear evidence, albeit without strong linkage to particular clinical events other that PD exposure, of interstitial and vascular alterations in the peritoneal membrane. These were significantly extended by the landmark studies of Honda et al., who, although studying limited amounts of biopsy material, made significant observations on the nature of changes in the vasculature of the peritoneal membrane induced by PD therapy [15, 16]. In a small group of patients

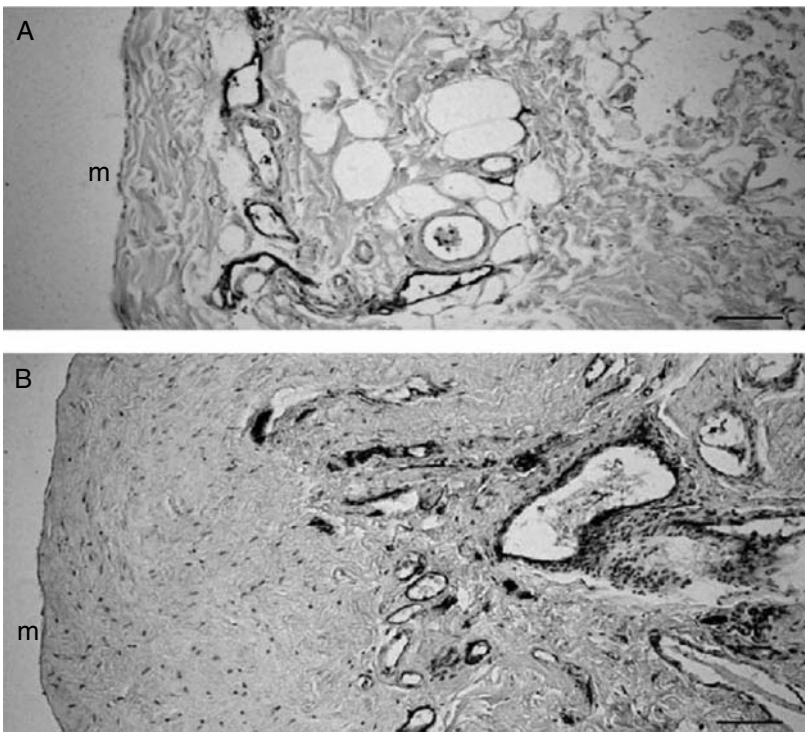


Fig. 27.3 Structural changes in the peritoneal membrane exposed to long-term peritoneal dialysis. Panel A shows the structure at the beginning of therapy, whereas panel B shows the structural alterations – loss of mesothelial integrity, submesothelial fibrosis, vasculopathy, and vascular proliferation – after 5 years on peritoneal dialysis. Brown staining indicates immunoreactivity for Factor VIII indicating the presence of blood vessels. Bar: 100 microns

with clinically defined ultrafiltration (UF) failure, these authors described extensive interstitial fibrosis, loss of mesothelium, and vascular changes. The changes to the vasculature included severe fibrosis and hyalinization of the media of venules with extensive deposition of type IV collagen and laminin in the vascular wall and degeneration of smooth muscle cells in the media [15]. In more studies, these authors demonstrated that changes in the peritoneal vasculature were associated with accumulation of the advanced glycosylation end-products (AGEs) as assessed by staining with an anti-CML antibody [16]. Despite the relatively small size of the study, AGE accumulation correlated with both interstitial fibrosis and vascular degeneration.

The Peritoneal Biopsy Registry

In 1999, the Peritoneal Biopsy Registry was established in an attempt to systematically examine and characterize changes in membrane structure in a large cohort of PD patients. A large series of parietal peritoneal samples collected at the time of transplantation (and thereby not selected for reasons of treatment failure or other complications of PD) was examined by an independent pathologist and compared to control biopsies obtained from uremic predialysis patients (those being preemptively transplanted) or hemodialysis patients (prior to transplantation). In addition, a cohort of "true" normal samples was collected from the living related donor population. This extensive study allowed for the first time a thorough evaluation of those changes induced by PD (time on therapy, infection history, and dialysis solution exposure) compared to relevant control samples.

The key observations of these studies suggest that time on PD using conventional dialysis solutions results in progressive (if highly variable) thickening of the submesothelial cell compact zone and progressive vascular alterations (characterized as a hyalinizing vasculopathy with eventual vascular obliteration) [17, 38, 39]. Evidence of significant increases in vessel numbers, as suggested by previous studies [45] and by several animal studies, was only observed in patients with UF failure, although it is now becoming clear that this may be related to anatomical location (parietal versus visceral peritoneum) [46] and its inherent susceptibility to angiogenesis. Importantly, uremia *per se* appears to play a significant contributory role in these alterations as biopsies from predialysis and hemodialysis patients already show significant interstitial and vascular alterations compared to the normal controls. This effect of uremia corroborates effects on peritoneal membrane structure and function seen in experimental animals rendered uremic following nephrectomy [14, 47]. In addition, when examining the origin of the biopsies, those patients with clinical complications requiring catheter removal or suffering from UF failure had the greatest degree of peritoneal pathology [17].

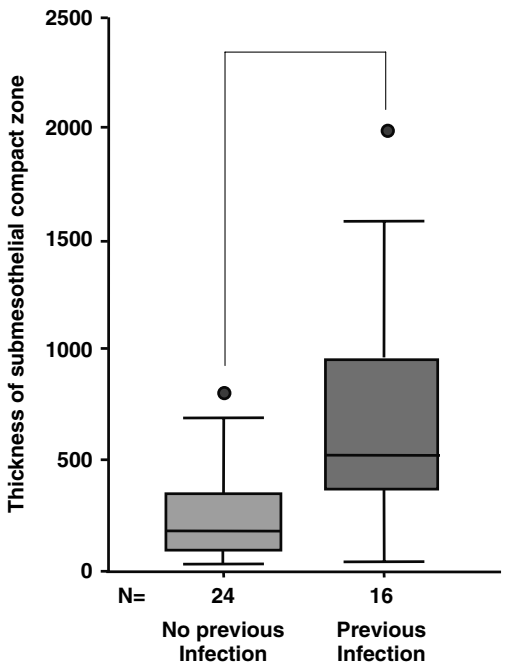


Fig. 27.4 Relationship between previous infection history and the degree of submesothelial cell compact zone thickening in peritoneal biopsies from PD patients. Data presented with the permission of the Peritoneal Biopsy Registry. $P<0.01$

Although such cross-sectional studies cannot provide direct mechanistic evidence of those factors directly responsible for the observed pathological changes, strong correlations were observed between duration of dialysis, total glucose exposure and previous infection history, and the observed alterations in both fibrosis and vascular degeneration (vasculopathy) (Fig. 27.4) [17, 38, 39]. However, there remain significant gaps in our knowledge. While the data suggest that progressive structural changes do occur, the severity of which are linked to the length of time the membrane is exposed to PD, the correlations are based on small numbers of patients and do not provide mechanistic insight. The implication of those factors as being directly responsible for, or a result of the structural changes, although logical and attractive and, to some extent, supported by the emerging literature in animal models, must nevertheless be interpreted with caution. Likewise, the emerging understanding of encapsulating peritoneal sclerosis (EPS), which is beyond the scope of this chapter, and its relationship to the described observations made from biopsy studies is equally unclear. As yet, no unifying hypothesis for the relationship between "simple" fibrosis and vasculopathy and EPS exists and, in fact, current thinking suggests that they may indeed be diseases of separate peritoneal compartments (visceral versus parietal peritoneum). Increasing our understanding of peritoneal pathology must be an area of priority and intense investigation over the coming years.

Peritoneal Functional Changes over Time

Solute Transport

Although many PD patients may have stable transport rates for 5 years of more [48, 49], cross-sectional studies and longitudinal cohort studies have now clearly established that, on average, there is a slowly increasing small solute transport rate over time [8, 50–55]. Detailed analyses of the 574 PD patients available from the Stoke cohort revealed that solute transport increased significantly in the 6 months following the initiation of PD, and continued throughout the course of treatment [53]. It has been suggested that the increase in the average small solute transport could be due to a minority of patients experiencing a rise, whereas the majority have stable function. This interpretation is probably false, since patients with high small solute transport will leave CAPD more rapidly because high transport status is associated with a higher technique failure and higher mortality [8, 56, 57]. The cause is not clear, but an association with decreased ultrafiltration is possible since an increased transport will lead to a more rapid absorption of glucose with abolition of the osmotic gradient and reduced UF. In turn, a reduced UF will lead to fluid overload and thus a role of cardiovascular problems is increasingly suggested [56, 58, 59]. As discussed below, the morphological cause for a progressive increase in small solute transport may be an enlarged vascular surface area, reflecting the increased number of capillaries demonstrated in biopsies from long-term PD patients [17].

The factors believed to cause these structural changes with time on PD include repeated episodes of peritonitis and long-term exposure to bioincompatible dialysates [17, 49, 60]. Hypertonic glucose-based solutions are particularly suspected, due to their hyperosmolality, high glucose content, and associated levels of glucose degradation products (GDPs). Circumstantial evidence supports the role of dialysate glucose exposure in membrane damage, both in morphologic studies of the membrane [38, 39] and longitudinal studies showing that increased use of hypertonic glucose precedes changes in membrane function [49]. The residual renal function must also be considered, since its loss will require increased use of hypertonic glucose to sustain UF and will change the clearance of cytokines, thereby increasing systemic inflammation.

Ultrafiltration

One of the commonest changes with time on PD is a gradual decline in UF when using glucose dialysate, which represents a major cause for technical failure and increased mortality/morbidity [8, 53]. It has been suggested that, by 3 years, some 10% of patients have UF failure [61], and by 6 years this has increased to 30% [62]. A study from Japan reported that up to 50% of those individuals who had survived at least 6 years on PD would have technique failure due to fluid overload from UF loss [63]. Besides catheter-related problems, mechanisms operating in the membrane play an important role in UF failure. As discussed above, PD patients develop over time an increased transport rate for small solutes, which induces a faster absorption of glucose and an early dissipation of the osmotic gradient [8, 53]. This

mechanism, responsible for an increased mass transfer area coefficient (MTAC) for small solutes, is considered as the most frequent cause of UF failure [64, 65]. However, the longitudinal studies by Davies et al. revealed that the changes in UF capacity are not exactly reflecting those in small solute transport [53]. Indeed, the fall in UF capacity observed in long-term patients (>4 years of PD) is disproportionately large for the rise in solute transport. These differences suggest that causes other than increased solute transport participate in the genesis of UF failure. A reduced sodium sieving during a hypertonic dwell, suggesting impaired free water transport, has been documented in long-term PD patients with UF failure [66, 67]. Subsequent cross-sectional studies suggested that a reduced osmotic conductance to glucose, causing a reduction of free-water transport, was involved in UF failure [62, 65, 68]. Although the mechanism of this reduced conductance remains unknown, it could be due to a decreased reflection coefficient (sigma), itself reflecting an alteration of the function of the aquaporin-1 (AQP1) water channels in the endothelium lining peritoneal capillaries [68, 69]. It must be pointed, however, that the expression of AQP1 is apparently unchanged in patients with long-term PD and UF failure [70, 71]. Furthermore, a recent study of 50 stable PD patients with UF failure showed no differences in the sigma coefficient between stable PD patients with or without UF failure and according to the duration of PD [64]. Thus, the potential role of functional impairment of AQP1 in UF failure remains to be substantiated. Other causes of UF dysfunction include increased effective fluid reabsorption by lymphatics, causing a decrease in intraperitoneal volume [62, 64] and modifications of the hydraulic conductance of the interstitium [72].

It must be emphasized that changes in intrinsic peritoneal transportwith time are rarely measured. In one case-matched study comparing patients treated for 5 years with PD compared to those starting treatment there appeared to be a significant reduction in peritoneal permeability with time [52], despite increased effective peritoneal surface area. This would be in keeping with an increase in peritoneal fibrosis, but longitudinal cohort studies have not confirmed this as yet. Clerbaux et al. showed no modifications of the sodium sieving in subgroups of 35 and 18 PD patients followed for 1 year and 2 years, respectively [55]. The recent description and validation of simple methods to determine the free water transport and the osmotic conductance to glucose [73, 74] is an important step in obtaining longitudinal informations on these parameters.

Macromolecular Clearance

Very few studies have assessed the changes in intrinsic permeability of the peritoneum to macromolecules such as albumin, IgG, and alpha 2-macroglobulin during PD. The issue is of importance, since longitudinal studies have shown a significant decrease in serum albumin concentration with time on PD [50, 55], which could play a role in the co-morbidity and the outcome of PD patients [75]. The macromolecule clearance can be assessed by the restriction coefficient of the membrane [76] that is inversely correlated with the permeability through the large pores. The restriction coefficients for macromolecules apparently do not change during the first 2 years of PD [77]. However, they may increase after a longer period of treatment, indicating that permeability to macromolecules could decrease with time on PD [77]. A reduced macromolecular clearance could be caused by a reduction in the large pore radius or by alterations in the interstitial tissue, for instance, due to the increased thickening of the submesothelial layer with collagen deposition [17].

The large pore fluid flux (JvL) can be assessed by the Peritoneal Dialysis Capacity (PDC) program [78]. A high JvL at the start of PD is related to comorbidity [79] but also to the development of hypoalbuminemia and survival on PD [80]. Indeed, patients with a high JvL showed an important fall in plasma albumin immediately after initiation of PD, suggesting peritoneal albumin loss. The correlation of JvL with older age, smoking, and atherosclerosis suggests that increased large pore permeability reflects generalized capillary disease [80]. Longitudinal studies showed no significant change in this parameter for up to 4 years on PD [79, 80].

Long-Term Effects of Automated Peritoneal Dialysis (APD)

Many APD individuals have been switched to this therapy from CAPD because of problems with achieving solute adequacy targets and/or difficulties with fluid removal. These patients may have variable residual function, and there is little information about the longitudinal changes in membrane function under this treatment modality. The European Automated Peritoneal Dialysis Outcome Study (EAPOS) examined longitudinal changes in the solute transport and UF capacity in a prospective cohort of 177 functionally anuric patients. The cohort experienced an increase in small solute transport and a reduction in UF capacity at 1 year and 2 years. These changes were more severe in patients using

hypertonic glucose or in those not using icodextrin at baseline. Importantly, these differences could not be explained by informative censoring nor by age, comorbidity, or peritonitis rate [6]. This study yielded important mechanistic information, since residual renal function was eliminated as a confounding factor. It supports the link between exposure to higher glucose concentrations and accelerated changes in solute transport, as well as the potential benefit of using icodextrin in that respect [81–83].

Mechanisms Driving Structural and Functional Damage to the Membrane

The Link Between Structural Changes and Ultrafiltration Failure in PD

The endothelium lining peritoneal capillaries is considered as the major functional barrier to water and small solutes transport during PD. The amount of perfused capillaries within the peritoneum determines the so-called "effective peritoneal surface area" (EPSA) that is the functional area of exchange between blood and dialysate [84]. The transport of water and solutes across the capillary endothelium is best described by the three-pore model, which includes transcellular, ultrasmall pores (radius: 3–5 Å) exclusively permeable to water, small pores (radius: 40–50 Å) permeable to water and small solutes, and large pores (radius >150 Å) permeable to macromolecules [85, 86]. Studies in transgenic mice have demonstrated that the water channel AQP1 is the molecular counterpart of the ultrasmall pores, which mediate up to 50% of UF during a hypertonic dwell [87, 88]. Colloid osmosis (e.g., with icodextrin) occurs at the level of interendothelial small pores that allow the diffusion of water and small solutes [89]. Numerous studies have shown that long-term PD is associated with modifications of the peritoneal membrane, including submesothelial fibrosis, vascular proliferation, vascular diabetiform changes, and alterations of the mesothelium (Fig. 27.3) [16, 29, 45, 90]. In the Perotoneal Biopsy Registry, Williams et al. reported a positive correlation between the extent of submesothelial fibrosis and vascularization. This suggests an interaction between the two structural changes [17, 45]. However, fibrosis and angiogenesis may represent two independent responses to peritoneal injury. For instance, in a rat model of dialysate exposure, Margetts et al. were able to dissociate the fibrotic and angiogenic responses by using adenovirus-mediated gene therapy targeting either fibrosis (decorin) or angiogenesis (angiostatin) [91]. Importantly, these data showed that reduction of angiogenesis improved UF, whereas decreasing fibrosis had little impact on transport [91]. Submesothelial vascularization, vasodilatation, and increased reactivity for nitrotyrosine secondary to peroxynitrite release have also been observed in rat and mouse models of acute peritonitis [70, 92, 93]. Thus, vascular proliferation and, possibly, vasodilatation or recruitment of preexisting vessels, might represent the structural basis for increased EPSA encountered in acute peritonitis and long-term PD [70, 90, 93].

Over the past few years, several experimental models have given new insights into the pathophysiology of UF failure in PD. These models include rats and mice with acute peritonitis [70, 92–94], chronic exposure to diabetes [95, 96] or uremia [14, 28, 97], and chronic dialysate exposure [91, 98]. A common feature of these models is the local release of growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor β (TGF-β) in the peritoneal membrane, leading to the development of areas of neovascularization and/or submesothelial fibrosis. These structural modifications, which have been documented at the morphological and molecular level, are associated with functional changes including higher permeability for glucose and small solutes, decreased sodium sieving, and reduced UF. Thus, an inverse relationship between the vascular density in the peritoneum and the amount of UF has been demonstrated in rats [91], and such a correlation also exists in the human peritoneal membrane [17]. It must be pointed out that, to date, there is no molecular evidence for a functional or structural modification of the water channel AQP1 in the peritoneum exposed to PD.

Epithelial to Mesenchymal Transition (EMT)

There is now a body of emerging evidence that suggests that changes to the peritoneal membrane are at least in part driven by chronic alterations to the mesothelium. Although not yet causatively implicated, it is suggested that dialysis solution-driven chronic activation results in the activation of the process of epithelial to mesenchymal transition (EMT) whereby epithelioid cells alter their phenotype and become myofibroblast in form and function [24–26].

This hypothesis is based on studies of mesothelial cells isolated from PD where with time on dialysis there appeared to be morphological alterations to a more fibroblastoid phenotype accompanied with loss of epithelioid markers such as cytokeratin expression. This switch in phenotype from epithelioid to fibroblastic confers on these cells a migratory

phenotype, allowing them to move into the submesothelial stroma (compact zone), where they may contribute directly to the fibrotic process [24]. Although definitive proof that such a process occurs in PD patients is still lacking, it remains an attractive hypothesis that might partly explain the morphological alterations seen in the mesothelium in the biopsy registry although this cannot explain the observation of complete denudation of mesothelium. This attractive hypothesis does gain support from recent studies from animal models that implicates both EMT and AGE-RAGE-driven EMT in driving peritoneal fibrosis [27, 28, 99, 100].

Dialysis Solutions and Membrane Structural and Functional Changes

Over the past 30 years, the focus of PD research has changed from the technical issues related to the establishment of clinical peritoneal dialysis to complex problems of peritoneal membrane pathobiology. Up to the mid-1980s, dialysis fluids and methods of access had to be developed along with the clinical procedures. Investigations were directed primarily at treatment efficacy and infection control. The first research articles on PD fluid biocompatibility were published, most using peripheral blood leukocytes as model system to assess the impact of dialysis solution components on cell viability and function [101, 102]. After this, peritoneal cell cultures were developed, and used extensively as preclinical testing for the development of new peritoneal dialysis solutions. Description of this extensive data is beyond the scope of this chapter as reviewed in [20, 103–105]. Instead, in the context of what factors are responsible for structural changes in the dialyzed peritoneum, we will focus on more recent data generated by an increasing number of research groups using animal models of PD in an effort to more closely mimic the specific in vivo environment of the dialyzed peritoneum [106]. These studies have cast significant light on the mechanisms that contribute to peritoneal membrane damage and those factors responsible for the initiation of peritoneal fibrosis.

As described above, longitudinal studies of PD patients have shown that small solute transport increases with time on PD [8, 53]. These data suggest that long-term exposure to conventional, glucose-based dialysis fluids plays a central role in the pathogenesis of the modifications of the peritoneal membrane. This hypothesis is supported by the observation that an early and high cumulative glucose exposure is associated with higher small solute transport across the peritoneum of PD patients [49] and by the results of the EAPOS study on anuric patients [6].

Animal Models and the Impact of Dialysis Solutions

Obtaining peritoneal biopsies in patients is not simple procedure, and these cannot be obtained electively. As described earlier, data from peritoneal biopsies although vital to our understanding of peritoneal pathology [17, 38, 39] only provide a cross-sectional snapshot of membrane changes (and they are limited to small areas of parietal or visceral peritoneum). Animal models, however, while failing to totally mimic human PD [107], do provide the opportunity to study longitudinal changes in peritoneal membrane pathology and thereby delve into the fundamental pathophysiological processes that drive membrane damage. In the field of PD, animal models have for a long time been underdeveloped and it is only in the past decade that significant progress has been made [108–113].

A number of research groups now have sophisticated animal models to more closely simulate the specific environment of the dialyzed peritoneum [89]. Descriptions of these different animals, with their advantages, limitations, and technical aspects have been reviewed on several occasions [110, 113]. Methodological differences such as study duration, species and strain of experimental animals, methods of peritoneal exposure, assessment of solute transport and ultrafiltration, and histological assessment differ substantially among the various research groups and to some extent make interpretation difficult. There have nevertheless been some substantial advances in understanding peritoneal membrane changes.

Most experimental models of PD that have been described make use of rats, and the majority of models are short-time (in general no longer than 4–6 weeks) [114]. These more chronic rat models were introduced to investigate biocompatibility of dialysis solutions in nonuremic animals in which PD was performed twice daily for 4 weeks [115]. Most models are peritoneal exposure models in which there is no fluid exchange. Peritoneal dialysis fluid is instilled at volumes ranging from 10 mL [116, 117] to 25 mL [118]. The longest long-term peritoneal exposure models in Wistar rats allow peritoneal infusion for up to 20 weeks [119, 120].

Some groups have tried to establish uremic models in rats [121] and rabbits [122], but difficulties still exist because nephrectomy results in technical problems and leads to a high dropout rate [123]. Nevertheless, this in vivo research has provided important breakthroughs in understanding peritoneal pathophysiology [107]. These breakthroughs are 1) the observation and integration of the long-term structural and functional alterations of the peritoneal

membrane, 2) a better understanding of the pathophysiology of peritoneal solute transport and ultrafiltration, and 3) a detailed description of the impact of standard dialysis solutions and inflammation on morphological and functional alterations of the peritoneal membrane that may in the future contribute to the development of improved dialysis solutions.

The traditional PD solutions are deemed to be bioincompatible because of their low pH, high glucose and lactate concentrations, hyperosmolality, and the presence of glucose degradation products formed during heat sterilization [106]. Glucose in high concentrations is toxic for the mesothelium both in in vitro and in animal studies [124]. Degradation of glucose results in formation of glucose degradation products and finally in formation of AGEs that have been described to accumulate in peritoneal tissues of patients [90, 125]. Glucose is also likely to be involved in the development of peritoneal neoangiogenesis. This is supported by the "diabetiform" alterations of the microvessels that are present in patients [15, 16, 45] and that can be induced to some extent in animal models [120]. Glucose degradation products are toxic to peritoneal cells and induce the formation of AGEs at a faster rate than glucose itself [126, 127]. The relative importance of glucose degradation products to glucose has not been clarified. It has been suggested that lactate may contribute to the toxicity of glucose [128].

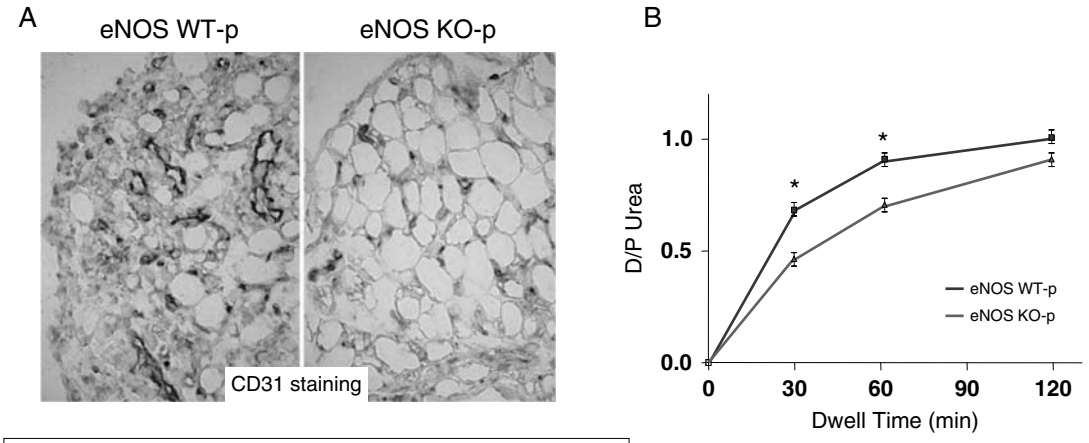
The Impact of Angiogenesis and Fibrosis

Long-term exposure to conventional glucose/lactate-based dialysis solutions can induce peritoneal alterations [17, 31, 34, 38, 39, 45]. The morphologic changes consist of an increased thickness of the submesothelial compact collagenous zone of the parietal peritoneum, sometimes accompanied by loss of surface mesothelium (Fig. 27.3). Interstitial fibrosis can also be found in omental tissue. Extensive vascular abnormalities have been described. These include not only subendothelial hyalinosis of arterioles, but also of the venules and small veins [15–17]. Also, an increased number of vessels have been found [45], especially in patients with UF failure [17]. The thickness of the submesothelial compact zone was related to the duration of PD, the absence of mesothelium and the prevalence of vasculopathy. A correlation has also been described between the number of peritoneal vessels and fibrotic alterations [17].

As described earlier, angiogenesis appears to be a key feature of dialysis solution–driven changes in peritoneal morphology. Although this concept is primarily based on animal studies, there is clear evidence of increased vessel formation in PD patients (particularly those with fibrosis and membrane dysfunction) [17, 45, 90].

Long-term PD is associated with alterations in peritoneal permeability and loss of UF. In view of the role of increased peritoneal surface area, modifications of activity and/or expression of nitric oxide synthase (NOS) isozymes might play a role in these modifications, via enhanced local production of nitric oxide (NO). This hypothesis was supported by the studies of Combet et al. [90], who determined NOS activities in peritoneal biopsies from control subjects, uremic patients immediately before the onset of PD, and uremic patients on short- or long-term PD. Peritoneal NOS activity is increased fivefold in long-term PD patients compared with control subjects. In uremic patients, NOS activity is positively correlated with the duration of PD. Increased NOS activity is mediated solely by Ca^{2+}-dependent NOS and, as shown by immunoblotting, an upregulation of endothelial NOS. The biologic relevance of increased NOS in long-term PD was demonstrated by enhanced nitrotyrosine immunoreactivity and a significant increase in vascular density and endothelial area in the peritoneum. Immunoblotting and immunostaining studies demonstrated an upregulation of VEGF, mostly along the endothelium lining peritoneal blood vessels in long-term PD patients. In the latter, VEGF co-localized with deposits of the AGE product pentosidine. These data provided a morphologic (angiogenesis and increased endothelial area) and molecular (enhanced NOS activity and endothelial NOS upregulation) basis for explaining the permeability changes observed in long-term PD. They also supported the implication of local AGE product deposits and liberation of VEGF in that process.

The use of animal models of PD has allowed to elucidate some of the molecular mechanisms involved in these degenerative processes. The important roles of aquaporins [13, 129, 130], VEGF [95], nitric oxide [13, 131], AGE formation and their receptor (RAGE) upregulation [28, 90, 100], and TGF-β [99] in the fibrotic alterations of the membrane as observed in patients on long-term PD have been investigated. More recently, genetically modified mice have emerged as an important tool to investigate the molecular basis of peritoneal changes during dialysis and during acute peritonitis [92, 93, 113, 132] (Fig. 27.5). The effects of RAGE in modulating fibrosis were not so clearcut in studies in RAGE-deficient mice, although this might be related to the nature of the genetic defect in these animals and its significant impact on inflammatory responses [98].



C	WT-p	KO-p
Vascular density (N/mm²)	411±32	289±38**
Endothelial area (%)	3.9±0.3	2.2±0.4**
D/P urea (AUC)	81±1	68±1**
Protein in dialysate (g/L)	3.8±0.4	2.8±0.5*

Fig. 27.5 Use of genetically modified mice to elucidate the impact of eNOS on vascular density and peritoneal transport. Wild-type mice (eNOS WT-p) or littermates lacking eNOS (eNOS KO-p) were submitted to a catheter-induced peritonitis model for 5 days. The lack of eNOS is reflected by a significant reduction in the vascular proliferation (panel A, staining with the endothelial marker CD31; panel C, morphometry analyses) and a marked reduction in the transport of small solutes (panel B, dialysate-over-plasma (D/P) ratio for urea during a 2-h dwell, $n = 6$ mice in each group; panel C, area under curve, AUC) and in the loss of protein in the dialysate (panel C). *P<0.05; **P<0.01.Data compiled from [93]

The Effect of GDP, RCOs, AGEs, and RAGE

Heat sterilization of conventional, glucose-based dialysis solutions generates the formation of GDP and reactive carbonyl species (RCOs) such as glyoxal, methylglyoxal (MGO), 3-deoxyglucosone, and 3,4-dideoxyglucosone-3-ene (3,4-DGE) [133, 134]. Furthermore, high levels of RCOs are also present in uremic plasma [135]. Multiple studies have demonstrated that both GDPs and RCOs accelerate the formation of AGEs in the peritoneal membrane, where they localize both in the mesothelium and endothelium [90, 127, 136, 137]. Both RCOs and AGEs modify proteins and/or interact with receptors, which may in turn initiate a range of cellular responses including stimulation of monocytes, secretion of inflammatory cytokines, proliferation of vascular smooth muscle cells, stimulation of growth factors, secretion of matrix proteins and alterations of mesothelial cell function [135, 138, 139]. The link between RCOs/AGEs and VEGF is also supported by the demonstration of increased VEGF expression in the peritoneum of rats chronically injected with MGO [136], as well as by the co-localization of pentosidine and VEGF in peritoneal capillaries from long-term PD patients [13, 90, 140] (Fig. 27.6). Recently, Kakuta et al. used a uremic rat model on PD to demonstrate that the combination of uremia and dialysis solution exposure generated vascular proliferation with ensuing transport abnormalities, AGE genesis, and upregulation of the angiogenic VEGF and bFGF. These modifications were significantly improved by giving pyridoxamine, an inhibitor of AGE, to the uremic rats, pointing to the pathophysiological importance of carbonyl stress in the alterations of the peritoneal membrane [97].

Studies on human peritoneal mesothelial cells (HPMC) in culture also yielded important insights into the pathophysiology of GDP in PD. Witowski et al. used HPMC to demonstrate the cytotoxic effect of GDP, which decreased cell growth and viability [141], while more recently Morgan et al., have shown that specific GDP species (notably 3,4-DGE) modulate mesothelial cell repair processes [138]. Lai et al. showed that incubation of HPMC with GDPs or dialysate fluids resulted in increased AGE synthesis and VEGF expression, as well as the expression of RAGE and other AGE receptors, in a dose-dependent manner [142]. Boulanger et al. showed that heat-sterilized dialysates (containing high glucose and GDP concentrations) reduced HPMC proliferation by inducing mesothelial cell apoptosis and oncosis [143]. These changes in cell function were significantly attenuated by blocking AGE-RAGE interaction using recombinant soluble-RAGE. Using a co-culture system, these investigators further demonstrated that mesothelial RAGE activation by AGEs enhanced VEGF release, which potentialized capillary tube formation by endothelial cells, a process that was attenuated by using blocking antibodies directed against RAGE or VEGF. The

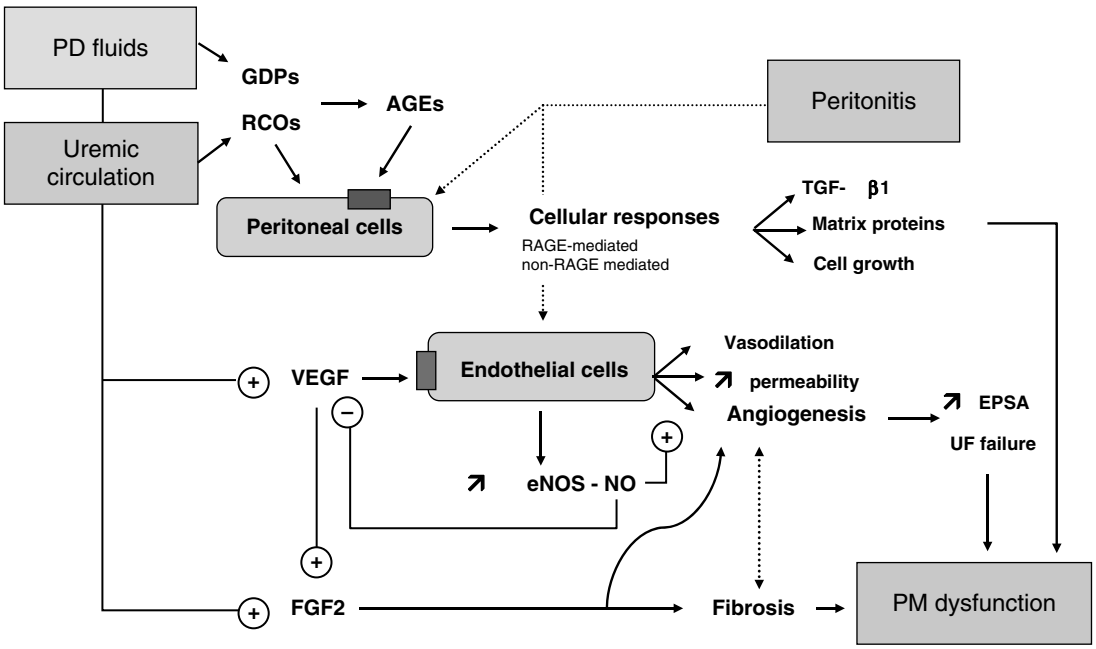


Fig. 27.6 Integrative approach to understanding the influence of factors that drive. Structural and functional changes in the peritoneal membrance (PM). See text for details

pathogenic role of AGE-RAGE interaction and its potential to drive EMT has been substantiated in a rat infusion model (see earlier) [28, 100].

The growth factor VEGF is a potent regulator of angiogenesis and vascular permeability [144]. The *VEGF* gene codes for several VEGF isoforms, which arrange into disulfide-linked homodimers. The binding of VEGF dimers to tyrosine-kinase receptors (VEGFR-1 and VEGFR-2) located in endothelial cells initiates a signal transduction cascade responsible for endothelial proliferation and migration, activation of plasminogen and collagenase, and vasodilation, resulting in physiological angiogenesis [144]. In addition, VEGF binds to the extracellular matrix, thereby inducing the release of bFGF, another potent angiogenic factor [145]. Stimuli for VEGF expression include hypoxia, hypoglycemia, cytokines such as interleukin-6 (IL-6), growth factors, and hormones. VEGF is expressed in the human peritoneal membrane, where it binds to the endothelium lining peritoneal capillaries [90]. Thus, by analogy with other angiogenic diseases, upregulation of VEGF may trigger vascular proliferation in the peritoneal membrane in long-term PD (Fig. 27.6). In this respect it is of interest that plasma and dialysate concentrations of VEGF and IL-6 have been shown to be associated with high peritoneal solute transport rate [146].

Nitric Oxide and Oxidative Stress

Nitric oxide is an attractive candidate to regulate EPSA and UF during PD, given its crucial role in the regulation of vascular tone and permeability [147], and its interactions with angiogenic growth factors [148]. The paradigm has been provided by the loss of UF in a rat model of acute peritonitis, characterized by a major upregulation of the endothelial and inducible NOS isoforms and a parallel increase in the permeability for glucose and small solutes [70]. Addition of the NOS inhibitor NG-nitro-L-arginine methyl ester (L-NAME) to the dialysate was able to restore most of the UF capacity in this rat model [94] and a similar effect was observed in a LPS-induced peritonitis mouse model [92]. In addition to its vascular effects, NO might also affect the peritoneum by generating peroxynitrite (a powerful, cytotoxic oxidant) and by modifying critical residues, as suggested by an increased reactivity for nitrotyrosine [70] or nitrosocysteine [94].

Multiple interactions between NO, endothelial NOS, and VEGF occur within endothelial cells (Fig. 27.6). Both NO and the endothelial NOS are required for VEGF-driven angiogenesis and vascular permeability [149]. On the other hand, VEGF is known to activate endothelial cells and upregulate the production of NO [150]. In turn, NO modulates and even suppresses the hypoxic induction of VEGF, which creates a negative feedback between NO and VEGF induction [148]. Interestingly, such crosstalk exists in the peritoneum, since upregulation of eNOS in a rat model of acute peritonitis is associated with down-regulation of VEGF [70].

The link between oxidative stress and peritoneal damage was substantiated by the studies of Lee et al. [151] who demonstrated that high glucose increased reactive oxygen species (ROS) in HPMC through the activation of a signaling cascade involving protein kinase C (PKC). In turn, the ROS generated were able to upregulate the expression of fibronectin by HPMC. A subsequent study by the same group provided in vivo evidence for the damaging consequences of ROS generated by conventional dialysates. Rats exposed to such dialysates for 12 weeks showed increased small solute transport, reduced UF, increased membrane thickness, and increased expression of eNOS, TGF-β1, VEGF, collagen I, and angiotensin II [152]. All of these changes were prevented by the administration of N-acetylcysteine or losartan, suggesting that these agents may play a protective role in long-term PD [152].

Contribution of Uremia and Glycemic Control

By analogy with the increased permeability of serosal membranes such as the pleura or the pericardium, it has been suggested that uremia *per se* might increase the permeability of the peritoneum [153]. That hypothesis has been supported by the association of several molecular mechanisms – upregulation of NOS, high levels of circulating RCOs and AGEs, increased growth factors – with higher peritoneal permeability in a chronic uremic rat model [14]. Subsequent studies confirmed that uremia alone induces AGE formation, upregulation of growth factors including VEGF and TGF-β1, myofibroblast transdifferentiation and development of interstitial fibrosis, as well as vascular proliferation and increased transport for small solutes [28, 97]. The attenuation of these changes by neutralizing anti-RAGE antibodies [28] or the RAGE-inhibitor pyridoxamine [97] suggests a role for the AGE-RAGE interaction in these processes (Fig. 27.6).

Diabetes may represent another factor that affects the peritoneal membrane. The CANUSA prospective study showed a greater proportion of diabetics among high transporter PD patients [57], and it has been suggested that diabetic patients have higher permeability for creatinine and lower UF than nondiabetic patients [48, 55, 154]. Studies performed in a streptozotocin-induced diabetic rat model [95, 96] showed that chronic hyperglycemia alone is sufficient to induce functional (increased transport for small solutes) and structural (areas of vascular proliferation) changes in the peritoneum. It is interesting to note that these modifications were associated with the selective regulation of NOS isoforms and AGEs deposits [96]. All the alterations were prevented by chronic insulin treatment, demonstrating that adequate control of glycemia in this diabetic rat model is sufficient to preserve the integrity of the peritoneum. Taken together, these data suggest an independent contribution of uremia and hyperglycemia in peritoneal changes during PD.

Peritoneal Inflammation and Membrane Dysfunction

As mentioned previously, inflammation appears to play a central role in modulating the function and possibly structure of the peritoneal membrane. Over the past decade, information gleaned from measurements of intraperitoneal inflammatory mediator levels (in PD effluent isolated from patients during stable PD and during peritonitis), as well as a large body of in vitro cell culture data has identified an outline of the process by which peritoneal inflammation is initiated, amplified, and how it resolves [155]. These data suggest that, following bacterial contamination of the peritoneal cavity, a coordinated train of events is set in motion to eradicate the invading organisms and resume normal tissue homeostasis. Also clear is that both the resident and infiltrating cells (both tissue cells and resident macrophages and infiltrating leukocytes) participate in these processes [103, 156, 157].

Inflammation in the dialyzed peritoneum involves an initiation phase resulting from the activation of resident phagocytes, and probably the mesothelium, by invading micro-organisms or their secreted products [19, 20]. Next, there is an amplification phase in which mesothelial cell activation by peritoneal macrophage-derived pro-inflammatory cytokines (such as IL-1β and TNFα) appears to play a key role. This process results in the generation of chemotactic signals, via the creation of a gradient of chemotactic cytokines (specific for individual leukocyte subpopulations) leading to the recruitment of these inflammatory cells to the site of activation [21, 22, 158–161]. This infiltration process is facilitated by the upregulation of leukocyte specific adhesion molecules of the immunoglobulin superfamily (ICAM-1 and VCAM-1/2) on the mesothelial surface [156, 162–164]. There is also the involvement of other pathways, including CD40-CD154 ligation, which also appears to regulate chemokine secretion and leukocyte trafficking [165–169]. The process of leukocyte infiltration is tightly controlled, such that initially polymorphonuclear leukocytes predominate (6–24 h) and are subsequently replaced by mononuclear cells (mononuclear phagocytes and T and B lymphocytes) [22]. This switch in leukocyte phenotype during peritonitis (Fig. 27.7), is known to be controlled by a sophisticated and

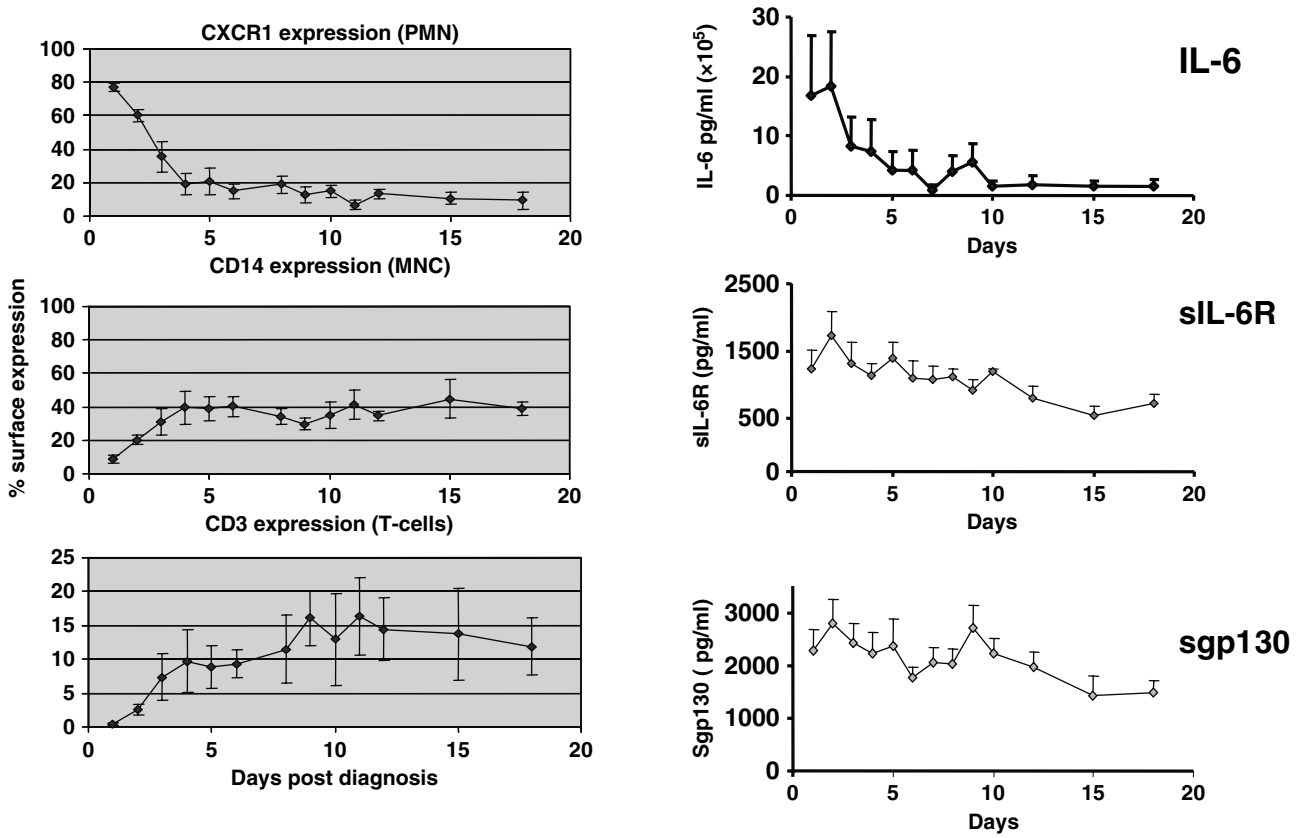


Fig. 27.7 Changes in recruited leukocyte phenotype and IL-6 family cytokines during the whole time course of bacterial peritonitis. Data (left panel) from flow cytometry using markers specific for PMN (CXCR1), monocytes (CD14), and T lymphocytes (CD3). Data (right panel) of IL-6, soluble IL-6 receptor (sIL-6R), and soluble gp130 (sgp130) measured by ELISA in 12 episodes of Gram-positive peritonitis

differential regulation of chemokine secretion and polymorphonuclear leukocytes apoptosis regulated by IL-6/sIL-6R signaling through its signal transducer gp130 [21, 22, 160, 161] as reviewed by Jones et al. [170, 171].

The Link Between Inflammation and Membrane Dysfunction

Given the number of factors that potentially impact on the peritoneal membrane (Figs. 27.2 and 27.6), it is perhaps difficult to separate out cause and effect and particularly difficult to attribute the degree of importance of single processes. That being said, there is little doubt that the process of inflammation in all its guises likely plays a significant role in peritoneal physiology and pathophysiology. In the former case, as was discussed earlier, alterations in cytokine or growth factor production (under genetic control) influence membrane function [131].

Each year, the understanding of inflammation and inflammatory process moves on in massive leaps and bounds in all aspects of disease and in all organ systems, and the same is the case for the peritoneal cavity. In the 1980s and early 1990s, we coined the phrase "the peritoneal cytokine network" and were primarily concerned with peritoneal host defense [20, 103] and the impact upon it of "bioincompatible" dialysis solutions [18]. We are now in a totally different era. The current paradigm suggests that inflammation comes in many guises and has both beneficial and detrimental effects. It is good if it promotes host defense and resolves inflammation, protecting the host from "insult" and restoring tissue homeostasis. It is bad if it loses control of itself, drives a more "chronic" phenotype, and contributes to tissue and end organ damage.

In the context of the peritoneum, our current understanding of the situation is equally if not more complex as there are both intrinsic and extrinsic factors impacting on the inflammatory process (Fig. 27.1). While it is clear that acute inflammation associated with infective episodes is a normal response to insult and, in the case of the peritoneum designed to promote bacterial removal, it is becoming equally clear that each insult is not the same, and this may compromise the ability of acute inflammation to resolve and in fact the nature of each individual response. This might result in the cumulative severity of acute inflammation changing with each subsequent insult. Although this is

speculation, our basic understanding of inflammation makes it a likely scenario. While we now understand the nature of some of the factors that control acute inflammation (eg,. chemokine and IL-6 *trans*-signaling) and have defined these in the context of single episodes of peritoneal inflammation in animal models and man, we are some way from being able to demonstrate their dysregulation, although preliminary animal data (in peritonitis and arthritis) suggests that this is the case [21, 22, 160, 161, 170, 171]. It is equally important that we do not limit our description to acute inflammation (or innate immunity) as these regulatory mechanisms also responsible for the recruitment and retention of both macrophage and T-cell populations in the peritoneal cavity.

To date, the definition of chronic inflammation is loosely defined as the retention of activated leukocytes (monocyte/macrophages and lymphocytes) within an organ system. Does a similar scenario appertain to the dialyzed peritoneal cavity? There is indeed the continuous retention (and indeed recruitment) of mononuclear cells and lymphocytes, and evidence of altered phenotype (Roberts and Topley, unpublished observations). We are only just beginning, however, to understand what this means in terms of peritoneal membrane longevity, and significant further study is required to define the activation status of these cells and how dialysis impacts upon them and whether they contribute to membrane dysfunction [172, 173]. Given the role of IL-6 as a marker of poor outcome in many diseases and its central role in regulating cellular inflammation, it is not a huge conceptual leap to suggest that there may indeed be some inter-relationship between inflammation and disease outcome, which is of relevance to the peritoneal cavity. This is especially relevant when one considers that trials of new dialysis solutions have shown variable alterations in local IL-6 levels following conversion to the use of more "biocompatible" dialysis [174, 175].

While we are only beginning to understand the full nature of local inflammation in the peritoneum and its long-term impact on membrane survival, we are also trying to get to grips with the impact of systemic inflammation in PD patients and the potential inter-relationships between them. Although factors such as IL-6 and C-reactive protein (CRP) predict poor outcome [176–178], the mechanism that drives these poor prognoses are likely extraperitoneal. It is nevertheless important to understand whether local effects (within the peritoneum) can impact positively on systemic inflammatory parameters and patient survival. In this respect, recent data that suggest alterations in plasma CRP in patients converted to new dialysis solutions are intriguing but require corroboration in much larger cohorts [179].

The scope of this review does not allow a detailed description of the immunology of the peritoneal cavity, although this is a rapidly expanding area of research. There are many questions to address that, by and large, will require human studies, as the rodent peritoneum does not mimic all of the subtleties and sophistications of the human immune system. The dialyzed peritoneal cavity provides us with unique access for this type of endeavour, and one hopes that over the coming decade we will be able to understand how inflammation in its various guises contributes to membrane structural and functional changes in PD patients so that we can modulate therapeutic interventions to limit its detrimental but accentuate its positive attributes.

Reversibility of Structural Changes in the Peritoneum

If the nature of the structural changes that occur in the peritoneal membrane exposed to long-term PD is now becoming better defined, the intriguing question of their reversibility upon peritoneal rest (i.e., terminating PD) or indeed specific therapy remains an important question. Since dialysis solutions can never be physiological (in order to perform there dialytic function), it may be that membrane protective strategies are an essential feature of the therapy [106, 180]. The issue is important, not only for technique survival but also in terms of potential benefits resulting from the different therapeutic approaches. Early human studies showed that peritoneal rest may result in a recovery of ultrafiltration in PD patients with hyperpermeability [181, 182]. In a limited study, Zhe et al. showed an improved UF capacity due to decreased solute transport rate in PD patients transferred to daytime PD with overnight membrane rest [183]. Kim et al. used a rat model exposed for 3 weeks to glucose dialysate to show that a 4-week-period of rest resulted in a significant reversibility of transport abnormalities, with improved UF and reduction of peritoneal thickness [184]. Similar conclusions were reached by Zareie et al. [46], who showed that a long peritoneal rest (12 weeks) in rats exposed to PD fluids resulted in a significant reduction of angiogenesis and fibrosis.

Individual Variation in Membrane Transport : Genetic versus Clinical Factors

The transport properties of the peritoneal membrane (i.e., the three populations of pores) are usually assessed by the peritoneal equilibration test (PET) or alternative methods such the standard peritoneal permeability analysis (SPA) or the Peritoneal Dialysis Capacity (PDC) tests [185, 186]. Assessing the individual variability in

peritoneal transport has a major clinical importance [185]. The CANUSA study first documented the association between higher transport for small solutes and lower combined patient and technical survival [57], an association that has been confirmed in various populations [56]. Indeed, a high D/P ratio for creatinine is paralleled by a low D/D_0 ratio for glucose with, as a consequence, reduction in the osmotic gradient, loss of UF, and fluid retention. A high transport status may also be associated with increased peritoneal albumin losses and, thus, potential denutrition. Furthermore, individual variability in peritoneal transport status also influences PD prescription: high transporters benefit from short dwells and icodextrin, while low transporters are prescribed longer dwells.

Twardowski et al. first showed that approximately two-thirds of patients have average transport rate, the remaining one third being almost equally distributed between high and low transporters [186]. This considerable patient variability renders it difficult to extrapolate mean values in cohort studies to the individual.

Subsequent series confirmed the existence of a significant interpatient variability in the baseline solute transport characteristics of the peritoneum, and showed that a high co-morbidity score, including hypoalbuminemia, older age, diabetes, and ACE inhibitor prescription were likely influencing this individual variation [53, 57, 187–190]. In particular, systemic inflammation, associated with co-morbid states and hypoalbuminemia as surrogate marker, may result in structural changes such as neoangiogenesis, leading to modifications in transport. Of note, one should remain cautious in interpreting albumin levels in relation to solute transport: rather than being a marker of inflammation, lower systemic albumin concentration may reflect the fluid overload encountered in high transporters. The latter may also lose albumin in the dialysate. At any rate, the complexity of the relationships between UF and small solute transport [190], as well as the fact that independent clinical variables account for only ~20% of the individual variability of solute transport [189], strongly suggest that factors that are not routinely measured do play a role in the baseline functional characteristics of the peritoneum.

The small solute transport rate depends mainly on the amount of perfused capillaries within the peritoneum, the blood flow, and the physical area of membrane contact with the dialysate. Accordingly, an increased EPSA is associated with higher transport of small solutes and, eventually, UF failure. As discussed above, growth factors such as VEGF and TGF-β1, cytokines such as IL-6, together with the release of NO by endothelial cells, play a central role in angiogenesis and fibrosis changes in the peritoneal membrane exposed to PD. Furthermore, polymorphisms within the regulatory region of the genes coding for VEGF, IL-6, and eNOS modify the amount of gene expression in vitro, and they have been associated with diseases – such as diabetic retinopathy and/or nephropathy – that are potentially relevant for the peritoneal membrane. Based on the finding that most of the variability in peritoneal transport remains unexplained by clinical factors, recent studies have investigated whether genetic variants (polymorphisms) could influence transport properties at baseline [191].

Wong et al. were the first to observe a positive association between a variable number of tandem repeats in the intron 4 of *ENOS* (ENOS4a/b) and transport properties in incident PD patients [192]. Of note, the *ENOS* genotype remained an independent predictor for peritoneal transport after adjustment for clinical parameters (gender, age, diabetes) by multivariate analysis. Szeto et al. investigated whether two promoter polymorphisms of *VEGF* may influence peritoneal transport in a series of 135 incident PD patients [193]. There was no association between *VEGF* polymorphisms and transport at baseline. However, in a subanalysis restricted to 83 patients for which a 12-month follow-up was available, there was a positive association between the two variants and the longitudinal changes in D/P creatinine and the VEGF mRNA level in a subset of dialysate effluent samples. Recently, Gillerot et al. investigated the respective contributions of common polymorphisms in *ENOS*, *VEGF,* and *IL6* to the small solute transport rate in a multicentric series of 152 incident PD patients [189]. Their studies identified a common polymorphism of *IL6* as an independent predictor of peritoneal transport, together with co-morbidity and serum albumin level. The effect was reflected by significant changes in IL-6 at the mRNA and protein levels, pointing to the role of local and systemic inflammation in regulating small solute transport [189] (Fig. 27.8).

Taken together, these studies support the hypothesis that inherited genetic variants might regulate specific mediators and, in association with clinical factors, affect the transport properties of the peritoneal membrane. Conflicting results in association studies are common and the methodological limitations have been clearly delineated [194], leading to specific guidelines [195]. Confirming the strength of the positive associations and deciphering the genetic influence on peritoneal transport will require well-designed, adequately powered studies, in different populations and different settings, as well as a detailed assessment of the biological role of the polymorphisms. In addition to the candidate gene approach, future studies will probably benefit from large genome-wide association studies currently performed in diabetic nephropathy or retinopathy.

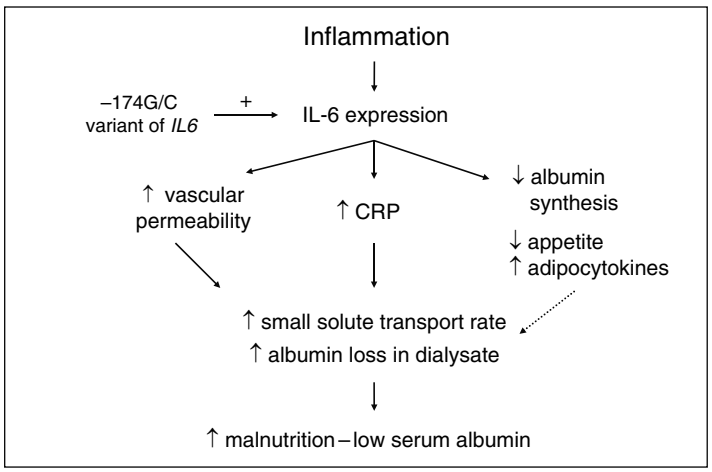


Fig. 27.8 Potential influence of genetic factors on alterations in peritoneal transport during inflammation. A biologically active variant in the promoter of the *IL6* gene regulates the systemic and local expression of the pro-inflammatory cytokine interleukin-6 (IL-6). The upregulation of IL-6 contributes, via local and systemic effects, to the increase in the transport of small solute and the loss of albumin in the dialysate, and to the general state of malnutrition-inflammation. Modified from [189]

Future Therapeutic Strategies and Perspectives for Membrane Preservation in PD

The introduction of glucose-free PD solutions including icodextrin, glycerol, and amino-acids solutions as well as their potential clinical benefits have the clear goal of reducing the deleterious effect of long-term exposure to glucose and its associated deleterious local and systemic effects [89]. The parallel development of two-chamber or dual-chamber bags has allowed a dramatic reduction in dialysate GPD concentrations by reducing GDP formation during heat sterilization [196]. The two-chamber system separates concentrated glucose from other components, allowing sterilization of glucose at a very low pH. Mixing of the two compartments results in a solution characterized by low levels of GDPs and also allows the production of a solution with a more physiologic pH [197–202]. When tested in vitro, such biocompatible dialysates have been shown to reduce AGE formation [203], decrease acute vasoactive effects on the peritoneal circulation [12, 204, 205], and improve ex vivo peritoneal macrophage function [202]. Two short-term randomized trials using such solutions have shown no significant modifications of peritoneal transport parameters but an increase in dialysate CA125 (taken as a marker of mesothelial cell mass) and a decrease in dialysate hyaluronan (taken as a marker of peritoneal inflammation) [201, 206].

As discussed earlier, the development of animal models has provided a rationale for other therapeutic strategies against structural and functional alterations of the peritoneum. Inhibition of the AGE formation [97] with compounds such as aminoguanidine, OPB-9195, or pyridoxamine are being currently evaluated, as well as the possibility of detoxifying RCOs by the glyoxalase pathway [97, 207]. Inhibition of the L-arginine:NO pathway, for instance, with L-arginine analogues has been shown to dramatically improve UF in rat model of acute peritonitis [94]. The potential usefulness of NOS inhibitors in PD patients will have to take into account the current lack of specificity of most inhibitors, as well as the potential problems inherent with inhibition of a ubiquitous mediator such as NO [208]. Inhibition of the oxidative stress by N-acetylcysteine or angiotensin II receptor blocker (losartan) was shown to be effective in preserving membrane structure and function in a rat model [152]. The antisclerosis and anti-inflammatory potential of atorvastatin, lisinopril, and valsartan has been suggested in rat models [209–212], with further demonstration of the effect of ACE-inhibitors and angiotensin II receptor blockers in cultured HPMC [213, 214]. The anticalcic agent diltiazem has been shown to decrease collagen synthesis and IL-1β-induced production of TGF-β1 in HPMC [215].

Modulation of angiogenesis with agents that inhibit endothelial cell growth, adhesion, or migration, or interfere with growth factors such as VEGF and bFGF and their receptors have been proposed. Margetts et al. first demonstrated the validity of the antiangiogenic approach by showing improvement of structural and functional parameters in a chronic infusion rat model of PD treated with adenovirus-mediated gene transfer of angiostatin [91]. However, it should be kept in mind that i) different molecular pathways are involved in various types of angiogenesis; ii) angiogenic growth factors may participate in other physiological processes; and iii) there is little information on safety, long-term side-effects, and impact of antiangiogenic therapy on processes such as healing [216]. Elegant studies showed the potential of the antiangiogenic compounds TNP-470 [217] or endostatin [218] to reduce peritoneal sclerosis – together with angiogenesis – in the chlorhexidine gluconate mouse EPS model. The pharmacologic induction of AQP1 may also provide a target for manipulating water permeability and treating some cases of UF failure [96]. Finally, one may predict that a better knowledge of the genetic determinants potentially involved in the individual variability in peritoneal transport at the onset of PD may pave the way for individualized therapeutic approaches.

Conclusions and Perspectives

This chapter has attempted to describe what is currently known about peritoneal membrane structure and functional change during peritoneal dialysis and to provide insight into the mechanisms that drive these alterations. This has borrowed heavily on both clinical data as well as results from developing work an extensive array of experimental models. Our knowledge of the peritoneal membrane and its alterations during (and preceding) dialysis have increased tremendously over the past 5 years. This has undoubtedly increased our understanding of potential membrane preservation strategies but also of the natural history of changes in the membrane. Hopefully, this, combined with the increasing number of treatment options available, should make it possible to enhance treatment quality, reduce the incidence of infection and membrane failure, and improve patient and technique survival on this treatment modality.

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Abbreviations

ACE	angiotensin converting enzyme
AGE	advanced glycation end product
AQP1	aquaporin 1
D/P	dialysate-over-plasma
EMT	epithelial to mesenchymal transition
EPS	encapsulating peritoneal sclerosis
EPSA	effective peritoneal surface area
GDP	glucose degradation products
HPMC	human peritoneal mesothelial cells
IL-6	interleukin-6
JvL	large pore fluid flux
MTAC	mass transfer area coefficient
NO	nitric oxide
NOS	nitric oxide synthase
PD	peritoneal dialysis
PET	peritoneal equilibration test
RAGE	receptor for advanced glycation end products
RCO	reactive carbonyl species
ROS	reactive oxygen species
sgp130	soluble gp130
sIL-6R	soluble IL-6 receptor
TGF-β	transforming growth factor-β
UF	ultrafiltration
VEGF	vascular endothelial growth factor

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Chapter 28
Peritoneal Dialysis in Diabetic End-Stage Renal Disease

M. Misra and R. Khanna

The management of diabetic patients with end-stage renal disease (ESRD) has undergone significant changes over the past few decades. Diabetics with extensive co-morbid diseases are generally accepted for chronic dialysis despite the inevitably poor long-term prognosis [1–4]. As a result, diabetes has become the most prevalent cause of ESRD in the United States. Between 1984 and 1997, the percentage of new patients starting renal replacement therapy (RRT) with ESRD due to diabetes increased from 27% to 42.9% in United States [5]. The 1- and 2-year mortality for diabetic patients in peritoneal dialysis (PD) between the years 1989 and 1998 has decreased by 26.6 and 20% per 1,000 patient years, respectively [5]. However, diabetic renal disease still has one of the highest mortality rates at the end of first year of dialysis when compared to renal transplantation and dialysis in nondiabetics [6]. Diabetic patients, regardless of dialysis modality, continue to have the lowest 5 year survival [7]. Nearly half of the diabetic patients begun on dialysis do not survive beyond 2 years, and less than one in five diabetic patients undergoing maintenance dialysis is capable of any activity beyond personal care [8]. Renal transplantation is the generally preferred treatment for diabetic patients with end-stage renal failure because it leads to better quality of life than any form of dialysis [9].

In such a setting, choosing a dialytic mode that has a better potential for survival, and that promotes better quality of life, is extremely important. However, choosing a dialysis therapy at present is subject to the strong personal biases of both physician and patient. This is because a clear difference between the outcomes of hemodialysis and peritoneal dialysis for diabetic patients has not been observed. In the 1960 s and early 1970 s, intermittent peritoneal dialysis (IPD) performed on diabetic ESRD patients, either in hospital or at home, with a cycler over 30–40 h/week, showed a promising decline or even arrest of uremic neuropathy and retinopathy. However, possibilities for patient survival beyond 2–3 years were dismal [10–14]. Thus, it appears that, with the loss of residual-renal function, which takes about 2–3 years in PD patients, the amount of dialysis provided with IPD was not adequate, and the majority of patients were dying from either electrolytic abnormalities or progressive uremia. The introduction of continuous ambulatory and continuous cyclic peritoneal dialysis (CAPD/CCPD) during the late 1970 s allowed both diabetic and nondiabetic patients to be treated adequately, and was quickly established as a viable alternative renal replacement therapy to hemodialysis [15–23].

The Proposed Benefits of CAPD/CCPD

There are both medical and social benefits of CAPD/CCPD [24]. Since it is essentially a home therapy, and allows flexibility in treatment, CAPD/CCPD has several social benefits: it allows home dialysis at a lower cost, permits long-distance travel, permits uninterrupted job-related activity, etc. However, in choosing a dialysis therapy both medical and social benefits should be taken into consideration. The proposed medical benefits of CAPD/CCPD that make it a preferred therapy over hemodialysis are listed in Table 28.1. During the course of this chapter we will attempt to examine these issues in more detail, to determine whether there is sufficient evidence to make such claims.

M. Misra (✉)
University of Missouri School of Medicine, Columbia, Missouri
e-mail: misram@health.missouri.edu

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Table 28.1 Proposed benefits of CAPD

1.	Slow and sustained ultrafiltration and a relative lack of rapid fluid and electrolyte changes compared to hemodialysis
2.	Ease of blood-pressure control
3.	Preservation of residual renal function for a period longer than hemodialysis
4.	Access for dialysis is easier
5.	Blood sugar control is possible through intraperitoneal route
6.	Steady-state biochemical parameters

Drawbacks of CAPD

Despite the many attractive advantages of CAPD, some of its drawbacks are of significant consequence and, therefore, may limit its widespread application. CAPD-related episodes of peritonitis, although less frequent with the use of devices that employ the "flush-before-fill" technique, and no higher in incidence than in nondiabetic CAPD patients, are one of the major causes of morbidity and therapy failure. Continuous loss of protein through the dialysate may aggravate nutritional problems of some of the chronically ill patients. Long-term integrity of the peritoneum, a biological membrane, has not been unequivocally established. Some of the social problems related to CAPD, such as distorted body image and burnout due to continuous therapy, may also limit its long-term use. Aggressive normalization of blood pressure in some diabetic patients with autonomic dysfunction and orthostatic hypotension may pose problems with maintaining fluid balance, and may aggravate ischemic complications. Excessive weight gain and hyperlipidemia as a consequence of continuous glucose absorption in some patients can be causes for concern. Ultrafiltration failure may be a troublesome problem, particularly in diabetics. During the past few years, advances in the field have enabled us to address some of these concerns and propose remedial measures to improve the risk–benefit ratio of this therapy. These aspects will be discussed in more detail later in this chapter.

When Is the Ideal Time to Initiate Dialysis in Diabetics?

Nearly every diabetic patient approaching end-stage renal failure has hypertension [25]. Additionally, the relative or absolute lack of insulin causes hyperglycemia, ketosis, and changes in transmembrane electrical potential in diabetics [26]. These problems lead to a higher frequency of fluid retention and electrolyte and acid–base disturbances in diabetics at a glomerular filtration rate higher than nondiabetics. Keeping this concern in mind, since April 1995 the United States Health Care Financing Administration's (HCFA) guidelines for diabetic patients with ESRD initiating dialysis have been revised. The HCFA now recommends that such patients may be started on dialysis at a C_{Cr} of less than 15 mL/min or a serum creatinine of 6.0 mg/dL (the respective comparable figures for nondiabetic patients being 10 mL/min and 8 mg/dL). Nevertheless, the average creatinine clearance at which dialysis is initiated is 4.9 mL/min [27]. There has been, however, an increase in the GFR at the time of dialysis initiation, from 7.5 mL/min in 1995 to 10.1 mL/min in 2005 [7]. The correlation between early initiation of dialysis and better patient outcome was reported as early as 1985 [28], later confirmed by several other studies [29, 30].

Theoretically at least, optimal pre-ESRD care and timely initiation of dialysis (before renal Kt/V falls below 2.0) seem attractive options. However, issues such as cost, patient burnout, and access-related morbidity need to be addressed in a controlled trial [31]. The Kidney Dialysis Outcomes Quality Initiative (K DOQI) guidelines of the National Kidney Foundation make a strong case for such a timely start of dialysis in both diabetic as well as nondiabetic ESRD patients [32].

Peritoneal Access

One of the advantages of peritoneal dialysis is the ease with which the peritoneum can be accessed. It is possible to use the catheter for supine peritoneal dialysis immediately after its insertion. This avoids the need for temporary access or preplanned-access surgery that is so often necessary in hemodialysis. Access to the peritoneal cavity is obtained through the use of either a Tenckhoff catheter or one of its newer modifications [33, 34]. The technique of catheter insertion, break-in procedure, and postoperative catheter care in diabetics is similar to that used in nondiabetic patients and described in detail in Chapter 9 of this book.

The common catheter complications are exit/ tunnel infection, catheter-cuff extrusion, poor dialysate flow, dialysate solution leak, pain in association with fluid flow, and peritonitis. CAPD experience gained over years has confirmed the earlier observations that catheter survival rates and infectious and noninfectious complications of peritoneal access are no different for diabetic patients than nondiabetic patients on peritoneal dialysis [35]. The spectrum of microorganisms causing peritonitis in diabetics is no different; the earlier concern of predilection for fungal infections in diabetics has turned out to be ill-founded. Although a cause-and-effect relationship is not established, the route of insulin delivery seems to influence the incidence of exit-site and/or tunnel infection. In an exhaustive survey of CAPD/CCPD patients with ESRD attributed to diabetes mellitus, performed by the U.S. National Institutes of Health CAPD Registry [35], exit-site and/or tunnel infection rates per patient-year by route of insulin administration were calculated. Although differences in rates were small, diabetics never using insulin had the lowest rate of exit-site/tunnel infection per patient-year (0.47), while patients using subcutaneous insulin reported the highest rate (0.65). The exit-site/tunnel infection rate per patient-year for patients using intraperitoneally administered insulin (0.60) was similar to the rate reported for patients using a combination of subcutaneous and intraperitoneal insulin (0.54). Blind patients using subcutaneously administered versus blind patients using intraperitoneal insulin reported similar rates per patient-year of exit-site/tunnel infection. Catheter replacement rates per patient year were similar for all patient groups (0.16–0.20).

Dialysis Schedules

Intermittent Peritoneal Dialysis

During the 1970 s, the recommended scheme of peritoneal dialysis was IPD with an automated peritoneal dialysis cycler providing 40 h of dialysis a week, divided into one or two sittings [10]. Blood sugar control while on IPD was achieved with insulin administered both subcutaneously and intraperitoneally. The amount of insulin administered was adjusted to individual requirements. On dialysis days the patients were given the usual daily dose of insulin by subcutaneous injection; an additional amount of regular insulin was added to the dialysis solution until the last five exchanges of dialysis to compensate for the glucose absorbed from the peritoneal cavity during the dialysis solution exchanges. Insulin was omitted from the last few exchanges to prevent post-dialysis hypoglycemia. Insulin requirements were determined at the initiation of each patient's first few treatments. The amount of insulin required was directly proportional to the amount of glucose load instilled during dialysis to achieve ultrafiltration. It took up to 2 weeks after initiation of dialysis to determine the exact amount of insulin required by an individual patient. Once established, the insulin requirements did not generally change unless new complications were encountered. In these patients, retinopathy and neuropathy seemed to stabilize during the course of IPD treatment. Hemoglobin and hematocrit were maintained at satisfactory levels without blood transfusions. Compared to nondiabetics on IPD, these patients experienced a higher incidence of fibrin-clot formation in dialysis effluent and a higher incidence of peritonitis. The patients also experienced higher rates of arterial calcification and hypertension. The majority of patients died from cardiac and cerebrovascular complications. Significant percentages of patients died suddenly at home, presumably due to a coronary event or from an electrolyte abnormality. The probability of patient survival at 1 and 2 years was 44% and 20%, respectively [10]. Outcomes of IPD in other centres with smaller numbers of patients were similar [11–14]. The main reason for the low survival rate may have been related to inadequate dialysis, since this IPD scheme as advocated in the past provided (under the best circumstances) a dialysis creatinine clearance of 20 L/week or less. Presumably most patients were underdialyzed and became more uremic with the gradual loss of renal function. Since the advent of CAPD the use of such a scheme of IPD has declined. In any case, due to its inadequacies, such a prescription is no longer recommended or acceptable as an effective renal replacement therapy.

Automated Peritoneal Dialysis (APD)

A variant of IPD with a much longer weekly duration and a larger amount of dialysis, daily night-time IPD (NIPD), is now used for home treatment in patients who are unsuitable for CAPD [36–39]. Other than the patient's preference, the indications for NIPD include those patients having high peritoneal membrane solute transport characteristics and those who develop complications as a result of increased intra-abdominal pressure during CAPD. The rise in intra-abdominal pressure in the supine position is considerably lower than in the upright position

[40]. During the NIPD treatment at home, the patient is confined to bed and sleeps during most of the therapy time. In order to provide the recommended amount of dialysis, NIPD needs to be carried out, depending on the peritoneal solute transport rate, 8–12 h/day using dialysis solution flow rates ranging from 12 to 17 L/day. A typical NIPD prescription is for a 1.5–2.5 L fill volume and 1 h cycles for 8–10 h of treatment time. In patients with low peritoneal transport characteristics, additional dialysis may be provided by the last bag fill option and leaving the solution dwelling in the peritoneal cavity during the day. Like IPD, the major benefit of NIPD is the lower incidence of complications related to high intra-abdominal pressure compared to CAPD. Importantly, the peritonitis rate is considerably lower probably due to a reduced number of connections and improved host-defense mechanisms [41].

Continuous Cyclic Peritoneal Dialysis (CCPD)

CCPD is a reversal of the CAPD schedule [42]. It uses multiple short cycles during the night with an automated cycler and a long daytime exchange while the patient is ambulatory. With this technique, variable volumes of dialysis solution are delivered for a prescribed dwell time with the aid of an automated cycler during the night (three or four 2-L commercial dialysis solution infusions are generally administered during the night, each dwelling for 2–3 h) and then are drained by gravity at the end of the dwell. An additional 2 L of dialysis solution is infused in the morning and is allowed to dwell intra-peritoneally for the next 14–15 h with the catheter capped. Hypertonic dialysis solution containing 2.5–4.25% dextrose is recommended for the daytime exchange in order to prevent significant absorption of the solution. Diaz-Buxo [42] observed that it is difficult to design a uniform method for intraperitoneal insulin administration for blood glucose control in CCPD patients due to the fact that during the day, when most of the dietary caloric load is consumed, they carry out only one peritoneal dialysis exchange for 12–14 h and essentially no food is eaten during the night, when several dialysis exchanges are carried out. Nevertheless, Diaz-Buxo claims excellent glycemic control can be obtained in the majority of patients if time is spent to individualize the precise dose of insulin required, and if a regular and predictable caloric intake is maintained with little day-to-day variation. He recommends that the insulin dose be appropriately divided among all the dialysis solution bags, depending upon the caloric load. Such a distribution avoids sudden and massive infusions of insulin and consequent hypoglycemia or hyperglycemia. The average intraperitoneal insulin dose required for good control of glycemia has been about three times the predialysis total subcutaneous dose. In most cases, 50% of the intraperitoneal dose is used for the long-dwell daytime exchange, with the remaining 50% equally divided among the nocturnal exchanges. For more detailed instructions readers are advised to refer to the protocol recommended by Diaz-Buxo [42]. The 1-year patient survival for diabetic patients on CCPD is reported to be 76% [42]. The main indications for CCPD in diabetics include patient preference; young diabetics awaiting cadaver or living-related renal transplantations; and older, blind, and dependent diabetics requiring partner support for the dialysis technique. The medical circumstance under which CCPD is often recommended over CAPD is in CAPD patients who have shown a tendency to develop complications related to increased intra-abdominal pressure. Another group of patients who may benefit from CCPD are those who complain of chronic low-back pain on CAPD.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

The standard CAPD technique has been previously reported [15]. In short, in the past the technique usually consisted of exchanging four 2-L dialysis solution bags/day using appropriate glucose concentrations from the range available (0.5, 1.5, 2.5, 4.25%) to achieve adequate ultrafiltration. Patients are taught to add insulin into the dialysis solution according to the protocol to be discussed later. The technique of CAPD is usually modified to accommodate the handicapped diabetic patient's desire to self-perform dialysis at home. Visual impairment, peripheral vascular disease with amputation of a part or entire limb, and peripheral neuropathy with sensory and/or motor function impairment are some of the physical disabilities observed in these diabetic populations. Devices such as the ultraviolet box [43], splicer [44], Oreopoulos-Zellerman connector [45], Y-system [46], and Injecta aid [47] are used with success in many patients. These devices have enabled a number of blind diabetics to self-perform CAPD. Although published reports of usage of such devices are scarce, anecdotal experiences of their usefulness are encouraging. In our center, the training period averages 5 working days while a complex patient may take as much as 20 working days.

Theoretical modeling [48, 49], later confirmed by studies using multivariate analyses [50], convincingly demonstrate an association between urea and/or creatinine clearance and survival in dialysis patients. For

example, a weekly Kt/V_{urea} of 2.1 (corresponding to a creatinine clearance of 70 mL/min) predicted a 2-year survival of 78% in the CANUSA study [50]. No particular target value of creatinine clearance or Kt/V_{urea} for diabetes is currently available. However, based on a review of the available data, the recently released K-DOQI guidelines recommend that an adequate amount of dialysis should achieve at least a combined (dialysis and residual-renal function) Kt/V of 1.7/week [32] in all patients. Many CAPD patients must use 2.5–3.0 L exchanges to achieve these targets.

Glucose as An Osmotic Agent

Several years of experience with peritoneal dialysis has indicated that glucose has proved to be an effective osmotic agent for inducing ultrafiltration during peritoneal dialysis. However, use of glucose has been identified with numerous undesirable metabolic effects, which necessitate a search for alternative osmotic agents. An average CAPD patient typically absorbs 100–150 g of glucose per day during the course of CAPD with glucose-based PD solutions. This inevitably large amount of carbohydrate absorption unavoidably leads to unwanted metabolic problems such as obesity, hypertriglyceridemia, and premature atherosclerosis [51]. There is also concern that continuous contact of the peritoneum with glucose may induce peritoneal mesothelial damage by nonenzymatic glycosylation leading to formation of advanced glycosylation end-products (AGE). Both in vitro and ex vivo evidence points towards AGE formation in conventional dextrose-containing dialysate [52–54]. The accumulation of AGE products may be a significant factor in the treatment failure of the long-term peritoneal dialysis patient by their effect on peritoneal membrane function and morphology [55]. In addition, higher doses of insulin required to maintain the blood sugar at normal levels may cause hyperinsulinemia which, even in healthy persons, has been shown to be a risk factor for atherosclerotic heart disease [56, 57]. Glucose has also been implicated to cause adverse hemodynamic effects in peritoneal dialysis [58]. To obviate the unacceptable metabolic consequences of glucose absorption, efforts have been made to substitute glucose with xylitol [59], amino acids [60], gelatin [61], polyglucose [62], glycerol [63], or polypeptide [64]. Although every agent tried has been found to be an effective osmotic agent, and also prevented or minimized the unwanted metabolic effect of glucose, none has been found to have the favorable metabolic profile of glucose. As a result of unacceptable toxicity or metabolic profiles, or prohibitively higher cost, compared to glucose, their use as osmotic agents has been limited. Amino acid mixtures of 1–2% in the dialysis solution have been used effectively to induce ultrafiltration in nondiabetic CAPD patients [60]. In four diabetic patients followed for >12 months on a 1% amino acid solution, serum albumin and cholesterol increased when compared with the control group [65]. The absorbed amino acids cause significant increases in total body nitrogen and transferrin, reduce the inevitable glucose load, and lower serum triglyceride levels. Use of such mixtures in diabetic CAPD patients has the potential to reduce many of the undesirable effects of glucose. However, their effectiveness over long periods has not been established. Furthermore, the high cost of amino acid mixtures could be a major limiting factor in their general use. Glycerol-containing dialysis solution has been used successfully in diabetic CAPD patients. This agent was well tolerated by the patients, was nontoxic to the peritoneal membrane, did not cause hepatotoxicity, and did not increase protein losses in the dialysate [63, 66]. Blood sugar was easily controlled with insulin. Some patients did develop signs and symptoms of hyperosmolality. However, glycerol showed no benefits over glucose because it delivered similar amounts of total caloric load and the problem with hyperlipidemia was unaltered. Larger molecular-weight polyglucose (Icodextrin) appears to be a safe and effective osmotic agent providing sustained ultrafiltration by a mechanism resembling "colloid" osmosis [67]. A total of 240 patient-years experience, ranging from single-dwell to full-scale multicenter studies, has thus far been accumulated with the use of Icodextrin. Its ability to provide sustained ultrafiltration over prolonged dwells, and absence of any significant long-term effect on peritoneal permeability, make it a viable alternative osmotic agent as compared to dextrose in diabetic CAPD patients [68]. Use of Icodextrin may also be associated with improved glucose control in diabetic patients [69]. Also, Icodextrin use in diabetic patients may lead to better preservation of peritoneal membrane function over time [70]. Observational data suggest that more biocompatible dialysates with low glucose degradation products and neutral pH may have a survival advantage in peritoneal dialysis. This needs to be validated in randomized control trials [71]. Polypeptides as an osmotic agent have been found to be safe in CAPD patients during an acute study [64]. However, long-term studies are needed to evaluate its usefulness, and also to study whether it has nutritional value in addition to its osmotic effect. Overall, at least for now, glucose remains the most widely used osmotic agent for peritoneal dialysis although Icodextrin may be used as an alternative agent in specific situations as a part of the peritoneal dialysis fluid regimen.

Blood Sugar Control During Peritoneal Dialysis

The aim of blood sugar control during peritoneal dialysis is to maintain a state of euglycemia throughout the dwell time, control post-meal glycemia, and avoid morning hypoglycemia. Uremia alters the insulin responsiveness; hence, the amount required to control blood sugar in a dialysis patient becomes unpredictable [72]. Glycosylated hemoglobin C (HbA_1C) is widely used as an indicator of monitoring glycemic control in peritoneal dialysis. HbA_1C metabolism is unaltered in renal failure. Although carbamylation of Hb is known to interfere with a particular HbA_1C assay, when immunological or other chemical methods of assay are utilized, this problem is easily overcome. Increasing HbA_1C levels usually imply worsening control (regardless of the method used) and correlate with glycemic control [73]. It is important to note that Icodextrin and its metabolite, maltose, can interfere with or cause false elevated glucose results. Caution is therefore advised while monitoring blood glucose, which must be done with a glucose-specific method (monitor and test strips) to avoid interference [74].

Methods have been used for blood glucose control during peritoneal dialysis, especially during CAPD. The survey of the U.S. NIH CAPD Registry [35] in 499 patients with ESRD attributed to diabetic nephropathy found five different treatment regimens for blood sugar control during CAPD therapy; 86% of the surveyed patients were taking insulin only, 2% took insulin with an oral hypoglycemic agent, 4% were on an oral agent only, 6% were on diet therapy alone, and the remaining 2% were on no specific therapy at all. Of the 434 patients taking insulin, 36% received it through subcutaneous injections only, 54% through intraperitoneal delivery only, and 10% through a combination of subcutaneous injections and intraperitoneal delivery. Although there are no studies that show one regimen of insulin administration clearly superior to others for CAPD patients, for reasons discussed below, if insulin is required to control blood sugar, attempts should be made to administer it intraperitoneally.

Kinetics of Intraperitoneal Insulin

There is evidence to suggest that intraperitoneal insulin delivery allows more rapid and consistent absorption of insulin; when absorbed, insulin preferentially enters the hepatic portal venous circulation and this hepatic delivery may beneficially affect lipid metabolism and peripheral insulin levels.

There are several similarities between the absorption kinetics of intraperitoneally administered insulin and the normal secretion of insulin by the islet cells. Insulin release in a normal person is a complex coordinated interplay of food absorbed from the gut, gastrointestinal hormones, and other hormonal and neural stimuli. Insulin secreted by the islet cells is taken into the portal vein, and, thereafter, the liver removes 50–60% of the secreted insulin presented to it [75]. In the basal state the portal/peripheral ratio of insulin is 3:1. Following bursts of secretion in response to glucose or amino acids, the portal/peripheral ratio may reach a value of 9:1. Insulin administered into the peritoneal cavity is absorbed preferentially by diffusion across the visceral peritoneum into the portal venous circulation. Additionally, direct absorption through the capsule of the liver has also been reported [76]. Once in the liver a significant fraction of insulin is cleared by the liver during its first pass. Initial delivery of insulin to the liver simulates physiological insulin secretion more closely; absorption is continuous until the end of the dwell [77–83].

Some of the causes for glycemic lability in diabetic patients taking subcutaneous insulin injections [84, 85] are degradation of insulin in the subcutaneous tissues and variations in absorption due to factors such as depth and location of injection, exercise, or regional blood flow. Peritoneal delivery of insulin alleviates these variables and allows for predictable metabolic management [75, 86, 87].

Benefits of Intraperitoneal Insulin

There are benefits when insulin is delivered to the liver during its first pass. Relatively few studies have carefully examined this issue. Studies in dogs show that insulin delivery via the portal route may be necessary to maintain normal levels of hormones and metabolites [88, 89]. However, both portal and peripheral insulin delivery have similar effects on hepatic and extrahepatic carbohydrate metabolism [90].

Excessive basal hepatic glucose output is the principal cause of elevated fasting plasma glucose levels in non-insulin-dependent diabetes mellitus (NIDDM) [91, 92] in normal and NIDDM subjects, hepatic glucose output is much more sensitive to suppression by insulin than is stimulation of peripheral glucose uptake [93]. While reviewing the benefits of intraperitoneal insulin, Duckworth and colleagues argue in favor of treating NIDDM with intraperitoneal insulin because intraperitoneal insulin delivery can selectively inhibit increased hepatic glucose output with a relatively lower

degree of hyperinsulinemia in NIDDM compared to subcutaneous insulin injections [94]. Duckworth [75] stresses that, for any given dose of insulin, the amount that reaches the peripheral circulation is considerably less when the insulin is delivered intraperitoneally rather than subcutaneously. This observation is all the more important in view of the increasing evidence suggesting that circulating insulin levels may be directly related to the risk of atherosclerosis [95–97].

In normal subjects a low basal level of insulin is maintained between ingestion of meals [98]. Peritoneal delivery of insulin results in rapid and consistent absorption and allows for maintaining a low basal level between meals. The significance of maintaining a basal level of insulin was clearly shown by studies showing that programmed insulin-infusion systems, which provide insulin in basal as well as pre-meal doses, are far more effective in normalizing blood glucose concentrations in type I diabetes than pre-meal insulin doses alone [99]. Persistent hyperinsulinemia, a rare occurrence in normal subjects, occurs frequently when insulin is subcutaneously injected. One study suggests that intraperitoneal insulin is necessary to normalize lactate levels [100].

A number of studies suggest that intraperitoneal insulin therapy is associated with lipoprotein profiles of lower atherogenic potential [101–103]. These studies demonstrated a reduction in the cholesterol content of high-density lipoprotein (HDL) in patients treated with intraperitoneal insulin compared with subcutaneous insulin, with no change in apolipoproteins A-I and A-II. Moreover, intraperitoneal insulin was associated with lower very-low-density lipoprotein (VLDL) triglycerides, VLDL apolipoprotein B, and near-normal levels of cholesterol ester transfer. The conclusion of these studies was that intraperitoneal insulin was more physiological and corrected a key step in reverse cholesterol transport in patients with IDDM. Hepatic functions, other than carbohydrate and lipid metabolism, that are dependent on insulin may also be improved with intraperitoneal administration [75]. For example, intraperitoneal insulin results in higher levels of plasma hydroxyvitamin D levels than subcutaneous insulin, even with comparable glucose control [104].

Both intensive subcutaneous insulin therapy and peritoneal insulin delivery can return the blood glucose levels and glycosylated hemoglobin values to normal. But the benefit of peritoneal delivery is fewer glycemic excursions, so that the difference between low and high glucose values during a day are lower compared to subcutaneous insulin [105]. Moreover, frequency of hypoglycemic episodes is reduced with peritoneal insulin.

A three-step euglycemic clamp in six matched groups (healthy subjects, insulin-dependent diabetics with normal kidney function, nondiabetic uremics, nondialyzed uremic diabetics, and diabetics on hemodialysis and CAPD) showed that the insulin-mediated glucose uptake is closer to normal in CAPD patients taking intraperitoneal insulin than in subjects on hemodialysis taking subcutaneous insulin [106]. In another retrospective study [107], insulin requirements were examined in two groups of dialyzed and nondialyzed diabetic patients, one treated with subcutaneous insulin and the other with intraperitoneal insulin. The blood glucose levels were significantly lower with the CAPD/intraperitoneal group compared to both CAPD/subcutaneous and HD/subcutaneous groups at every time interval for as long as 15 months.

Because of the similarities between the effects of intraperitoneally administered insulin and the physiologically secreted insulin, glycemic and metabolic control during CAPD is more physiological than during hemodialysis. Such an advantage should impact on the overall long-term progression of diabetic complications in patients on dialysis. The effects of intraperitoneal insulin in the progression of target organ diseases in CAPD patients are difficult to ascertain because of the high prevalence of end-stage multi-organ damage at the time of initiation of dialysis; nearly half the patients do not survive 2 years on the therapy. Moreover, young patients with early target organ damage, appropriately, are very quickly transplanted and do not stay on the therapy long enough to observe the impact of therapy. Unless observations in diabetic CAPD patients extending over 5–10 years are carried out, we will not know intraperitoneal insulin's effect on the slowing of the progression of target organ diseases. For now, it is clear that short-term metabolic control with intraperitoneal insulin is better than that achieved with subcutaneous insulin and, therefore, should favour CAPD over hemodialysis.

Problems of Intraperitoneal Insulin Therapy

Some anecdotal experiences suggest increased incidence of peritonitis in patients receiving intraperitoneal insulin [108]. Contrary to this observation, the National CAPD Registry survey of peritonitis rates per patient-year by route of insulin administration and type of diabetes management revealed patients using a combination of subcutaneous and intraperitoneal insulin experienced the lowest rate (0.93 episodes per patient-year) of peritonitis [35]. The peritonitis rate per patient-year for patients using subcutaneously administered insulin (1.03) was similar to the rate reported for patients using intraperitoneal insulin (1.06). Blind patients using subcutaneously administered versus blind patients

using intraperitoneal insulin reported similar rates of peritonitis. It has been suggested that insulin may have a bactericidal effect. In a more recent report, the rate of peritonitis in intraperitoneal insulin administration was mainly increased in CAPD patients. However, it was still in an acceptable range compared with patients without diabetes [109].

The other problem observed with the use of intraperitoneal insulin is subcapsular liver steatonecrosis [110] and malignant omentum syndrome [111]. Steatosis in a unique subcapsular distribution was observed during autopsy in 10 of 11 CAPD patients treated with intraperitoneal insulin and in none of the nine control CAPD patients receiving no insulin. More studies are needed to understand the importance of this focal lesion in the livers of CAPD patients receiving intraperitoneal insulin. In patients with malignant omentum syndrome, insulin is trapped in the omentum, probably in response to foreign protein.

From the above discussion it is evident that there are a number of metabolic and long-term benefits to peritoneal delivery of insulin for diabetic patients. Diabetic dialysis patients, despite the far-advanced target organ damage, should be given the benefit of peritoneal delivery of insulin for better metabolic control and to derive the antiatherogenic benefit, however small.

Steps of Blood Sugar Control in a New CAPD Patient Using the Intraperitoneal Route

Several protocols of blood sugar control with intraperitoneal insulin have been published [17, 21, 112–115]. These protocols were designed based on the vast experiences of the individual centers. There are no studies that compare the effectiveness of different methods, but from a clinical perspective they all seem effective in achieving the goal of good metabolic control. The method described below is the one practiced at our center.

The goal of therapy is to maintain blood sugar at about 150 mg/dL throughout the day and achieve a HbA_1C level of 7% or below without the hypoglycemic symptoms. During and for a week or two after the initiation of CAPD, blood sugar is controlled with daily multiple subcutaneous injections of regular insulin as per the standard practice of blood sugar control. This interval allows for CAPD to be established and the dialysis dose to be determined. An attempt is made to switch to the intraperitoneal route of insulin administration after explaining the practice to the patient. It is not uncommon for patients to refuse the intraperitoneal approach for fear of the unknown. On the first day of the switch, 100% of the CAPD daily subcutaneous insulin dose is divided among all four exchanges, with a reduced insulin dose (50–70%) added to the overnight dwell. Although many patients may need more than 100% of subcutaneous dose of insulin when switched to the intraperitoneal route, it is recommended to use caution initially in order to avoid severe hypoglycemia. Although the amount of insulin required to control blood sugar intraperitoneally is comparatively smaller than in the subcutaneous route, when the liver is insulinized during the first pass of exogenous insulin through the intraperitoneal route, only about half the injected amount is absorbed through the peritoneal route during a 6-h dialysis exchange [83]. Therefore, it is appropriate to initiate intraperitoneal mode with 100% of the subcutaneous dose.

Review of fasting, 2 h postprandial and/or pre-exchange blood glucose results of the previous day allows stepwise changes in insulin added to each cycle until the desired blood glucose control is achieved. Below are some helpful hints for the use of intraperitoneal insulin. The dialysis exchanges are performed during the day to coincide with the major meals, i.e., breakfast, lunch, and supper. The fourth exchange is made at around 2300 h, at which time a small snack may be taken. The patient is advised to consume a diet providing 20–25 kcal/kg body weight/day and containing protein of 1.2–1.5 g/kg body weight. During the initial control, blood sugar by the finger-stick method is estimated four times a day, pre-exchange. After cleaning the blood port of the dialysis solution bag with a sterilizing solution, using a syringe with a long needle, regular insulin is added to each dialysis solution bag. The time of insulin injection into the bag, prior to solution infusion, should be standardized. The bag is inverted two or three times to aid mixing. Increments in insulin are required for each additional hypertonic dialysis cycle incorporated into the daily routine. Increments differ among patients. Individual patient requirements are determined during training. Patients are trained to check their blood sugar levels with the finger-prick method. This method, which gives quick results and correlates well with venous blood sugar levels, helps the patient monitor unexpected fluctuations in blood sugar. The finger-prick test is performed 5–10 min before each bag exchange and, whenever necessary, the dose of insulin added to the next bag is adjusted according to the guidelines taught the patient at the time of training.

Intraperitoneal insulin requirements during episodes of peritonitis are widely believed to be increased, but hypoglycemia has recently been reported when the usual dose of intraperitoneal insulin was continued during peritonitis [116]. Also, in diabetic rats it has been shown that peritonitis does not change intraperitoneal requirements during standardized peritoneal dialysis exchanges [117]. Blood glucose during peritonitis is likely to be determined by the relative importance of increased insulin absorption and reduced carbohydrate intake due to anorexia versus increased

glucose absorption and the infection-related catabolic state. If care is not exercised, severe fatal hypoglycemia may be encountered with intraperitoneal insulin administration.

In diabetic CAPD patients such treatment objectives as maintaining morning-fasting glucose less than 140 mg/dL, post-meal hyperglycemia less than 200 mg/dL, and HbA_1C levels less than 9% is easily achieved with intraperitoneal insulin administration. Insulin injected into the tubing and flushed into the peritoneal cavity with a small volume of dialysis solution reduces the total amount of insulin needed to normalize blood sugar compared to mixing insulin with the dialysis solution prior to infusion [118]. Some type II diabetic patients have difficulty maintaining satisfactory blood sugar levels even with very large doses of insulin. The reason for such refractoriness to intraperitoneal injection of insulin is not clear, but is believed to be due to the trapping of insulin in the mesenteric or omental lymphatics [111]. There is evidence that addition of oral Rosiglitazone may improve blood glucose profile by improving insulin sensitivity and decreasing inflammatory response [119].

Site of Intraperitoneal Delivery

Most protocols recommend mixing insulin with the dialysis solution before delivery into the peritoneal cavity. This way, insulin is diluted nearly 2,000 times and a very low insulin concentration is achieved in the solution. Due to the low concentration gradient, insulin diffusion is slow and continuous. On the other hand, when insulin is injected into the connecting tube through a special injection port, a high concentration of insulin is achieved in the first 50 mL of dialysis solution that gets infused into the peritoneal cavity [112]. This approach may reduce the amount of insulin required.

Blood Sugar Control During APD

Blood-sugar control while on NIPD is achieved with insulin administered either subcutaneously or both subcutaneously and intraperitoneally. The amount of insulin administered is adjusted to individual requirements. During the day, patients are given the daily dose of insulin, usually long-acting, by subcutaneous injection, the dose determined both by patient's dietary caloric intake and insulin sensitivity. An additional amount of long-acting insulin is given subcutaneously or regular insulin intraperitoneally at the initiation of cycler therapy. The amount of insulin needed is dependent on the patient's insulin sensitiveness and the amount of glucose absorbed during the dialysis. Type I diabetics typically need considerably less insulin compared to type II diabetics. During the first few treatments, blood sugar is determined several times and insulin dose is titrated to maintain the desired blood sugar level. It takes several treatment days to determine the exact amount of insulin required by an individual patient. Once stable, blood sugar may be checked periodically during treatment.

Clinical Results

Blood Pressure Control

Blood pressure control on CAPD is simple, due to continuous sustained ultrafiltration and sodium removal, which maintains patients at their dry body weight [120, 121]. The reduction in blood pressure is most marked during the initial weeks of therapy and additional decreases occur over the next few months [121]. The blood pressure response to CAPD correlates well with the reduction in fluid body weight, emphasizing the importance of fluid volume in the pathogenesis of hypertension in ESRD. Hypertension can often be controlled without drug therapy, even when plasma renin and aldosterone levels are observed to be increased [122].

During CAPD exchanges, net water as well as sodium is removed. A typical CAPD patient loses about 1–1.5 L/day of ultrafiltrate with a sodium concentration of about 132 mEq/L since the dialysate equilibrates with serum sodium during a 4–6 h exchange [123, 124]. The total sodium loss during a day can also be readily calculated as the sum of (drain volume × drained dialysate sodium concentration) – (infusion volume × infused dialysate sodium concentration) for each day. Thus, a typical CAPD patient could easily lose up to 132–198 mEq/day of sodium through the ultrafiltrate. A patient accustomed to restricted sodium intake during the course of chronic renal failure continues his/her low-sodium diet during CAPD therapy. Consequently, CAPD patients become sodium-depleted over the course of therapy due to the combination of dialysate sodium loss and restricted consumption. Initially, such sodium depletion is

beneficial in controlling hypertension. Most CAPD patients, requiring multiple antihypertensive agents for control of hypertension prior to starting CAPD, gradually need fewer and fewer drugs, eventually discontinuing them altogether [123]. If, at this time, dietary sodium intake is not liberalized, severe sodium depletion could lead to hypotension, especially in patients with primary cardiac disease. Total body sodium depletion results in decreased vascular response to infusions of pressor agents such as norepinephrine [125]. Salt repletion in such patients results in restoration of the vascular pressure response, extracellular fluid volume, and blood pressure.

In certain CAPD patients, such as those with diabetic autonomic neuropathy or cardiac dysfunction, hypotension may occur readily and very early after initiating CAPD. Surprisingly, many patients are asymptomatic, despite a severe degree of hypotension (possibly due to a lack of renin response from the kidneys, since most patients are functionally anephric).

On the other hand, during intermittent dialysis therapies the dialysate sodium concentration decreases due to solute sieving with ultrafiltration, hence sodium loss is considerably diminished [123]. Consequently, hypertension control in patients on intermittent dialysis therapies is not readily achieved. Most patients require fluid and dietary salt restriction and very many need antihypertensive medications. Hypotension, if it occurs in these patients, is generally transient and is a result of rapid ultrafiltration during treatment. From the above discussion it is apparent that, due to its effect on salt and water balance, CAPD controls blood pressure readily and a significant number of such patients do not require medication.

Benefits of Slow and Continuous Ultrafiltration During CAPD

Rapid ultrafiltration, i.e., 3–4 L of fluid removal during a typical 3–4 h hemodialysis, three times a week, causes intravascular fluid volume depletion leading to hypotension in many diabetic patients. In most of these patients this acute transient hypotension is usually managed by infusion of saline or colloid solution to restore intravascular volume and maintain blood pressure. In patients with significant coronary, carotid, or peripheral artery disease ischemic symptoms, or in some instances irreversible ischemic complications such as myocardial infarction or stroke, may ensue if hypotension is sustained. Fluid infused to correct hypotension essentially negates the purpose of ultrafiltration and, more importantly, adds to the cost of dialysis. Contrary to hemodialysis, patients on CAPD do not need this rapid rate of ultrafiltration; typically these patients require 1–2 L of fluid removal over a 24-h period. Unless the patient is clearly dehydrated, transient acute hypotension during CAPD is infrequent. There are no data in the literature that compare in a prospective manner the impact of dialysis therapy on the ischemic complications of vascular diseases of similar severity in patients on hemodialysis and CAPD. Nevertheless, analysis of death rates by cause of death for all diabetic ESRD patients on hemodialysis (35,683 patient-years at risk) and CAPD (5,254 patient-years at risk) during 1987–1989 in the United States showed mortality from myocardial infarction and cerebrovascular events was greater among diabetic patients on CAPD/CCPD (151.6 deaths per 1,000 patient-years at risk) compared to diabetic patients on hemodialysis (129.7 deaths per 1,000 patient-years at risk) [8]. This higher death rate from cardiac causes in CAPD diabetic patients may in part be a reflection of selection bias, i.e. preferential use of CAPD/CCPD for patients known to have severe cardiovascular disease.

Residual-Renal Function

The importance of residual-renal function in the management of dialysis patients has been underrecognized; 1 mL/min of residual renal creatinine clearance adds 10 L/week to total (dialysis and renal) weekly clearance. Residual-renal function contributes to the overall clearance of small and middle molecular weight solutes and fluid removal. In addition, substantial amounts of sodium, potassium, phosphate, and acid excretion permit liberal fluid and dietary intake. Due to the contribution of renal function to solute clearance, the dialysis prescription may be modified to reduce the dose of dialysis and, in some, time spent on dialysis per treatment.

There are indications that the rates of decline of residual-renal function in patients on hemodialysis and CAPD may be different. Since the original publication of Rottembourg and colleagues in 1983 [126], which showed a stable residual-renal function (assessed by creatinine clearance) over a period of 18 months in 22 insulin-dependent diabetic patients on CAPD compared to 56 insulin-dependent diabetic patients treated with hemodialysis, several more studies have confirmed the observation that residual-renal function in CAPD patients is preserved for a longer period, in some up to 60 months, compared to hemodialysis patients [127–138]. If, indeed, residual-renal function decays faster in hemodialysis patients than in CAPD patients, on a theoretical ground several potential mechanisms could be operating in combination to make hemodialysis nephrotoxic:

1. As discussed earlier, patients on hemodialysis frequently experience rapid changes in extracellular fluid volumes during aggressive ultrafiltration. The result is an acute fall in blood pressure and, most likely, an acute fall in renal blood flow and glomerular capillary pressure, resulting in ischemia of remaining functioning nephrons.
2. There is evidence to suggest that the passage of blood through extracorporeal circulation triggers the secretion of interleukin (IL)-1 and tumor necrosis factor (TNF) [139]. Levels of TNF-α are increased in uremic patients; dialysis further increases these levels. Circulating cytokines may directly or indirectly generate vascular and immune injury in vivo [140]. Alternatively, blood membrane contact may trigger the release of reactive oxygen metabolites into circulation that may damage residual renal tissue [141]. Shah has suggested that reactive oxygen metabolites generated by neutrophils enhance glomerular basement membrane degradation by proteolytic enzymes and may cause a profound constrictive response in the glomerular capillaries [141]. The evidence cited above suggests that hemodialysis could be nephrotoxic and, hence, could cause deterioration of residual-renal function at a rate faster than the natural progression of the primary renal disease. Absence of such nephrotoxic effect in patients on CAPD may permit natural progression of renal disease and, in many, preservation of native kidney function for a longer period.

It is important to point out that the evidence cited above is only suggestive of a trend, because many cited studies were retrospective, were not matched for glomerular filtration rate (GFR) between two therapies at the initiation of dialysis, for frequency of complicating events such as severe hypotension and were not controlled for administration of other nephrotoxic drugs. Moreover, reliance on creatinine clearance as an estimate of GFR has always been questioned. In research studies measurement of residual GFR after administration of cimetidine in doses of 800 mg/day to CAPD patients closely approximates inulin clearance. In clinical practice, however, estimation of residual-renal function by calculating the mean of urea and creatinine clearance seems a practical way of circumventing this problem [142].

Visual Problems

Most insulin-dependent diabetics have irreversible retinal lesions before they start dialysis, especially during the terminal phase of renal failure when hypertension tends to be severe. In the great majority, by the time they reach the stage of dialysis, ocular lesions are far too advanced to expect any useful recovery. However, attempts should be made to preserve any useful vision the patient has. Specialized eye care is essential for all these patients. Many patients benefit from vitrectomy and panretinal photocoagulation, even with advanced retinal lesions [143–145]. The common lesions seen at the time of initiating CAPD are background retinopathy, proliferative retinopathy, and vitreous hemorrhage. Retinal detachment may also be seen in some cases. Therefore, better preservation of ocular function depends on the more aggressive approach to blood pressure and glucose control during the predialysis phase. Retinal ischemia may be made worse by the rapid fluctuations in intervascular volume during the intermittent therapy. CAPD avoids many of the problems inherent in the intermittent forms of dialysis. Stabilization or even improvement of ocular function in diabetic patients maintained on CAPD has been reported by several centers [21, 47, 143, 145].

Cardiac and Vascular Diseases

Morbidity and mortality due to atherosclerotic heart disease and microangiopathy remain the main cause of death among diabetics undergoing peritoneal dialysis. Small-vessel disease leading to ischemic gangrene of the extremities is a common complication of type I diabetes. Short-term experience with CAPD in diabetics does not suggest that ischemic complications occur any more frequently in diabetics than in non-diabetics. In the only long-term experience, reported by Zimmerman et al. [146], the incidence of ischemic and/or gangrenous complication was extremely low. The keys to preserving adequate circulation to extremities include avoidance of smoking and hypotensive episode and lipid regulation.

Metabolic and Nutritional Problems

Loss of proteins, amino acids, polypeptides, and vitamins in the dialysate contribute to the morbidity and slow rehabilitation of diabetic patients on CAPD. Such losses pose a special problem in those diabetics who may be wasted and malnourished because of poor food intake, vomiting, catabolic stresses, and intercurrent illness. Twenty-four hour amino acid losses in the dialysate average about 2.25 g/day, with about 8 g/day of proteins [147]. In uncomplicated cases, dialysate daily protein losses correlate with serum-protein concentration and body-surface area. During peritonitis, the protein losses are excessive, and in combination with inadequate food intake due to poor appetite or inability to eat, may produce severe hypoproteinemia, hypoalbuminemia, and hyperimmunoglobulinemia. Therefore, during the course of a prolonged peritonitis episode, physicians should consider early parenteral nutrition.

Continuous absorption of glucose during CAPD may aggravate the pre-existing hypertriglyceridemia, a frequently seen lipid problem in both dialyzed and nondialyzed uremics [21, 148–154]. The prevalence of hypertriglyceridemia in long-term CAPD patients is reported to be about 80% [155, 156] and hypercholesterolemia prevalence to be about 15–30% [155, 157]. Insulin levels correlate directly with the level of serum triglycerides [158], hence it is not surprising to find that diabetics who have hyperinsulinemia either due to exogenous or endogenous insulin have a significant problem of hypertriglyceridemia. At the start of therapy most patients have either normal or low cholesterol levels. During the initial months after the initiation of therapy, both serum cholesterol and triglycerides increase [51, 150, 159–162]. The increase in cholesterol is predominantly due to the increase in the fractions of VLDL and LDL, and, to a lesser extent, the increase in HDL fraction [51, 157]. The HDL fractions are being lost in the dialysate during CAPD [163], hence, the serum levels can be lower than normals. Nevertheless, due to increased intake of energy, CAPD patients are reported to have high levels of HDL [164–166]. The lipid disorders are more marked in those with pre-existing lipid disorders, especially in diabetics.

Peritonitis

CAPD-related peritonitis is one of the major causes of morbidity in CAPD patients. Experiences over 10 years have indicated that the spectrum of pathology, clinical manifestations, and management of peritonitis in diabetics and nondiabetics are similar. The earlier fear that diabetic CAPD patients would contract peritonitis with unusual organisms more often than nondiabetic patients has proved unfounded [167]. As in nondiabetics, peritonitis in diabetics is caused predominantly by skin bacteria. About 40% of bacterial peritonitis is due to *Staphylococcus epidermidis*. While this organism is a weak pathogen, in recent years it has been recognized with increasing frequency as the cause of wound infections and endocarditis. *S. epidermidis* does not produce toxins, and pathogenicity depends entirely on its ability to initiate a pyogenic process. The clinical illness is usually mild, and the disease responds well to antibiotic treatment. Other organisms isolated during episodes of peritonitis include *Staphylococcus aureus, Streptococcus viridans*, Gram-negative enteric organisms, and, very rarely, anaerobic organisms. A very small fraction of peritonitis is caused by fungi. Insulin administration into the dialysis solution bag breaks the sterility of the system and could potentially contaminate the peritoneal cavity and cause peritonitis. However, clinical experience has shown this not to be a significant problem. The incidence of peritonitis in diabetics is no more than the incidence of peritonitis in nondiabetics on CAPD [168]. More recently a large single-center prospective study has shown significantly higher peritonitis rates in diabetics (1.2 versus 0.8 episodes/patient-year). However, there was no difference between the diabetic and nondiabetic patients in the first episode in terms of catheter-related infection and exit-site infection [169]. The National CAPD Registry surveyed peritonitis rates per patient-year by route of insulin administration and type of diabetes management [35]. Although differences in the rates were not large, diabetics never using insulin had the highest rate of peritonitis per patient-year (1.31), while patients using a combination of subcutaneous and intraperitoneal insulin experienced the lowest rate (0.93). The reason for such a protective effect in patients using insulin is unclear; it is suggested that insulin may have a bactericidal effect. The recent trend has been to use devices meant to facilitate exchange procedures or protect against peritoneal contamination, especially the Y-set system, the introduction of which has significantly lowered the incidence of peritonitis [170].

Treatment of CAPD-related peritonitis including the right selection of antibiotics and duration of treatment, appropriate time for catheter removal, etc., is similar for diabetic and nondiabetic patients alike, and has been reported extensively elsewhere [167]. Due to the enhanced absorption of glucose during peritonitis, hyperglycemia is frequently observed in diabetics, and insulin requirements may increase. However, some patients may experience hypoglycemia if they are unable to eat, and insulin administration is continued at the same dosage as that prior to peritonitis. Close monitoring of blood glucose during the episode of peritonitis is essential to prevent either hypoglycemia or hyperglycemia. Due to increased protein losses during peritonitis, the patient's nutrition must be watched closely during the acute phase and, in some, parenteral nutrition should be considered. Generally, the outcome of peritonitis treatment is good. Most patients continue on CAPD after the peritonitis is cured. A small percentage (2–5%) will drop out of the CAPD program for a variety of reasons, including loss of membrane efficiency.

Patient and Technique Survival on CAPD

The 3-year cumulative patient survival rates on CAPD are significantly better than those achieved with intermittent peritoneal dialysis [15]. However, the actuarial survival and technique success rates for diabetics are lower than in nondiabetics of comparable age on CAPD. The reported 3-year survival rates for diabetics range from 40% to 60%,

depending on the ages of patients [171–173]. These results were not statistically different from 115 diabetic patients treated at the same center during the same period with hemodialysis. Data from the USRDS show a lower survival for diabetic patients on peritoneal dialysis *vis-à-vis* hemodialysis [174–176]. However, in all these studies dialysis dose was not adjusted for in the analysis. As long as the therapy dose is matched between two therapies, comparable survival is achieved between diabetic patients on peritoneal dialysis and hemodialysis [177, 178]. In contrast to USRDS data, lower adjusted mortality rates in diabetic patients on peritoneal dialysis as compared to hemodialysis have been reported by a Canadian Registry [179]. The USRDS Annual Report of 1991 compared the 1-year survival rates, adjusted for age, sex, and race, for diabetics on hemodialysis and CAPD/CCPD from day 90 of dialysis [180]. The 1-year survival for the hemodialysis group was slightly better than for CAPD/CCPD (69.6% versus 65.7%). Interestingly, 1-year survival for nondiabetic patients was almost identical in the two groups. However, these results are unadjusted for severity of coexisting diseases such as coronary artery diseases and cerebrovascular conditions. The median age for diabetic patients was 53 years for CAPD and 55 years for hemodialysis patients. However, when the mortality was analyzed according to the age of patient, mortality rates tended to be higher for hemodialysis patients than for CAPD patients among younger patients (age 40 years or below), while the opposite was the case among older patients (age over 40 years). Another study by the Michigan Kidney Registry [181] in the cohort initiating dialysis in 1989 with Cox's proportional hazards analysis showed diabetic patients age 20–59 years had a 38% lower relative risk of death on CAPD ($p = 0.01$) compared to hemodialysis. Diabetics aged 60 years and older had a 19% higher risk on CAPD versus hemodialysis, but this difference was statistically not significant ($p = 0.08$). In a more recent analysis of several registry and prospective cohort data, Vonesh et al. have reported that PD is associated with equal or better survival among nondiabetic patients and younger diabetic patients. The data showed that in the United States, survival for older diabetics was better on HD whereas there was no difference seen in this subset in the Canadian and Danish registries [182]. By showing a better survival rate on CAPD compared to hemodialysis, younger patients, who as a group tended to be relatively free from cardiac disease compared to older patients, may be displaying the beneficial effects of CAPD, i.e., better blood-pressure control, use of intraperitoneal insulin, etc., on diabetic patients. On the other hand, the higher mortality rate for older patients on CAPD is probably a reflection of selection bias regarding treatment modality for diabetic patients; older diabetic patients with severe cardiac and peripheral vascular diseases are preferentially chosen for CAPD/CCPD treatment.

The lower technique survival rate for CAPD is a reflection of peritonitis as the major problem of CAPD; peritonitis used to be the major cause of drop-out from CAPD [8]. Since the introduction of the Y-set system the peritonitis rate has improved significantly [183]; the rate of peritonitis in the past 2 or 3 years is about one episode every 16–24 patient-months compared to one episode every 12 patient-months before the introduction of the Y-set system. This improvement in peritonitis rates will have a favorable impact on the drop-out rate from CAPD. Moreover, adequacy standards for CAPD patients have received more attention [51, 184]. This also favorably influences the drop-out rates due to inadequate dialysis, which accounts for nearly 15–20% of CAPD drop-outs. These two improvements in technique may continue to o improve CAPD/CCPD survival rates.

Technique-Related Complications

Complications that are a direct result of increased intra-abdominal pressures, such as dialysate leaks, hernia, hemorrhoids, and a compromised cardiac pulmonary status, occur with the same frequency in diabetics as in nondiabetics. As discussed earlier, peritoneal membrane function as assessed by serum chemistries, and based on a peritoneal equilibration test (N. Lameire, personal communication) in the absence of peritonitis, remains stable over a period of time. Transient loss of ultrafiltration during an episode of peritonitis is frequent, but full recovery is expected when peritonitis is resolved. Irreversible loss of ultrafiltration, as in nondiabetic patients, may occur in diabetic CAPD patients mainly as a sequel of severe peritonitis and due to sclerosing peritonitis [185–187]. Although the exact etiology of sclerosing peritonitis has not been established, its occurrence, once most prevalent in Europe, has been almost eliminated since acetate buffer in the dialysis solution has been replaced by lactate.

Hospitalization Rates

Because of the numerous complications associated with diabetes, diabetic patients on CAPD tend to have increased morbidity and require more frequent hospitalization than nondiabetic patients. For type I and type II diabetics the rate of hospitalization (33 days per patient-year of treatment) appears to be similar. Hospitalization due to causes directly related to CAPD technique is progressively decreasing. The rate of hospitalization for diabetics on CAPD is comparable to diabetics on hemodialysis.

Protecting the Peritoneal Membrane in Diabetes: Role of Newer PD Solutions

Since glucose is the main osmotic agent and lactate the main buffering agent (lactate induced low Ph prevents caramelization during sterilization) used in peritoneal dialysis, diabetic patients seem to be at a particular disadvantage. These substances, besides inducing ultrastructural changes in the peritoneal membrane (thus affecting peritoneal function), also promote neoangiogenesis and mesothelial damage. Moreover, the manufacturing process introduces glucose degradation products (GDPs), which pose the greatest challenge to the integrity of the peritoneal membrane. GDPs vary in their toxic potential and may also have a role in peritoneal inflammation [188–191]. The toxicity to the peritoneal mesothelium occurs as a result of bipronged attack. Besides the GDP content of the PD solution, locally produced advanced glycation products (AGEs) may damage the mesothelium as well [188]. AGE products stimulate local angiogenesis in the peritoneal membrane inducing diabetiform changes. Lower GDP-containing solutions may improve mesothelial viability and enhance mesothelial proliferation besides promoting healing. Solutions with low GDP content may have anti-inflammatory effects too [70, 192–198].

Icodextrin use in diabetic PD patients may have some added advantages. Besides improved preservation of peritoneal function [199], it may improve fluid status [199], preserve residual renal function, increase MTAC, and increase convective contribution to small solute and free water removal [200]. Finally, Icodextrin may tend to ameliorate the harmful effects of glucose like hyperinsulinemia (a cardiovascular risk factor in its own right) and dyslipidemia [201].

Can Peritoneal Dialysis Be a Long-Term Therapy for ESRD Patients?

During the early years of CAPD it was feared that long-term CAPD in diabetics may not have been feasible because of extensive microvascular disease. Lower solute and water clearance was predicted for diabetics compared to nondiabetics [202]. In addition, concerns of membrane injury from high rates of peritonitis led most to believe there would be a short life for the peritoneal membrane and a high drop-out from the therapy after a short period. However, contrary to earlier expectations, a recent study in a group of 130 CAPD patients reported similar peritoneal transport characteristics for both diabetics and nondiabetics [203], and peritoneal membrane function for solute and water transfer remained stable for up to 60 months [204, 205]. Although experience with long-term survival of diabetics on CAPD is very limited, there are now reports of diabetic patients who have been successfully managed on CAPD for longer than 5 years [146, 206]. Characteristically, the patients who survive for a long period tend to be free from associated cardiac disease and are nonsmokers. Actuarial survival was 44% at 5 years (26 patients at risk) in one of the series [146]. The NIH CAPD registry survey reported that, of the 7,161 CAPD patients surveyed, 19% were on treatment for 3 years or more [35]. These long-term patients included a smaller percentage (18%) of patients with diabetes than short-term cohorts (26%).

Thus, it is becoming apparent that, compared to nondiabetics, diabetic patients on CAPD tend to have lower patient survival results because they tend to have significantly more cardiovascular complications than their counterparts. Compared to diabetic patients on hemodialysis, the younger diabetic patients with a relative lack of coexisting diseases tend to have a lower mortality on CAPD/CCPD. Increased mortality and morbidity of older diabetic patients on CAPD is a reflection of the impact of comorbid conditions. Improvements in peritonitis rates during CAPD and establishment of adequacy standards will have a favorable impact on dropout rates from CAPD/CCPD.

Can CAPD/CCPD Be Recommended Over Hemodialysis for Diabetic Patients?

Diabetes is an exceedingly complex disease, and the management of diabetic patients is exceptionally challenging. While acknowledging that both dialysis modalities, CAPD and hemodialysis, have unique advantages and disadvantages for managing diabetic ESRD patients, there is a need to individualize dialysis therapy to derive maximum benefit from a therapy. Based on the available evidence it is clear that there are some unique features of CAPD that are conducive to better long-term outcomes in diabetic patients. For example, maintenance of residual-renal function for 5 years or more after initiating dialysis should have a great impact on patient management. Residual-renal function allows for liberal dietary intake, including fluid. The presence of significant residual-renal function also gives one the flexibility to modify the dialysis prescription, to adjust better to a patient's needs. Lastly, the benefits of intraperitoneal insulin have not been emphasized enough. Besides being convenient, peritoneal delivery of insulin during CAPD achieves better metabolic control compared to subcutaneous injections and, in the long run, produces several effects which are antiatherogenic. Indeed, this is an added advantage in the management of a diabetic patient. Besides these

medical benefits, patients with severe coronary or carotid artery diseases may find slow but continuous peritoneal dialysis more tolerable than intermittent hemodialysis. In conclusion, there are several reasons to recommend CAPD/CCPD over hemodialysis for diabetic ESRD patients who cannot be transplanted, and who choose chronic dialysis as the mode of renal replacement therapy.

Summary

It is becoming apparent that, with proper selection of patients, diabetic patients can survive for a long period on CAPD. Variances in reported mortality for diabetic peritoneal dialysis patients are primarily due to the failure to include variables such as dialysis adequacy in statistical analysis. The morbidity and mortality observed on CAPD therapy is primarily related to associated-risk factors such as cardiovascular disease, atherosclerotic complications, and infection. Ability to administer intraperitoneal insulin during CAPD enables simulation of normal insulin secretion by the islet cells. There is a strong belief based on current available evidence that PD patients tend to retain residual-renal function for a longer period of time as compared to HD. The incidence of peritonitis is decreasing and will affect the CAPD drop-out rate. Introduction of Icodextrin peritoneal dialysis solution will allow better preservation of peritoneal membrane and minimize dropouts from ultrafiltration failure.

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Chapter 29
Peritoneal Dialysis in Children

B.A. Warady, S.R. Alexander, and F. Schaefer

Like many chapters in this book, the origins of the present chapter can be traced to the 1976 discovery of continuous ambulatory peritoneal dialysis (CAPD) by Moncrief, and their associates [1]. Early on, PD was widely considered to be the renal replacement therapy (RRT) of choice for acute renal failure in pediatric patients, primarily because PD is intrinsically simple, safe, and easily adapted for use in patients of all ages and sizes. However, following on the heels of the seminal work of Moncrief and Popovich, it became apparent that CAPD was a method of chronic RRT that was ideally suited to the needs of the pediatric patient with end-stage renal disease (ESRD) as well.

In the first edition of this book and chapter, the practical aspects of providing chronic peritoneal dialysis (CPD) to children were highlighted, in large part reflecting the vast clinical experience of one of the current authors (S.R.A.), who helped pioneer the use of CAPD for children. In the second edition, we built on that foundation by making every effort to include the most current information considered vital to the provision of "optimal" dialytic care in the pediatric clinical arena. In doing so, we incorporated what we believed were the most noteworthy clinical experiences published by our pediatric nephrology colleagues from around the globe. In addition, we purposely made reference to a variety of research efforts pertinent to CPD because of their impact on the clinical needs of patients and to serve as a stimulus for future research in this area of pediatric ESRD care. In the current edition, we have taken a similar approach. We have once again included the most current information pertinent to the clinical care of children on CPD by incorporating lessons learned from a variety of sources including national/international registries, published guidelines, and clinical experiences and research initiatives. In many cases, the information we have added has proven to be a valuable follow-up to recommendations provided in the prior edition. In the end, we hope that this chapter successfully serves its role as a frequently used resource designed to make possible the best of care for children who receive CPD, and their families.

Notes on the History of PD use in Children

The peritoneal cavity has been used in the treatment of serious illness in children for at least 75 years. In 1918, Blackfan and Maxcy described the successful use of intraperitoneal injections of saline solution in dehydrated infants, a method that is still used in rural areas of some developing countries [2]. The initial reports describing the use of PD to treat children suffering from acute renal failure were published by Bloxsom and Powell in 1948 (in the premier issue of the journal *Pediatrics*) and by Swan and Gordon in 1949 [3, 4]. These reports appeared at a time when the worldwide published clinical experience with PD did not total 100 patients [5].

The experience of Swan and Gordon was the more successful of the two initial pediatric PD reports [4]. The technique ("continuous peritoneal lavage") and apparatus used by these pioneering Denver pediatric surgeons allowed large volumes of dialysate to flow continuously by gravity from 20-L carboys through a rigid metal catheter that had been surgically implanted into the upper abdomen of the patient. Dialysate was constantly drained by water suction through an identical catheter implanted in the pelvis. Fluid balance was maintained by adjusting the dialysate dextrose concentration to between 2 and 4 g%, and excellent solute clearances were achieved by providing an average dialysate delivery of 33 L/day. Dialysate temperature was regulated by adjusting the number of illuminated 60 W incandescent light bulbs in a box placed over the dialysate inflow path.

B.A. Warady (✉)
Children's Mercy Hospital, Kansas City, Missouri
e-mail: bwarady@cmh.edu

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Although two of the three children treated by Swan and Gordon survived after 9 and 12 days of continuous peritoneal lavage, it was more than a decade before the use of PD in children was again reported. During the 1950s, the development of disposable nylon catheters and commercially prepared dialysate made PD a practical short-term treatment for acute renal failure [6]. The adaptation of this technique for use in children was described in 1961 by Segar and associates in Indianapolis and in 1962 by Ettledorf and associates in Memphis [7, 8]. Both groups also demonstrated the effectiveness of PD as a treatment for boric acid and salicylate intoxication, two of the most common intoxications in small children during the 1960s [9, 10].

Subsequent reports established PD as the most frequently employed RRT for acute renal failure in pediatric patients [11–17]. PD appeared ideally suited for use in children. As compared to hemodialysis (HD), PD was intrinsically simple, safe, and easily adapted for use in patients of all ages and sizes, from newborn infants to fully grown adolescents. In contrast, HD at this early stage of development required large extracorporeal blood circuits that were either poorly tolerated or frankly impossible to achieve in many children. The widespread popularity of PD as the acute RRT of choice for children was enhanced by the prevalent notion that the peritoneum was "more efficient" in the child, a concept addressed later in this chapter.

While successful as a treatment for acute renal failure, PD appeared to have much less to offer the child with ESRD. Initial chronic PD techniques required reinsertion of the dialysis catheter for each treatment, making prolonged use in small patients difficult, and routinely resulted in inadequate dialysis [18]. The development of a permanent peritoneal catheter, first proposed by Palmer and associates and later refined by Tenckhoff and Schecter, made long-term PD an accessible form of RRT for pediatric patients [19–21]. When Boen and then Tenckhoff devised an automated dialysate delivery system that could be used in the home, chronic intermittent peritoneal dialysis (IPD) became a practical alternative to chronic HD for children [22, 23]. Largely as a result of the pioneering efforts of the pediatric ESRD treatment team in Seattle, pediatric chronic IPD programs were established in a few prominent pediatric dialysis centers [24–30]. However, there was little enthusiasm for chronic IPD among pediatric nephrologists during this period because it was associated with many of the least desirable features of chronic HD (e.g., substantial fluid and dietary restrictions, immobility during treatments, and the need for complex machinery), without providing the efficiency of HD.

A new era in the history of PD for children was heralded by the description of CAPD in 1976 by Moncrief, Popovich, and associates [1]. Advantages over HD and of special importance to children included near steady-state biochemical control, no disequilibrium syndrome, greatly reduced fluid and dietary restrictions, and freedom from repeated dialysis needle punctures. CAPD also allowed children of all ages to receive dialysis at home, offering them the opportunity to experience more normal childhoods. Finally, CAPD made possible the routine treatment of very young infants, thereby extending the option of RRT to an entire population of patients previously considered too young for chronic dialysis.

CAPD was first used in a child in 1978 in Toronto and soon became available in other pediatric dialysis programs in North America and Western Europe [30–38]. In Canada, dialysate was available in small-volume plastic containers soon after the first pediatric CAPD patients were trained. In contrast, early efforts to adapt CAPD for pediatric patients in the United States were hampered by the commercial availability of dialysate only in 2,000-mL containers. Parents were taught to discard surplus fluid from the 2,000-mL containers and infuse the remainder, or to prepare small-volume bags at home by filling blood bank transfer packs [30, 33]. Hospital pharmacies would periodically prepare small-volume dialysate bags for individual families [34]. These wasteful, expensive, and potentially risky methods became unnecessary in July 1980, when dialysate in 500- and 1,000-mL plastic containers became commercially available in the United States [39]. The subsequent addition of 250-, 750-, and 1,500-mL containers completed a range of standardized dialysate containers that accommodated most pediatric CAPD patients.

The next step in the resurgence of PD for children was the reintroduction of the automated cycler. Continuous cycler peritoneal dialysis (CCPD) was first used in a child by Price and Suki in 1981 [40]. Cycler dialysis subsequently became extremely popular among pediatric PD programs in North America [41]. Further modifications of the CCPD regimen focused on elimination of the daytime exchange (i.e., nightly intermittent peritoneal dialysis [NIPD]) in most cases. During the past 25 years, valuable clinical information regarding the frequency and efficacy of CPD usage has been collected from centers throughout the world [42–46]. Before 1982, fewer than 100 pediatric patients had been treated with CAPD worldwide, and CCPD for children was virtually unknown [40]. By the end of 2004, PD was the most frequently prescribed chronic dialysis modality for children in Finland, Canada, Australia, and New Zealand, and in many other parts of the world as well (Fig. 29.1) [47]. It is noteworthy, however, that while 957 children (0–19 years) were receiving CPD in the United States, they represented only 40% of the chronic pediatric dialysis population.

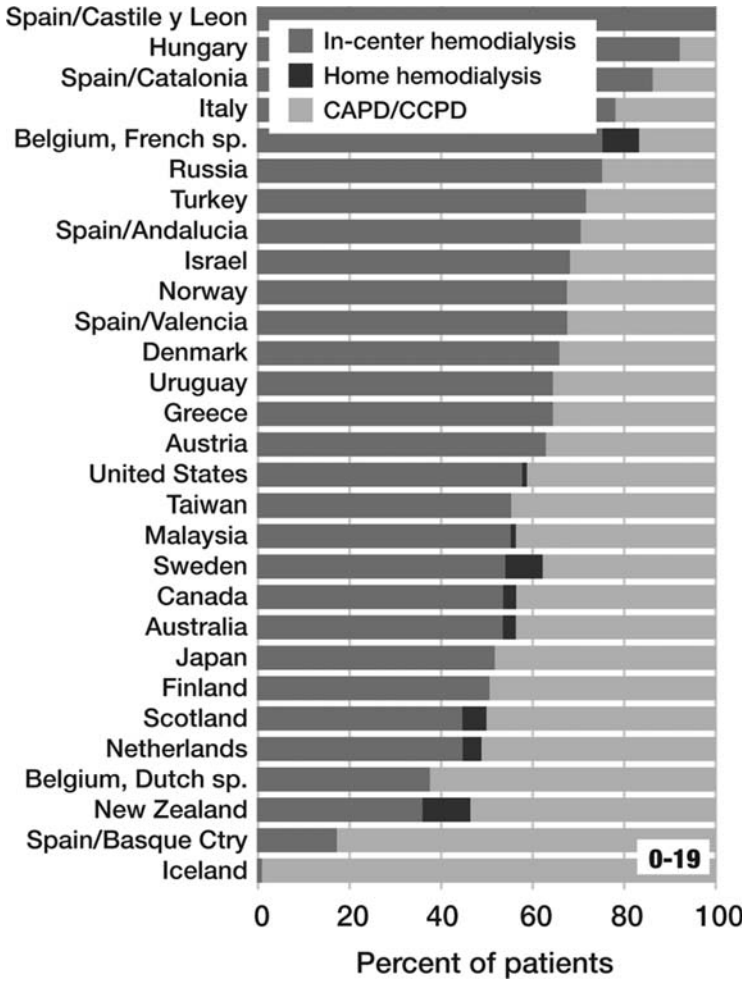

Fig. 29.1 Percent distribution of prevalent pediatric (0–19 years) dialysis patients, by modality. By permission, USRDS, 2006 Annual Data Report, www.usrds.org

Demographic Issues

Incidence of ESRD in Children

ESRD is not a common pediatric disorder. In the United States from 1985 to 2004 there were only 12–15 new pediatric ESRD cases per million population reported each year [47]. This contrasts sharply with the incidence of congenital heart disease (8,000 per million children) and childhood leukemia (40 per million) [48, 49]. Published information on the incidence of ESRD in pediatric patients reveals marked geographic variability. Using reports from single pediatric ESRD treatment centers, national surveys, and national and multinational registries, Gusmano and Perfumo previously documented an incidence ranging from 2.1 to >10 new cases per million children per year [50]. More recent data has revealed the greatest incidence rate (15.5 per million population) to be reported by Valencia (Spain), with the U.S. rate at 15.0 [47]. In Japan, the rate was only three patients per million population in 2004, whereas the EDTA registry reported an incidence rate of 9.9 patients per million of the age-related population based on data collected from 12 countries between 1985 and 2000 [43].

The incidence of ESRD also varies according to age, as shown in Table 29.1, which provides data from the United States Renal Data System (USRDS) for 1980, 1995, and 2004 [47]. Note that ESRD incidence increases significantly in the adolescent population, but the incidence of ESRD is much greater in adults than it is in any pediatric age group.

Table 29.1 also shows the differences in ESRD incidence rates over time. Of interest is the relatively greater increase in the ESRD incidence seen in the youngest pediatric age group, compared to older pediatric patients. While these data could be interpreted as showing an absolute increase in the disorders leading to ESRD in children <4 years of age, it

Table 29.1 ESRD incidence in the United States in 1980, 1995 and 2004 by age at start of ESRD therapy

Age group (years)	PMP/year 1980	1995	2004
0–4	2.8	8.2	10.8
5–9	5.5	7.5	6.9
10–14	9.5	13.9	13.3
15–19	20.1	29.9	28.2
20–44	55.6	119.2	119.1
45–64	156.4	461.1	518.0
64–74	232.8	1003.6	1298.9

PMP = Per million population, unadjusted.
Source: Data from USRDS 2006 [47].

seems more likely that renal replacement therapy is being provided to an increasing number of very young children who previously would have been excluded from many ESRD treatment programs.

The variability in ESRD incidence seen among different geographic areas, age groups, and observation periods serves to emphasize that these are not true incidence figures, but rather the incidence of the decision to treat children with RRT. That decision has been influenced by economic and social conditions, as well as by developing technologies [51, 52].

Prevalence of ESRD in Children

Children account for only a small fraction of the total ESRD patient population. Of the 335,963 registered dialysis patients receiving treatment in the United States on 31 December 2004, only 2,365 (0.7%) were less than 20 years of age [47]. Of the 25,765 registered PD patients, only 957 (3.7%) were pediatric patients [47]. Table 29.2 displays USRDS ESRD patient counts for 31 December of 1994 and 2004 by age group and treatment modality. Total pediatric dialysis (HD + PD) patient counts are small and increased by 24% between 1994 and 2004, compared to an astounding 70% increase for adults during the same period. However, the relative importance of PD for children in the United States is clearly shown in Table 29.2. In 2004, PD was used to treat 41% of all pediatric dialysis patients 0–19 years old and 60% of children <15 years of age. In contrast, only 7.5% of registered adult dialysis patients were treated with PD, significantly less than the 14.5% of patients recorded in 1994. It should be noted, however, that the pediatric PD population increased by only 11% between 1994 and 2004, not keeping pace with the overall increase in the pediatric dialysis population. During the same period the adult PD population decreased by 12.5%, despite the substantial overall increase in the number of adult dialysis patients. While a host of factors likely account for the decreased preference for PD in children and adults in the United States, the greater clinical experience with HD in pediatric centers and the associated improvement in HD technology, particularly as it concerns safety and efficacy, have been particularly influential.

Finally, the data in Table 29.2 demonstrate the importance of transplantation to pediatric ESRD management. Patients with a functioning transplant accounted for 77% of pediatric ESRD patients in 2004, compared to 28% of adults.

Table 29.2 Living United States ESRD patients on 31 December of 1994 and 2004 by patient age and treatment modality

	1994			2004		
Age group (years)	HD	PD	Tx	HD	PD	Tx
0–4	26	154	198	67	213	279
5–9	68	137	584	94	139	775
10–14	203	214	1,013	255	262	1,362
15–19	674	356	1,648	938	343	2,491
0–19	995	861	3,443	1,354	957	4,907
20–85+	167,392	29,442	68,670	307,914	24,807	131,229

HD = In-center, in-center self and home hemodialysis, PD = CAPD, CCPD, and other PD modalities, TX = Functioning transplant.
Source: Data from [47].

Causes of ESRD in Children

Approximately one-half of children requiring RRT have a congenital or hereditary renal disorder and one-half an acquired renal lesion. This is in contrast to the adult ESRD population in which over 80% of patients have an acquired renal disease. Table 29.3 lists the primary renal disorders of 5,993 pediatric dialysis patients (HD and PD patients combined) reported between January 1992 and January 2006 to the dialysis patient database of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [53]. The most frequently identified primary renal disorders were focal segmental glomerulosclerosis (14.5%), aplastic/hypoplastic/dysplastic kidneys (14.4%), and obstructive uropathy (13.1%).

The frequency with which structural anomalies of the urinary tract occur among children with ESRD has important implications for pediatric ESRD programs. CPD techniques must be made compatible with a wide variety of urinary diversions. Close collaboration with pediatric urologists and surgeons is essential to the successful integration of CPD with reconstruction or revision of these urinary tracts prior to transplantation.

Principles of Peritoneal Membrane Solute and Fluid Transport in Children

The peritoneal exchange process in pediatric patients, as in adults, is the sum of two simultaneous and interrelated transport mechanisms: diffusion and convection. Diffusion refers to the movement of solute down a concentration (electrochemical) gradient, while convection refers to movement of solutes that are "trapped" in a fluid flux, the magnitude of which is determined by the ultrafiltration rate [54]. A comprehensive discussion of these principles may be found in Chapter 6. For the present chapter, we have focused on efforts to understand peritoneal membrane function in pediatric patients.

Table 29.3 Primary renal disease diagnosis in pediatric dialysis patients

Diagnosis	N	%
Focal segmental glomerulosclerosis	867	14.5
Aplasia/hypoplasia/dysplasia	860	14.4
Obstructive uropathy	783	13.1
Reflux nephropathy	209	3.5
SLE nephritis	199	3.3
Hemolytic uremic syndrome	189	3.2
Chronic glomerulonephritis	185	3.1
Polycystic disease	175	2.9
Congenital nephrotic syndrome	153	2.6
Prune belly	124	2.1
Medullary cystic disease	124	2.1
Idiopathic crescentic glomerulonephritis	120	2.0
Familial nephritis	110	1.8
Membranoproliferative glomerulonephritis Type I	108	1.8
Pyelonephritis/interstitial nephritis	89	1.5
Cystinosis	89	1.5
Renal infarct	83	1.4
Berger's (IgA) nephritis	75	1.3
Henoch-Schonlein nephritis	66	1.1
Membranoproliferative glomerulonephritis Type II	62	1.0
Wilms tumor	43	0.7
Wegener's granulomatosis	41	0.7
Other systemic immunologic disease	37	0.6
Drash syndrome	36	0.6
Oxalosis	28	0.5
Membranous nephropathy	25	0.4
Sickle cell nephropathy	19	0.3
Diabetic GN	6	0.1
Other	640	10.7
Unknown	448	7.5

Effective Membrane Surface Area and Solute Permeability: Diffusive Transport

Early attempts to describe peritoneal membrane function in children were thought to suggest that the peritoneum was intrinsically "more efficient" in pediatric patients, a perception that undoubtedly contributed at least in part to the early popularity of PD as a dialysis modality for children. However, studies performed during the past 25 years have served to establish the fundamental similarity between adult and pediatric peritoneal membrane performance characteristics when dialysis mechanics are properly controlled and results are properly scaled to body surface area. In an early example of the peritoneal equilibration test (PET) in pediatric patients, Gruskin and associates examined time-related changes in dialysate-to-blood concentration ratios for seven different solutes in children, 4 months to 18.5 years of age [55]. By rigidly controlling dialysis mechanics in these studies, Gruskin demonstrated the distortions created by even minor perturbations in exchange volume and dwell time. Diffusion curves constructed for each solute were found to be fundamentally similar to adult reference curves. Gruskin concluded that apparent age-related differences in PD "efficiency" described in previous reports were probably the result of differences in dialysis mechanics employed in those studies [56–62].

Subsequent studies of diffusive transport made use of the fact that, in the absence of an osmotic gradient between blood and dialysate, the rate of diffusive transfer is directly related to the mass transfer area coefficient (MTAC), the effective functional membrane size and the concentration gradient of the solute across the peritoneal membrane [63]. The MTAC is a single parameter that is essentially independent of dialysis mechanics (e.g., exchange volume or dialysate dextrose concentration) and represents the functional peritoneal surface area and the diffusive permeability of the membrane. A variety of studies in adults have provided evidence that it is the functional and not the anatomical peritoneal surface area that participates in solute and water exchange, the functional component accounting for only 25–30% of total peritoneal surface area [64]. The MTAC has also been characterized as the clearance rate that can be expected in the absence of ultrafiltration or solute accumulation in the dialysate.

Results of studies in which MTAC values were measured in pediatric patients have been mixed. In an early study, Morgenstern et al. found the MTACs for urea, creatinine, uric acid, and glucose in eight children, 1.5–18 years of age, to be similar to adult reference values [65]. In contrast, later studies by Geary et al. and Warady et al. suggested that age-related differences in MTAC did indeed exist. Geary et al. determined MTAC values in 28 pediatric patients and suggested that solute transport capacity varies inversely with age and does not approach adult values until later childhood [66]. Warady et al. determined the MTACs for urea, creatinine, glucose, and potassium in 83 children <1–18 years of age who were evaluated in a standardized manner with the test exchange volume scaled to body surface area (BSA) (e.g., 1,100 mL/m^2) [67]. The mean normalized (to BSA) MTAC values for creatinine, glucose, and potassium significantly decreased as age increased and suggested either an inverse relationship between patient age and functional peritoneal surface area or an inverse age-related difference in peritoneal permeability. It should be noted, however, that the age-related differences in MTAC values measured by Geary et al. and Warady et al. were small and though statistically significant were unlikely to be clinically important.

In addition to the MTAC, the rate of dissipation of the solute gradient between blood and dialysate also has a significant impact on diffusive transfer. This rate is influenced by a host of factors including cycle frequency and dialysate volume. The impact of dialysate volume is a result of the principle of geometry of diffusion [68]. This principle suggests that the larger the dialysate volume, the greater the amount of solute transfer that can occur before the dialysate solute concentration begins to rise significantly, and the longer the transperitoneal concentration gradient will persist to drive diffusion. This principle is particularly important when studies of diffusive transport, such as the Peritoneal Equilibration Test (PET), are conducted. The infant's peritoneal membrane surface area is twice that of an adult when scaled to body weight. Accordingly, historical attempts to devise a pediatric PET to evaluate peritoneal solute transport, in which test exchange volumes were scaled to body weight, resulted in relatively small dialysate volumes being used in the youngest patients [56]. In turn, there was rapid equilibration of solute and the inaccurate perception of enhanced membrane transport capacity [56–62].

Scaling the test exchange volume by BSA allows for an equivalent relationship between dialysate volume and peritoneal membrane surface area for children of all ages and sizes so that any detectable differences in solute equilibration rates in this setting are the result of true differences in diffusive transport [67, 69, 70]. The use of BSA as the most appropriate "scaling factor" has been validated in studies conducted by Kohaut et al., de Boer et al., Warady et al., and Schaefer et al. [56, 67, 71, 72]. Studying their patients in accordance with the three-pore model of peritoneal transport developed by Rippe et al., [73, 74], Schaefer and colleagues [72] clearly demonstrated that the functional peritoneal exchange surface is a linear function of BSA and independent of patient age.

Convective Mass Transfer and Ultrafiltration

The removal of fluid during a CPD exchange reflects the interaction of the hydraulic permeability of the peritoneal membrane with the permeability of the peritoneum to the osmotically active solutes on either side of the membrane. Convective mass transfer has its greatest influence on large solute removal in contrast to the mass transfer of small solutes. Studies conducted by Pyle have demonstrated that the contribution of convection to urea transport in a 4-h CAPD exchange with 4.25% glucose is 12%, 45% for inulin, and 86% for total protein [75].

Early studies and much clinical experience suggested that adequate ultrafiltration could be difficult to achieve in infants and younger children. A more rapid decline in dialysate dextrose concentration and osmolality was observed in the youngest patients, and the inadequate ultrafiltration was attributed to this mechanism [76, 77]. Later, Kohaut et al. demonstrated that apparent differences in the ultrafiltration capacity in children from infancy to adolescence disappear when the exchange volume is scaled to BSA rather than body weight [56]. Nevertheless, the infant's BSA to body mass ratio is so much greater than that of older patients, it can be difficult to achieve comparable exchange volumes in the clinical setting. For example, an exchange volume of 1,100 mL/m^2 BSA that equates to a volume of 35 mL/kg body weight in an older child often represents an "intolerable" volume of >50 mL/kg body weight in a very young infant. The latter situation often necessitates the use of relatively smaller exchange volumes in infants and young children, which have a negative impact on ultrafiltration capacity and necessitate an alteration of the dialysis prescription. Finally, data suggests that the body size-normalized fluid reabsorption rate may also be slightly increased in young infants compared to older children and adults, and have an impact on net ultrafiltration [72]. Whereas this finding may be a manifestation of a greater lymphatic absorption rate in the youngest children (see below), it is more likely the result of a reversed movement of fluid along hydrostatic and oncotic pressure gradients as a result of greater intraperitoneal pressures being generated in the smallest patients [78].

Peritoneal Lymphatic Absorption

Studies of ultrafiltration in children have to some extent been hindered by the absence of information on the contribution of lymphatic absorption to net ultrafiltration. Mactier and associates suggested that children have relatively greater rates of lymphatic fluid absorption than adults, which results in a reduced mean ultrafiltration by 27% [79]. However, the lymphatic absorption rates of the children were similar to adult reference values when the rates were scaled for BSA. Similarly, Schröder et al. studied 17 children on PD and found that net transcapillary ultrafiltration and lymphatic absorption were not dependent upon patient age [80]. While additional investigative efforts are surely needed on this topic, lymphatic flow most likely accounts for only 20–30% of dialysate uptake by the body [81].

Summary

In summary, a great deal of progress has been made characterizing the contributions of diffusive and convective transport to peritoneal membrane mass transfer in children following the acceptance of BSA as the uniform scaling factor in kinetic studies. Whereas minor age-related differences in solute and water transport may exist, the previous reports of substantial differences between children and adults can be accounted for by perturbations in the dialysis mechanics used for the test exchanges and the reliance on body weight as the scaling factor. These pitfalls must be avoided when studies of peritoneal transport function are used to guide therapy, as will be discussed below in the section on the PET in children.

Peritoneal Dialysis for Acute Renal Failure

Indications and Contraindications

The conservative management of acute renal failure (ARF) in pediatric patients requires meticulous attention to fluid and electrolyte balance. Minor errors can have severe consequences. Dietary restrictions, phosphate binders, diuretics, sodium bicarbonate, calcium salts, antihypertensive medications, and sodium–potassium exchange resins

Table 29.4 Indications for dialysis in children with acute renal failure

Hyperkalaemia (serum $[K^+] > 7.0$ mEq/L)
Intractable acidosis
Fluid overload; often with hypertension, congestive heart failure, or pulmonary edema
Severe azotemia (BUN > 150 mg/dL)
Symptomatic uremia (encephalopathy, pericarditis, intractable vomiting, hemorrhage)
Hyponatremia, hypocalcemia, hyperphosphatemia (severe symptomatic)
Fluid removal for optimal nutrition, transfusions, infusions of medications, etc.

These are general guidelines. Each case must be individualized (see text).

all play important roles in delaying or avoiding dialysis in some children, although such tactics are not likely to be successful in oligo-anuric children. Several factors are at work in the pediatric patient that tend to defeat even the most carefully conceived conservative management plans. Children with ARF are profoundly catabolic, resulting in the accumulation of uremic solutes at surprisingly rapid rates. In the oliguric child, it is difficult to meet energy requirements while abiding by stringent limitations on allowable fluid intake. As a result, dialysis and ultrafiltration tend to be promptly employed in pediatric patients with ARF.

Widely accepted clinical indications for RRT in children with ARF are listed in Table 29.4. Such lists may not adequately portray the need to consider the rate at which conditions lead to a deteriorating clinical condition in the individual child. A marginal clinical situation should not be tolerated in any child when prompt institution of RRT will control fluid and solute derangements and allow adequate nutrition.

The convenience, simplicity, and relative safety of PD have allowed the nephrologist to begin dialysis in the child as soon as it is needed, without undue anxiety over potential complications from the procedure itself. The popularity of PD over HD for critically ill pediatric patients has traditionally rested on two important features: ready access to the peritoneum (versus typically more difficult vascular access), and better tolerance of PD by unstable children. Recent advances in vascular access techniques and equipment, along with improvements in hemodialysis (primarily bicarbonate buffers and ultrafiltration control modules) have narrowed the choice between acute dialysis modalities in many pediatric centers. Clear indications for one dialysis modality over the other are now rarely present, and often it is the experience of the center that dictates the modality selection.

During the past decade, the development of continuous renal replacement therapies (CRRT) for children has begun to challenge the pre-eminence of PD and HD for treatment of the most critically ill pediatric patients in many centers [82, 83]. Although vascular access is required, CRRT is well tolerated by hemodynamically unstable children and has been successfully employed in settings previously limited by patient instability to PD [84].

Despite the recent attention and emphasis on the use of CRRT in children, PD continues to play an important role in the treatment of ARF in severely ill pediatric patients, especially among neonates and small infants [85, 86]. Moreover, advances in neonatal cardiopulmonary bypass surgery have led to an increasing reliance on PD after surgical repair of congenital heart disease in these tiny patients [87–89]. It has become routine in many high-volume pediatric cardiac surgery centers to *prophylactically* place a peritoneal dialysis catheter at the end of the cardiac operation in infants considered at risk for low cardiac output syndrome. Early postoperative use of peritoneal drainage and low-volume PD in this setting has gained wide acceptance as a relatively safe and effective measure for management of the diuretic-resistant oliguria and fluid overload often seen in these infants [90–92].

In summary, the clear superiority of one RRT modality over the others for pediatric patients has not been established and often it is the experience of the center that dictates modality selection [93]. The critical role of acute PD in pediatric centers is well established, especially those called upon to manage ARF in neonates and infants. Thus, acute PD services will likely be required in all centers providing care for severely ill pediatric patients for many years to come. Practical guidelines for the treatment of ARF in children, including guidelines for the use of acute PD, were recently published by a European expert panel [94].

There are few contraindications to acute PD. Absolute contraindications all relate to the lack of an adequate peritoneal cavity. Neonates with an omphalocele, diaphragmatic hernia, or gastroschisis cannot be treated with PD. Recent abdominal surgery is not an absolute contraindication, as long as there are no draining abdominal wounds. Children with vesicostomies and other urinary diversions, polycystic kidneys, colostomies, gastrostomies, prune-belly syndrome, and recent bowel anastomoses have been successfully treated with PD. Peritoneal dialysis can be used to treat acute allograft dysfunction immediately following renal transplantation, as long as the allograft has been placed in an extraperitoneal location. Extensive intra-abdominal adhesions may prevent PD in some patients. Surgical lysis of such adhesions can be attempted but can result in prolonged intraperitoneal hemorrhage.

Technical Considerations

Catheters

Acute catheters: temporary versus permanent

A reliable catheter is the cornerstone of successful acute PD. The choice between a percutaneously placed temporary catheter and a surgically placed "permanent" catheter is usually somewhat arbitrary, reflecting local practice. The rigid temporary Teflon catheter with a stylet (Trocath®, Cook, Bloomington, Indiana) has been largely abandoned due to a high rate of catheter-related complications. For example, the use of a single Trocath for longer than 72 h was shown 30 years ago to be associated with an unacceptably high incidence of peritonitis [16]. Fortunately, small catheters designed for percutaneous placement at the bedside using the Seldinger technique with a peel-away sheath (Cook Critical Care, Bloomington, Indiana) have become readily available [95]. Flexible intravenous and body cavity drainage catheters (Cook Mac-Loc Multipurpose Drainage Catheter®, Cook, Bloomington, Indiana) also have been successfully adapted for use as PD catheters in infants and small children [96–98]. Poor drainage is a common problem with percutaneous catheters that is usually caused by omental envelopment [99]. When this occurs, it is best to avoid repeated abdominal punctures and proceed to surgical catheter placement.

Surgical placement of a cuffed permanent catheter in the setting of ARF has the advantage of assuring good immediate function, but must be weighed against the risks and delays incurred by an operative procedure requiring general anaesthesia. Anesthesiologists may be reluctant to administer general anesthesia to a child with the metabolic derangements of ARF. In patients considered high-risk for general anesthesia, initial placement of a percutaneous catheter under local analgesia allows immediate dialysis. A surgical catheter can then be placed once the child is stable and it is clear that more than about 5 days of dialysis will be needed. Surgical catheter placement at the bedside is readily performed in the pediatric or neonatal intensive-care unit patient [100–102].

There have been no controlled studies comparing percutaneously with surgically placed catheters in pediatric ARF patients. In a single-center retrospective study, patients with surgically placed catheters were found to have fewer catheter-related complications (9% of patients) when compared to patients with temporary catheters placed at the bedside (46% of patients, $p = 0.01$) [103].

Temporary catheters for infants

When treating small infants (e.g., those weighing <1,500 g), such commonly found ICU items as 14-gauge plastic intravenous catheters can serve as dialysis catheters. A small curled catheter designed to drain pleural effusions without a water seal (the Starzl Pleural Catheter®, Cook) can also be used. This catheter is inserted over a guidewire and can be placed flat just beneath the anterior abdominal wall. Multiple fenestrations in the curled intraperitoneal segment increase drainage and reduce obstructions. A neonatal acute catheter is also available from Cook.

Permanent catheters for ARF

Standard, single-cuff Tenckhoff catheters (straight or curled) can be used to treat ARF. There is no difference in the techniques used to place permanent catheters, whether the patient is to receive acute or chronic PD. (Permanent catheters will be discussed later in this chapter in the section on chronic peritoneal dialysis.) The use of fibrin glue at the entrance of the catheter to the peritoneum may decrease the incidence of dialysate leakage [104].

Prophylactic antibiotics

As with catheters placed surgically for chronic PD, a single dose of a cephalosporin antibiotic should be given up to 1 h prior to surgical implantation of the acute PD catheter. Similar use of a prophylactic dose of a cephalosporin antibiotic at the time of percutaneous catheter placement is also recommended. Subsequent contamination of the dialysis circuit requires the use of prophylactic antibiotics, usually a first-generation cephalosporin given IP for 48 h.

Prophylactic IP heparin

Intraperitoneal heparin, 250–500 units/L (even lower doses may be used in infants), should routinely be used in all patients for the first 24–48 h after catheter placement by either method to prevent catheter blockage by blood clots or fibrin. Heparin should be continued for as long as the PD drainage remains blood-tinged. Care should be taken in very

small infants or in patients who are coagulopathic as substantial amounts of heparin can be absorbed from the dialysate during rapid cycling.

Acute Peritoneal Dialysis Solutions

Peritoneal dialysis solutions (PDS) are commercially available in standard dextrose concentrations of 1.5, 2.5, and 4.25%. Acute dialysis is usually begun with the 2.5% solution in order to obtain better ultrafiltration at the outset when fluid overload is frequently present and the exchange volume must be kept relatively low to avoid leaks from the new catheter insertion site. PD solutions must be warmed to body temperature before infusion. Adults usually complain of discomfort during the infusion of cool PDS, but infants may respond to unwarmed PDS with a fall in blood pressure. The heater platform of the automated cycler or blood transfusion warming devices placed in the PDS inflow path may be used. Alternatively, water-filled heating pads may be wrapped around the hanging bags of fresh PDS.

Bicarbonate-based PDS have become the standard of care for pediatric patients in Europe and elsewhere and should be used whenever possible in pediatric patients receiving acute PD. Lactate-based PDS remain the only commercially available PDS in North America. Some infants and small children do not tolerate the lactate absorbed from the dialysate [105]. These patients are often hypoxemic with an ongoing metabolic acidosis. Such infants will do better if they are treated from the outset with a PDS that contains bicarbonate as the buffer that has been prepared by the hospital pharmacy [106]. An example of a bicarbonate-based PDS formula is shown in Table 29.5. Note that calcium must be given by an alternative route and serum ionized calcium levels must be closely monitored when dialysate containing a moderately high concentration of bicarbonate is used.

Pharmacy-prepared dialysate offers a therapeutic flexibility that can be helpful in other situations. Dialysate containing a lower concentration of sodium (e.g., 127 mmol/L) may be used to avoid the hypernatremia associated with rapid free-water removal and concomitant sodium sieving that can accompany aggressive ultrafiltration in fluid-overloaded infants [107, 108]. The admixture of amino acid– and dextrose-based dialysate has been shown to be feasible and to result in absorption by the peritoneum of up to 69% of delivered amino acids. Although no direct effect on outcome was seen in their patients, the authors suggest that the combined amino acid and dextrose dialysate may help to control the hyperglycemia often seen in pediatric ARF patients [109].

The Acute PD Prescription

The PD prescription must specify the dialysate composition, exchange volume, exchange inflow, dwell and drain times, and the number of exchanges to be performed in 24 h. During the initial 24 h after catheter placement, the exchange volume is kept low, usually 10–15 mL/kg, to reduce the risk of dialysate leakage. Over the ensuing 3–5 days, the exchange volume can be increased gradually to reach a maximum of about 30 mL/kg (800 mL/m^2). Higher exchange volumes have been advocated in the past, but are unnecessary when PD is performed continuously. Respiratory embarrassment and hydrothorax have been reported with the use of exchange volumes >40 mL/kg [110, 111].

Initial stabilization on PD requires 24–72 h of frequent exchanges, 40–60 min each, in order to remove the accumulated solutes and excess fluid. This corresponds to a traditional acute IPD regimen used around the clock. Even shorter cycles can be used in hyperkalemic patients. It must be remembered that frequent cycles, especially when high dextrose concentrations are used, will place the patient at risk for hypernatremia and hyperglycemia due to sieving of sodium and rapid dextrose absorption.

Once the patient is stabilized, dialysis can proceed indefinitely. By gradually extending dwell times and increasing exchange volumes toward 800–1100 mL/m^2, a typical maintenance CPD regimen can be reached in a few days.

Table 29.5 Peritoneal dialysis solution containing bicarbonate for use in infants intolerant of lactate dialysate

NaCl (0.45%)	896.0 mL
NaCl (2.5 mEq/mL)	12.0 mL
$NaHCO_3$ (1.0 mEq/mL)	40.0 mL
$MgSO_4$ (10%)	1.8 mL
$D_{50}W$	50.0 mL

Final composition: Na = 139 mEq/L, Cl = 99 mEq/L, Mg = 1.5 mEq/L, SO_4 = 1.5 mEq/L, HCO_3 = 40 mEq/L, hydrous dextrose = 2.5 g/dL. Calculated osmolality = 423 mOsm/kg H_2O.

Familiarity with CPD regimens used in the treatment of ESRD has led to the popularity of standard CPD regimens for the treatment of ARF [112–114].

There is no need to periodically suspend PD in order to see if renal function will return; kidneys seem to begin performing again when ready to do so, independent of ongoing PD. While there have been no systematic studies of this approach to the acute PD prescription, the advantages of the near steady-state biochemical and fluid control achievable with CPD are compelling.

Special Equipment

Complete manual PD sets are commercially available (Dialynate® , Utah medical Products, Inc., Midvale, Utah) and are best used in small infants whose exchange volumes are <50–60 mL. The automated cycler can be used with exchange volumes of 50–100 mL, but tubing dead space reduces efficiency of treatment and the accuracy of delivered volumes can be suspect. As with chronic PD, when exchange volumes reach 100 mL, the automated cycler provides the most convenient method of delivering acute PD in the inpatient setting, although CAPD can be as effective. However, many intensive care unit nurses are unfamiliar with the automated cycler. As with CRRT, maintaining ICU nursing competencies on the automated PD cycler requires an intensive and persistent educational program and 24-h support from the dialysis nursing specialists.

PD for ESRD in Children

Until recently, firm guidelines did not exist as to when to initiate RRT in children with ESRD. The decision to start dialysis was based on a combination of factors including urea and creatinine levels (which vary with age), potassium and acid–base balance, growth, and the patient's general well-being. In general, dialysis has been felt to be necessary once the glomerular filtration rate falls below 10 mL/min/1.73 m^2 , but may be required sooner in individual patients.

In 2006, the updated National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines on peritoneal dialysis adequacy were published. They suggest that the initiation of dialysis should be considered in the pediatric patient when the estimated glomerular filtration rate (eGFR) is 9–14 mL/min/1.73 m^2 BSA, and should be recommended when the GFR is 8 mL/min/1.73 m^2 or less [115]. In addition, it is emphasized that dialysis should be initiated at the higher GFR when the patient's clinical status is complicated by the presence of malnutrition, fluid overload, hypertension, hyperkalemia, hyperphosphatemia, acidosis, growth failure, or the neurologic consequences of uremia, and the complications are refractory to medical/dietary management. The GFR can be estimated by either averaging the measured creatinine and urea clearances, by using the Schwartz estimating equation, or by using a timed urine collection for creatinine clearance after a dose of cimetidine [116–118].

Indications and Contraindications for CPD

The majority of pediatric patients who require dialysis can be managed with CPD. Thus, the choice of PD over chronic HD is most often based on patient and family preference, center philosophy, and availability of the desired modality. Absolute indications for CPD include the following [119–121]:

1. very small patients
2. lack of vascular access
3. contraindication to anticoagulation
4. cardiovascular instability
5. lack of proximity to a pediatric HD center

There are a number of conditions that constitute absolute contraindications to CPD. These include the presence of the following:

1. omphalocele
2. gastroschisis
3. bladder extrophy
4. diaphragmatic hernia
5. obliterated peritoneal cavity and peritoneal membrane failure

Relative contraindications include:

1. impending abdominal surgery
2. impending living-related kidney transplantation
3. lack of an appropriate caregiver
4. patient/caregiver choice if an alternate modality is available and medically suitable

The presence of a colostomy, gastrostomy, ureterostomy, and/or pyelostomy does not preclude CPD. Patients with a bladder augmentation, as well as patients with the prune-belly syndrome have also been successfully managed with CPD [122, 123]. Controversy exists as to whether the presence of a ventriculoperitoneal cerebrospinal fluid shunt constitutes a contraindication to CPD. Limited experience suggests that CPD is acceptable in this situation if no feasible alternative dialysis option exists, recognizing the risks for peritonitis [124–126].

In the absence of a compelling indication to initiate CPD, the quality of life for both patient and family assumes great importance in dialysis modality selection, and regular assessment of this patient/family parameter is encouraged [127–130]. Ideally, however, CPD should be considered as merely one form of treatment in the continuum of RRT, and patients and families should understand that a change of modality may be necessary at some point in the child's management.

Choice of Dialysis Modality

CPD is the preferred initial modality for children in most pediatric dialysis centers, mainly for psychosocial reasons. In general, home dialysis techniques are better compatible with social life and school attendance. However, this major advantage must be carefully weighed against the burden and responsibility of care imposed on the families by home dialysis. This burden may give rise to severe burnout symptoms, depression, and familial dysfunction [131]. Careful evaluation of the family's social, psychological, and economic background, ideally by a multiprofessional team including experienced physicians, dialysis nurses, psychologists, and social workers is required to come to a fully informed decision regarding the optimal dialysis modality. Hemodialysis should be the modality of choice whenever families appear unable or unwilling to take over the dialysis care at home.

As noted previously, CPD is almost exclusively used in infants for technical reasons which limit the use of hemodialysis in this age group. These include cardiovascular instability, the difficulty of placement and increased complication rates of indwelling venous catheters, and the technical impossibility to create and puncture repeatedly an arteriovenous fistula in an infant. At the other end of the pediatric age spectrum, adolescents sometimes dislike the impairment of their body image brought about by PD and feel impaired in their evening social activities if on APD, prompting the selection of HD.

The strongest medical argument in favor of PD is the better preservation of residual kidney function as compared to HD, which has been demonstrated for children [132, 133]. The importance of preserving residual kidney function as an essential determinant of patient survival, morbidity, and quality of life is increasingly recognized in adult and pediatric patients alike, and should be taken in consideration, particularly if an extended dialysis period and or poor fluid and dietary compliance is expected.

In those centers where automated PD is freely available, this CPD modality is usually preferred over manual CPD. Pediatric PD registries in North America and Italy have reported that an average of 70% of children who are prescribed CPD perform APD, with a substantial increase in APD usage over time [42, 44]. While personal preference and lifestyle are the factors that most frequently influence the choice of PD modality, individual variation in peritoneal transport characteristics may determine a patient's suitability for a particular therapy. In oliguric or anephric patients who are "high transporters" based on their peritoneal equilibration test, ultrafiltration is insufficient with the long dwell times of CAPD, making APD with a dry daytime abdomen (NIPD) the treatment of choice [134]. Conversely, "slow transporters" are best dialyzed by CAPD. Use of APD in these patients may result in inadequate solute removal and symptomatic uremia, while ultrafiltration is well maintained.

PD Catheters

Peritoneal access is a key factor in the success and longevity of CPD [135]. Goals for the PD access include the attainment of rapid dialysate flow rates, no fluid leaks, minimal catheter movement at the skin exit-site (ES), a low incidence of catheter-related infections, and placement of the catheter at a site that is both reachable and visible to the child or caregiver.

A multitude of CPD catheters have appeared since Tenckhoff's original catheter in 1968, and no consensus yet exists as to the optimal catheter for pediatric CPD [136]. A decision regarding catheter choice and usage should take into account the following factors:

- catheter design
- number of cuffs
- exit-site orientation
- implantation

Catheter Design

The straight internal portion of CPD catheters have largely been replaced with coil catheters in pediatric patients, more so in the United States than in Europe; the latter design eliminates infusion pain and pain related to catheter tip pressure on the peritoneum. They also have a lower failure rate in terms of poor dialysate flow due to catheter migration. Despite the fact that there is no difference in the rates of peritonitis or exit-site infection associated with the two catheter designs [137–139], a 1995 survey of the North American Pediatric Peritoneal Dialysis Study Consortium (PPDSC) documented the use of coil catheters by 88% of centers, and the 2006 NAPRTCS database recorded coil catheters in 62.8% of PD patients [53, 140].

Number of Cuffs

In 1985, Twardowski provided evidence that exit-site infection rates in adults were lower with double-cuff catheters versus single-cuff catheters amidst a number of other studies supporting this finding [141–143]. The NAPRTCS registry reports a significantly lower incidence of peritonitis in association with double-cuff catheters (1/19.7 patient-months) compared to single-cuff catheters (1/15.0 patient-months), although the experience varies in individual centers [53, 144–147] However, four prospective studies have failed to show a difference in ESI rates or peritonitis for single- and double-cuff catheters [138, 139, 145, 148–151]. Despite conflicting data and most importantly, the lack of the necessary randomized controlled trials, most adult nephrologists are convinced of the superiority of double-cuff catheters with their use representing more than 70% of catheters, significantly more than the 44% figure in pediatrics [53, 152].

When two cuffs are used with a straight tunnel configuration, external cuff extrusion is a frequent complication. Early experience with a high rate of external cuff extrusion in children resulted in a preference for single-cuff catheters in pediatric patients [36, 153–158]. This is reflected in the 1995 data from both the PPDSC and NAPRTCS, which documented a 64–69% incidence of single-cuff catheters [138–140, 159]. The cuff extrusion that was seen was likely secondary to excess torque being placed on the catheter at the time of placement as a result of the angle between the exit-site and the abdominal wall portion of the catheter. It also proved most likely to occur if the outer cuff was less than 2.0 cm from the exit-site [160]. While there are very few reports describing the incidence of distal cuff extrusion with double-cuff catheters in children, two series from 1986 to 2004 reported cuff extrusion rates of 8 and 4%, respectively [144, 161].

Exit-Site Orientation

Early data in adults demonstrated a lower rate of ESI with downward pointing exit sites compared to upward pointing ones, and a trend towards lower ESI rates when compared to lateral pointing exit sites [141]. However, a subsequent study of single-cuff catheters did not demonstrate a difference in ESI rates for upward- versus downward-pointing exit sites [162]. In a recent study of adult patients, Crabtree and Burchette found that the risk of infectious and mechanical complications were similar with lateral and downward exit-site configurations [163].

In children, observational data on the relationship between exit-site orientation and infection appears to support the use of the downward pointing exit sites. In many cases, the downward orientation is achieved by using a swan neck catheter, which is characterized by a permanent bend of the subcutaneous portion of the catheter and an arcuate tunnel [164]. An upward facing exit site emerged as an independent risk factor for peritonitis in an analysis by Furth et al. of the 1992–1997 NAPRTCS data [165]. More recently, the 2006 NAPRTCS data revealed that a straight catheter tunnel was associated with a peritonitis rate of 1/15.4 patient months, while the rate associated with a swan neck/curved

tunnel was only 1/21.1 patient months [53]. Likewise, the peritonitis rates associated with an upward and downward oriented exit site were 1/13.8 patient-months and 1/20.0 patient-months, respectively [53].

Proximity of the CPD catheter exit site to diapers and gastrostomy tube/button exit sites are pediatric-specific risk factors for infection. Additionally, catheter trauma may occur during crawling. The swan-neck presternal catheter developed by Twardowski, may be useful in selected pediatric patients who are still in diapers, have gastrostomies, colostomies, vesicostomies or ureterostomies, are obese, crawling, or subject to recurrent ESI [166–169]. It also allows for tub bathing. A 5-year follow-up of this catheter in 10 children documented an extremely low ESI rate of one infection per 162 patient-months [170]. However, trauma to the exit site was not reduced, catheter disconnection in the subcutaneous tunnel occurred in two children, and catheter survival greater than 1 year occurred in only 36% of patients. In a more recent review, Warchol et al. documented an exit-site infection rate of 1/70.2 patient-months with the presternal catheter [171].

Catheter Implantation and Postoperative Care

The two most common approaches to PD catheter insertion are the open and laparoscopic approaches. The advantage of the open technique is the ability to directly visualize placement of the catheter into the pelvis. This is particularly beneficial in those patients who have previously undergone pelvic surgery. The major problem with the technique is the necessity for a significant incision into the peritoneum. Whereas there is limited experience in pediatrics, the laparoscopic placement of CPD catheters allows for the use of much smaller peritoneal incisions, without sacrificing placement of the catheter under direct vision [172–174]. Whichever approach is used, the catheter insertion site, exit site, and tunnel configuration should be determined well in advance of the surgical procedure, taking into account patient preference, previous surgical scars, abdominal configuration including skin folds and belt line [160, 175, 176]. Midline catheter insertion has been associated with a significant incidence of catheter leakage [141]. Adoption of a lateral placement technique through the body of the rectus muscle has resulted in a decrease in catheter leakage and is practiced by many surgeons [138, 139, 160, 172, 177–180]. The placement of fibrin glue at the peritoneal cuff suture can also be helpful in this respect [181]. Avoidance of leakage is essential since it not only delays ingrowth of fibrous tissue into the catheter cuffs, but it also provides a medium for bacterial growth. The exit site should afford easy visual access and should not be compromised by bending movements of the patient.

Prospective trials on the effectiveness of prophylactic antibiotics for insertion of PD catheters are scant. However, a review of four such adult studies found that treatment significantly reduced the risk of early (first month following catheter insertion) peritonitis [139, 182–185]. Likewise, a pediatric study by Sardegna et al. found a significant reduction in peritonitis occurring during the first 2 weeks post-catheter insertion in patients given preoperative antibiotics, regardless of the antibiotic type [186]. Based on these study results, it has been recommended that a single dose of a first or second generation cephalosporin be given intravenously to children and adults at the time of catheter placement [145, 187–189]. Routine prophylactic use of vancomycin is discouraged because of the possible development of vancomycin-resistant enterococcus.

The role of omentectomy remains controversial, although it is recognized that catheter occlusion by omentum is more common in children than adults. If an omentectomy is performed, the incidence of catheter occlusion is approximately 5% compared to an occlusion rate of 10–22.7% in pediatric patients without an omentectomy [190, 191]. Fifty-three percent of centers surveyed by the PPDSC routinely performed an omentectomy, similar to the 59% figure from a survey of North American surgeons [140, 172]. An omentectomy was also performed with the insertion of 82.4% of catheters in the Italian pediatric PD registry [144]. In our hands, the omentectomy is a simple procedure that can be carried out at the time of the initial surgical procedure and should be considered in all cases.

Following catheter insertion, the catheter should be flushed with 10 mL/kg of heparinized dialysate until the effluent is clear to ensure patency. The usual heparin concentration is 500 units/L of dialysate. During the postoperative healing period, stress on the surgical wound due to high intra-abdominal pressure may disrupt the healing process and lead to dialysate leakage [192]. Accordingly, attention to the prevention of vomiting and straining, and the use of adequate analgesia, is essential. Where possible, a delay of 10–15 days prior to using the chronic catheter is desirable, although only 24% of pediatric centers surveyed in 1995 practiced this routinely [140]. In addition, a more recent pediatric study found no difference in catheter related complications when comparing early (<7 days postinsertion) and delayed (>7 days postinsertion) usage. When delaying catheter usage is not feasible, the use of lower volume exchanges initially is advisable [176, 179, 193]. Protocols for initiation of dialysis are highly variable, but generally involve some fraction of the full dialysis volume, which is increased over time (Fig. 29.2) [121].

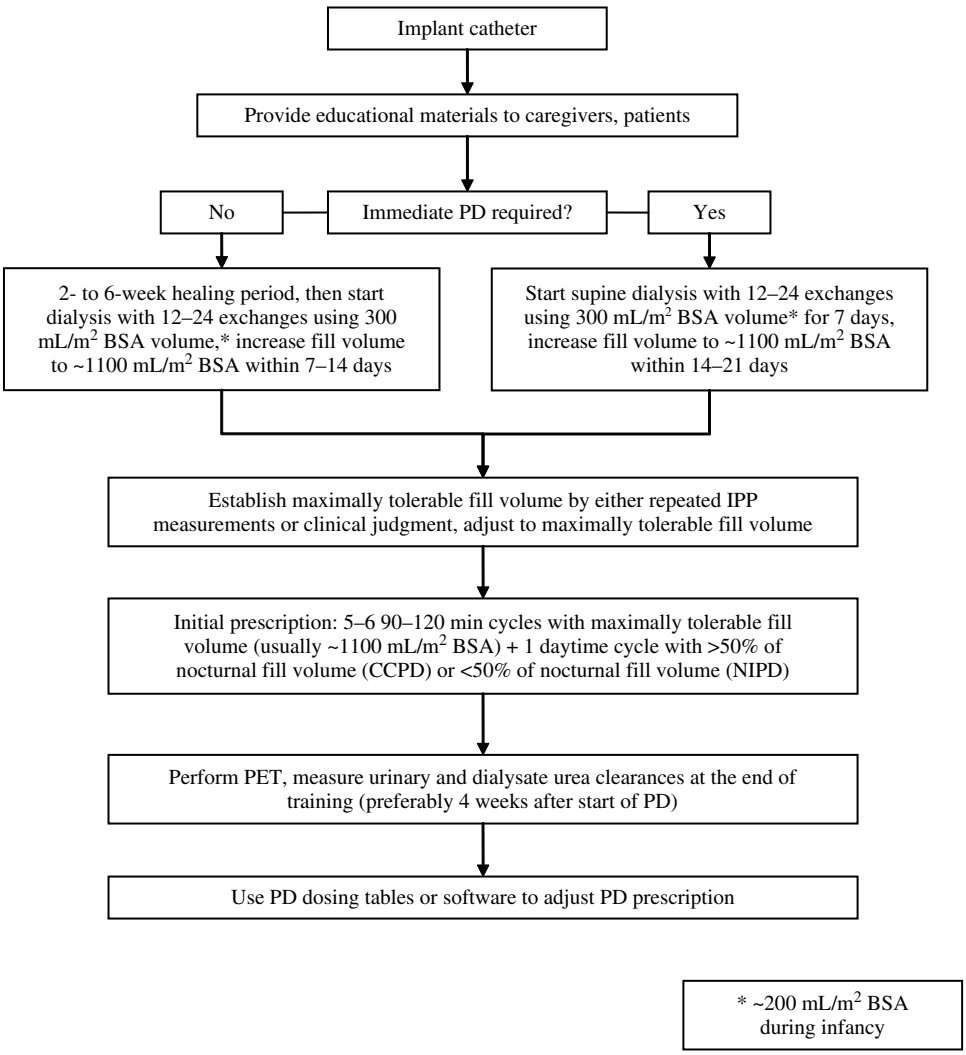

Fig. 29.2 Initiation of APD. By permission of Baxter Healthcare Corporation. Care of the Pediatric Patient on Peritoneal Dialysis, pp. 23, 2004

To prevent early catheter colonization, sterile, nonocclusive dressings should be utilized until the catheter exit-site is well healed [189, 193]. Ideally, exit-site care during the immediate postoperative period should be conducted weekly with mask and gloves and should be conducted by trained dialysis staff. This approach should be followed until the exit site is well healed, typically 4–6 weeks [189, 192]. Catheter immobilization is imperative to prevent trauma to the healing exit site. A detailed review of acute and chronic exit-site care for pediatric patients is available [194].

Finally, current recommendations do not call for routine flushing of catheters after the initial postoperative break-in period [145, 160]. Where practiced, flushing protocols vary widely from center to center.

Specialized Equipment for Pediatric Patients

In the early years of pediatric CPD, adult solutions and equipment were adapted for pediatric use. With the realization that CPD was ideally suited to the pediatric population, and with the expanding use of CPD, newer equipment was developed with specific pediatric capabilities.

Pediatric Catheters

As discussed above, almost all adult PD catheter configurations (straight, coil, swan-neck, single- and double-cuff) are available in infant and pediatric sizes and differ primarily in their length. Small transfer sets for pediatric patients are also available.

Dialysate Bag Size

Early in the course of pediatric CPD, most patients were maintained on CAPD. The availability of dialysate in small bags (250, 500, and 750 mL bags) was considered a major advance in the care of children on CPD. However, and as mentioned above, over the past several decades there has been an overwhelming move toward APD with 75% of CPD patients in the NAPRTCS database receiving APD and only 25% receiving CAPD [53]. As a result, a variety of bag sizes (0.5, 1.0, 2.0, 2.5, 3.0, 5.0, and 6.0) are available for APD (Personal communication, Baxter Healthcare Corp). In addition, the development of "disconnect" systems, such as the Ultrabag® system (Baxter Healthcare Corp, Deerfield, Illinois) and Freedom Set® (Fresenius USA, Concord, California) has circumvented the problem of having to carry unused dialysate from larger volume bags. The smallest Ultrabag® available is 1,500 mL. The Ultrabag® also comes in 2.0, 2.5, and 3.0 L volumes.

Pediatric Cyclers

The major improvement in cycler technology over the past 10 years has been the development of portable cyclers. The previously used Pac-X® and Pac-Xtra® (Baxter Healthcare Corp.) cyclers are large and the calibration mechanisms very sensitive, precluding movement of the cycler even within the home setting.

The HomeChoice® Pediatric (Baxter Healthcare Corp.) cycler is a small and extremely portable cycler that is being used by the vast majority of pediatric APD patients in North America. The range of delivered volumes inherent to this cycler make it suitable for pediatric use in all but the smallest patients. The minimum and maximum delivered volumes are 60 and 3,000 mL, respectively. Delivered dialysate volumes can be increased by 1 mL increments from 60 to 100 mL, by 10 mL increments from 100 to 500 mL, by 50 mL increments up to 1,000 mL, and by 100 mL increments thereafter. The total therapy volume, ranges from a minimum volume of 200 mL to a maximum 80 L. Total volume can be increased by increments of 50 mL to 2.0 L, by 100 mL increments to 5.0 L, and by 500 mL increments thereafter. Pediatric-specific software permits the low effluent flow rates inherent to small children without moving to the next fill cycle. Pediatric-specific tubing is available for the Home Choice® cycler with a low recirculation volume (approximately 20 mL) set. Home Choice Pro® also allows for software monitoring of home treatments.

Additional cyclers include the Gambro Serena® (Gambro Pharmaceuticals, Lakewood, Colorado) and the sleep·safe® and PD-NIGHT® cyclers, both from Fresenius, (Fresenius, Concord, California). The sleep·safe® cycler has a wide range of delivered volumes starting at 25 mL. It can be specifically programmed for pediatric dialysis with tubing containing a recirculation volume of only 15 mL. The PD-NIGHT® cycler has a tubing set specific for children with a recirculation volume of only 6.4 mL.

Choosing Among Commercially Available PD Solutions

The composition of commercially available PDS is the same for children and adults. The majority of PDS have historically been bio-incompatible in that they are hyperosmolar, use glucose as the osmotic agent and use lactate buffered at a low pH of 5.5. Evidence is strong that these factors contribute to the development of glucose degradation products (GDPs), which are toxic to the peritoneal membrane and which enhance the local and systemic production of advanced glycation end products (AGE). AGEs may also contribute to structural damage to the peritoneal membrane and vasculature and may worsen the cardiac profile of children on dialysis [195–197]. As a result, newer solutions utilizing alternative osmotic agents and buffer sources which result in reduced GDP production have been developed [198]. These solutions appear to reduce intraperitoneal inflammation and to be associated with improved macrophage function, although any definitive impact on peritonitis rates is yet to be

demonstrated [196]. Thus, these solutions are closer to the 'ideal PDS' whose characteristics might consist of the following [199, 200]:

- Provides optimal ultrafiltration and solute clearance
- Does not impair peritoneal defense mechanisms
- Allows for maintenance of long-term peritoneal membrane integrity
- Supplements nutritional deficiencies
- Iso-osmolar
- Physiological pH using bicarbonate as a buffer
- Contains antimicrobial and antifungal properties

Buffers

Acidosis is common in ESRD and can be offset by the provision of alkali in the dialysate. Many of the currently used PD solutions contain lactate in concentrations of 35–40 mmol/L with a pH of approximately 5.5. This acid pH is known to be toxic to peritoneal cells.

Sodium bicarbonate appears to be the ideal buffer for PDS. However, insoluble calcium salts form in solutions containing bicarbonate, calcium, and glucose. Additionally, an acid pH is necessary to prevent caramelization of glucose during heat sterilization. To circumvent these problems, multi-bag systems have been developed that separate out the buffer (either lactate or bicarbonate/lactate mix), allowing the glucose to be stored at a low pH [201]. At present, both Baxter and Fresenius produce two-bag systems resulting in a more physiological intraperitoneal pH and apparently improved peritoneal membrane biocompatibility [198]. Physioneal® utilizes a lactate/bicarbonate mixed buffer (pH 7–7.4), while the Stay Safe Balance® system separates glucose and electrolytes from the lactate buffer and also results in a neutral pH. Since the GDPs appear to be the predominant factor contributing to peritoneal membrane toxicity, it is not surprising that these low-GDP glucose-based solutions have resulted in an improved proliferation of mesothelial cells as reflected by increased levels of Ca-125 in the peritoneal effluent of adults [202]. Additional new products include the bicaVera® system, which utilizes a pure bicarbonate buffer and the Gambrosol Trio®, a lactate-based three-bag system that separates the hypertonic glucose component [198]. In a study of children, Haas et al. demonstrated that the use of a neutral-pH bicarbonate solution (34 mM pure bicarbonate) in patients receiving APD was associated with more effective correction of acidosis and better preservation of the peritoneal cell mass than a conventional lactate based fluid [203]. In another pediatric study, Fischbach et al. found that the use of Physioneal® caused less inflow pain than a pure lactate based fluid [204].

Osmotic Agents

The most widely used osmotic agent in PDS has been glucose. While glucose is safe and inexpensive, its ultrafiltration (UF) effects are short-lived and it is generally felt to be toxic to the peritoneum, especially in high concentrations and when used long term. In addition, its use has been associated with the development of hyperglycemia, hyperlipidemia, hyperinsulinism, and obesity. Of the variety of alternative osmotic agents investigated, the two most successful are glucose polymers (Icodextrin) and amino acids [198, 199].

Glucose polymers are large molecular weight oligosaccharides. Currently, PDS contain Icodextrin at a concentration of 7.5% with an average molecular weight of 20 kDa. The solution is lactate-based and has a low GDP content. Glucose polymers are isosmotic and produce ultrafiltration by colloid osmosis. More than 15 years of clinical experience have been accumulated with Icodextrin, with the following observations: [205–212]:

1. UF is equivalent to that obtained with 2.27% glucose solutions, and is sustained over dwell periods as long as 12 h
2. Maintains UF during peritonitis
3. Less able to glycate proteins compared to glucose-based PD solutions
4. Single daily exchanges have been used for the daytime dwell for adult and pediatric patients on APD, with resultant sustained UF and improved solute clearance
5. Single daily exchanges in adults with type 1 UF failure have prolonged CAPD usage by 12–22 months
6. Increases convective flow through the small-pore system, improves clearance of B2-microglobulin, and has no effects on the peritoneal permeability characteristics
7. Ultrafiltration capacity with therapy may be compromised in youngest children

The main disadvantage of solutions containing Icodextrin is the accumulation of maltose, although no related adverse clinical effects have yet been described. Maltose levels reach steady state within 2 weeks of commencing a single daily dose of Icodextrin, fall to normal levels within 2 weeks of ceasing Icodextrin, and do not accumulate in tissue stores [207]. Concerns about maltose accumulation have, however, limited the use of this solution to one exchange daily. Hypersensitivity to Icodextrin has been manifested by the development of an exfoliative dermatitis [213].

Nutrineal® (1.1% amino-acid containing solution) is an additional Baxter product and is an alternative PDS that avoids glucose exposure and contains no GDPs [214]. It provides ultrafiltration equivalent to 1.36% glucose containing fluids and can potentially enhance nutrition in CPD patients who experience hypoalbuminemia. However, studies with it have not proven its use to be uniformly beneficial [214].

Calcium

The use of calcium-containing phosphate binders has been standard practice following recognition that aluminium accumulates in ESRD and has multiple toxicities. At the same time, hypercalcemia is a potential complication of such therapy, especially in patients who are also receiving supplementation with vitamin D. As a result, PDS containing 1.25 and 1.75 mmol/L calcium have been developed [200, 215–217]. Pediatric data have demonstrated a significantly more negative calcium mass transfer during exchanges with dialysate containing 1.25 mmol/L of calcium as compared to 1.75 mmol/L [218]. Thus, supplemental calcium is generally necessary in patients receiving dialysis with PDS containing low concentrations of calcium, especially when non-calcium-containing phosphate binding agents are being used, to prevent the development of a negative calcium balance. Additionally, negative calcium mass transfer may stimulate parathyroid hormone (PTH) secretion, which influences the need to initiate or increase the dosage of supplemental vitamin D in this patient population [217, 219]. Thus, while dialysate with 1.25 mmol/L calcium is probably acceptable in the majority of pediatric patients, selected patients with refractory hypocalcaemia and/or hyperparathyroidism without hypercalcemia may benefit from a higher calcium concentration in the dialysate.

Magnesium

Hypermagnesemia is common in patients with ESRD and on CPD, in the absence of tubulointerstitial diseases of the kidney [220]. Currently available PDS have magnesium concentrations of 0.75, 0.5, and 0.25 mmol/L. Dialysis against a solution with 0.75 mmol/L magnesium results in a net magnesium gain and, in some cases, hypermagnesemia. The adverse effects of hypermagnesemia are not entirely known. However, studies have shown that hypomagnesemia stimulates PTH secretion, while hypermagnesemia suppresses PTH secretion. In adults, a significant inverse correlation between serum magnesium and PTH levels has been documented, and suggests that hypermagnesemia may also be a risk factor for adynamic bone disease [221]. Dialysis against the 0.25 mmol/L or a zero magnesium solution has been shown to result in a normal serum magnesium level in most cases, although hypomagnesemia has occasionally been reported. The optimal dialysate magnesium concentration for both adults and children is not known. The 0.5 mmol/L solution may represent a "happy medium," but will probably not be suitable for all patients. Monitoring of serum magnesium levels, with the goal of maintaining a normal serum magnesium level, should dictate the magnesium content of the PDS for a specific patient.

Chronic PD Prescription

The PD prescription for children has evolved empirically from guidelines that adapted adult CAPD for pediatric patients [30, 33–35, 37, 38]. In all cases, the CPD prescription should be tailored to the needs of the individual patient, with consideration of the medical needs as well as the patient/family quality of life [129, 130]. A CAPD regimen of four or five exchanges/day with an exchange volume of 900–1,100 mL/m^2 BSA (35–45 mL/kg) of 2.5% dextrose dialysis solution has routinely yielded net UF volumes of up to 1,100 mL/m^2 with acceptable biochemical control. However, the vast majority of pediatric PD patients receive cycler dialysis and the recently published K/DOQI Clinical Practice Recommendations pertaining to CPD in pediatric patients target an individual exchange

volume of 1,000–1,200 mL/m^2 for patients >2 years, and a lower initial volume (600–800 mL/m^2) for younger infants [115, 222, 223]. In concert with these recommendations, the 2005 ESRD Clinical Performance Measures (CPM) Project's report on 488 pediatric APD patients in the United States revealed the mean nighttime exchange volume to be 1,074 +/− 329 mL/m^2 and 57% of patients had a mean nighttime exchange volume between 900–1,299 mL/m^2 [224]. The greatest percentage of children on APD are prescribed a regimen consisting of 6–12 exchanges over 8–10 h per night, with a daytime dwell consisting of approximately 50% of the nighttime exchange volume. Whereas NIPD (e.g., no daytime dwell) has been used in children, the 24-hour schedule of CCPD and CAPD may optimize middle-molecule clearance [225].

The goal of achieving dialysis adequacy in the most cost-effective manner has highlighted the need to be cognizant of a patient's residual kidney function (RKF) and peritoneal membrane solute transport capacity when designing the dialysis prescription [115, 226–228]. In addition, in most patients (except for the rapid transporter) the most effective way to increase solute clearance is to increase the exchange volume to the values noted above, and not the exchange frequency. In association with this recommendation, some clinicians advocate a direct assessment of the patient's maximum tolerated intraperitoneal volume as part of the prescription process since an exceedingly high intraperitoneal pressure may compromise ultrafiltration capacity and be poorly tolerated by the patient [209, 229–231].

Measurement of RKF assumes greatest significance in those situations in which target solute clearances fail to be achieved solely by the dialysis process. Calculated as the average of residual creatinine clearance and residual urea nitrogen clearance as a means of taking the tubular secretion of creatinine and reabsorption of urea into consideration, the contribution of RKF towards a target goal may be substantial early in the course of dialysis. Subsequently, a progressive loss of RKF usually occurs and mandates modification of the dialysis prescription if target solute clearances are to be attained [115, 232–234]. Efforts to preserve RKF include the prevention of nephrotoxic insults such as exposure to radiocontrast dye, aminoglycoside antibiotics, and ECF volume depletion [115]. Use of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker might also be considered based on the experience in adults, with close monitoring for the development of hyperkalemia [235–237]. As discussed below, characterization of a patient's peritoneal membrane transport capacity is also recommended. While it may be influenced by a host of factors including inflammation, medication, and even genetic polymorphisms, it can best be evaluated clinically by the performance of a PET [238].

The use of computer-based dialysis modeling to achieve target CPD doses, has been successfully applied to the pediatric CPD population [72, 239, 240]. In contrast to instituting the CPD prescription based on PET transport categorization only, with subsequent empirical prescription changes guided by clinical experience, the use of computerized modeling makes it possible to tailor the CPD prescription to an individual patient in an efficient manner using computer calculations. Prescription recommendations are made with the "PD Adequest" (Baxter Healthcare) program using PET data to generate MTAC values, whereas the "Pack PD" (Fresenius) and the "PDC" (Gambro) program use data generated from the Personal Dialysis Capacity (PDC) test.

Principles of the PET and Its Role in Prescription Management

The peritoneal equilibration test or PET was developed by Twardowski et al. as a clinically applicable means of characterizing solute transport across the peritoneum [134]. The procedure yields the data necessary to determine the fractional equilibration of creatinine and glucose between dialysate and blood expressed as a dialysate to plasma (D/P) ratio for creatinine and a ratio of dialysate glucose to initial dialysate glucose (D/D$_o$). Since the transport capacity of a patient's peritoneal membrane is such an important factor to consider when determining the dialysis prescription, a PET evaluation should be conducted soon after the initiation of dialysis [115, 226, 227, 241]. However, since there is evidence that a PET performed within the first week of CPD may yield higher transport results than a PET performed several weeks later, K/DOQI has recommended that the PET be conducted 4–8 weeks following the initiation of PD [115, 228, 242]. The PET evaluation should be repeated when knowledge of the patient's current membrane transport capacity is necessary for the determination of the PD prescription, especially when clinical events (e.g., repeated peritonitis) have occurred and are followed by evidence of altered transport characteristics (e.g., presence of unexplained fluid overload, worsening of hypertension, increasing need for hypertonic dialysate dwells).

Whereas a test exchange volume of 2,000 mL is used in all adult PET studies irrespective of patient size, current recommendations in children are for the use of a BSA standardized PET exchange volume of 1,000–1,100 mL/m^2,

which takes into consideration the previously mentioned age-independent relationship between BSA and peritoneal surface area. It also allows for comparison of individual patient data to population norms determined with a comparable test procedure. The Pediatric Peritoneal Dialysis Study Consortium (PPDSC) and the Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS) have both conducted large multicenter trials and have established reference curves for solute equilibration in children [67, 243].

The availability of the PET makes it possible to predict a patient's likely response to a specific PD schedule. Thus, children who are classified as rapid transporters based on their 4-h D/P creatinine or their 4-h D/D_o glucose value are likely to dialyze most efficiently using short, frequent dialysis cycles as in CCPD or NIPD. On the other hand, a low-average transporter may benefit most from a schedule that includes longer dwell times as in classical CAPD. In patients new to CPD, use of a 2-h PET has proven reliable and less labor intensive in a preliminary pediatric experience [244, 245].

In addition to using the correct BSA-related test exchange volume, proper use of the data derived from the PET requires that dialysate creatinine values are corrected for glucose interference when a photometric method of creatinine determination is used since falsely elevated creatinine values may result [134]. This situation can be avoided by the use of the enzymatic assay method of creatinine determination. In addition, measured plasma solute concentrations should be divided by 0.9 to account for their presence in plasma water only and not in whole plasma. Failure to do so has resulted in solute D/P ratios greater than unity [246].

The presence of residual dialysate volumes has been noted in several adult and pediatric PET studies, and can complicate the interpretation of results [67, 247]. A large residual volume containing solute that is equilibrated with serum during the long overnight dwell that precedes the PET can artificially inflate solute D/P ratios. This is especially true during the initial 1–2 h of the PET, and can thereby influence the categorization of solute transport capacity.

Finally, the Personal Dialysis Capacity (PDC) test has been validated as an alternative to the PET to assess individual peritoneal transport characteristics in children and adults [248]. The PDC test is based upon the three-pore model of peritoneal mass transport developed by Rippe et al. that assumes peritoneal fluid and water transport occurs across three types of pores of varying size. As opposed to the single dwell used to carry out the PET, the PDC test uses data from multiple dwells performed during a 24-h period, all of which makes possible the determination of peritoneal fluid absorption rates and macromolecule permeability. It may also provide the means by which the etiology of a rapid transport status (inflammation versus anatomic reasons) can best be determined [249]. The pediatric experience with the PDC has been published by Schaefer et al. [72].

PD Adequacy

The goal of achieving dialysis adequacy in children rightly emphasizes the clinical status of the patient as an important qualitative target [115]. The pediatric component of the K/DOQI PD Adequacy guidelines states that, "adequate dialysis is likely provided if the patient's clinical status is characterized by adequate growth, blood pressure control, and nutritional status; avoidance of hypovolemia and sodium depletion; and adequate psychomotor development" Clinical manifestations of inadequate dialysis may include the following:

Congestive heart failure
Hyperphosphatemia/excessive serum calcium x phosphorus product
Uncontrolled hypertension/hypervolemia
Overt uremia (uremic pericarditis, pleuritis)
Repeated hyperkalemic episodes
Clinical or biochemical signs of malnutrition or wasting
Poor school performance

Factors contributing to inadequate dialysis include the following:

Loss of RKF
Prescription inadequate for peritoneal membrane transport characteristics
Reduced peritoneal surface area caused by extensive intra-abdominal adhesions
Loss of membrane solute transport/ultrafiltration capacity because of peritonitis
Noncompliance with PD prescription
Poorly functioning PD catheter

Despite the emphasis on clinical parameters, CPD adequacy and solute clearance have been used almost interchangeably since the performance of the National Cooperative Dialysis Study in the adult HD population. Historically, dialysis adequacy was characterized by K/DOQI in terms of small-solute clearance as a total (residual kidney plus peritoneal dialysis) weekly $Kt/V_{urea} \geq 2.0$ and a total weekly creatinine clearance ≥ 60 L/1.73 m^2 for the patient receiving CAPD [250]. The recommended target clearances were slightly greater for patients receiving cycler dialysis. Subsequent to those recommendations, reanalysis of data from the CANUSA trial of adult CAPD patients showed that RKF and not peritoneal clearance had the greatest influence on patient survival [251]. More recently, the Adequacy of PD in Mexico (ADEMEX) study and a randomized trial of adult CAPD patients conducted by Lo et al. has provided data which supports a lower solute target and prompted the current recommendation for a target total (peritoneal and kidney) Kt/V_{urea} of at least 1.7 per week in adults [115, 252, 253]. It has also been suggested that the determination of peritoneal creatinine clearance has little added value to the prediction of outcome in adults receiving CAPD such that adequacy targets should be based on urea kinetics only. Since very few data coupling dialysis dose to outcome are available in pediatrics, making it impossible to define PD adequacy in children with confidence, the current clinical experience suggests that the pediatric population should use clearance goals that meet or exceed current K/DOQI adult standards. Specifically, it is recommended that the minimal delivered dose of total (peritoneal and kidney) small-solute clearance should be a Kt/V_{urea} of at least 1.8/week [115]. Once the urine Kt/V_{urea} is <0.1/week, it should be considered negligible, with all clearance being contributed by dialysis alone. Data from the CPM project has revealed median Kt/V_{urea} values of 2.43 and 2.45 for pediatric patients receiving CCPD and NIPD, respectively [224].

As mentioned above, Kt/V_{urea} has found widespread acceptance as a marker of small-solute clearance and is calculated as the urea clearance normalized for the volume of urea distribution or total body water (TBW). Whereas some investigators have recommended the use of bioelectrical impedance as a means of determining V, this procedure is not regularly conducted in most pediatric dialysis centers [254]. Others have published anthropometric equations that have been found to overestimate TBW in PD patients [255, 256]. Prior publications have also recommended the use of formulae derived from healthy individuals [257, 258]. Most recently, the determination of TBW by heavy water (H_2O^{18} or D_2O) dilution in 64 pediatric patients receiving PD has now allowed for the development of new equations for children that permits one to predict TBW with acceptable accuracy and precision [259]. The sex-specific formulas are as follows:

For Boys:
$$TBW = 0.010 \times (\text{height} \times \text{weight})^{0.68} - 0.37 \times \text{weight}$$
For Girls:
$$TBW = 0.14 \times (\text{height} \times \text{weight})^{0.64} - 0.35 \times \text{weight}.$$

Sex-specific nomograms that are designed to estimate TBW and that were developed based on the prediction equations have also been published [115] (Figs 29.3a–29.3d). Since the height × weight parameter predicts BSA, the prediction equation can be simplified, albeit with somewhat less precision, to the following:

For Boys:
$$TBW = 20.88 \times BSA - 4.29$$
For Girls:
$$TBW = 16.92 \times BSA - 1.81$$

The Gehan and George equation should be used to determine BSA and sex-specific nomograms based on the equation have been developed [115, 260] (Figs 29.4a and 29.4b).

Ideally, 24-h collections of urine and dialysis fluid should be obtained two times per year, or when there has been a significant change in the patient's clinical status (e.g., repeated peritonitis, loss of RKF) that may influence the dialysis performance or prescription. Computer-generated estimates of solute removal are not an adequate substitute for a collected specimen [239, 240, 261]. Recognizing the difficulty of accurately collecting urine in infants and young children, many clinicians attempt to achieve the adequacy targets through the contribution of CPD clearance alone.

Finally, UF capacity should also be considered a component of adequate CPD and a patient's membrane transport capacity may be particularly important in this context. Studies in adult CPD patients have revealed that the relative risks of technique failure and patient mortality are significantly increased in patients categorized as high transporters by the PET [262]. The reasons for the increased risk noted in this population of patients are unknown, but it has been postulated that the rapid glucose absorption that characterizes the high transport state may predispose patients to chronic fluid overload and cardiovascular morbidity [263].

(a)

Male Total Body Water (L) Nomogram

Height (cm)

Weight (kg)	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	1.6	1.7	1.8	1.9													
3	1.9	2.1	2.2	2.4													
4	2.2	2.4	2.6	2.8	3.0												
5	2.4	2.7	2.9	3.1	3.3												
6	2.6	2.9	3.1	3.4	3.6	3.9	4.1										
7	2.8	3.1	3.4	3.6	3.9	4.2	4.4	4.7	4.9								
8	2.9	3.2	3.5	3.9	4.1	4.4	4.7	5.0	5.3	5.5	5.8						
9				4.0	4.4	4.7	5.0	5.3	5.6	5.9	6.2	6.5	6.7				
10				4.2	4.6	4.9	5.2	5.6	5.9	6.2	6.5	6.8	7.1	7.4	7.7		
11				4.4	4.8	5.1	5.5	5.8	6.2	6.5	6.8	7.1	7.5	7.8	8.1	8.4	8.7
12				4.5	4.9	5.3	5.7	6.0	6.4	6.8	7.1	7.5	7.8	8.1	8.5	8.8	9.1
13								6.3	6.6	7.0	7.4	7.8	8.1	8.5	8.8	9.2	9.5
14								6.5	6.9	7.3	7.7	8.0	8.4	8.8	9.2	9.5	9.9
15								6.7	7.1	7.5	7.9	8.3	8.7	9.1	9.5	9.9	10.2
16								6.8	7.3	7.7	8.1	8.6	9.0	9.4	9.8	10.2	10.6
17											8.4	8.8	9.2	9.7	10.1	10.5	10.9
18											8.6	9.0	9.5	9.9	10.4	10.8	11.2
19											8.8	9.3	9.7	10.2	10.6	11.1	11.5
20											9.0	9.4	9.9	10.4	10.9	11.3	11.8

(b)

(cont'd) Male Total Body Water (L) Nomograms

Height (cm)

Weight (kg)	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170	174	178	182	186	190
20	10.9	11.3	11.8	12.3	12.7	13.2	13.6	14.0	14.5	14.9	15.3	15.7										
22	11.4	11.9	12.4	12.8	13.3	13.8	14.3	14.7	15.2	15.7	16.1	16.6										
24	11.8	12.3	12.9	13.4	13.9	14.4	14.9	15.4	15.9	16.4	16.8	17.3	17.8	18.3	18.7							
26	12.2	12.8	13.3	13.9	14.4	15.0	15.5	16.0	16.5	17.0	17.5	18.0	18.5	19.0	19.5							
28	12.6	13.2	13.8	14.4	14.9	15.5	16.0	16.6	17.1	17.7	18.2	18.7	19.3	19.8	20.3	20.8	21.3					
30	13.0	13.6	14.2	14.8	15.4	16.0	16.6	17.1	17.7	18.3	18.8	19.4	19.9	20.5	21.0	21.6	22.1					
32	13.3	14.0	14.6	15.2	15.8	16.5	17.1	17.7	18.3	18.8	19.4	20.0	20.6	21.2	21.7	22.3	22.9	23.4	24.0			
34	13.6	14.3	15.0	15.6	16.3	16.9	17.5	18.2	18.8	19.4	20.0	20.6	21.2	21.8	22.4	23.0	23.6	24.2	24.7			
36	13.9	14.6	15.3	16.0	16.7	17.3	18.0	18.7	19.3	19.9	20.6	21.2	21.8	22.4	23.1	23.7	24.3	24.9	25.5	26.1	26.6	
38	14.2	14.9	15.7	16.4	17.1	17.8	18.4	19.1	19.8	20.4	21.1	21.8	22.4	23.0	23.7	24.3	24.9	25.6	26.2	26.8	27.4	
40			16.0	16.7	17.4	18.1	18.8	19.5	20.2	20.9	21.6	22.3	23.0	23.6	24.3	24.9	25.6	26.2	26.9	27.5	28.1	28.8
42			16.3	17.0	17.8	18.5	19.2	20.0	20.7	21.4	22.1	22.8	23.5	24.2	24.9	25.5	26.2	26.9	27.5	28.2	28.8	29.5
44			16.6	17.3	18.1	18.9	19.6	20.4	21.1	21.8	22.6	23.3	24.0	24.7	25.4	26.1	26.8	27.5	28.2	28.8	29.5	30.2
46			16.8	17.6	18.4	19.2	20.0	20.8	21.5	22.3	23.0	23.8	24.5	25.2	26.0	26.7	27.4	28.1	28.8	29.5	30.2	30.9
48			17.1	17.9	18.7	19.5	20.3	21.1	21.9	22.7	23.5	24.2	25.0	25.7	26.5	27.2	27.9	28.7	29.4	30.1	30.8	31.5
50			17.3	18.2	19.0	19.8	20.7	21.5	22.3	23.1	23.9	24.7	25.4	26.2	27.0	27.7	28.5	29.2	30.0	30.7	31.5	32.2
52						20.1	21.0	21.8	22.6	23.5	24.3	25.1	25.9	26.7	27.5	28.2	29.0	29.8	30.6	31.3	32.1	32.8
54						20.4	21.3	22.1	23.0	23.8	24.7	25.5	26.3	27.1	27.9	28.7	29.5	30.3	31.1	31.9	32.7	33.4
56						20.7	21.6	22.5	23.3	24.2	25.0	25.9	26.7	27.6	28.4	29.2	30.0	30.8	31.7	32.4	33.2	34.0
58						20.9	21.8	22.8	23.7	24.5	25.4	26.3	27.1	28.0	28.8	29.7	30.5	31.4	32.2	33.0	33.8	34.6
60						21.2	22.1	23.1	24.0	24.9	25.8	26.7	27.5	28.4	29.3	30.1	31.0	31.8	32.7	33.5	34.4	35.2
62						21.4	22.4	23.3	24.3	25.2	26.1	27.0	27.9	28.8	29.7	30.6	31.5	32.3	33.2	34.0	34.9	35.7
64						21.7	22.6	23.6	24.6	25.5	26.4	27.4	28.3	29.2	30.1	31.0	31.9	32.8	33.7	34.5	35.4	36.3
66									24.8	25.8	26.8	27.7	28.6	29.6	30.5	31.4	32.3	33.2	34.1	35.0	35.9	36.8
68									25.1	26.1	27.1	28.0	29.0	30.0	30.9	31.8	32.8	33.7	34.6	35.5	36.4	37.3
70									25.4	26.4	27.4	28.4	29.3	30.3	31.3	32.2	33.2	34.1	35.1	36.0	36.9	37.8
72									25.6	26.6	27.7	28.7	29.7	30.7	31.6	32.6	33.6	34.5	35.5	36.4	37.4	38.3
74									25.9	26.9	27.9	29.0	30.0	31.0	32.0	33.0	34.0	34.9	35.9	36.9	37.8	38.8
76									26.1	27.2	28.2	29.3	30.3	31.3	32.3	33.3	34.4	35.3	36.3	37.3	38.3	39.3
78									26.3	27.4	28.5	29.5	30.6	31.6	32.7	33.7	34.7	35.7	36.7	37.7	38.7	39.7
80									26.5	27.6	28.7	29.8	30.9	31.9	33.0	34.1	35.1	36.1	37.1	38.2	39.2	40.2

Fig. 29.3 (**a**) Male Total Body Water (L) Nomograms; (**b**) (cont'd) Male Total Body Water (L) Nomograms; (**c**) Female Total Body Water (L) Nomograms; (**d**) (cont'd) Female Total Body Water (L) Nomograms. By permission of Am J Kidney Dis 2006; 48 (suppl. 1): S152–S155

(c)

Female Total Body Water (L) Nomograms

Height (cm)

Weight (kg)	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	2.0	2.1	2.2	2.4													
3	2.4	2.6	2.8	2.9													
4	2.8	3.0	3.2	3.4	3.6												
5	3.1	3.3	3.5	3.8	4.0												
6	3.3	3.6	3.8	4.1	4.3	4.6	4.8										
7	3.5	3.8	4.1	4.4	4.8	4.9	5.2	5.5	5.7								
8	3.7	4.0	4.3	4.6	4.9	5.2	5.5	5.8	6.1	6.4	6.6						
9				4.9	5.2	5.5	5.8	6.1	6.4	6.7	7.0	7.3	7.6				
10				5.1	5.4	5.8	6.1	6.4	6.8	7.1	7.4	7.7	8.0	8.3	8.6		
11				5.3	5.6	6.0	6.4	6.7	7.1	7.4	7.7	8.1	8.4	8.7	9.0	9.3	9.6
12				5.4	5.8	6.2	6.6	7.0	7.3	7.7	8.0	8.4	8.7	9.1	9.4	9.7	10.0
13								7.2	7.6	8.0	8.3	8.7	9.1	9.4	9.8	10.1	10.4
14								7.4	7.8	8.2	8.6	9.0	9.4	9.7	10.1	10.5	10.8
15								7.6	8.0	8.5	8.9	9.3	9.7	10.0	10.4	10.8	11.2
16								7.8	8.3	8.7	9.1	9.5	9.9	10.3	10.7	11.1	11.5
17											9.3	9.8	10.2	10.6	11.0	11.4	11.8
18											9.6	10.0	10.5	10.9	11.3	11.7	12.2
19											9.8	10.2	10.7	11.1	11.6	12.0	12.5
20											10.0	10.4	10.9	11.4	11.8	12.3	12.7

(d)

(cont'd) Female Total Body Water (L) Nomograms

Height (cm)

Weight (kg)	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170	174	178	182	186	190
20	11.8	12.3	12.7	13.2	13.6	14.0	14.5	14.9	15.3	15.7	16.1	16.5										
22	12.3	12.8	13.3	13.7	14.2	14.7	15.1	15.6	16.0	16.4	16.9	17.3										
24	12.8	13.3	13.8	14.3	14.8	15.2	15.7	16.2	16.7	17.1	17.6	18.0	18.5	18.9	19.4							
26	13.2	13.7	14.2	14.8	15.3	15.8	16.3	16.8	17.3	17.8	18.3	18.7	19.2	19.7	20.1							
28	13.6	14.1	14.7	15.2	15.8	16.3	16.8	17.3	17.9	18.4	18.9	19.4	19.9	20.4	20.9	21.3	21.8					
30	13.9	14.5	15.1	15.7	16.2	16.8	17.3	17.9	18.4	18.9	19.5	20.0	20.5	21.0	21.5	22.0	22.5					
32	14.3	14.9	15.5	16.1	16.6	17.2	17.8	18.4	18.9	19.5	20.0	20.6	21.1	21.7	22.2	22.7	23.2	23.7	24.3			
34	14.6	15.2	15.8	16.4	17.0	17.7	18.2	18.8	19.4	20.0	20.6	21.1	21.7	22.3	22.8	23.4	23.9	24.4	25.0			
36	14.8	15.5	16.2	16.8	17.4	18.1	18.7	19.3	19.9	20.5	21.1	21.7	22.3	22.8	23.4	24.0	24.5	25.1	25.6	26.2	26.7	
38	15.1	15.8	16.5	17.1	17.8	18.4	19.1	19.7	20.3	21.0	21.6	22.2	22.8	23.4	24.0	24.6	25.1	25.7	26.3	26.9	27.4	
40			16.8	17.4	18.1	18.8	19.5	20.1	20.7	21.4	22.0	22.7	23.3	23.9	24.5	25.1	25.7	26.3	26.9	27.5	28.1	28.6
42			17.0	17.7	18.4	19.1	19.8	20.5	21.1	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.3	26.9	27.5	28.1	28.7	29.3
44			17.3	18.0	18.7	19.5	20.2	20.9	21.5	22.2	22.9	23.6	24.2	24.9	25.5	26.2	26.8	27.4	28.1	28.7	29.3	29.9
46			17.5	18.3	19.0	19.8	20.5	21.2	21.9	22.6	23.3	24.0	24.7	25.3	26.0	26.7	27.3	28.0	28.6	29.3	29.9	30.5
48			17.8	18.5	19.3	20.0	20.8	21.5	22.3	23.0	23.7	24.4	25.1	25.8	26.5	27.2	27.8	28.5	29.2	29.8	30.5	31.1
50			18.0	18.8	19.6	20.3	21.1	21.8	22.6	23.3	24.1	24.8	25.5	26.2	26.9	27.6	28.3	29.0	29.7	30.4	31.0	31.7
52						20.6	21.4	22.1	22.9	23.7	24.4	25.2	25.9	26.6	27.4	28.1	28.8	29.5	30.2	30.9	31.6	32.2
54						20.8	21.6	22.4	23.2	24.0	24.8	25.5	26.3	27.0	27.8	28.5	29.2	29.9	30.7	31.4	32.1	32.8
56						21.1	21.9	22.7	23.5	24.3	25.1	25.9	26.6	27.4	28.2	28.9	29.7	30.4	31.1	31.9	32.6	33.3
58						21.3	22.1	23.0	23.8	24.6	25.4	26.2	27.0	27.8	28.5	29.3	30.1	30.8	31.6	32.3	33.1	33.8
60						21.5	22.4	23.2	24.1	24.9	25.7	26.5	27.3	28.1	28.9	29.7	30.5	31.3	32.0	32.8	33.5	34.3
62						21.7	22.6	23.4	24.3	25.2	26.0	26.8	27.7	28.5	29.3	30.1	30.9	31.7	32.4	33.2	34.0	34.8
64						21.9	22.8	23.7	24.6	25.4	26.3	27.1	28.0	28.8	29.6	30.4	31.3	32.1	32.9	33.6	34.4	35.2
66									24.8	25.7	26.5	27.4	28.3	29.1	30.0	30.8	31.6	32.4	33.2	34.1	34.9	35.7
68									25.0	25.9	26.8	27.7	28.6	29.4	30.3	31.1	32.0	32.8	33.6	34.5	35.3	36.1
70									25.2	26.1	27.0	27.9	28.8	29.7	30.6	31.5	32.3	33.2	34.0	34.9	35.7	36.5
72									25.4	26.4	27.3	28.2	29.1	30.0	30.9	31.8	32.7	33.5	34.4	35.2	36.1	36.9
74									25.6	26.6	27.5	28.4	29.4	30.3	31.2	32.1	33.0	33.9	34.7	35.6	36.5	37.3
76									25.8	26.8	27.7	28.7	29.6	30.6	31.5	32.4	33.3	34.2	35.1	36.0	36.8	37.7
78									26.0	27.0	27.9	28.9	29.9	30.8	31.7	32.7	33.6	34.5	35.4	36.3	37.2	38.1
80									26.2	27.2	28.1	29.1	30.1	31.1	32.0	33.0	33.9	34.8	35.7	36.7	37.6	38.5

Fig. 29.3 Continued

(a)

Body Surface Area
Height (cm)

Weight (kg)	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	0.18	0.18	0.19	0.19	0.20	0.20	0.21	0.21	0.22	0.22	0.22	0.23	0.23	0.24	0.24	0.24	0.25
3	0.22	0.22	0.23	0.24	0.24	0.25	0.25	0.26	0.27	0.27	0.28	0.28	0.29	0.29	0.30	0.30	0.31
4	0.25	0.26	0.27	0.27	0.28	0.29	0.30	0.30	0.31	0.31	0.32	0.33	0.33	0.34	0.34	0.35	0.35
5	0.28	0.29	0.30	0.31	0.32	0.32	0.33	0.34	0.35	0.35	0.36	0.37	0.37	0.38	0.39	0.39	0.40
6	0.31	0.32	0.33	0.34	0.35	0.36	0.36	0.37	0.38	0.39	0.40	0.40	0.41	0.42	0.42	0.43	0.44
7	0.33	0.34	0.36	0.37	0.38	0.38	.039	0.40	0.41	0.42	0.43	0.44	0.44	0.45	0.46	0.47	0.47
8	0.36	0.37	0.38	0.39	0.40	0.41	0.42	0.43	0.44	0.45	0.46	0.47	0.48	0.48	0.49	0.50	0.51
9	0.38	0.39	0.40	.042	0.43	0.44	0.45	0.46	0.47	0.48	0.49	0.50	0.51	0.51	0.52	0.53	0.54
10	0.40	0.41	0.43	0.44	0.45	0.46	0.47	0.48	0.49	0.50	0.51	0.52	0.53	0.54	0.55	0.56	0.57
11	0.42	0.44	0.45	0.46	0.47	0.49	0.50	0.51	0.52	0.53	0.54	0.55	0.56	0.57	0.58	0.59	0.60
12	0.44	0.46	0.47	0.48	0.50	0.51	0.52	0.53	0.54	0.55	0.56	0.58	0.59	0.60	0.61	0.61	0.62
13	0.46	0.47	0.49	0.50	.052	0.53	0.54	0.55	0.57	0.58	0.59	0.60	0.61	0.62	0.63	0.64	0.65
14	0.48	0.49	0.51	0.52	0.54	0.55	0.56	0.58	0.59	0.60	0.61	0.62	0.63	0.64	0.66	0.67	0.68
15	0.49	0.51	0.53	0.54	0.56	0.57	0.58	0.60	0.61	0.62	0.63	0.65	0.66	0.67	0.68	0.69	0.70
16	0.51	0.53	0.54	0.56	0.57	0.59	0.60	0.62	0.63	0.64	0.66	0.67	0.68	0.69	0.70	0.71	0.72
17	0.53	0.54	0.56	0.58	0.59	0.61	0.62	0.64	0.65	066	0.68	0.69	0.70	.071	0.72	0.74	0.75
18	0.54	0.56	0.58	0.59	0.61	0.63	0.64	0.66	0.67	0.68	0.70	0.71	0.72	0.73	0.75	0.76	0.77
19	0.56	0.58	0.59	0.61	0.63	0.64	0.66	0.67	0.69	0.70	0.72	0.73	0.74	0.75	0.77	078	0.79
20	0.57	0.59	0.61	0.63	0.64	0.66	0.68	0.69	0.71	0.72	0.73	0.75	0.76	0.77	0.79	0.80	.0.81

(b)

(cont'd) Body Surface Area
Height (cm)

Weight (kg)	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170
20	0.79	0.80	0.81	0.82	0.84	0.85	0.86	0.87	0.88	0.89	0.90	0.91	0.92	0.93	0.94	0.95	0.96
22	0.83	0.84	0.85	0.87	0.88	0.89	0.90	0.91	0.92	0.94	0.95	0.96	0.97	0.98	0.99	1.00	1.01
24	0.86	0.88	0.89	0.90	0.92	0.93	0.94	0.95	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.05	1.06
26	0.90	0.92	0.93	0.94	0.96	0.97	0.98	0.99	1.01	1.02	1.03	1.04	1.06	1.07	1.08	1.09	1.10
28	0.94	0.95	0.97	0.98	0.99	1.01	1.02	1.03	1.05	1.06	1.07	1.08	1.10	1.11	1.12	1.13	1.14
30	0.97	0.99	1.00	1.01	1.03	1.04	1.06	1.07	1.08	1.10	1.11	1.12	1.14	1.15	1.16	1.17	1.18
32	1.00	1.02	1.03	1.05	1.06	1.08	1.09	1.11	1.12	1.13	1.15	1.16	1.17	1.19	1.20	1.21	1.22
34	1.03	1.05	1.07	1.08	1.10	1.11	1.13	1.14	1.16	1.17	1.18	1.20	1.21	1.22	1.24	1.25	1.26
36	1.07	1.08	1.10	1.11	1.13	1.15	1.16	1.18	1.19	1.21	1.22	1.23	1.25	1.26	1.27	1.29	1.30
38	1.10	1.11	1.13	1.15	1.16	1.18	1.19	1.21	1.22	1.24	1.25	1.27	1.28	1.30	1.31	1.32	1.34
40	1.12	1.14	1.16	1.18	1.19	1.21	1.23	1.24	1.26	1.27	1.29	1.30	1.32	1.33	1.35	1.36	1.37
42	1.15	1.17	1.19	1.21	1.22	1.24	1.26	1.27	1.29	1.30	1.32	1.34	1.35	1.37	1.38	1.39	1.41
44	1.18	1.20	1.22	1.24	1.25	1.27	1.29	1.30	1.32	1.34	1.35	1.37	1.38	1.40	1.41	1.43	1.44
46	1.21	1.23	1.25	1.26	1.28	1.30	1.32	1.33	1.35	1.37	1.38	1.40	1.42	1.43	1.45	1.46	1.48
48	1.24	1.25	1.27	1.29	1.31	1.33	1.35	1.36	1.38	1.40	1.41	1.43	1.45	1.46	1.48	1.49	1.51
50	1.26	1.28	1.30	1.32	1.34	1.36	1.38	1.39	1.41	1.43	1.44	1.46	1.48	1.49	1.51	1.52	1.54
52	1.29	1.31	1.33	1.35	1.37	1.38	1.40	1.42	1.44	1.46	1.47	1.49	.1.51	1.52	1.54	1.56	1.57
54	1.31	1.33	1.35	1.37	1.39	1.41	1.43	1.45	1.47	1.49	1.50	1.52	1.54	1.55	1.57	1.59	1.60
56	1.34	1.36	1.38	1.40	1.42	1.44	1.46	1.48	1.49	1.51	1.53	1.55	1.57	1.58	1.60	1.62	1.63
58	1.36	1.38	1.40	1.42	1.44	1.46	1.48	1.50	1.52	1.54	1.56	1.58	1.59	1.61	1.63	1.65	1.66
60	1.39	1.41	1.43	1.45	1.47	1.49	1.51	1.53	1.55	1.57	1.59	1.60	1.62	1.64	1.66	1.67	1.69

Fig. 29.4 (**a**) Body Surface Area, (**b**) (cont'd) Body Surface Area. By permission of Am J Kidney Dis 2006; 48(Suppl 1):S156–S157

Nutritional Management of Children on CPD

Nutritional Goals

The goal of nutritional management of children on CPD is to optimize quantitative and qualitative nutrient intake and restore the physiological growth capacity, while minimizing the metabolic consequences of uremia. Infants represent a unique subgroup within the ESRD population, based on the severe anorexia and rapid growth failure observed in this age group, but also in view of the unique option to provide optimally balanced nutrition by way of enteral feeding. Several reviews of the nutritional approach to pediatric patients on CPD are available and are summarized below and in Table 29.6 [264–266]. Recommendations must take into account both losses and absorption of nutrients in the dialysis fluid [267, 268].

Optimal energy requirements have not been established, but consensus recommends that prepubertal children on CPD receive 100% of the recommended dietary reference intakes (DRI) according to height age and sex [269]. Carbohydrates should be complex in nature and provide at least 35% of dietary energy intake. These targets are easily reached in most infants on enteral nutrition; high-calorie oligosaccharide additives can be added to the formula

Table 29.6 Guidelines for nutritional therapy for children receiving chronic peritoneal dialysis

Nutrient	Infant	Pre-puberty	Puberty	Post-puberty
Energy (kcal/kg/day)	110–150	70–100	Males, 60 Females, 48	Males, 60 Females, 48
Protein (g/kg/day)	1.5–2.0	1.4–1.5	1.0–1.2	1.0–1.2
Fat		50% dietary energy intake		
Vitamins:				
Pyridoxine (B6)		0.3–0.6 mg/day	1.0–1.3 mg/day	
Ascorbic acid		15–45 mg/day	45–75 mg/day	
Folic acid		60–200 mg/day	300–400 mg/day	

if required to save fluid volume. In addition, glucose is continuously absorbed from dialysate, providing the equivalent of up to 12% of the required daily caloric intake [270]. As a consequence, hypertriglyceridemia and obesity frequently result from excessive carbohydrate load, particularly in infants. Hence, the course of weight, body composition, and plasma lipids requires close monitoring and frequent adjustment of caloric intake.

In infants and young children, approximately 50% of the dietary energy intake should come from fat, with a polyunsaturated: saturated fatty acid ratio of 1.5:1.0. Although serum lipids levels are elevated in patients on CPD, they remain stable on such a regimen [271, 272]. The dietary fat component should be lower in older children, but the age at which intake should be curtailed is controversial as inappropriate restriction could result in growth impairment [273, 274].

Protein intake must be carefully controlled, avoiding protein malnutrition on the one hand but also avoiding potential toxicity from nitrogenous waste products, metabolic acidosis, and extra phosphate load, which result from a high protein intake. Previous recommendations overestimated the amount of protein required for growth and a positive nitrogen balance in children in general, and in pediatric CPD patients in particular [275]. The Dietary Reference Intake (DRI) recommendations introduced in 2002 are lower than the previously used recommended dietary allowances (RDA) for protein intake, and the average amount of protein lost via noninflamed peritoneal membranes is only 0.15 g/kg per day. While spontaneous protein intake usually exceeds the RDA considerably, a prospective study in children with predialytic CKD has demonstrated the long-term safety of reducing protein intake to 100% RDA with regards to growth and weight gain [276]. The widespread notion that a high protein intake per se can stimulate tissue anabolism and longitudinal growth has never been substantiated by clinical and experimental evidence. Conversely, a very high protein intake is clearly associated with metabolic acidosis leading to tissue catabolism [277, 278]. In addition, the increasingly evident role of hyperphosphatemia as a major cause of cardiovascular toxicity and the limited efficacy of dialytic phosphate removal by PD emphasize the need for restricting phosphate, and consequently protein intake in children on CPD. Accordingly, a daily protein intake of 1.5–2 g/kg should be sufficient in the first year of life, 1.4–1.5 g/kg at age 1–10 yrs, and 1.0–1.2 g/kg in adolescents on CPD. Protein supplements are almost never required. In children in whom an *ad libitum* diet is unsatisfactory, the protein intake prescription should only be increased once a sufficient non-protein energy supply has been established [279, 280]. At least 50% of dietary protein intake should be of high biological value due to the higher percentage of essential amino acids that are beneficial in promoting muscle anabolism and decreasing muscle wasting [281]. Protein sources with relatively low phosphate content should be preferred.

The use of amino acid containing PD solutions (Nutrineal, Baxter Healthcare, Deerfeld, Illinois), applied exclusively or in combination with glucose based solutions in automated PD, has been proposed as a means to improve the nutritional status of CPD patients. However, studies in adults and children have failed to demonstrate a consistent improvement in body composition or nutritional markers [214]. Instead, blood urea levels rise and metabolic acidosis is aggravated with amino acid solutions, questioning the usefulness of this approach [282, 283].

In general, fluid, sodium and potassium intake in the child on CPD needs slightly less restriction than in patients on HD. Fluid intake varies widely in children, depending mainly on residual urine output. While restriction of salt and fluid intake is usually necessary in oligo- and anuric children and in patients with poor ultrafiltration due to membrane failure, infants with dysplastic kidney disease commonly remain polyuric even when reaching ESRD. In these patients, ultrafiltration should be limited and adequate salt and fluid intake ascertained in order to maintain residual urine output as long as possible. Another peculiar aspect of CPD in neonates and young infants is their relatively greater electrolyte losses related to ultrafiltration. For example, an anuric infant of 5 kg body weight requiring 250 mL of ultrafiltrate per day will lose approximately 35 mmol NaCl, i.e., 7 mmol/kg sodium and chloride per day. Failure to substitute these losses can lead to hypotonic or, more insidiously, isotonic dehydration. Arterial hypotension occurs in these children predominantly in the late nighttime hours while on the cycler, and can lead to vascular events such as

sinus venous thromboses and ischemic optic nerve atrophy. Likewise, hypokalemia sometimes occurs in neonates and young infants undergoing intensive PD, necessitating oral potassium supplementation. Hyperkalemia is a rare problem in children on CPD, seen occasionally in adolescents following missed dialysis cycles or as a result of suboptimal compliance with dietary potassium restrictions.

Dietary phosphorus restriction is a key issue in pediatric CPD, since hyperphosphatemia is a strong predictor of cardiovascular morbidity on dialysis. Age-appropriate serum phosphorus levels should be targeted, i.e., 4.8–7.4 mg/dL during the first 12 months of life, 4–6 mg/dL at 1–12 years and 3.5–5.5 mg/dL in adolescents. The recommended daily dietary phosphorus intake (DRI) is 100 mg in the first 6 months of life, 275 mg at 6–12 months, 460 mg at 1–3 years, 500 mg at age 4–8 years, and up to 1,250 mg in older children. Phosphorus intake should ideally be limited to 100% of the DRI in normophosphatemic, and to 80% of DRI in hyperphosphatemic children. This is difficult to achieve by dietary counseling except in infants on controlled enteral feeding, since the processed food and soft drinks particularly preferred in the pediatric age group are rich in phosphate, and dialytic removal of phosphate is limited. Hence, most school children and adolescents on CPD require the regular intake of phosphate binders. Calcium-based phosphate binders are still first choice in most pediatric units; however, since their use contributes to calcium-phosphate ion product elevations and is linked to the development of uremic vasculopathy even in the pediatric population, calcium-free alternatives are increasingly considered [284]. Sevelamer is effective in children, but slightly aggravates metabolic acidosis [285, 286]. Lanthanum carbonate may be an efficacious alternative, but thorough experimental and clinical assessment of the long-term effects of lanthanum deposition in the growing bone will be required before its routine use can be recommended in children [287]. Irrespective of the choice of phosphate binders, their efficacy depends on the timing of their intake and the matching of their dose with the phosphorus content of the meals. Recent nutritional education programs have focused on this issue by assigning phosphate 'units' to individual meals and recommending load-adjusted phosphate binder dosing, analogous to flexible insulin dosing prescribed according to carbohydrate intake in diabetic patients.

While avoidance of hyperphosphatemia is a challenging target in most children on CPD, hypophosphatemia sometimes develops in patients with renal tubular phosphate wasting, severe anorexia, or very intense dialysis, as well as in young infants fed low-phosphorus formula milk. Since hypophosphatemia may be as deleterious to bone integrity as hyperphosphatemia, it should be corrected via cessation of oral phosphate binders, dietary modification, and, if necessary, enteral supplementation [288].

Supplementation of water-soluble vitamins is mandatory for children on CPD (Table 29.6). Provision of 100% of the DRIs is probably sufficient for all of these vitamins. Vitamin D should be provided in the active form either as calcitriol or calcidiol. Iron supplementation is necessary in most children on CPD receiving erythropoietin. While serum carnitine levels are frequently reduced in children on CPD, carnitine supplementation is indicated only in children who are symptomatic with findings such as a myopathy [289–291]. Zinc and copper deficiency has been reported in children on CPD and some centers recommend routine supplementation [292, 293].

Monitoring of Nutritional and Hydration Status

The minimal monitoring requirements for nutritional management include tracking of growth, BMI and serum albumin. The BMI (weight^2/height) provides a rough estimate of a patient's nutritional status, but does not differentiate between water content, lean and fat mass. Since the BMI is markedly age dependent, it should be normalized to height age to account for growth retardation in the dialysis population. BMI reference percentile curves for children, as well as a program to calculate standard deviation scores, are available via the website of the International Pediatric PD Network (IPPN; www.pedpd.org). Extremes of BMI are associated with increased mortality and morbidity. Wong et al. demonstrated that the adjusted relative mortality risk of dialyzed children is 60% higher at a BMI SDS of -2.5 and $+2.5$ compared to an ideal BMI SDS of 0.5 [294].

Dietary habits and the frequency of vomiting in infants should be regularly checked and recorded. Whenever appropriate, 3-day dietary intake histories should taken and nutrient intake analyzed [295]. Monitoring of the protein intake can be accomplished by measuring urea nitrogen appearance in dialysate and should be performed every 4 to 6 months together with the regular PD adequacy assessment. The protein equivalent of nitrogen appearance (PNA) can be calculated by the modified Borah equation [296]:

$$\text{PNA (g/day)} = (6.49 \times \text{UNA}) + (0.294 \times V) + \text{protein losses (g/day)},$$

where UNA is the total dialytic and urinary urea nitrogen appearance (g/day) and V = total body water [259]. V can be estimated from height and weight using the formulas indicated in the adequacy section of this chapter. PNA should

be normalized to body weight and is a valid approximation of dietary protein intake provided a patient is in a steady state condition.

The determination of dry weight can be challenging in children on CPD. Patients may gain fat and water weight while losing lean body mass, compromising the validity of body weight-based indices. Subscapular and suprailiac skinfold thickness measurements can be performed to calculate the fat and fat-free mass with good sensitivity and reproducibility, at least in the hands of experienced observers. Bioelectrical impedance analysis provides sensitive information about the state of hydration but cannot differentiate between lean body mass and extracellular water [254, 297]. The regular combined monitoring and integrative interpretation of bioelectrical impedance, weight, blood pressure, daily fluid intake, and ultrafiltration rates usually provides reliable information about the hydration status.

Controlled Enteral Nutrition

In the infant and young child on CPD, optimal feeding is essential for growth and neurological development. The anorexia of chronic kidney failure results in an inadequate spontaneous dietary intake. Abdominal fullness from the dialysate, peritoneal dextrose absorption, gastroesophageal reflux, and behavior problems may contribute to poor nutrition. In addition, the poor taste and palatability of formula preparations optimized for use in children with chronic kidney disease compromise oral acceptance by the infant. These factors, plus the extensive time commitment and negative parent–child interaction that frequently accompany feeding routines in dialyzed children have led to the concept of controlled enteral nutritional feeding (tube feeding) in infants with advanced CKD. Enteral feeding is accomplished using a nasogastric (NG) or cutaneous gastrostomy (PEG) tube ending in the stomach or the jejunal intestine, or with a PEG button [298–303]. In patients on NIPD or CCPD, continuous overnight tube feedings have the advantage of providing nutrients during the period of most intensive dialysis by innocuously consolidating the feeding routine. Night-time tube feeding also allows the stomach to be empty during the day, which may permit spontaneous oral eating. It is usually necessary to combine night-time tube feeding with daytime boluses to reach nutritional goals.

Energy supply can be maximized by adding concentrated sources of carbohydrate and/or fat to feedings [304]. Infant formulas such as Good Start® or Similac PM 60/40® contain lesser amounts of phosphorus and potassium. Commercial carbohydrate (e.g., Moducal® , Polycose® , Scandical®), fat or combinations products (Duocal®) can be added to these to increase energy density without changing electrolyte and mineral content. Recently, complete formulas adapted to the needs of infants with chronic renal failure have become available in Europe (Nephea [Meta-X]).

Very appropriate weight gain and correction of malnutrition can usually be achieved by enteral feeding in infants on CPD [305–307]. Calorie intake needs to be adjusted to avoid overfeeding and obesity. If applied before severe malnutrition has occurred, adequate statural growth can often be achieved. In children who are already growth retarded due to prolonged anorexia, only limited catch-up growth can be expected.

While the usefulness of tube feeding in children unable to attain adequate nutrition spontaneously is beyond any doubt, opinions differ regarding the optimal approach to tube feeding . Endoscopically placed percutaneous gastrostomy (PEG) tubes offer convenience and cosmetic advantages and avoid the struggle of tube insertion. On the other hand, PEG feeding may be compromised by nausea, persistent vomiting, and diarrhoea. These complications partially respond to a reduction of the volume and osmolality of the formula, as well as the mode of administration. In the case of persistent vomiting, gastrojejunal tubes can be used [300, 308]; however, maintaining fixation of the tube in the jejunum is difficult and displacement into the stomach commonly occurs. In addition, gastritis may develop from irritation by the tube, requiring histamine receptor or protein pump blockade. G-tube displacement, obstruction, and gastrocutaneous fistulas are additional potential complications that require specific interventions. The most relevant complication in children undergoing CPD is, however, peritonitis caused by penetration of organisms from the exit-site to the abdominal cavity. Since PEG exit sites are frequently colonized with *Staphylococcus aureus* or *Candida*, catastrophic peritoneal infections can occur [302, 309, 310]. The risk of such infections appears to be increased in severely malnourished subjects, and when the PEG tube is placed in patients who already receive CPD. Once a stable ring of scar tissue has formed between the abdominal and the gastric wall, it appears to be relatively safe to perform CPD. Therefore, it is strongly recommended to insert PEG tubes prior to PD initiation and before severe malnutrition has occurred. Also, careful PEG exit-site care and early treatment of local infections is important.

Nasogastric tube feedings avoid the risks of PEG-related infections. Patient acceptance has improved with the use of small (8F), soft silastic tubes, which need to be exchanged only every 4–6 weeks. However, tube placement remains an unpleasant experience and vomiting is a universal complication. The major barrier limiting the acceptance of nasogastric tubes by patients and parents is the presence of a visible "sign of disease," which can create severe psychological and social problems. It is unclear whether speech development may also be delayed in some NG-tube

fed infants as the tube may interfere with phonation [311]. The incidence of sinusitis and otitis are not increased by the presence of nasogastric tubes [308, 311].

Enteral feeding has been accused to interfere with the natural learning process for coordinated swallowing. Exclusively tube-fed infants shun solid foods as a consequence of a hyperactive gag reflex [302, 311]. Tube feeding must sometimes be continued for months after a successful kidney transplant in these infants while they learn to chew and swallow solids without gagging. Hence, regardless of the route of enteral feeding, time must be provided regularly for oral stimulation in order to encourage development of oral motor skills and speech performance. Pacifiers and gum massage encourage non-nutritive sucking. Oral intake of food prior to tube feeding is encouraged, even when most of the intake is via the tube. A multidisciplinary behavioral team approach is often useful in managing these children [301, 311].

Management of the Very Young Infant: Special Considerations

During the early 1980s, the development of CPD techniques and equipment suitable for use in very small infants changed forever the landscape of pediatric ESRD care, bringing the benefits of dialysis and transplantation to the youngest ESRD patients who before CPD rarely survived. Referral of these babies to specialized pediatric RRT centers is now considered routine. Since the NAPRTCS Dialysis Patient Registry was established in 1992, 767 of 5,993 (12.8%) registered pediatric dialysis patients began dialysis prior to 24 months of age [53]. Over 90% of those babies were treated with CPD.

Infants with ESRD present a special challenge to the pediatric nephrologist since successful management includes aggressive nutritional support, careful attention to metabolic abnormalities and bone disease, delivery of adequate dialysis, and the frequent use of recombinant human growth hormone (rhGH), all with an eye towards kidney transplantation when the infant reaches the optimum size and medical condition. Four recent reports, two from the United States and one each from the United Kingdom and Finland, have highlighted the effectiveness of this aggressive approach. In 1997, Holtta et al. reported successful maintenance peritoneal dialysis in 34 patients who began CPD under the age of 5 years (mean age at onset of CPD 1.6 years) [312]. Primary renal disease in 27 of these babies was congenital nephrotic syndrome of the Finnish type. Mortality was low (5.9%) during a median treatment time of 9.3 months, and growth during the first 6 months of CPD was excellent with the height standard deviation score (HtSDS) improving from -2.13 to -1.66. However, the peritonitis rate was high (1 episode per 11.5 patient-months) and hospitalization rates at best averaged 150 days per year. In 1997, Becker et al. [313] described an excellent outcome in 19 infants, 10 of whom commenced CPD at or below 1 year of age. There was no mortality in this patient population, and those who had reached school age were in age-appropriate grades. Catch-up growth was achieved in those treated with rhGH. In 1999. Warady et al. studied the neurodevelopmental outcome of the 28 survivors among 34 infants who began long-term CPD at ≤ 3 months of age [314]. At 1 year, the mental developmental score was within the normal range in 79% of patients, and of the 16 patients followed beyond 5 years, 94% attended school full time in age-appropriate classrooms. Successful transplantation figured prominently in the long-term management of these infants, 24 of whom received their initial transplant at a mean age of 2.1 ± 0.8 years. In 2000, Ledermann et al. described a similar experience with long-term CPD in 20 infants who began dialysis during the first year of life [315]. Four infants died. Growth among survivors was excellent with the HtSDS improving from -1.8 at initiation of CPD to -1.1 at 1 year and -0.8 at 2 years. Head circumference SDS increased dramatically from -1.9 at start to -0.9 at 1 year. Fourteen of 16 survivors achieved normal developmental milestones.

These important studies illustrate the considerable improvement in outcome seen in this subpopulation of children treated over the past two decades with CPD. They also highlight areas of care where ongoing research and improvement are still needed, especially related to nutrition and growth, cognitive development, infectious complications and mortality. The optimization of nutrition for the infant CPD patient is described in another section of this chapter, as is the critical role of nutrition (plus rhGH therapy in some patients) in achieving near-normal growth rates. The remainder of the present section will be devoted to a discussion of selected areas of CPD management that are of particular importance to these very young patients.

When to Recommend and When to Consider Withholding/Withdrawing CPD in the Infant with ESRD

The decision to recommend chronic dialysis in very young infants with irreversible renal failure remains controversial. While there is no doubt that outcomes have improved dramatically with the introduction of CPD, mortality

and morbidity are higher than in any other age group, and there is little objective information available to guide the decision-making process. In a survey of pediatric nephrologists worldwide reported by Geary in 1998, 93% of respondents offered treatment to some such infants, but only 53% stated that they offered treatment to all such infants [316]. Decisions to treat or withhold treatment involve clinical, theoretical, legal, economic, and, most often, ethical considerations. Early ethical opinion that favored consideration of dialysis and transplantation for infants as "experimental" [317] has given way to a much more comprehensive and therefore more complex process in which the overriding principle guiding treatment decisions is an attempt by the multidisciplinary treatment team and the parents to reach consensus on what constitutes the best interests of the child [318]. Aiding this process are the limited, but still informative data on mortality risk factors compiled by Wood and her colleagues in the NAPRTCS in 2001, and by Ellis and her colleagues in 1995 [319, 320]. In the NAPRTCS study of 137 patients who began dialysis under 6 years of age, 103 of whom were younger than 2 years at dialysis initiation, 1-year survival was lowest in the youngest infants (<3 months = 83%) compared to older infants (2–5 yrs = 95%). Co-morbid disease involving major systems other than the kidneys was more common in non survivors at all ages, but was particularly important in the youngest infants. When ESRD was complicated by nonrenal disease, particularly pulmonary disease and/or pulmonary hypoplasia, oliguria or anuria in infants <2 years at dialysis initiation, survival at 1 year was poor, confirming the earlier observations of Ellis et al. who noted that among 21 infants who began CPD during the first year of life, all of the babies with isolated renal disease survived, compared to only 25% of the infants with both renal and nonrenal disease.

Thus, the decision to offer chronic dialysis to an infant should begin with a realistic appraisal of the infant's chances for survival in the presence of non-renal disease ± oligo-anuria. When only renal failure is present, prospects are good for survival to an age and size appropriate for kidney transplantation. While even these situations must be individualized, as many nonmedical factors must be considered, referral for chronic dialysis is now considered routine when an infant has little or no nonrenal disease.

Dialysis Considerations

Infants can be treated with either CAPD or APD, but most centers prefer to begin dialysis in the in-patient setting with manual, two-chamber sets, slowing increasing the exchange volume towards a goal of 100–150 mL. While the newer automated cyclers come equipped with programs and tubing allowing fill volumes as low as 50–60 mL, in practice APD performs best when fill volumes exceed 100 mL [222]. There are no infant-specific adequacy guidelines available to guide the CPD prescription, but good results have been reported using the Kt/V_{urea}targets set for adults and older pediatric patients [321].

Polyuric infants may absorb significant amounts of dialysate resulting in repeated low drain alarms. This can be overcome by reducing the drain alarm limit [322]. Polyuric infants are also prone to volume contraction with significant amounts of ultrafiltration. Profound volume contraction in an infant on CPD has been associated with sudden blindness due to optic ischemic neuropathy [323]. Volume contraction can be circumvented by careful attention to the individual ultrafiltration patterns of the infant, use of the minimal dextrose concentration necessary to achieve UF targets, (even combinations of 0.5 and 1.5% dextrose PDS), and/or high-volume, low-caloric density feedings with salt supplementation [324]. Unfortunately, the 0.5% solution is generally available only in Canada.

Selected Complications

Hyponatremia

Hyponatremia is a relatively frequent complication, especially in infants with high-output renal insufficiency, and may contribute to growth failure. The hyponatremia is due to multiple factors, including the low sodium content of infant formulas, high ultrafiltration requirements relative to body weight with obligate sodium losses in the dialysate, renal sodium losses in nonoliguric patients, and inadequate ultrafiltration. Oral sodium supplementation with sodium chloride or bicarbonate may be necessary to achieve a normal sodium status and optimize growth [320, 325–328]. Required sodium supplementation averages 3–5 mmol/kg/day, but may be as high as 5–10 mmol/kg/day [322].

Hypophosphatemia

Similac PM 60/40® (Ross Laboratories, Montreal, Quebec), is commonly used in infants with ESRD to minimize phosphate intake. Its phosphate content is 6 mmol/L compared to most standard infant formulas which contain 9–13 mmol/L of phosphate. Carnation Good Start® (Carnation Nestle Food Company, Glendale, California) has an intermediate phosphate content of 8 mmol/L, providing a substantially cheaper alternative to PM 60/40®. As a result, hypophosphatemia is common in infants on CPD even when not receiving phosphate binders. Chronic hypophosphatemia may be as deleterious to bone integrity in the growing infant as hyperphosphatemia [288]. Its occurrence requires the cessation of phosphate binders if they are being used, and/or an increase in dietary phosphate content. This may require formula supplementation with sodium phosphate preparations.

Poor Ultrafiltration

Equilibration of glucose across the peritoneal membrane is faster in young children than in adults when exchange volumes are scaled to body weight rather than BSA [58]. Using volumes scaled to BSA, glucose equilibration in infants is similar in children and adults [56, 329, 330]. Clinically and probably as a result of the use of relatively smaller exchange volumes, many infants demonstrate type 1 ultrafiltration "failure" with long dwell times. This is of concern in a population whose caloric intake is primarily in liquid form. Ultrafiltration can be maximized by using appropriate exchange volumes scaled to BSA and/or nocturnal APD with short dwell times (45–60 min). Tidal PD should be considered when UF is inadequate, particularly in oliguric or anuric infants. Tidal PD has also recently been used successfully as "rescue" therapy for poorly functioning catheters in infants [331].

Infectious Complications

The frequency of infectious complications remains higher in infants on dialysis than in older children and adults, although the use of automated cyclers and disconnect systems has reduced pediatric peritonitis rates overall [53, 332, 333]. Possible explanations for the infant experience include the proximity of the PD catheter exit site to the diaper area and gastrostomy tube/button, as well as the greater use of single-cuff catheters with an upward-facing exit-site [334–337]. The NAPRTCS database shows peritonitis rates of 0.9 episodes per patient-year for infants 0–1 years of age compared to 0.69 per patient-year for 2–5-year-olds and 0.64 per year for children >12 years of age [53]. Multiple patient data registries also document shorter catheter survival in infants compared to older children [334–336, 338] in association with the elevated infection rates.

Hypogammaglobulinemia

Hypogammaglobulinemia has been reported in infants on PD, and is postulated to be associated with increased infection rates [339, 340]. However, a prospective study of 17 infants on CPD has shown that while hypogammaglobulinemia is common (71%), it may be transient and generally does not interfere with the development of a protective antibody response to vaccination [341]. Furthermore, there was no association between hypogammaglobulinemia and an increased risk of sepsis or peritonitis.

Transplantation

The final goal of ESRD management is a functioning transplant. Infants may be an ideal group for transplantation as they have a greater capacity for growth and healing and are often less malnourished, growth-retarded and chronically ill than older children with a longer period of ESRD. In addition, recent data show significantly improved growth rates post-transplantation compared to CPD in the 6-month to 4-year age group [342]. However, controversy exists as to the optimal timing of transplantation. Traditionally, infants were maintained on CPD until they reached an appropriate size (approximately 10 kg) to optimize surgical outcome, the major complication being vascular thrombosis [343, 344]. Numerous authors have, however, reported patient and graft survival rates similar to older children and improved growth and neurological development in infants transplanted at less than 1 year of age [345–349]. Living-related transplantation appears particularly successful in infants, with superior graft survival compared to deceased donor grafts [159, 332, 346–348, 350, 351]. However, it is important to recognize that while the 2006 NAPRTCS database documents that 0–1-year-olds account for only 5.3% of pediatric transplants, for a total of 521 transplants from 1987 to 2006, the registry documents a 5-year graft survival of only 54.6% for infants under 2 years of age who received deceased donor grafts [53].

Transplantation requires an intensive multidisciplinary approach and should be undertaken at the "optimal" time for each patient, taking into account parental wishes, availability of dialysis and donors, nutritional status, growth, and surgical experience and outcome for the particular institution [347]. Some infants will require time on dialysis to allow necessary surgical intervention or to correct malnutrition, while others may proceed directly to transplantation without dialysis. The risks of transplantation and prolonged immunosuppression must be weighed against the risks and outcome of prolonged CPD in the developing infant.

In summary, caring for an infant on CPD, though demanding and labor-intensive for both medical team and family, can be very successful when there is sufficient attention to detail. However, the care necessary for this population is associated with a physical, financial and emotional cost that may on occasion be overwhelming for a family [352]. Surveys of pediatric nephrologists continue to reveal that the prevailing opinion among physicians who routinely care for these infants is that it is still acceptable, with informed consent, for parents to elect conservative therapy or withdrawal of therapy, if the burden of care outweighs the benefits of dialysis and transplantation for an individual child and family [316, 317, 353].

Renal Anemia and Its Treatment in Children on CPD

Erythropoiesis stimulating agents (ESAs) correct the anemia of chronic kidney disease and eliminate the need for red blood cell transfusions in almost all adult and pediatric dialysis patients by suppressing erythroid apoptosis [354–361]. Improvements in exercise tolerance, cognitive function, work capacity, sexual function, and overall sense of well-being have been consistently described in adult dialysis patients treated with recombinant human erythropoietin (r-HuEPO) [362, 363]. Pediatric dialysis patients may enjoy even greater benefits from ESA therapy. While 25–60% of adult dialysis patients were transfusion-dependent prior to the availability of ESA, virtually all children treated with HD required transfusions from the earliest months of dialytic therapy and over 75% of children treated with CPD for more than 12 months also became transfusion-dependent [37, 364, 365]. Repeated red blood cell transfusions had profoundly adverse effects in children, including frequent exposure to infectious agents, sensitization to human HLA antigens, and chronic iron intoxication. Of these, perhaps the most consistently damaging to children was the development of high titers of preformed anti-HLA antibodies. This resulted in increased waiting time on the deceased donor transplant list and decreased overall allograft survival, both of which have been shown to be associated with a history of only six or more transfusions prior to transplantation [366]. Initiation of r-HuEPO therapy and consequent cessation of transfusions has been shown to decrease titers of panel-reactive antibodies in multiply-transfused children [367].

Children with ESRD have additional problems unique to the pediatric patient that may be ameliorated by the correction of renal anemia. Poor growth is a consistent feature of uremia in children to which severe anaemia may contribute, although consistently beneficial effects of ESAs on growth in dialyzed children have not been demonstrated [368–371]. Cognitive function is diminished in uremic children and correction of anaemia has been associated with improved cognitive function in adults on CPD and with improvement in brainstem auditory evoked responses in children [372–374]. The limited energy and exercise capacity of uremic children are closely related to the degree of renal anemia and adversely affect the capacity of these children to study and play normally with other children [375]. Finally, the presence of anemia has been associated with an impaired quality of life and an increase in morbidity and mortality in children receiving dialysis [376–378].

Pretreatment Concerns

Experience with the use of r-HuEPO in pediatric dialysis patients has previously been detailed in a number of reviews [359, 379–381]. There have also been more recent experiences with darbepoetin alfa, an analogue of r-HuEPO that is characterized by a more prolonged half-life than r-HuEPO as a result of the addition of two additional sialic acid-containing carbohydrates to the parent compound [382–385]. The updated K/DOQI Guidelines and Clinical Practice Recommendations for Anemia Management that were published in 2006 recommended that the target Hgb for a child or adult with CKD should be 11.0–13.0 g/dL [386]. This recommendation was made with recognition of the age-related normal Hgb values and the Hgb values indicative of anemia in children. Subsequent to the K/DOQI publication, the results of two randomized trials were published that described an increase in adult morbidity and mortality associated with high (>13 g/dL) target Hgb values [387, 388]. While modifications of the K/DOQI recommendations are currently under review as a result of these new data, it is likely that target Hgb values >12 g/dL will now be discouraged. It should also be emphasized that any new recommendations are based on adult experiences only, as there are no prospective pediatric data comparing anemia management with outcome in patients with CKD or on dialysis.

Hypertension is one of the few complications of ESA therapy in children and it develops or worsens in one-fourth to one-third of children treated with r-HuEPO [259, 380]. It thus seems prudent to insist on superbly controlled hypertension as a prerequisite for initiating therapy. Particular attention should be paid to maintaining children at their dry weights during the initiation of ESA therapy. Blood pressure must be carefully monitored in all treated patients, but especially those not receiving antihypertensive therapy when ESA therapy is begun. Early concerns about an increased risk of seizures in treated patients have not been substantiated [354, 389]. Initial reports of seizures may have actually been describing hypertensive encephalopathy rather than a primary neuroelectric event. ESAs should also not be withheld from children with stable, well-controlled seizure disorders.

Iron deficiency will inhibit ESA effectiveness [390]. Prior to initiating treatment with an ESA, a patient's iron status should be assessed by measuring serum iron, total iron binding capacity (TIBC), and serum ferritin levels. Transferrin saturation (TS) $=20\%$ and serum ferritin level >100 ng/mL are indirect, yet usually reliable, indicators of adequate iron stores to support vigorous erythropoiesis [388, 390]. The transferrin saturation is calculated in the following manner:

$$\mathrm{TS}(\%) = (\text{serum iron}/\mathrm{TIBC}) \times 100$$

Although useful in adults, the reticulocyte hemoglobin content (CHr) does not appear to be a reliable marker of iron status in children on dialysis [391].

Correction of iron deficiency at the outset of CPD may delay the need for ESA therapy in some children and will increase the efficacy of ESA in all. The route of iron administration can be either oral or IV in patients receiving CPD [388, 392].

Dosing

ESAs are effective when given intravenously, intraperitoneally, or by the subcutaneous route. Over 95% of pediatric CPD patients followed in the dialysis patient database of the NAPRTCS receive ESA therapy via subcutaneous administration [53]. Intraperitoneal dosing is safe, but to be effective it must be given in a small-volume (50 mL) of dialysate, which can compromise solute clearance [393, 394].

There is some information to suggest that the therapeutic dose of r-HuEPO for children and adults is weight independent [395]. Nevertheless, most experts recommend that a reasonable starting subcutaneous dose of r-HuEPO for the patient receiving CPD is 80–120 U/kg per week given in one to three divided doses [381, 388]. Infants and young children require higher doses and should be started at approximately 200 U/kg per week [381, 388]. The ratio of darbepoetin alfa to r-HuEPO is approximately 0.45 ug/100 units. The primary goal of therapy is to select a dose that increases the hemoglobin steadily at no more than 2–2.5 g/dL in a 4-week period, generally considered to be a rate at which adjustments in volume status and antihypertensive medications can be safely made to maintain normal blood pressure [379, 388]. It is recommended that ESA doses be decreased, but not held if a downward adjustment of the Hgb level is needed [388]. Complete stoppage will not be fully apparent for at least one erythrocyte lifetime (60 days), at which point the Hgb may fall precipitously. It is better to reduce the dose and follow the Hgb value weekly until the new steady state is achieved. Missed doses should be replaced at the earliest possible opportunity.

When initiating therapy with an ESA, a patient's hemoglobin should be measured every 1–2 weeks until the target Hgb has been reached and the ESA dose is stable; the frequency of Hgb monitoring should be at least monthly thereafter. Similarly, iron status tests should be performed every month during initial ESA treatment and at least every 3 months during stable ESA therapy [388].

Iron Supplementation

Almost all children on CPD receiving an ESA require iron supplementation. Factors which may contribute to the development of iron deficiency in CPD patients include inadequate intake of dietary iron, frequent diagnostic blood tests, inadequate intestinal iron absorption as a result of factors such as increased levels of hepcidin and increased iron requirements during therapy with ESAs [396, 397]. Oral iron preparations differ in tolerability and absorption with the most potent preparation, ferrous sulphate, also the one most often associated with gastrointestinal side effects [398]. Absorption of oral iron is enhanced by increased gastric acidity, as is seen when iron is taken before or several hours after a meal or with small doses of vitamin C [399]. Absorption of iron is diminished by phosphate

binders, tannins (tea, coffee), and green leafy vegetables. The usual starting dose of oral iron is 2–3 mg elemental iron/kg per day.

When oral iron supplements are unsuccessful in meeting or repleting iron needs, intravenous iron is indicated. There is now a substantial experience in North America with ferric gluconate, a much safer alternative than iron dextran because of the risk of anaphylaxis associated with the latter iron preparation [391, 392]. Additional alternatives such as iron sucrose are currently being studied in children. While effective clinically, further study of all of these agents are necessary because of concerns related to subclinical toxicity (e.g., oxidative stress) [396, 400].

ESA "Resistance"

A suboptimal response to ESAs can occur as a consequence of iron deficiency, infection (e.g., peritonitis) or other inflammatory processes, hyperparathyroidism, aluminium intoxication, and vitamin B12, folate, or carnitine deficiency [401–403]. Of these, iron deficiency is the most common [224, 381]. A failure to increase the Hgb level to greater than 11 g/dL despite an r-HuEPO equivalent dose of greater than 500 U/kg per week should prompt an investigation for these factors [388].

Immune Status and Vaccine Responsiveness

The propensity for infection that characterizes children on CPD has led to a number of studies that have evaluated the immune status of this population. Abnormalities of humoral immunity including hypogammaglobulinemia, deficiency of IgG_2, and abnormal responses to childhood immunization have all been described [339, 341, 404–406].

Katz et al. first described hypogammaglobulinemia in infants receiving CAPD [339]. Whereas immunoglobulin losses into the effluent were present, these losses could not fully explain the low serum IgG levels seen. It was hypothesized that "uremic toxins" might suppress immunoglobulin synthesis. Neu et al. described hypogammaglobulinemia in 12 of 17 (71%) patients <42 months of age and maintained on cycler PD [341]. No cause-and-effect relationship between low serum IgG levels and infection was evident in this study. Similar clinical observations will need to be conducted in the future to determine if patients on CPD who are found to have low serum immunoglobulin levels by routine screening should receive prophylactic intravenous immunoglobulin therapy [189].

Current recommendations are that children on dialysis should receive all of the standard childhood immunizations, in addition to expanded age group usage of the influenza and pneumococcal vaccines [406–408]. While it is hoped that this approach will help alleviate the risk of vaccine-preventable disease, it should be noted that very few studies have specifically evaluated vaccination response in children immunized while on dialysis [409]. Most of the studies that have been conducted involved relatively small numbers of patients. Based on the information that has been collected to date, guidelines for immunizing patients on CPD are as follows [406–408]:

1. Patients should receive all standard immunizations according to the recommended immunization schedule of the American Academy of Pediatrics [406, 408].
2. Older patients who have not had natural varicella may receive the varicella vaccine if not previously immunized [408, 410]. Since this is a live viral vaccine, it should be avoided in patients receiving immunosuppressive medication, including corticosteroids at a dose greater than 2 mg/kg body weight or a total daily dose of 20 mg for more than 2 weeks [411]. Transplantation should be delayed for >8 weeks following this live viral vaccine.
3. Patients should receive supplemental immunization with the influenza and pneumococcal vaccines. The influenza vaccine should be provided yearly and booster inoculations of the pneumococcal vaccine will be required [408, 412–415].
4. Antibody response to the measles–mumps–rubella (MMR) vaccine and varicella should be evaluated prior to transplantation [407, 416, 417]. Re-immunization is recommended if the patient is unprotected.
5. Doubling of the recommended dose of hepatitis B vaccine should be considered and up to three additional doses should be provided to patients who do not develop protective antibody levels after the primary series. Antibody levels to hepatitis B should be monitored yearly and booster doses should be provided to patients whose antibody levels fall below protective [406].

Growth

Progressive growth retardation is a classical characteristic of children on dialysis. A substantial percentage of patients who develop ESRD during childhood attain a compromised final adult height [418, 419]. Nutritional imbalances, particularly *protein-energy malnutrition*, are frequently seen in children suffering from CKD and may contribute to the development of this complication. Infants and young children are particularly vulnerable to malnutrition because of low nutritional stores and high energy demands which are in turn necessary to promote high growth rates in this age group. In addition, protein synthesis is decreased and protein catabolism increased in uremia. In children with CKD, spontaneous energy intake is correlated with growth rates if it is less than 80% of recommended dietary allowance. However, a further augmentation of energy above this level results in increasing obesity rather than the stimulation of additional longitudinal growth. *Metabolic acidosis* contributes to uremic growth failure and tissue catabolism via increased endogenous glucocorticoid production, activation of the ubiquitin-proteasome pathway, suppression of endogenous growth hormone and IGF-1 secretion, and downregulation of GH and IGF-I receptor expression. Moreover, children with CKD secondary to renal malformations often suffer from excessive *salt and water losses*, which can persist well into end-stage renal failure. These losses can cause severe growth retardation, as is evident in children with isolated renal tubular defects. *Renal osteodystrophy*is related to growth failure in a complex manner. Excessive hyperparathyroidism can cause destruction of the growth plate architecture and complete growth arrest. On the other hand, low bone turnover is also associated with diminished longitudinal growth. Both in pre-dialytic CKD and in children with ESRD undergoing CPD, growth rates are correlated positively with plasma PTH levels. Hence, both low and high bone turnover derangements may contribute to growth impairment in children with CKD.

Post-infantile growth is predominantly regulated by *endocrine mechanisms*. The function of the somatotropic hormone axis is fundamentally disturbed in CKD. Whereas the circulating growth hormone levels are normal or slightly elevated due to impaired metabolic clearance [420], pituitary GH secretion is inappropriately low since free circulating IGF-1 is reduced [420]. Uremia is characterized by a state of multilevel resistance to GH and its effector IGF-1, as reflected by GH receptor downregulation and defective postreceptor GH signaling leading to diminished IGF-1 synthesis, accumulation of circulating IGF binding proteins resulting in low free, biologically active IGF-1, and a post-receptor defect in IGF-1 action [421]. Since these alterations are quantitatively correlated with the degree of renal impairment, GH resistance is most marked in children with ESRD.

Although dialysis treatment partly corrects the uremic state, longitudinal growth is usually not improved by the institution of dialysis. A slight gradual loss of standardized height typically occurs in children and adolescents undergoing CPD or hemodialysis. Residual kidney function seems to be a better predictor of longitudinal growth than dialytic clearance. In children on CPD, a high peritoneal transporter status is also associated with subnormal longitudinal growth. Since the high transporter status can be caused by a state of microinflammation and cytokine-induced intracellular inhibitors are involved in the post-GH receptor signaling defect in uremia [422], upregulation of inflammatory cytokines may be an important mechanism contributing to growth failure via GH resistance in children on CPD [422].

Despite the resistance to endogenous GH, treatment with *recombinant human growth hormone* (rhGH) at pharmacological doses (0.05 mg/kg/day) markedly increases IGF-I production whereas IGFBPs are only modestly stimulated, resulting in improved IGF-I bioactivity and stimulation of longitudinal growth in children with CKD. The response to rhGH is best in prepubertal patients with pre-dialytic CKD. In these children, rhGH doubles the pretreatment height velocity during the first treatment year and continues to reduce the relative height deficit during extended administration, resulting in near normal height within 5 to 6 years of therapy. Long-term rhGH treatment is remarkably safe and leads to a marked improvement of final adult height [423, 424]. The efficacy of rhGH therapy has also been demonstrated in young infants with CKD, supporting the recommendation for early rhGH initiation in infants and young children if adequate energy intake fails to result in normal growth [275]. The growth promoting effect of rhGH is less marked in dialysed children compared to children with pre-endstage CKD, probably due to the more marked GH resistance secondary to microinflammation, GH receptor down-regulation and accumulation of IGF binding proteins in ESRD. The response to therapy does not differ between children on CPD and hemodialysis.

Renal Osteodystrophy

Renal osteodystrophy represents a spectrum of skeletal disorders ranging from high-turnover lesions of secondary hyperparathyroidism to low-turnover lesions and adynamic bone disease [425]. Whereas factors related to the development of the former lesion include phosphate retention, hypocalcaemia, decreased levels of 1,25-dihydroxy-vitamin D,

skeletal resistance to parathyroid hormone and reduced expression of vitamin D and calcium sensing receptors in the parathyroid glands, pathogenic factors responsible for low turnover bone disease include the use of calcium containing phosphate binders, active vitamin D therapy, and the use of high dialysate calcium concentrations [426]. The clinical presentation of renal osteodystrophy is generally insidious, although it may be manifested by renal bone pain, bony deformities, and muscle weakness. Low turnover bone disease is associated with an increased risk of fractures. Both uncontrolled high-turnover osteodystrophy and low-turnover bone disease interfere with skeletal mineralization and increase the risk of extraskeletal calcification [427]. Also, while skeletal resistance to the physiological effects of PTH occurs in uremia, PTH at high concentrations is a uremic toxin causing damage to multiple tissues including the myocardium and vasculature. Hence, dietary and pharmacological measures to prevent and treat renal osteodystrophy in dialyzed children aim at maintaining bone and PTH homeostasis while preventing cardiovascular damage from altered mineral metabolism.

Control of osteodystrophy can be achieved by maintaining serum phosphorus, serum calcium and their ion product in their age-appropriate normal ranges (see also "Nutrition Goals"). The target range for PTH in children is more controversial. While histopathology findings suggest that optimal bone turnover may be achieved at plasma PTH levels of 200–300 pg/mL, or about 3–6 times the upper limit of normal, mean PTH concentrations >250 pg/mL have been strongly associated with coronary artery calcification in young adults with childhood-onset ESRD [217, 427, 428]. Other experts recommend that the PTH goal for children on dialysis should be close to the normal range (1–2 times), an outcome that can be achieved as long as normophosphatemia is strictly preserved [429, 430].

General measures to maintain a normal mineral and salt balance in children on CPD include the restriction of dietary phosphorus intake, supplementation of vitamin D_2 if required to maintain the 25-hydroxyvitamin D level at >30 ng/mL, and the use of dialysis fluids containing 1.25 mmol/L calcium. If normophosphatemia cannot be maintained, calcium based phosphate binders should be added, taking care to limit the total intake of elemental calcium to 2,500 mg/day or twice the recommended dietary intake (DRI) [217]. Serum calcium should be maintained in the low normal range. If levels exceed 10.2 mg/dL (2.54 mmol/L), calcium-based phosphate binders should be replaced by non-calcium-based compounds such as sevelamer and low-calcium dialysis fluid should be used for several weeks. Hypocalcemia should also be avoided, and treated by vitamin D repletion, enteral calcium supplementation and active vitamin D sterols. If hyperparathyroidism develops despite maintenance of normophosphatemia, normocalcemia and adequate 24-hydroxyvitamin D levels, oral calcitriol remains the treatment of first choice in children on CPD. The induction of low-turnover bone disease with frequent episodes of hypercalcemia is the major limitation of calcitriol therapy [431, 432]. While the hypercalcemic potential of calcitriol is less affected by the dosing interval (daily versus twice or thrice weekly) than originally thought, evening dosing is more effective and better tolerated than morning administration [432–435]. The combination of calcitriol with calcium-free phosphate binders increases the therapeutic margin of calcitriol therapy. The therapeutic advantage of the new synthetic vitamin D analogues (i.e., doxercalciferol, paricalcitol, 22-oxacalcitriol) in children awaits clarification by clinical trials.

The calcimimetic agent cinacalcet decreases plasma PTH levels independent of baseline PTH and phosphate levels by binding to the parathyroid calcium sensing receptor and increasing its sensitivity to ionized calcium. Cinacalcet allows for control of parathyroid gland function even in patients with otherwise refractory hyperparathyroidism. Calcimimetics may be ideal to use in combination with vitamin D sterols since they lower serum calcium and phosphate levels [436]. Safety concerns about its use in children have been raised since the calcium sensing receptor is abundantly expressed in epiphyseal growth plates and serum testosterone levels are reduced by 30%. Despite the fact that animal studies do not suggest a negative impact on longitudinal growth, clinical trials need to be conducted to elucidate the efficacy and safety of cinacalcet in children [437].

Parathyroidectomy should be considered in children with severe hyperparathyroidism (persistent serum levels of PTH >1,000 pg/mL (100 pmol/L), and disabling bone deformities associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy [217]. Effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy or total parathyroidectomy with parathyroid tissue autotransplantation.

Complications

Peritonitis

The single most serious complication of CPD in children is peritonitis [336, 438–442]. Eleven percent of peritonitis episodes in children lead to incomplete functional recovery or technique failure [443]. Children have a significantly greater tendency to develop peritonitis than adults, with a higher proportion of children experiencing an episode of peritonitis during the first year of therapy [53]. Reductions in peritonitis rates have been reported in both adults and

children with technological advances such as disconnect systems and flush-before-fill techniques and improved prevention of exit-site infections by topical *Staphylococcus aureus* prophylaxis [138, 139, 438, 442, 444, 445]. The most recent evaluation of the NAPRTCS database showed an annualized peritonitis rate of 0.71 episodes or 1 infection every 16.9 patient-months [53]. The rate of peritonitis was higher in patients during their first year of life with one infection every 13.3 months versus one episode every 18.8 patient-months in children >12 years of age. In the recent International Pediatric Peritonitis Registry (IPPR), Gram-positive organisms were cultured in 44%, Gram-negative organisms in 25%, and cultures remained negative in 31% of the 501 episodes. Fungal infections were seen in <2% of cases [443]. Notably, Gram-negative and specifically pseudomonas peritonitis were much more common in the United States, and associated with the use of mupirocin exit site prophylaxis.

When peritonitis is suspected, empiric antibiotic therapy should be administered via the intraperitoneal route and provide coverage for Gram-positive and Gram-negative organisms, usually by a combination of a first generation cephalosporin or vancomycin with a third generation cephalosporin or an aminoglycoside [189]. In view of the marked regional variation of antibiotic resistance patterns, the choice of empiric therapy should be guided by the local antibiotic resistance profile [446]. The primary use of vancomycin, especially in the potentially oto- and nephrotoxic combination with aminoglycosides, should be restricted to centers with widespread methicillin resistance [447–451]. Antibiotic therapy should be modified as soon as culture results become available and continued for 10 to 21 days, depending on the causative organism [443].

Exit-Site and Tunnel Infections

Catheter exit-site/ tunnel infections are a significant cause of catheter failure. In a review of the NAPRTCS data from 1992 to 1997, the incidence of exit-site/tunnel infections was 30% by 1 year after catheter insertion [165]. The Italian PD registry documented the incidence of catheter infections to be 1 episode/27.4 patient months [144]. Exit-site (ESI) and tunnel infections tend to occur more frequently in children than in adult CPD patients, possibly related to specific problems of hygiene in young children ("diaper related") and/or the shorter length of the sinus tract with a higher risk of colonization of the subcutaneous cuff [452]. In a retrospective review of 157 episodes of ESI occurring in 50 children treated with CPD at a single center during 950 patient-months of dialysis, *S. aureus* was the most frequent (nearly 50%) organism in both purulent and nonpurulent infections [453]. *Pseudomonas aeruginosa* was the most common Gram-negative organism (10.6%). Notably, neither patient age nor the presence of a gastrostomy, pyelostomy or the use of diapers favored the development of an ESI in these children. When ESIs did occur in diapered infants, they were more often due to Gram-positive than enteric organisms.

Prevention of exit-site infections is the primary goal of exit-site care, which should consist of regular assessment of the exit-site, cleansing, immobilization of the catheter and protection of the exit-site and tunnel from trauma. The exit-site should be assessed using objective, standardized criteria. An exit-site scoring system developed for children has also been recommended for use in adult patients [188, 451] (Table 29.7). Cleansing should be performed with a noncytotoxic and nonalcoholic agent (e.g., poloxamer 188, octenidine, chlorhexidine). The use of a dressing may be associated with fewer infections in the pediatric patient [454]. A recent survey of exit-site care practices in 22 pediatric and 125 adults sites found that significantly fewer pediatric programs conducted daily care and used tap water or antibacterial soap, while a greater percentage "air dried" the cleaned exit-site and used a semi-permeable dressing over an absorbent layer, compared to adult programs. (B. Prowant, Personal Communication). In the International Pediatric Peritonitis Registry, *Pseudomonas*-related peritonitis episodes were more common in centers performing exit-site care more than twice weekly and in those centers using nonantibacterial cleansing agents (soap, tap water) [446].

Clinical data in children and adults support the use of prophylactic antibiotic agents to decrease PD-associated *S. aureus* infections. While early recommendations suggested the need to assess patients/caregivers for *S. aureus* nasal carriage status, some centers now prescribe the therapy to all patients, with recognition of the risk for the emergence of

Table 29.7 Exit-Site Scoring System

	0 Points	1 Point	2 Points
Swelling	No	Exit only (<0.5 cm)	Including part of or entire tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain on pressure	No	Slight	Severe
Secretion	No	Serous	Purulent

Infection should be assumed with a cumulative exit-site score of 4 or greater.

antibiotic resistance [455–458]. However, the routine topical use of mupirocin cream at the catheter exit-site has been associated with increased *Pseudomonas* exit-site infection in adults and peritonitis in children [446, 459, 460]. Gentamicin is an efficacious alternative to mupirocin, covering both the Gram-positive and the Gram-negative spectrum [459, 460].

Exit-site infections are routinely treated with oral antibiotics according to culture results [189]. Intraperitoneal antibiotics are added only if improvement is not seen promptly. Refractory or recurrent infections suggest involvement of the subcutaneous cuff. In these cases surgical catheter replacement, usually performed as a one-stage intervention, is the standard procedure [144, 189]. Alternative approaches include surgical unroofing and peeling of the external cuff from the catheter and selective replacement of the external infected portion by cutting and gluing just above the internal cuff [461–464].

Hernias, Leaks, and Hydrothorax

Hernias

Abdominal wall hernias are common in children on CPD, occurring in 22–40% of pediatric patients [465, 466]. Inguinal hernias are most common, but umbilical and even paraesophageal hernias can also occur as a result of the increased intra-abdominal pressure associated with CPD. Hernias in children are likely to occur early in the course of CPD. Young age, prior abdominal surgery, corticosteroid therapy, malnutrition, and obesity are risk factors for hernia formation. In all cases, incarceration is uncommon. Young male infants are at highest risk of inguinal hernias, since the obliteration of the processus vaginalis is frequently incomplete at time of PD initiation. If Tenckhoff catheters are placed laparoscopically, the processus vaginalis should be explored for patency in male infants and prophylactic closure of the open processus should be considered. It has also been proposed that the intraabdominal pressure in children starting CPD should be repeatedly measured in order to minimize the risk of hernia formation [231]. At a given fluid volume normalized to body surface area, infants appear to develop a higher intraabdominal pressure than older children. The intraperitoneal pressure should not exceed 10 cm H_2O. APD with reduced exchange volumes and increased exchange frequency should be considered for patients felt to be at risk. If a hernia is diagnosed, elective repair should be scheduled promptly. In most cases of inguinal hernias in males <2 years of age, a bilateral repair is recommended.

Leaks

Dialysate leakage from the catheter exit-site can complicate the placement of newly inserted catheters [467]. Dialysate can also leak from the peritoneal cavity into various tissue planes, most often into subcutaneous tissue around a previous surgical incision. The subcutaneous fluid expands because it is hypertonic dialysate and consequently absorbs water. Conservative management, occasionally including temporary suspension of CPD, is usually sufficient to allow these leaks to resolve. Aspiration of the subcutaneous fluid is not helpful and should be avoided.

A leak into the genital area can be difficult to distinguish from an inguinal hernia. Both CT scan and scintigraphy have been used for this purpose [468, 469]. Most of these patients can be managed conservatively by reducing the exchange volume and discontinuing daytime exchanges in CCPD patients. If a patent processus vaginalis is present, it may require ligation to prevent recurrence of a genital leak.

Hydrothorax

Hydrothorax is an uncommon complication of CPD in children and adults [470] but it is usually right-sided when it occurs. It is suggested that the leaks occur as a result of the impact of raised intra-abdominal pressure on small defects in the pleuroperitoneum covering the diaphragm [471]. Others believe that a tiny bleb arises on the surface of the diaphragm and then ruptures, forming a one-way valve leading to a tension hydrothorax. Alternatively, there is the potential that the pleuroperitoneal connection is present as a congenital defect in the diaphragm and only becomes evident because of the presence of dialysis fluid.

It is important to consider other causes of pleural effusion in CPD patients, including congestive heart failure, fluid overload, and hypoalbuminemia. In patients in whom the cause is uncertain, tests are necessary to prove the pleuroperitoneal connection. Various techniques have been used to detect the presence of PD fluid in the pleural space, including thoracocentesis to measure the pleural fluid for dextrose, colorimetric testing (indigo carmine), direct visualization (methylene blue), and chest fluoroscopy after infusing dilute radiopaque contrast media or radioisotope into the peritoneal cavity [472, 473]. More recently, MRI after intraperitoneal administration of dilute gadolinium contrast agent has been introduced as a noninvasive, radiation-free alternative [474]. However, the risk of developing nephrogenic systemic fibrosis associated with the use of gadolinium must be considered prior to pursuing the latter approach [475, 476].

Resolution of a hydrothorax will take place following transfer to hemodialysis. For patients who need/wish to return to CPD, sealing of the pleuroperitoneal connection with an intrathoracic sclerosing agent (i.e., tetracycline or autologous hemoglobin) or surgical patch-grafting have been reported [470, 477–479].

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS), referred to as sclerosing encapsulating peritonitis in earlier literature, is a severe complication of long-term PD. According to a Japanese study, signs of EPS are present in 57% of children receiving CPD for 5 years, in 80% after 8 years and in 100% of patients after 10 years of CPD [480]. These figures are higher than reported for adults, in whom EPS was observed in 17% of patients dialyzed for 8 years [481]. EPS appears to reflect the long-term toxicity of conventional PD solutions which are buffered at acidic pH with cytotoxic lactate, hyperosmolar glucose, and toxic glucose degradation products arising from heat sterilization. The bowel becomes encapsulated in a fibrous, calcified cocoon. The occurrence of EPS usually leads to PD technique failure [482, 483]. Fatalities have occurred in severe cases accompanied by massive inflammation. Immunosuppressive treatment and surgery has been helpful in anecdotal cases.

Other Major Disorders of the Gastrointestinal Tract

Diverticulitis is a frequent source of bowel perforation and fecal peritonitis in adults, but has not been reported in children. In contrast, appendicitis must be considered as a rare but important disorder in the differential diagnosis of peritonitis in children on CPD who present with fever and abdominal pain. After an appendectomy, CPD should be suspended until the stump has healed.

Pancreatitis has been described in adults and anecdotally in children on CPD [484, 485]. Concerns that CPD may predispose a patient to develop pancreatitis have been disputed [486]. Cessation of CPD and transfer to hemodialysis may be indicated in individual cases.

Miscellaneous Complications

It is not possible to list all the other complications that may be associated with CPD. However, a brief review of some of the more important or uniquely pediatric complications are provided.

Hypogammaglobulinemia

Hypogammaglobulinemia has been reported in infants and younger children on CPD [339, 341, 487]. This may be particularly significant since mortality rates are highest in this age group of CPD children, and the majority of the deaths are from infection. This complication should be monitored for and treatment with intravenous gammaglobulin considered when hypogammaglobulinemia is detected, especially in the setting of an active infection.

Prune-Belly Syndrome

Children with prune-belly syndrome can be treated with CPD, despite their deficient abdominal musculature [122, 123]. To prevent catheter leaks in this setting, a percutaneous catheter insertion technique can be helpful in achieving a watertight seal within the thin abdominal wall. A slow break-in period to permit healing is also advised. NIPD is the preferred dialysis modality in these boys to increase patient comfort.

Ventriculoperitoneal Shunt

Children with myelomeningocele typically have a neurogenic bladder which may lead to ESRD. In addition, these children often have hydrocephalus requiring ventriculoperitoneal (VP) shunting. When children with VP shunts require dialysis, the option of CPD is commonly entertained. The theoretical possibility of bacterial peritonitis episodes involving the VP shunt has led some authors to consider the presence of a VP shunt as a relative contra-indication to CPD [124]. Grunberg reviewed nine children on PD with meningomyeloceles, six of whom had

functioning ventriculo-peritoneal shunts. None developed ventriculitis or ventriculo peritoneal shunt dysfunction, even though four had PD-related peritonitis. One child presented with a massive PD-related hydrothorax [126, 488].

Genitourinary Surgery

Children with inadequate bladders are often treated with a bladder augmentation procedure using bowel, stomach or dilated ureter [489]. Creation of the augmented bladder requires extensive surgery with attendant risks for the development of adhesions. In addition, the augmented bladder segment is attached to a vascular pedicle that resides in the peritoneal cavity. Despite the magnitude of the surgery, and potential for complications, these children do well on CPD.

Many children on CPD require elective nephrectomies, usually for hypertension or to remove a potential focus of infection prior to renal transplantation. If it is necessary only to remove the kidneys, the use of a posterior approach avoids invasion of the peritoneal cavity and allows CPD to continue immediately postoperatively. For patients requiring nephroureterectomy via a transperitoneal approach, CPD must often be suspended for a brief period, relying on temporary HD. CPD can also be offered to children who require a vesicostomy or pyeloureterostomy. Few dialysis complications related to these forms of urinary diversion have been observed.

Bloody Dialysate

Children on CPD will occasionally experience bloody dialysate following minor trauma. The bleeding is probably due to catheter trauma in most cases. Mild bleeding can mimic the cloudy fluid of peritonitis. Conservative management is usually successful. The peritoneal cavity is flushed with dialysate with the option of adding low-dose heparin to reduce the risk of clot obstructing the catheter. Patients, parents, teachers, and coaches often need reassurance that such episodes are of little consequence, and should not interfere with the normal physical or sporting activities.

Bloody dialysate can also occur in postmenarchal girls secondary to retrograde menstruation or at the time of ovulation. Conservative management as above is all that is required.

Quality of Life and Other Psychosocial Issues

Some authors claim that the survival of patients with ESRD depends on factors other than the mode of treatment. Therefore, determination of the quality of life for ESRD patients is important for clinical decision making and also for allocation of resources [490]. One study of 73 children and adolescents compared the psychosocial adjustment to ESRD for patients on HD, CPD, and following transplantation [491]. Significant advantages of transplantation over dialysis, and of CPD over HD, were found. Children with transplants exhibited less social and functional impairment and fewer treatment-associated practical difficulties. Parents of transplanted children also had fewer practical difficulties. Children on CPD had less social impairment, less depression, better adjustment, less behavioral disturbance, and fewer practical problems related to treatment than their HD counterparts. Depression and anxiety scores were lower in parents of children on CPD. While this study suggests better-adjusted parents of CPD children, possibly due to greater involvement in their child's care, the potential for parental "burn-out" exists with prolonged CPD. It is difficult for parents to meet the medical, psychological and social needs of the child on CPD and still have sufficient time to meet the needs of other family members [492, 493].

More recently, two studies of the health related quality of life (HRQOL) of pediatric patients with CKD used the PedsQL 4.0 Generic Core Scales as the evaluation tool [494–496]. This 23-question survey has forms for patients and parents and asks respondents to score patient function in four domains: physical, emotional, social, and school. There are also two summary scores (psychosocial health and total score). In an assessment of 20 children with CKD but not yet with ESRD, an additional 12 children receiving HD or PD and 27 transplant recipients, McKenna et al. found that the children with kidney disorders scored lower than controls in all domains, and that children on dialysis scored equal to or higher than the transplant recipients [129]. Whereas parents of the transplant recipients rated their children's HRQOL higher than the children themselves, the opposite was the case in the dialysis patients. In the second study, Goldstein et al. studied 96 children (HD-32, PD-19, Transplant-45) and 84 parents [130]. As in the study by Mckenna et al., the scores of the patients were significantly lower than healthy controls for all domains. No differences were noted between the PD and HD patients, while the transplant recipients reported better physical and psychosocial health than the dialysis population. Although a variety of factors influence results such as these, the number of prescribed medications and the success of anemia management may be particularly influential [129, 377].

The real success of advances in transplantation and dialysis therapy must be judged by the patient's rehabilitation. Children with ESRD differ from those with many chronic disorders by the persistence of their disease, the reliance on technology despite successful transplantation, and a much higher incidence of multiple disabilities as compared to the general population. A large multicenter study of children and adolescents with ESRD noted school attendance was good during the first years, but subsequent education was frequently disrupted and inadequate [497]. Attendance at schools providing an opportunity for a university career was low, and only 52% of eligible patients attended vocational school. Only 14% of adolescents over 18 years of age achieved independent living. Factors that appear to contribute to this poor outcome include delays in social and sexual maturation, retardation of growth, and psychological and behavior disturbances such as depression, anxiety, withdrawal and denial, which have their roots in chronic illness during childhood [498, 499]. Among adolescent patients on PD and in the NAPRTCS registry, 79% were attending school full-time at baseline and 81% 6 months after initiating dialysis, as compared to children receiving HD (52 and 52%, respectively) [53].

Finally, short stature, combined with alterations in body image related to the need for CPD, such as catheters, central venous lines, feeding tubes, or fistulas, may contribute to psychological maladjustment in children with ESRD. While parents can ensure the compliance of younger children for dialysis and medications, adolescents present a particular challenge with respect to compliance. Peer pressure often results in dietary indiscretion, and fear of being labelled different may cause a child to forgo dialysis exchanges at school. Embarrassment about catheters, fatigue, or the dialysis *per se* may result in failure to participate in physical-fitness classes, which results in poor levels of physical activity with attendant health risks.

Transplantation

Improving patient and allograft survival rates in children have confirmed the long-standing impression that renal transplantation is the treatment of choice for all pediatric dialysis patients [159]. Thus, dialysis is best considered a bridge to get children safely to or between renal transplants. To be a successful dialysis modality for children, PD must be readily compatible with transplantation. When CAPD was first developed for children in the early 1980s, some nephrologists and transplant surgeons were hesitant to transplant children on CAPD, primarily because of a perceived risk of post-transplant peritonitis under immunosuppression [500]. These fears have proved unfounded. Nearly three decades of experience with transplantation in children maintained on CPD has failed to demonstrate any adverse impact of PD-associated peritonitis on transplant outcome. Currently, 39% of children receiving transplants in the nearly 100 North American pediatric dialysis centers that participate in the NAPRTCS are maintained pretransplant on PD, compared to 30% maintained on HD [53]. A randomized comparison of PD and HD in children has not been performed. Reports of patient and graft survival rates >90% at 1 year among children maintained on CPD prior to transplantation have become commonplace [501–504].

In several important areas, the use of CPD as the maintenance dialysis modality immediately prior to transplantation has been reported to be associated with outcomes superior to HD. In adult patients, PD favorably influences early graft function [505] and is associated with a lower risk for graft failure and recipient death compared to HD [505, 506]. However, PD has also been shown to be associated with an increased risk of graft loss due to thrombosis. Recent data from the NAPRTCS has documented an increased risk of graft thrombosis as a cause of graft loss in children treated with PD immediately prior to transplantation, confirming earlier observations on a smaller cohort [507, 508]. In a review of 7,247 pediatric renal transplants performed between 1987 and 2001, McDonald et al. found that in patients receiving CPD, 3.4% of all grafts were lost as a result of thrombosis, as compared to 1.9% in the HD group and 2.4% in the preemptive transplant group, a difference that was highly significant ($p = 0.005$). Although young recipient age was associated with a trend towards higher thrombosis risk, the PD patients had a higher risk of graft loss due to thrombosis in all age groups, even among patients >12 years at the time of transplant. Studies in adult patients have also found an increased risk of thrombosis in patients receiving PD pretransplant [509].

The etiology of the increased risk of graft thrombosis in PD patients is not clear, although peritoneal protein losses leading to a hypercoagulable state similar to that seen in nephrotic patients has been hypothesized [510]. Routine pretransplant screening for the presence of hypercoagulable disorders (e.g., protein C, protein S, and antithrombin III deficiencies, antiphospholipid antibodies, factor V Leiden, prothrombin, and MTHFR mutations) has led to wider recognition of the importance of intensified post-transplant anticoagulation prophylaxis in such patients. Similarly, all pediatric PD patients should receive routine anticoagulation prophylaxis after transplantation. The optimum anticoagulation approach has not been identified, although routine use of perioperative heparin followed by small daily doses of aspirin has been effective in patients for whom PD was the only known thrombotic risk factor [511].

Some Important Aspects of the Preparation of the PD Patient for Transplantation

Every pediatric dialysis patient should be considered to be continuously in active preparation for kidney transplantation, regardless of how far in the future the transplant is likely to be accomplished. Management decisions made while the child is being dialyzed, especially those involving blood transfusions and vascular access, can have a profound impact on future transplant options. Every dialysis center caring for a pediatric patient should establish and maintain a close collaborative working relationship with the center that will ultimately transplant the child, and once the formal transplant referral process has begun, the child on dialysis should be seen regularly at the transplant center, or if this is not possible, the transplant center must be kept well informed of events in the dialysis course of the child. This situation is optimized when dialysis and transplant centers work closely together to bring the child to transplant in the best possible condition.

Immunizations

Most, but not all infants and children who receive routine childhood immunizations while on PD develop protective antibody titers that may be critical to avoiding serious infection following transplantation [512]. Immunizations should be as complete as possible prior to transplantation, and all vaccines must be given no closer than 4 weeks prior to transplantation. While non-live vaccines can be given following transplantation, immunogenicity is poor due to immunosuppression. Although many centers will not administer non-live vaccines for at least 1 year post-transplant, all pediatric transplant patients should eventually complete the primary immunization series with non-live vaccines.

Because live vaccines cannot be given after transplantation, careful attention must be paid to administering these vaccines as early as possible pretransplant [409]. All live vaccines must be given either together on the same day or separated by at least 4–6 weeks. Patients should be kept on the regular vaccination schedule when possible, but accelerated administration of live vaccines (MMR) in infants as young as 9 months of age has been shown in a small group of patients to result in measurable antibody titers in over 80% [513]. Current recommendations are for two doses of MMR 4 weeks apart and two doses of varicella vaccine preferably three months apart, all at least 4 weeks prior to transplantation [406, 410].

Transfusions

Administration of whole blood or packed red blood cells prior to transplantation has been shown to be associated with an increased risk of graft loss in pediatric recipients. In an analysis of graft survival in nearly 10,000 pediatric recipients followed by the NAPRTCS, a total of greater than five transfusions at any time pretransplant had a relative hazard of graft failure $= 1.3$ ($p = 0.003$) [53]. Each transfusion is a potentially sensitizing event that can result in the development of persistent antibodies to human tissue antigens that ultimately limit the potential donor pool for that child. Thus, transfusions should be avoided as much as possible prior to transplantation.

Vascular Access and Central Venous Thrombosis

Many children who come to transplant have had multiple vascular access procedures throughout their lives, some involving indwelling catheters in deep central veins. In some cases the entire inferior vena cava becomes completely thrombosed leading to the development of collateral venous drainage consisting of a network of small veins, none of which is capable of supporting the venous drainage of the allograft [514, 515]. This is particularly true when the transplant is an adult-sized kidney placed into an infant.

Thus, care must be taken to avoid central venous catheters in the lower extremities as much as possible, especially in patients whose primary renal disorders place them at increased risk for vascular thrombosis (e.g., nephrotic syndrome, systemic lupus erythematosus, and any congenital or acquired hypercoagulable state). Most transplant centers will require imaging studies to assess the patency of the abdominal and pelvic vasculature in all infants and young patients likely to receive an adult-size donor kidney and in older patients otherwise at risk for central venous thrombosis [508].

Immediate Preoperative Management

Preoperative evaluation of the child on CPD includes assessment for evidence of a tunnel or exit-site infection and for peritonitis. Dialysate is sent for cell count, differential, Gram's stain, and culture. When dialysate studies indicate bacterial peritonitis, the transplant should be postponed. A localized exit-site infection does not mandate postponement as long as the catheter is removed at the time of transplant surgery, using a separate drape and scrub of the abdomen. However, the presence of a significant tunnel infection is a contraindication to transplantation.

While dialysis the night before transplant surgery is customary, not all children need it. For small children, the volume depletion associated with PD immediately prior to transplantation can make intraoperative fluid loading more difficult [501].

The Peritoneal Dialysis Catheter

An extensive literature review by Chavers revealed that the reported time of routine PD catheter removal in children varied widely, from immediately at the time of transplant to up to 4 months post-transplant [516]. Local experience and custom seem to drive these policies, rather than the demonstrated superiority of any particular approach. When the allograft is placed in an intraperitoneal location in infants and small children, the catheter typically is removed during transplant surgery [501, 502]. Later removal in patients receiving retroperitoneal transplants allows for use of PD post-transplant in cases of primary allograft nonfunction or early acute rejection. Post-transplant ascites can also be drained if necessary using the PD catheter. When these problems are infrequently encountered in a center, the PD catheter is more likely to be removed early. Because such problems typically occur during the first post-transplant days, if a patient is doing well there seems little reason to leave the catheter in place beyond the initial hospitalization [501, 516].

Complications Post-Transplant Related to PD

Peritonitis following transplantation is an infrequent complication, occurring in 1–11% of transplanted children in centers where PD catheters are routinely removed 2 weeks to 3 months post-transplant [517–520]. No correlation has been found between the number of pretransplant peritonitis episodes and the incidence of post-transplant peritonitis [517]. Fever in an immunosuppressed child with an indwelling PD catheter mandates a work-up for peritonitis. Management of post-transplant peritonitis has not been studied systematically. Most centers remove the PD catheter and treat the patient with parenteral antibiotics.

Cellulitis of the PD catheter exit site and/or tunnel has occurred in some series more often than peritonitis [518, 521]. Recent treatment for acute rejection has been cited as a risk factor for PD catheter exit-site/tunnel infection. The care of the exit site post-transplant has not been studied. High rates of exit-site/tunnel infection have been reported by centers employing daily cleansing regimens using povidone-iodine [518, 521].

Post-transplant ascites occurs in up to one-third of pediatric PD patients [516]. Ascitic fluid volumes can be substantial and can result in uncomfortable abdominal distension, respiratory distress and traction on the incompletely healed transplant incision. The cause is unknown, although fluid loading post-transplant, especially in infants, may play a role [522]. Drainage may be required, but repeated drainage may contribute to re-formation of ascitic fluid.

Congenital Hyperammonemia and Other Inborn Errors of Metabolism

Congenital urea cycle enzymopathies are characterized by a reduced capacity to synthesize urea, which leads to accumulation of ammonium and other nitrogenous urea precursors. Severely affected neonates develop vomiting, lethargy, seizures, and coma within the first few days of life. The central nervous system symptomatology is thought to be primarily due to the effects of increased blood ammonium concentration. Emergency treatment is aimed at rapid and sustained removal of accumulated ammonium. Exchange transfusion, acute PD, continuous extracorporeal procedures (continuous arteriovenous or venovenous hemofiltration, hemodialysis, and hemodiafiltration [CAVH/CVVH/CVVHD/CVCHDF]) as well as intermittent HD have all been employed [523, 524]. While PD is more

efficacious than exchange transfusions in removing ammonia [525], hemodialysis is at least 10 times more effective than PD [526–528]. Continuous extracorporeal techniques are preferred in neonates. CVVHD is clearly superior to PD and is considered the treatment of choice for neonatal metabolic crises [529]. However, the insertion of a central venous dialysis catheter in neonates can be technically difficult, and neonatal hemodialysis is not available everywhere. While referral to a center experienced in emergency extracorporeal dialysis should be strongly preferred, PD remains an option in infants who are too unstable to be transported safely.

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Chapter 30
Intraperitoneal Chemotherapy

M. F. Flessner

For the nephrologist, the major therapeutic use of the peritoneal cavity is dialysis, but the peritoneum is a portal of entry for a wide variety of local and systemic therapies. Because of intravenous access problems in neonates, transfusion of packed red blood cells was one of the earliest uses of intraperitoneal (i.p.) therapy [1, 2]. Insulin is often placed in the dialysate in order to treat glucose intolerance during peritoneal dialysis [3], and i.p. insulin delivery is currently undergoing investigation as a means of long-term therapy in diabetes [4–6]. Erythropoietin, prescribed as replacement therapy for the anemia related to end-stage renal disease (ESRD), has been administered intraperitoneally [7, 8]. In contrast to these forms of i.p. therapy, which are designed to treat systemic illnesses, antibacterial agents are injected intraperitoneally in order to treat peritonitis [9]. In the past 20 years, i.p. chemotherapy has increasingly been evaluated for treatment of malignancies localized to the peritoneal cavity [10–29].

Since i.p. therapy is more cumbersome than systemic, intravenous (i.v.) delivery, the critical point that the clinician must determine is the usefulness of such an approach. Is there a pharmacokinetic advantage of administering the drug regionally (i.p.) versus systemically? In other words, does the drug achieve therapeutic concentration in the region of interest while maintaining an acceptably low level in the general circulation and thereby minimize toxicity? The i.p. administration of a drug such as erythropoietin, which has a site of action in the bone marrow and not the peritoneal cavity, may not be an appropriate use of this route. Because of a slow rate of systemic absorption, very large concentrations of erythropoietin must be injected with the peritoneal dialysate to attain levels in the blood which are equivalent to those attained with i.v. or subcutaneous (s.c.) dosing. Much of this expensive agent must be wasted, since the solution must be drained from the patient before the drug is fully absorbed [7].

What follows is an analytical approach to the evaluation of the i.p. route of administration with respect to the i.v. route. The approach assumes that the target of the therapy is either a cellular component in the peritoneal cavity (bacteria or tumor ascites cells) or the tissues surrounding the peritoneal cavity. The properties of the target significantly influence the method of delivery and the feasibility of the technique.

Pharmacokinetic Advantage

At steady state, the quantitative formula for pharmacokinetic advantage (R_d) for a target within the peritoneal cavity is in its simplest form [30]:

$$R_d = \frac{\left(\frac{C_P}{C_B}\right)_{i.p.}}{\left(\frac{C_P}{C_B}\right)_{i.v.}} \quad (1)$$

where: C_P = concentration in the peritoneal cavity, C_B = concentration in the systemic circulation, and the subscripts indicate the route of administration. In planning a therapeutic strategy the physician would like to predict R_d prior to administration of the drug in humans. The pharmacokinetics of a particular drug are based on the transport physiology of the region in which it is administered, as well as pharmacokinetic processes in the rest of the body.

M.F. Flessner (✉)
University of Mississippi Medical Center, Jackson, Mississippi
e-mail: mflessner@umsmed.edu

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Multicompartmental Concept

Physiologic characteristics of the peritoneal cavity, which cause it to be advantageous for removal of waste metabolites and poisons from the body, also provide an excellent portal of entry into the body for many drugs. The tissue space surrounding the cavity is capable of absorbing almost any agent including cell size materials placed in the cavity. Fig. 30.1 illustrates the complexity of the peritoneal cavity, in terms of pharmacokinetic pathways. Solute and fluid transfer as indicated from the peritoneal cavity occurs into the various tissues surrounding the cavity and from there into the body compartment via the circulation. Although all surfaces are potentially targets for any drug or agent within the peritoneal cavity, the relative importance of a specific area is determined by whether the surface is in contact with the fluid in the cavity. This issue is particularly important in the regional administration of antineoplastic agents and will be discussed below.

In Fig. 30.1, the peritoneal tissue has been divided into four major compartments. Each of these compartments receives blood originating in the body compartment. The blood flows through capillary exchange vessels distributed throughout the tissue and returns to the body compartment. Lymph flows from each tissue space to the body compartment as illustrated in Fig. 30.1. Each tissue compartment receives solutes from the peritoneal cavity with a solute mass transfer rate of S and fluid at rate F (S and F are illustrated as positive from the cavity into the tissue).

The body is shown as a single compartment in Fig. 30.1, but it could be represented by multiple compartments, if the pharmacokinetic characteristics of the drug demand it. For example, a drug that has its major effect or chief site of metabolism in the liver would be a candidate for such a model, in which the relative rates of absorption into each tissue would determine the overall effectiveness of the medication. The volume of the body compartment equals the volume of distribution of the drug in the total body excluding the tissues surrounding the peritoneal cavity. Its concentration is assumed to equal the arterial concentration. The drug is cleared at some rate CL_{BC} and there may exist some rate of input into the compartment (I_{BC}). Blood flows from the body compartment through each peritoneal compartment with rate Q_i. Lymph flows from each organ system (L_i) through two major systems into the body compartment: the thoracic duct (L_{TD}) and the right lymph duct (L_{RLD}).

The peritoneal cavity compartment is assumed to be well mixed; i.e., the concentration is the same throughout the cavity. The cavity may have a solute input rate of I_{PC} and a drainage rate of D_{PC}. The cavity does not exchange directly with the body compartment; transport occurs only with the tissue compartments.

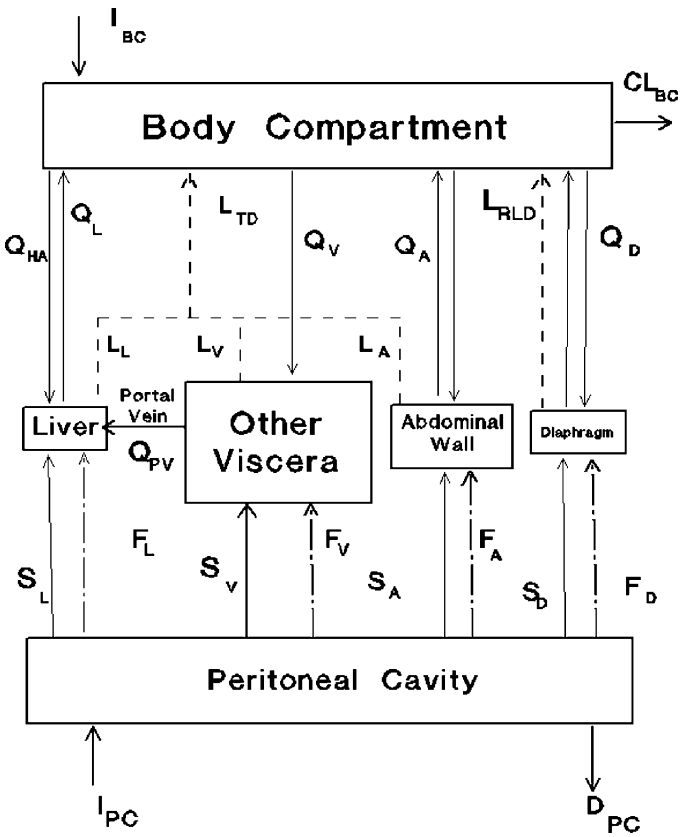

Fig. 30.1 Compartmental model concept of intraperitoneal drug delivery in which transport occurs between the cavity and specific tissues surrounding the cavity. *Symbols*: I = infusion; CL = clearance; D = drainage from the cavity; Q = blood flow through organ or vessel; L = lymph flow from tissue to body compartment; F = rate of convection from the cavity to tissue; S = rate of solute transfer from the cavity to tissue. *Subscripts*: A = abdominal wall and psoas; BC = body compartment; D = diaphragm; HA = hepatic artery; L = liver, PC = peritoneal cavity; PV = portal vein; RLD = right lymph duct; TD = thoracic duct; V = other viscera including the intestines, stomach, pancreas, and spleen. See text for a full description

The diaphragm is included as a separate compartment because of the specialized subdiaphragmatic lymphatic system [31, 32], which accepts cell sizes to 25 μm in diameter [33] and which accounts for 70–80% of the total lymph flow from the cavity [34–36]. The diaphragm also experiences relatively large but variable hydrostatic pressure gradients during respiration, because of its position between the thoracic and abdominal cavities. Expiration facilitates direct fluid movement into the diaphragmatic interstitium and into the lacunae of the subdiaphragmatic lymphatic apparatus [31, 32].

The abdominal wall is shown as a separate compartment because it is the single largest recipient of fluid transfer from the cavity. The abdominal wall is of major importance as well because it is likely that much of the solute transfer flows through this tissue due to contact with the fluid [37]. In animal experiments this amounts to 40–50% of the total fluid movement out of the cavity [35, 38, 39]. The reason for this fluid movement has been attributed to the hydrostatic pressure gradient across the abdominal wall. In addition, the lymphatics are not well developed in this tissue and therefore do not provide the safety valve that they do in intestinal tissue [40]. Proteins or other macromolecular drugs, which are carried into the muscle tissue as a result of the hydrostatic pressure-driven convection will transfer to the body compartment slowly [38, 41, 42].

The liver is separated from the other visceral tissues because of its unique portal circulation coupled with its role in drug metabolism. The liver may be primarily responsible for protein losses into the cavity.

The "other viscera" include the spleen, stomach, intestines, and the pancreas, which are lumped together in a single tissue compartment. The viscera present the largest portion of the peritoneal surface area, but it is unknown at this time how much of this surface area is in contact with the fluid at any time during a therapeutic treatment. As drugs transport into the tissue from the cavity they will also be taken up by the networks of vessels within each of these tissues and then return to the general circulation. The rate of the drug transfer to the blood is governed by diffusion and convection (solvent drag) within the tissue space, the permeability-surface area density of the blood exchange vessels, and the rate of blood perfusion. The process of drug uptake from the peritoneal cavity includes the same physiological mechanisms responsible for transport during dialysis except that the direction of transport is reversed.

Table 30.1 lists the human parameters, which are independent of solute size but are necessary to solve the system in Fig. 30.1. The first two columns concern peritoneal surface area. The first column specifies the percentage of the total peritoneal surface area, while the second tabulates the total surface area in cm^2. The data of Rubin et al. [43] are used because the measurements were more conservative than those of Esperanca and Collins [44], since the mesentery was not included. The areas have been scaled to a 70 kg body weight by the factor $(\text{body weight})^{0.7}$ [30]. It should be noted that these are total surface areas that have resulted from the dissection of each tissue and its surface area measured by planimetry; these area values may not represent the true area of contact between the peritoneal fluid and the tissue.

The tissue weights were estimated as follows. The liver weight was taken directly from a table in Ludwig [45]. The "other viscera" weight was computed from the sum of the spleen (0.14 kg) and intestines. The latter were estimated from the product of the total surface area [43], the average thickness of 2.5 mm [46], and the specific gravity of these tissues, which was assumed to equal 1 g/cm^3. The thicknesses of the abdominal wall and diaphragm were estimated to be 2 cm and 0.3 cm [47], respectively, and the tissue weight was calculated in the same fashion as in the case of the hollow viscera.

There have been a number of estimates of the rate of perfusion (q_i) of the abdominal tissues. Measurements in the control animals [48] for the parietal wall (0.06 mL/min/g tissue) and diaphragm (0.31) are listed in Table 30.1. Other estimates [49] for the parietal wall tended to be much higher, because of the specific preparation and use of vasodilators. The perfusion rates in the "other viscera" and the liver (includes both hepatic artery and portal flow) can be estimated from total organ blood flows [50, 51] and divided by the weight of each system. The estimates for the gastrointestinal tract agree with several other measurements made in a variety of tissues from other species [52–54]. The total blood flows for the diaphragm and abdominal wall (Q_i) can be calculated from the product of the organ weight and q_i.

Table 30.1 Adult human parameters which are independent of solute size (scaled to 70 kg body weight)

Tissue	Percentage total surface area	A_i (cm^2)	Weight (g)	q_i (mL/min/g)	Q_{tot} (mL/min)	L (mL/min)	F (mL/min)	L/F
Liver	13.2	1056	1800	0.83	1500	0.46	0.07	6.83
Other viscera (intestines spleen, stomach)	67.9	5432	1700	0.65	1100	0.97	0.33	2.91
Abdominal wall	11	880	1960	0.06	118	0.04	0.67	0.05
Diaphragm	7.9	632	190	0.3	57	0.27	0.27	1.01

Thoracic duct lymph flow has been measured in humans and typically has a flow rate of 1–1.6 mL/h/ kg body weight [55, 56]. Nonruminant animals have flow rates on the order of 2–3 mL/h/kg body weight [35, 57–59]. Morris [57] estimates that the contributions of the liver and gastrointestinal tract amount to 30% and 64%, respectively, of the thoracic duct flow. The remaining 6% of the total flow is from all the skeletal muscle below the diaphragm, including the psoas, the abdominal wall, and the lower limbs. In order to estimate the lymph flow for humans, the mean value for the thoracic duct (1.3 mL/h/kg body weight) was multiplied by the percentages obtained by Morris for each organ system: 30% for liver and 64% for other viscera. One-third of the remaining 6% was arbitrarily assumed to be the contribution of the abdominal wall. Total lymph flows were then calculated by multiplying each tissue-specific lymph flow rate by the body weight (70 kg) and converting to mL/min.

Of the lymph that exclusively leaves the peritoneal cavity, 70–80% occurs through the subdiaphragmatic system [34]. This is a major site for transport of fluids, macromolecules, and cellular materials from the cavity to the blood. Values for flow range from 0.6–1.8 mL/h/kg body weight in the anesthetized rat [35] to 0.1 mL/h/kg in anesthetized sheep and 0.50 mL/h/kg in awake sheep [60]. Flow rates in awake, healthy continuous ambulatory peritoneal dialysis (CAPD) patients vary from 0.14 to 0.28 mL/h/kg body weight [54, 55]. The rates appear to increase in cirrhosis to 0.43 mL/h/kg [56]. We have chosen the mean rate of 0.23 mL/h/kg and multiplied it by 70 kg to find the diaphragmatic lymph flow rate of 16.1 mL/h.

The next to last column in Table 30.1 lists estimated total flow rates of fluid in mL/min to each organ system. The total flow from the cavity has been estimated from the average of three studies in healthy CAPD patients [53–55, 57] to be 1.33 mL/min. This flow is driven by the hydrostatic pressure in the cavity [29, 58, 59] and occurs in the face of hyperosmolar solutions, which draw fluid into the cavity [31, 33, 59–61]. These studies have shown that protein acts as a marker for fluid movement. The total hourly flow rate has been partitioned to each set of tissues on the basis of the fraction of protein deposition from the cavity of the rat [31] with corrections for the rates of lymph flow from each tissue.

Blood Flow: Does It Limit Solute Transfer?

Estimates of the effective blood flow surrounding the peritoneal cavity suggest that transport between the blood and the cavity is not limited by the supply of blood, except in cases of severe hypotension. Physiologists have attempted to estimate the "effective" blood flow by measuring the clearances of various gases from the peritoneal cavity, assuming that these were limited by blood flow only. Gas clearances of hydrogen [61, 62] and CO_2 [63] have been determined in small mammals and found to be equal to 4–7% of the cardiac output. However, this method of determining the effective peritoneal blood flow may actually underestimate the true blood flow. Collins [64], who studied absorption of several inert gases from peritoneal gas pockets in pigs, found almost a three-fold range in clearance, which correlated with the gas diffusivity in water. If the transport of these gases was limited by blood flow, the clearance of each gas would have been the same. The results imply that the transport of these gases is not limited by blood flow but by resistance to diffusion in the tissue. Gas clearance data therefore underestimate the true peritoneal blood flow, and the conclusion, based on lumped clearance data, would be that blood flow limitation in the peritoneal cavity is unlikely.

The lumped clearance argument, however, does not rule out specific limitations in a portion of the peritoneal cavity, which may be offset by another set of tissues. To investigate the possibility of blood flow limitation of transport across specific surfaces of the peritoneum, the chamber technique was utilized to answer the question of "local" limitations of blood flow on urea (which should diffuse rapidly due to its small molecular weight and which would be more likely to demonstrate blood flow limitations) transport across the liver, stomach, cecum, and abdominal wall [65]. The mass transfer rates of urea were determined under conditions of control blood flow, blood flow reduced by 50–80%, and no blood flow (postmortem); the blood flow was monitored simultaneously with laser Doppler flowmetry. While all four tissues showed marked decreases in urea transport after cessation of blood flow, only the liver displayed a decrease in the rate of transfer during periods of reduced blood flow. Further studies with the chamber technique tested the effects of blood flow on osmotically induced water flow from the same four tissues; results demonstrated statistically nonsignificant decreases in water flow in the cecum, stomach, and abdominal wall [66]. Analogous to the solute data, the liver demonstrated a significant drop in water transfer with reduced blood flow. Thus, transport of both solute and water across the surface of the liver is limited by blood flow. Zakaria and co-workers [67] have shown in rats that the liver is responsible for only a very small amount of the actual area of transfer; this implies that a drop in blood flow to the liver would have minimal effects on overall transperitoneal transport. These data support and extend earlier studies of peritoneal dialysis in dogs [68] and rats [69] during conditions of shock and demonstrate relatively small changes in solute transfer. These all support the use of the technique for solute or fluid removal during periods of low systemic blood pressure and the probable low blood perfusion of the organs surrounding the peritoneal cavity.

Simplified Compartmental Model

The Problem of Surface Contact Area

The area of the peritoneum in contact with the therapeutic solution is typically a fraction of the anatomic area. Research in animals [37, 70] and humans [71, 72] has clearly demonstrated that during dialysis only about 30% of the total surface area is covered at any one time. Although over 24 h, the entire peritoneum will make contact with an i.p. solution [37], the duration of contact with specific parts of the peritoneum is unknown. Dialysis solutions containing glucose are gradually absorbed from the cavity and, therefore, there is a receding volume and contact surface area after the effective osmolar gradient is lost. An alternative to the typical dialysis solution is one containing 4% of icodextrin (a 20 to 30 kDa starch), which has been shown to maintain the peritoneal volume at a constant for up to 48 h [73], with a loss of 50% over the next 48 h. A 7.5% icodextrin solution has been shown to be effective as a drug carrier for 5- fluorouracil [74] for up to 96 h; this type of solution maintains the volume and the area of contact relatively constant. However, even the icodextrin solutions do not guarantee contact with the target areas for any given length of time. The volume of the solution, the size of the patient, and the patient's position all affect the peritoneal contact area. For example, if the patient is ambulatory, even a large volume (3 L) may pool in the bottom of the peritoneal cavity. Large portions of the peritoneum may not be covered [37], and therefore the residence time of the medication may be a problem for certain regions of the cavity.

The lack of certainty about the surface contact area and the residence time at each tissue surface complicates the implementation of the multicompartmental model of Fig. 30.1. There are just no data on which to base a weighting system for fluid contact to a particular tissue. In addition, research in animals has demonstrated that for small molecules (~500 Da), the relative permeability of visceral and parietal peritoneal surfaces are nearly the same [75]. For many substances, the model concept of Fig. 30.1 requires many defined parameters, and a simpler approach can be employed to calculate R_d. A number of examples will follow the simplified theory. While Eq. 1 can also be applied to the treatment of malignant ascites, its use in treating metastatic tumor implants is complicated by the altered tumor properties that impact the penetration and effectiveness of the agent.

Simplified Model Concept

The model concept presented in Fig. 30.2 is a simple, two-compartmental approach, without regard to the anatomy and physiology of the system. It is the most straightforward concept to estimate the R_d from Eq. 1. The body consists of two compartments: 1) the systemic blood circulation that circulates through the drug's volume of distribution (V_D) and 2) the peritoneal cavity where the therapeutic drug is in solution. The transfer of drug across the so-called "*peritoneal membrane*" is modeled as a simple transfer of mass as follows:

$$\text{rate of mass transfer} = \frac{d(C_P V_P)}{dt} = -MTAC(C_P - C_B) \tag{2}$$

where MTAC = the overall mass transfer-area coefficient for the drug or solute, C_P = the concentration in the peritoneal cavity, V_P = the volume in the peritoneal cavity, and C_B = the concentration in the blood. A mass balance on the blood yields:

$$\frac{d(C_B V_D)}{dt} = MTAC(C_P - C_B) - CL_{BC}(C_B V_D) \tag{3}$$

where CL_{BC} = the total body clearance, which is often approximated by the glomerular filtration rate divided by V_D for unbound, water-soluble drugs. Fig. 30.3 provides MTACs for water-soluble drugs in normal dialysis patients and in patients undergoing i.p. chemotherapy [76–78]. These may underestimate or overestimate the mass transfer of particular drugs in tumor-bearing patients. As can be seen in Fig. 30.3, the MTAC for heated drugs is considerably higher than the nonheated solutions [79–81]. This likely due to the combination of vasodilation with increased peritoneal blood flow and greater surface contact area with the use of dual catheters and a continuous flow system. The area is not well defined in these perioperative procedures, but the technique can significantly enhance the pharmacokinetic advantage and the efficacy [82]. Drugs that are more lipid soluble will have an order of magnitude higher rate of clearance from the peritoneal cavity [83–85].

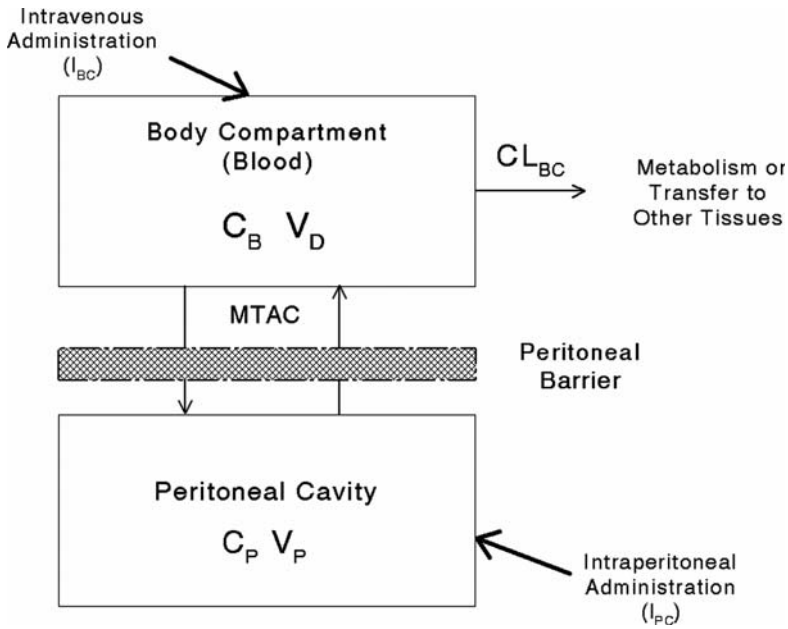

Fig. 30.2 Simplified two-compartment model. Nomenclature is the same as in Fig. 30.1. MTAC = mass transfer-area coefficient; C_B = concentration in blood; V_D = volume of distribution for drug in body compartment; C_P = concentration in peritoneal cavity; V_P = volume in peritoneal cavity. See text for details

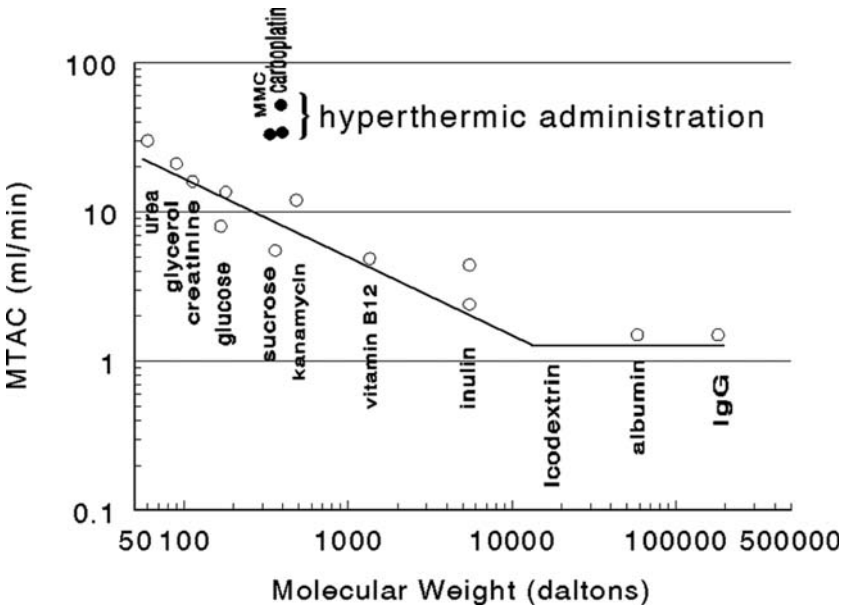

Fig. 30.3 Mass transfer-area coefficient (peritoneal clearance) versus molecular weight

Variation of MTAC with Body Size

Figure 30.4 shows the clearance (~MTAC) for urea and inulin for the rat, rabbit, dog and human; these species cover a body-weight range from 200 g to 70 kg [30]. The parameter increases as the 0.62–0.74 power of body weight for inulin and urea, respectively. The average of these two values is very close to the two-thirds expected for body-surface-area scaling. Keshaviah and colleagues [82] demonstrated a linear correlation between the volume at which MTAC was maximum and the body surface area in a study of 10 patients with body surface areas ranging from 1.4 to 2.3 m^2. Since the characteristic time for absorption from the peritoneal cavity is equal to V_P/MTAC, similar time scales can be

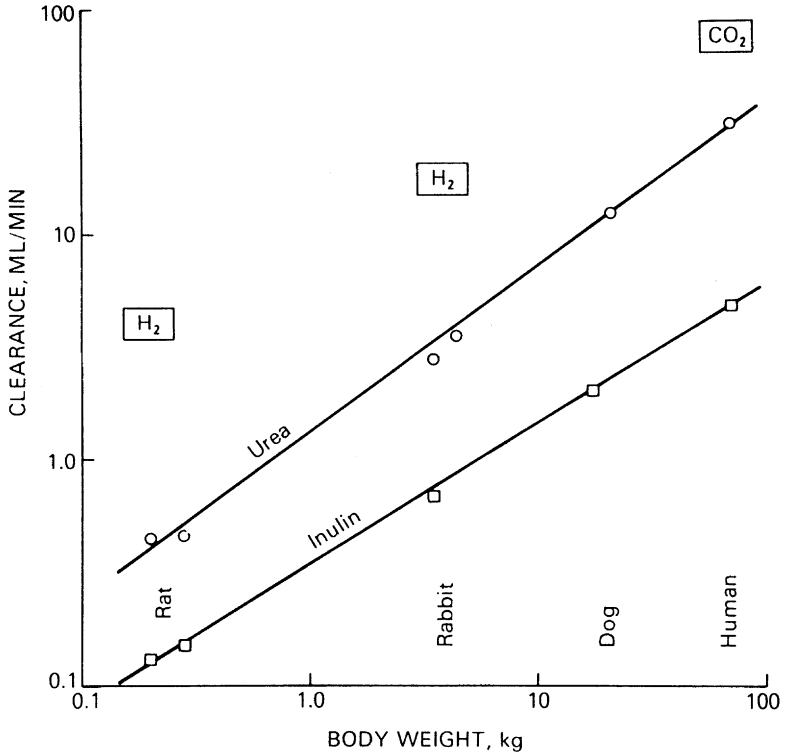

Fig. 30.4 Peritoneal clearance (or mass-transfer-area coefficient) for the indicated gases, urea, and inulin versus body weight. From [116]

achieved in humans and experimental animals if the volume is scaled as the two-thirds power of the body weight. For example, 2 L in the peritoneal cavity of the 70 kg human patient (29 mL/kg) would be equivalent to 40 mL in a 200 g rat (200 mL/kg) because $(200/70{,}000)^{2/3}$ (2,000) = 40. These scaling criteria permit the design of experiments, which more accurately reflect in small animals dialysis that is carried out in humans.

Calculation of the Pharmacokinetic Advantage

The solution of Eqs. 2 and 3 requires the parameters of V_D, CL_{BC}, and the MTAC for each solute and the doses to be given (dose = $C \times V$ for each compartment), which are given i.v. or i.p. at time = 0. The concentration versus time may then be calculated in each compartment for each route of administration; these concentrations define the R_d.

Alternatively, if a drug is infused at a constant rate into a fixed volume of fluid in the peritoneal cavity until steady state is achieved, then a regional advantage will be observed:

$$R_{\text{i.p.}} = (C_P/C_B)_{\text{i.p.}} \tag{4}$$

Similarly, if the drug is infused at a constant rate intravenously with the same fixed i.p. volume of fluid, then the corresponding concentration ratio may be defined

$$R_{\text{i.v.}} = (C_P/C_B)_{\text{i.v.}} \tag{5}$$

The pharmacokinetic advantage R_d is defined as the ratio:

$$R_d = R_{\text{i.p.}}/R_{\text{i.v.}} \tag{6}$$

Conceptually, R_d expresses the relative advantage that may be achieved by administration of a drug directly into the peritoneal cavity compared with i.v. administration. It has been shown [30] that the pharmacokinetic advantage may be expressed as a remarkably simple equation if there is no elimination of the drug from the peritoneal region:

$$R_d = 1 + CL_{BC}/MTAC \tag{7}$$

where CL_{BC} = total body clearance (cm^3/min). The same equation may be used for drug that is not administered by continuous infusion to steady state if the exposure terms are defined as the areas under the peritoneal and plasma concentration curves (AUC_P and AUC_B) following any schedule of administration if the system is linear in the sense that none of the relevant parameters change with drug concentration or time.

Equation 7 indicates a large pharmacokinetic advantage for most hydrophilic drugs administered to the peritoneal cavity. For example, a typical antibiotic would be expected to have a $MTAC$ of the order of 10 mL/min (Fig. 30.3). If the drug is cleared from the body by glomerular filtration at the rate of inulin, 125 mL/min [86], then the expected value of R_d is approximately 14.

Many drugs are eliminated by tissues within the peritoneal cavity, particularly the liver. This provides a first-pass effect, which has the effect of increasing the natural pharmacokinetic advantage given by Eq. 7. The regional advantage expected in the presence of some extraction of the drug by liver may be obtained from Dedrick [23]:

$$R_{i.p.} = \frac{1 + \frac{CL_{BC}}{MTAC}}{1 - fE} \tag{8}$$

where f = the fraction of the absorbed drug that enters the liver through the portal system or by direct absorption into its surface, and E = the fraction of that drug which is removed by the liver on a single pass. The quantity $(1 - fE)$ is the fraction of the absorbed drug that reaches the systemic circulation. If this fraction is small, then the natural advantage to regional administration can be considerably enhanced.

We do not have adequate information on the value of f. It is generally thought that small molecular weight compounds are absorbed primarily through the portal system [87]; however, there is evidence that some significant fraction of the absorbed drug can bypass the liver [12]. In the Speyer study, concentrations of 5-fluorouracil were observed to be higher in a peripheral artery than in the hepatic vein in three of four patients. Calculation of f was not reliable because analysis of the data depended upon knowledge of the blood flows in the portal vein and drug metabolism by gastrointestinal tissues, and these were not measured. The fact that about 15–20% of the peritoneal surface area covers tissues which are not portal to the liver is consistent with the transport observations.

Application of Model to the Pharmacokinetic Advantage

Antibiotics: Vancomycin

Intraperitoneal antibiotic therapy is used to treat localized peritonitis. The goal of such therapy is the same as that of antineoplastic agents: to maximize the concentration in the cavity in order to target the superficial tissues in the peritoneal cavity. Since the subject of i.p. antibiotic therapy has been covered thoroughly in another chapter of this text, we will illustrate the general approach to calculation of the regional pharmacokinetic advantage by application of the theory to vancomycin, a drug that is currently one of the recommended therapies for i.p. infections due to gram-positive organisms, which are resistant to cephalosporins and penicillins [9].

Vancomycin has a molecular weight of 1,500; 55% of the drug is bound to serum protein [88–90]. Its volume of distribution is variable and is cited over a range of 0.64 L/kg in normal young humans [90] to 0.93 L/kg in the elderly [88, 90]. Patients with renal failure (creatinine clearance less than 10 mL/min) have volumes of distribution averaging 0.9 L/kg [89]. The serum half-life of vancomycin is typically 6 h. However, since 90% of the injected dose is excreted by the kidney [91, 92], the normal half-life of 6 h becomes markedly prolonged in renal failure. Clearance of the drug in a normal (70 kg) patient is 100–140 mL/min. In the patient with renal failure the clearance is correlated with iothalamate, a marker for glomerular filtration rate [91]. Typical clearance rates for patients with creatinine clearance less than 10 mL/min average approximately 5 mL/min [89, 93].

The overall MTAC estimated from Fig. 30.3 is 4.0 mL/min. For the purpose of illustration, let us assume that the overall clearance from the body of our patient on peritoneal dialysis is 5 mL/min and that the drug is given by continuous infusion. Under these circumstances, the relative advantage of i.p. administration relative to i.v. administration is calculated from Eq. 11 modified to account for protein binding: $R_d = 1 + 5/(4.0 \times 0.45) = 3.8$.

Because of the long half-life and the toxicity of high serum levels that might result if continuous infusion were performed [88], the drug is usually given in either a single i.p. dialysate dwell every 24 h or as an i.v. infusion approximately once a week. Bunke et al. [94] studied vancomycin pharmacokinetics by dosing patients with either

10 mg/kg i.v. in a saline solution over 30 min or 10 mg/kg diluted in 2 L of 1.5% dextrose dialysate, which was allowed to dwell over 4 h. By computing the AUC_P/AUC_B for i.p. delivery during the first 24 h, the regional advantage ($R_{i.p.}$) is 429/109 = 3.9. Repeating the same for i.v. delivery, the AUC_P/AUC_B ($R_{i.v.}$) is 78.4/297 = 0.26. The pharmacokinetic advantage would then be $R_{i.p}/R_{i.v.}$ = 3.9/0.26 = 15. This provides a strong theoretical and experimental argument for i.p. vancomycin in appropriate cases of peritonitis.

Intraperitoneal Insulin

Human insulin is a small protein with a molecular weight of 5,808, which is secreted by the beta cells of the pancreatic islets of Langerhans in response to a glucose load in the plasma [50]. The secretion occurs directly into blood which circulates via the portal vein to the liver. The bulk of the hormone in the blood is in the unbound form [95]. Extraction of the hormone by the liver is receptor-mediated, saturable, and typically amounts to 40–60% of the drug delivered in the portal system [96]. After entering the general circulation, insulin distributes to the entire extracellular space [97]. In particular, insulin circulates to the kidney and muscle, which, aside from the liver, are its other major targets. Under normal conditions there is a portal-to-peripheral insulin concentration gradient, with the highest concentrations in the liver [95]. In an effort to control diabetic hyperglycemia in a more physiological way, replacement insulin is increasingly being administered intraperitoneally in order to mimic the normal physiology [96, 97].

Insulin is often administered dissolved in the dialysate to diabetic patients who suffer from ESRD and are treated with CAPD [98]. This results in the simultaneous transfer of insulin and dextrose from the cavity into the body and generally results in stable levels of blood glucose and insulin, which are below the corresponding levels with subcutaneous insulin [99]. Because of the extensive extraction by the liver, Eq. 8 must be used in order to predict the regional advantage of i.p. insulin therapy. Rubin [3] has shown that the transport properties of insulin (mass-transfer-area coefficient or $MTAC$ = 2.9 mL/min) are nearly identical to those of inulin ($MTAC$ = 3.3 mL/min). Because of similar molecular size, parameters for inulin are typically substituted for those of insulin. Transport is probably highest across the surfaces of the liver and of other viscera because their combined surface area makes up 60–65% of the total peritoneal area. In Eq. 8, assume that f = 0.9 and E = 0.5 and the $MTAC$ from Fig. 30.3 is 2.3 mL/min. While the normal total body clearance of insulin is typically 650–750 mL/min (referenced to 1.73 m^2), the clearance of [^{125}I] insulin is approximately half or 350 mL/min in chronic renal failure [100, 101]. The regional advantage can be calculated from Eq. 12: R_R = [1 + 350/2.3]/(1 − 0.9(0.5)) = 278. The measured ratio of intraperitoneally administered [^{125}I]insulin (AUC_P/AUC_B) was approximately 500 in dogs [98] and the value was 200–300 in humans [102].

Recent efforts in insulin replacement therapy for patients who suffer from diabetes mellitus, but who are not on dialysis, have tested i.p. administration as a more physiological method of drug delivery [97]. In a study that compared free insulin peaks after i.m., s.c, and i.p. injections, i.p. insulin produced serum insulin peaks at 15 min, while i.m. and s.c. insulin resulted in a much slower increase with peaks at 60 and 90 min, respectively [103]. The rapid rise in serum insulin, produced by i.p. administration, followed by a gradual fall in concentration, more closely mimics the true pancreas. The same study demonstrated that insulin delivered to the upper part of the peritoneal cavity was more quickly absorbed than insulin introduced into the lower part of the cavity. This is probably due to the rapid transfer into tissues of the gastrointestinal tract and direct diffusion into the liver. Delivery into the cavity by a pump has also led to more consistent serum levels than with administration into s.c. tissue, which produces variability in absorption rates [104].

In contrast to the relatively steady delivery of i.p. insulin in CAPD, this i.p. delivery therapy is typically given episodically in small volumes in the upper part of the cavity. The ratio of portal to systemic venous levels of insulin (AUC_{portal}/AUC_B) can give us a rough estimate of the utility of the delivery technique. It should be pointed out that the concentration in the portal vein probably reflects only a portion of the insulin delivered to the liver, since direct absorption across the surface of the liver is known to occur [105]. Selam et al. [106] have demonstrated in dogs that the ratio of i.p. insulin delivery to the portal vein over the amount appearing in the plasma is 17. This supports the concept of i.p. delivery of insulin in order to re-establish a more normal portal-to-peripheral insulin concentration gradient.

Antineoplastic Agents

The pharmacokinetic rationale for the i.p. administration of drugs in the treatment of microscopic residual ovarian cancer was described in 1978 [76]. The procedure has been the subject of numerous preclinical and clinical studies

during subsequent years, and these have been reviewed periodically [27, 28, 107]. The pharmacokinetic theory has been consistently validated, and there is clear evidence of response in terms of surgically staged complete remissions in a number of studies. Markman et al. [21] reviewed several of these and concluded that there may be an advantage to regional drug delivery of cisplatin-based therapy for small-volume refractory residual ovarian cancer. Subsequently, Markman et al. [108] concluded that attainment of a surgically staged complete remission may have a favorable impact on survival. Recently, Muggia et al. [25] demonstrated substantial activity with i.p. floxuridine (FUDR). Due to positive results of recent clinical trials[15, 22, 29, 109], i.p. drug therapy in the management of abdominal cancer has been designated as the standard of care by the National Cancer Institute [110].

Some of these principles are illustrated by a discussion of two specific drugs: *cis*-diamminedichloroplatinum(ii) (cisplatin) and 5-fluorouracil (5-FU). At issue are both the pharmacology of intracavitary administration and the depth of penetration of drug into both normal and neoplastic tissues.

Cisplatin

Cisplatin is among the most active agents used in the treatment of ovarian cancer. Its pharmacokinetics have been studied extensively, and a physiological model has been developed and applied to several species [111–113]. Briefly, the drug reacts with both small and large molecular weight nucleophiles in plasma and tissue compartments. The tissue-specific rate constants vary among the tissues but are relatively constant across species. Release of (presumably inactive) platinum from macromolecules is dominated by their catabolism.

Goel et al. [26] studied the i.p. administration of cisplatin in combination with etoposide, and examined the effect of concurrent i.v. administration of sodium thiosulphate to protect the kidney against platinum toxicity. They administered the drug combination in 2 L of normal saline and observed a cisplatin clearance from the peritoneal cavity of 15 mL/min and a clearance from the plasma of 329 mL/min. These clearances resulted in a regional advantage (AUC_P/AUC_B) of 26 in those patients who did not receive sodium thiosulphate. This advantage is similar to the value of 16 obtained by Piccart et al. [114] for cisplatin administered in combination with melphalan.

Los et al. [115] conducted pharmacokinetic studies of cisplatin in rats bearing CC531 colonic adenocarcinoma on serosal surfaces of the peritoneal cavity in order to determine the effect of route of administration on tumor and normal tissue levels of platinum. The AUC_B was approximately the same following both i.v. and i.p. administration, while the regional advantage was 7.6 based on ultrafiltered plasma and peritoneal fluid. Clearance from the peritoneal cavity may be calculated from their data to be 0.42 mL/min for a 200 g rat. The rat clearance is thus predictive of the human values on the basis of body weight to the 2/3 power in general agreement with the allometric variation in Fig. 30.4.

Average tumor levels of platinum in the i.p. group were twice those in the i.v. group; however, the excess platinum was confined to the periphery of the tumour. Measurements of platinum concentrations by proton-induced X-ray emission (PIXE) showed substantially higher levels in the outer 1.0 mm of the tumor; concentrations at 1.5 and 2.2 mm from the surface were independent of route of administration of the drug. This limited penetration is consistent with theoretical calculations for hexose [116] and experimental data for [^{14}C]EDTA [117] in normal tissues. It is instructive to apply a penetration model to cisplatin. As a rough approximation, let us assume that the diffusivity in tissue, D, is 1.9×10^{-6}cm^2/s based on transport in brain [118]; that the capillary permeability-area density (pa) product is of the order of 1.4×10^{-6} s^{-1} based on hexose in jejunum; and that the tissue-specific reaction rate, k, is 8×10^{-5} s^{-1} based on muscle [112]. Then the nominal diffusion distance $[D/(pa + k)]^{1/2}$ is 0.4 mm, which would imply that 9/10 of the gradient would be confined to the first millimeter from the surface of the tissue. While these calculations are provided for illustrative purposes, and are very approximate, they are almost certainly much better that order-of-magnitude. They support the idea that direct diffusion of cisplatin into tissue is very limited in extent.

The above reaction ($k = 8 \times 10^{-5}$ s^{-1}) and permeability (1.4×10^{-3} s^{-1}) parameters predict that $[1.4 \times 10^{-5}/(1.4 \times 10^{-3} + 8 \times 10^{-5})](100) = 95\%$ of the drug would be expected to be absorbed into the systemic circulation. This large bioavailability is consistent with the observations of Los et al. [115] in the tumor-bearing rat and of Pretorius et al. [119] in the dog, as well as with considerable human experience.

5-Fluorouracil (5-FU)

As discussed by Chabner [120], phosphorylation of 5-FU to nucleotide analogues appears necessary for its subsequent biological effects. Elimination from the body is primarily by metabolism believed to require reduction of the pyrimidine ring by dihydrouracil dehydrogenase. This enzyme is present in both the liver and other tissues such as the gastrointestinal mucosa. 5-FU exhibits strongly nonlinear elimination in human subjects with a half-saturating concentration of 15 μM as reviewed and discussed in the development of a physiological pharmacokinetic model [121].

Further, the observation of total-body clearances at low infusion rates that considerably exceed expected hepatic blood flow suggests the presence of extensive extrahepatic metabolism.

5-FU has pharmacological properties that commended it to i.p. trials in the treatment of intra-abdominal cancer. It is a hydrophilic drug with a molecular weight of 130 Da, which would be expected to have a relatively slow clearance from the peritoneal cavity (Fig. 30.3) and a total-body clearance ranging from 0.94 L/min at an infusion rate of 134 mg/kg/day to as high as 4–7 L/min at infusion rates of 10–30 mg/kg/day [121]. In addition to the high ratio of CL_{BC} to predicted MTAC, significant removal of the drug by peritoneal tissues would be expected to further limit systemic exposure.

The prediction of a high regional advantage has been shown in a number of clinical trials. Values of the AUC ratio between peritoneal cavity and plasma have been reported to be strongly dose-dependent, ranging from 124 at a dose of 3.5 mmol/L to 461 at a dose of 2.0 mM [19]. These are in general agreement with the observations of Speyer et al. [11], who observed peritoneal-to-plasma concentration ratios of 298 at 4 h and of Sugarbaker et al. [109] who reported a mean AUC ratio of 200 in patients administered 5-FU in the immediate postoperative period. Clearance from the peritoneal cavity has been in good agreement with the predictions from Fig. 30.3: 14 mL/min [11] and 24 mL/min [19]. Nonlinearity in systemic exposure deriving from the saturable metabolism (and possible saturable first-pass effect) of the agent was associated with an extraordinarily steep dose-response curve [11].

There has been considerable interest in the detailed mechanism of absorption of 5-FU from the peritoneal cavity because of the possibility of using this route as a way to perfuse the liver through the portal vein. Speyer et al. [11] placed catheters in the portal vein, hepatic vein, peripheral artery and peripheral vein of human patients. The hepatic extraction was calculated to decrease slightly from about 0.7 to 0.6 from the first to the seventh exchange. The estimated value of the fraction, f, of the absorbed drug entering the portal system was strongly dependent on assumptions relating to the blood flow rate in the portal vein and metabolism by tissues draining into the portal system, neither of which was directly assessed. Estimated values of f ranged from 0.3 to 1 depending on the assumptions made. There was direct evidence of drug bypassing the portal system in three of the four patients in whom the AUC in the peripheral artery actually exceeded the AUC in the hepatic vein. In studies in rats, Archer et al. [122] observed that systemic 5-FU levels were significantly lower during mesenteric vein infusion (0.9 ± 0.2 μM) compared with i.p. infusion at the same rate (2.1 ± 0.3 μM). Indirect evidence of a pharmacological first-pass effect is provided by the observations of Gianola et al. [123], who were able to administer a mean of 1.5 g per treatment cycle intraperitoneally but only 1.0 g intravenously; the i.p. route was actually accompanied by less hematological toxicity.

Approaches to Enhance Contact Area and Residence Time Intraperitoneally Administered Drugs

Drug delivery to metastatic cancer in the peritoneal cavity requires drug exposure and therefore is vitally dependent on sufficient contact between the therapeutic solution and the targeted tumor nodule(s). An approach to improve the contact area is to use a surface-active agent. In experiments with animals, diacetyl-sodium sulfosuccinate (DSS) has been shown to increase the surface contact area and to proportionally increase the rate of mass transfer into the local tissues [37, 70, 124]. More rapid uptake of the drug would result in a dissipation of the drug concentration from the fluid; this problem could be solved with the use of an automated exchange device such as a peritoneal dialysis machine, programmed to deliver periodic infusions over time of given concentration. Although DSS is used as an oral stool softener (docusate sodium), it unfortunately is quite toxic if administered i.p.; exposure of fluid containing surfactant to a larger proportion of the peritoneal surface area also accelerated the loss of protein and the dissipation of the drug concentration in the therapeutic solution [70].

In the perioperative setting, drug delivery can be enhanced considerably. Two catheters can be placed in the peritoneal cavity: one catheter for drug input and the other catheter for removal of solution. Solutions warmed to temperatures greater than body temperature (approximately 41°C) may be infused rapidly into the peritoneal cavity and withdrawn in the second catheter. This technique will set up higher concentrations if solution is fed from a large reservoir so that the loss of drug is relatively small. Additionally, with heating of the drug, causing vasodilation in the vessels, there is likely an increase in penetration into both normal tissue and neoplastic tissue [79–81, 125, 126]. This technique may help to solve the problem of residence time as well. If a greater portion of the peritoneal surface area is covered by the solution and the concentration of the drug is maintained constant, then the area into the curve for the surface contact concentration should be maximized. This will be restricted to perioperative patients, and the side effects of these drugs on normal peritoneum have not been studied.

Intraperitoneally Administered Drug Penetration in Neoplasms

Normal Versus Neoplastic Barriers in the Peritoneal Cavity

Penetration of 5-FU into tissues surrounding the peritoneal cavity has not been studied experimentally. Collins et al. [127] observed a strongly concentration-dependent rate of 5-FU disappearance from the peritoneal cavity of the rat. The peritoneal clearance increased from 0.20 mL/min, consistent with its molecular weight, to 10 times that value as the peritoneal concentration was decreased from 10 mM to 20 μM. This was explained by assuming that the drug is metabolized in tissues adjacent to the peritoneal cavity. A one-dimensional diffusion model with saturable intratissue metabolism (V_{max} = 36 nmol/min/g, K_M = 5 μM) simulated the peritoneal concentrations reasonably well. The model predicted that the concentration in the tissue would be 10% of its value at the tissue surface at a depth of 0.6 mm following a 12-mM dose; the corresponding 10% level would be reached at only 0.13 mm following a 24-μM dose. Observations that the toxicity profile associated with i.p. administration is similar to that observed following i.v. administration [12, 123] seem to confirm limited tissue penetration. If the drug reached the gastrointestinal crypt cells in high concentration, one would expect substantial toxicity there.

Predicting the concentration of the drug at the surface may or may not guarantee penetration of the drug into the tumor to the rapidly dividing tumor cells, which are the real target. The compartmental model concept lumps all of the potential barriers to the solute into one entity and does not differentiate between the variety of tissues, which may have different areas of contact and which may experience different transport forces. While Eq. 1 in conjunction with Eq. 2 permits calculation of the pharmacokinetic advantage, the model does not tell us anything about the specific penetration into the tissue. It merely describes the transfer between the two compartments. Illustrated in Fig. 30.5 is the distributed model concept [128], in which an idealized tissue space is modeled as a peritoneum overlying a tissue containing parenchymal cells and blood vessels surrounded by an interstitium; mathematical details of this theory are contained in previous publications [116, 128–130] and are beyond the scope of this chapter. Because intraperitoneal therapy involves the treatment of normal tissue as well as neoplastic tissue, it is important to differentiate between the properties of both of these. Figure 30.5 displays elements of the normal peritoneum with a tumor implant, which has destroyed the peritoneum and is growing within the tissue. The normal peritoneal barrier is made up of peritoneum, interstitial matrix, and the blood capillary wall. Lymphatic vessels are also located between normal tissue planes within

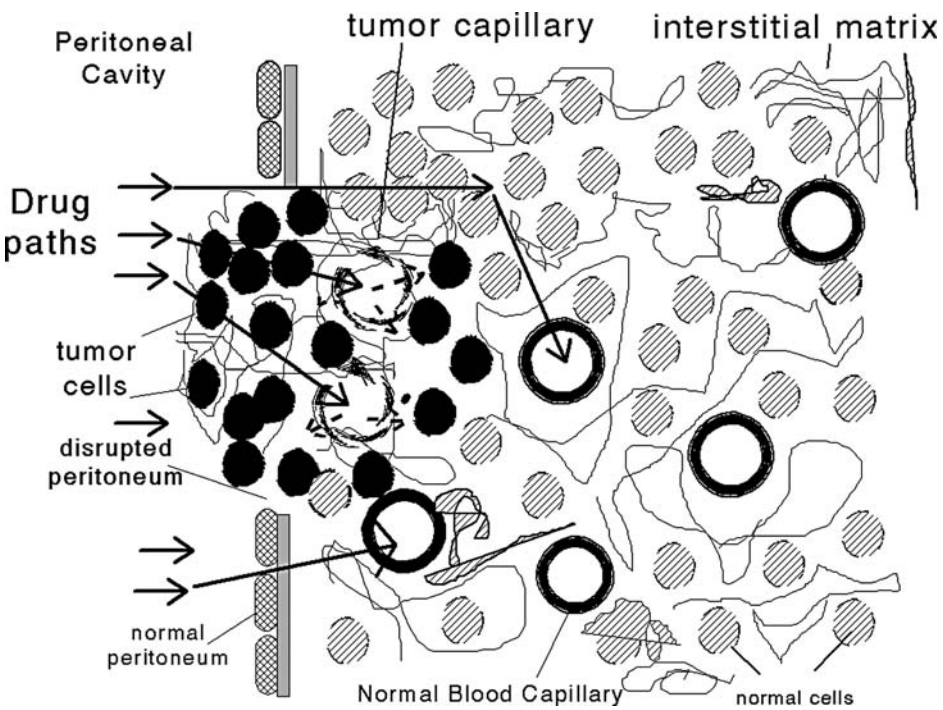

Fig. 30.5 Distributed model concept of metastatic cancer and potential barriers to i.p. therapy. Solid circles represent the tumor metastases, which have invaded and destroyed the mesothelium in its vicinity. Tumor capillaries (discontinuous circles) are typically more permeable than the normal microcirculation and set up high interstitial flows and pressures. The tumor microenvironment (interstitium between cells) is often markedly expanded compared to that of normal tissue. See text for details

smooth muscle or in the diaphragm. The differences between tumor and normal tissue include: lack of a mesothelial layer over the tumor, a very altered interstitium, and a hyperpermeable microcirculation. The following paragraphs will discuss the transport barrier for the normal peritoneum and the abnormalities of neoplastic tissue.

Anatomic Peritoneum

While the peritoneal barrier is often called the "peritoneal membrane," the actual anatomic peritoneum, made up of a layer of mesothelial cells and several layers of connective tissue [131], is not a significant barrier to molecules up to a molecular weight of 160,000 Da. Studies in rodents and dialysis patients have shown that protein leaves the cavity rates of approximately 10 times the rate at which it appears in blood [132–136]. The only route of transfer of protein in the cavity back to the central circulation is via the lymphatics [34, 137, 138]. There must be some other pathway for disappearance of this protein. In experiments with rodents, it has been shown that, as protein transports across the peritoneum, there is some adsorption [39] to the peritoneal cells but most of the protein deposition is into the subperitoneum. Further experiments demonstrated that removal of the peritoneum does not eliminate the dialytic properties of the peritoneal barrier [139]. Recent studies in patients undergoing partial or total peritonectomy for treatment of peritoneal carcinomatosis confirm the findings in rodents; the clearance of mitomycin C from the peritoneal cavity was not significantly affected by an extensive peritoneal resection [140].

Although proteins appear to easily pass the mesothelium into the subperitoneum, viral vectors containing gene products are taken up directly into mesothelial cells with little penetration beyond this single cell layer. Adenoviruses that code for the reporter gene β-galactosidase have been shown to be quantitatively taken up in mesothelium and not to penetrate into underlying tissues unless there is a break in the mesothelium [141–148].

The peritoneum at the site of tumor implantation will likely be destroyed in most cases of neoplastic cellular infiltration of the peritoneum (see Fig. 30.5). The loss of the mesothelium promotes adhesions, presents problems to the maintenance of the smoothly gliding peritoneal surface of the gut, and decreases the function of the immune system. Without the mesothelium, adhesions form between the visceral and parietal surfaces, and the fluid distribution may become markedly abnormal, which may preclude intracavitary therapy [149]. However, treatment with viral vectors containing anti-sense RNA or other gene products, which might not be capable of passing through the normal mesothelium, have the possibility to penetrate into the tumor from the peritoneal cavity [147].

In summary, the normal anatomic peritoneum is not a significant barrier to small solutes or to macromolecules, unless there exists a mechanism of uptake by the mesothelial cells, as in the case of viral vectors. The normal mesothelium may be destroyed by a metastatic tumor, which opens this abnormal tissue to penetration of viral vectors.

Interstitium or Tumor Microenvironment

Interstitium or the so-called "microenvironment" is made up of collagen fibers linked through adhesion molecules such as β-1 integrins to fibroblasts, parenchymal cells, and other interstitial cells [150, 151]. Hyaluronan molecules, which vary from 50,000 Da to 40 million, wrap around the collagen fibers and are likely attached to them at some link point. To the hyaluronan are attached large molecules called proteoglycans that also interact with the surrounding cells [152, 153]. Hyaluronan molecules are highly negatively charged and imbibe large amounts of water and restrict the passage of negatively charged proteins [154]. Proteins such as immunoglobulins are typically restricted to about 50% of the interstitial space [155, 156]. Thus, the interstitial space of normal muscle, which is anywhere from 12 to 20% of the total tissue volume, restricts proteins to 6 to 10% of the tissue. The transport of large solutes such as immunoglobulin G (150 kDa) or adenovirus (900 kDa) will be highly retarded by the microenvironment, as illustrated in Fig. 30.6, which compares the concentration profiles of small solutes and macromolecules in normal and neoplastic tissue.

Alterations in the interstitial pressure can change the relative tissue interstitial water space and the proportion of the tissue available to the solute. It has been shown in animal experiments that the abdominal wall interstitium will double when the intraperitoneal pressure is increased from 0 to 4 mm Hg [157, 158]. This will markedly enhance the transport of both small and large solutes through this space. The hydraulic conductivity or water permeability of the tissue also increases with increasing intraperitoneal pressure and washout of hyaluronan from the tissue interstitium [159]. Since the surface contact area is maximized with increasing peritoneal volumes [72, 82], attempts to increase the contact area will increase the pressure as well. The i.p. pressure varies directly with. the i.p. volume [160, 161] for normal dialysis patients. The effect of pressure is greatest in the abdominal wall where a nearly linear pressure gradient from the inside of the peritoneal cavity to the outside has been measured in the rat [162]; these profiles may be quite different from those in tumors [163] or in the human abdominal wall. Patients with adhesions or extensive surgical resection may have restricted volumes and very different pressure-volume characteristics, with increased pressures at lower volumes than those of dialysis patients. In summary, large volumes in the cavity increase the intraperitoneal pressure and expand the

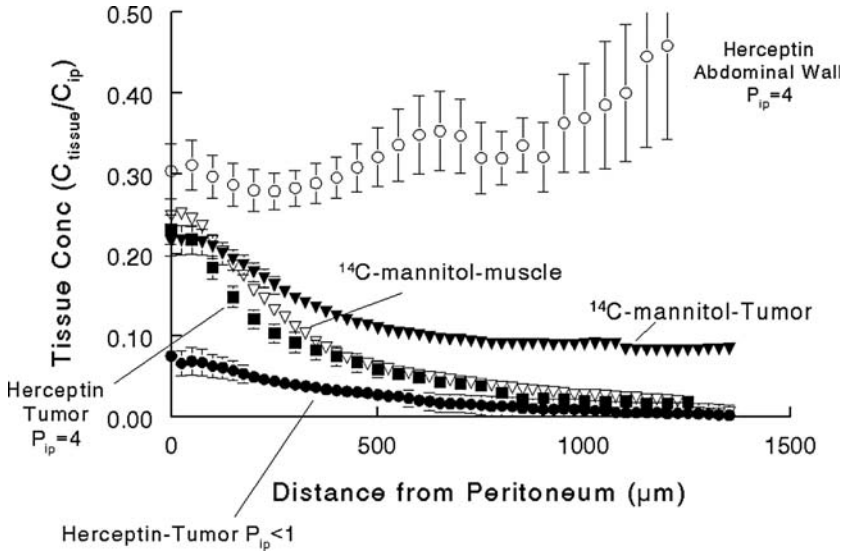

Fig. 30.6 Comparison of penetration of mannitol or Herceptin (IgG monoclonal, Her2/neu) into normal tissue (open symbols) or IP SKOV3 xenograft (closed symbols) of the rat after 3 h of treatment with a large i.p. volume. Mean ± SE concentrations versus distance in microns from the peritoneal surface. Replotted from [163, 169, 194]

interstitial space and, in turn, augment the space within the tissue to which both small and large solutes distribute. Antineoplastic agents will transport at faster rates through normal tissue due to increases in both diffusion and convection [129, 157, 159, 164–166].

There exist remarkable differences between the tumor microenvironment and that of normal interstitium. Interstitial pressures in normal tissue are in the range of −2 to 0 mm Hg [167, 168]. This allows convection due to the hydrostatic pressure gradient from the solution in the cavity (3–10 mm Hg) into the tissue. Unfortunately, several investigators have observed high interstitial pressures up to 45 mm Hg in neoplastic tissue [163, 169–172]. To deliver macromolecules by convection from the cavity into these tumors, the solution would have to attain a pressure greater than that of the tumor. The upper limit of pressure tolerated by an ambulatory patient is approximately 8–10 mm Hg in the peritoneal cavity [62, 163] and may limit the penetration of large solutes that depend on convection or solvent drag, if the tumor interstitium has a pressure higher than the i.p. pressure. In addition, steady i.p. pressures of >15 mm Hg in a closed cavity may suppress the portal circulation [62]. Pressures of >20 mm Hg may prevent the descent of the diaphragm [62] and compromise respiration. Therefore, an unanesthetized ambulatory patient will likely be unable to tolerate therapy, which depends on large volumes (>3–4 L) to produce high i.p. pressure. If tumor interstitial pressures are higher than those that can be attained, therapy with macromolecule may be precluded. Anesthetized patients, who receive mechanical ventilation, may be able to tolerate higher levels of i.p. pressure, but the mesenteric circulation supplying the gut should be carefully monitored.

Studies of tumor interstitium show that the space between the cells is often markedly expanded in comparison to normal tissue [173]. A recent study in human ovarian carcinoma xenografts demonstrated an interstitial water space of 2–3 times that of normal muscle [169]. Gullino and colleagues have shown similar results in several tumors [173]. Thus, the high interstitial pressure results in an expanded interstitium, which would typically result in higher rates of diffusion and convection in normal tissue. However, the high interstitial pressure and intrinsic properties of the tumor interstitium resist any transfer of large molecules into the tumor [170, 174–177]. On the other hand, smaller substances (molecular weight < 500 daltons) will diffuse into the tumor parenchyma in a fashion similar to normal tissue [117, 169].

Microcirculation

Normal blood capillary endothelia are lined with a glycocalyx, which has been demonstrated to provide the endothelium with its barrier characteristics [178–181]. In portions of the interendothelial cleft, it is theorized that the glycocalyx is quite dense and only small molecules up to the size of insulin (~5,500 Da) will typically pass through while in other areas a small number of gaps will have a less dense glycocalyx, which will permit protein leakage [166]. This provides the size selective nature of the normal peritoneal barrier. However, inflammation or drugs such as adenosine [182] cause the elimination or degradation of the glycocalyx and an increase the capillary permeability; the vessels of the

normal peritoneum are likely affected during inflammation due to invasion by metastatic carcinoma [183]. Capillary permeability is markedly altered in neoplastic tissue, with typically a high permeability but a variable microvascular density [184, 185]. Although detailed studies have not been carried out, all indications are that these highly permeable capillaries may be responsible for the rapid clearance of drugs into portions of the tumor from the systemic circulation [186]. While this can be an advantage in treatment of these tumors, the high pressures in the interstitium may actually result in difficulty in drug penetration [185, 187]. The nature of angiogenic vessels is under scrutiny; these may not have the glycocalyx that lines the normal endothelium and provides much of the barrier to solute transfer [184, 186–188]. Thus, many of the characteristics of these new vessels may be completely different from those of normal vasculature. In addition, the actual distribution of vessels is very irregular. In small (<1 cm diameter) ovarian xenografts, the vessels are located in the periphery of the tumor, which is expanding into the normal tissue [169]. The central part of the tumor may actually be necrotic and have no vasculature at all. Penetration to nonvascularized portions of the tumor is one of the problems of i.v. or i.p. administration. Targeting the vasculature simultaneously with intraperitoneal therapy may be a method of accessing these portions of the tumor and solving this problem.

Lymph drainage from the cavity is chiefly through the subdiaphragmatic lymphatics [166]. In normal conditions, the relaxation of the diaphragm will open specialized "stomata," which accept proteins, cells, and solution from the peritoneal cavity into collecting lymphatics [32, 189]. The subsequent contraction of the diaphragm will close the stomata and propel the material into the parasternal lymphatics and ultimately into the right or left lymph duct. Approximately 70–80% of peritoneal lymph drainage occurs through this route [34]. Lymphatics from the viscera drain to the cisterna chyli at the base of the thoracic duct and ultimately into the left venous system [138].

With peritoneal carcinomatosis, the subdiaphragmatic lymphatics and the mesenteric lymphatics may be obstructed [190, 191]. The obstruction produces severe ascites because the normal flow of fluid and proteins from the viscera into the peritoneal cavity cannot be cleared properly [191]. In addition, the lymphatics provide a route of metastasis to the remainder of the body; including the periaortic and thoracic nodes [192]; often supradiaphragmatic nodes are overwhelmed with tumor cells; these same nodes then allow tumor cells to pass into the systemic circulation. However, if these pathways are still functional, intraperitoneal therapy directly targets these routes of metastasis and is a direct route to the systemic circulation for all agents, particularly those with molecular sizes greater than that of albumin.

Summary of Normal Versus Neoplastic Peritoneal Barrier

The anatomic peritoneum is not a barrier to most drugs, including immunoglobulins. The mesothelial layer may be absent in a tumor implant on the peritoneum and the vasculature and the microenvironment may be greatly altered. While viral vectors are totally absorbed in the normal mesothelium, its absence at a tumor surface may permit these very large particles (~900 kilodaltons) to pass into the first few cell layers of the tumor; however viral vectors will still have restricted movement in the tumor interstitium [177]. The interstitium is markedly expanded and theoretically should promote high rates of diffusion and convection [169, 177]. However, the high interstitial pressure and the tendency of flow from the center part of the tumor towards the periphery may cause a functional obstruction in the direction of the treatment drug originating from the peritoneum cavity [163, 170, 172, 193]. In addition, there appear to be structural differences in the collagen matrix of the tumor interstitium that prevent significant convection and diffusion of negatively charged, macromolecular agents [176, 177]. The tumor blood capillary and microcirculation are markedly abnormal in distribution and permeability characteristics [184, 185, 187]. Depending on the location and density of the tumor microvasculature, systemically administered drugs may rapidly distribute to perfused regions of the tumor but not reach poorly vascularized locations altogether. Multi-agent therapies that simultaneously attack the interstitium, vasculature, and the peritoneal side of the tumor will therefore likely be more effective in remitting peritoneal carcinomatosis.

Penetration of Small Molecules: Distributed Model Theory

The distributed model concept permits estimates of drug penetration. The theory for small solutes (≤1,000 Da), which depend almost exclusively on diffusion for transport through the tumor, is presented below. Application of the theory for macromolecules, which transport chiefly by convection, is complicated by a lack of transport parameters within the tumor parenchyma and the variability of the microcirculation and tumor microenvironment [130].

Transfer of small molecules from the peritoneal cavity can be viewed as a process of diffusion from the fluid in the cavity into the adjacent tissues followed by absorption from the tissue extracellular space into blood in the exchange vessels (Fig. 30.5). Convection generally does not play a quantitatively significant role for small solutes [194], and

lymphatic uptake is negligible compared with removal from the tissue by the flowing blood. The result is that a concentration profile is established within the tissue. At steady state the rate of diffusion down the profile at any location is exactly balanced by the combination of irreversible chemical reaction in the tissue and removal by flowing blood. For a nonreactive solute and a uniformly distributed capillary network, it is easily shown that the rate of uptake into blood perfusing the viscera may be calculated from the equation [116]:

$$S_{\mathrm{i}} = \sqrt{D_{\mathrm{i}}(p_{\mathrm{i}}a_{\mathrm{i}})}A_{\mathrm{i}}(C_{\mathrm{P}} - C_{\mathrm{B}}) \tag{9}$$

where S_{i} = net rate of uptake of the solute in tissue "i" (μg/min), D_{i} = the effective diffusivity of the solute in tissue "i" (cm^2/min), p_{i} = the intrinsic permeability of the blood capillaries in tissue "i" (cm/min), a_{i} = the capillary surface area per unit tissue volume ($\mathrm{cm}^2/\mathrm{cm}^3$), A_{i} = the superficial surface area of tissue "i"exposed to peritoneal fluid (cm^2), C = the free solute concentration (μg/cm^3), and the subscripts P and B refer to peritoneal fluid and blood, respectively (see Fig. 30.1). The effective diffusivity is equal to the diffusivity in the tissue interstitial space multiplied by the tissue fractional interstitial space, which is available to the solute.

A number of observations may be made about Eq. 9. First, the effective diffusivity, capillary permeability, and capillary surface area enter as their square root so that doubling of the capillary permeability, for example, would be expected to be associated with only a 41% increase in mass transfer ($2^{1/2} = 1.41$); second, the net transport rate is proportional to the superficial area of the tissue; and, third, the rate of transport is proportional to the difference in the free concentration of solute between the peritoneal fluid and blood.

Equation 9 serves as the basis for the definition of an equivalent MTAC of the tissue. If there were a thin membrane separating the peritoneal fluid from the blood, the rate of uptake would be given by

$$S_{\mathrm{i}} = MTAC_i(C_{\mathrm{P}} - C_{\mathrm{B}}) \tag{10}$$

Comparison of Eqs. 9 and 10 shows that the equivalent tissue permeability can be calculated from

$$MTAC_{\mathrm{i}} = A_i\sqrt{D_{\mathrm{i}}(p_{\mathrm{i}}a_{\mathrm{i}})} \tag{11}$$

Either Eq. 9 or 10 can be used to calculate the rate of absorption of a drug from the peritoneal cavity into the blood as they are exactly equivalent. The spatially distributed view of the tissue offers certain advantages because it provides some insight into the underlying transport mechanisms and how these might be altered by pathological processes or pharmacological manipulations. It also serves as a natural link to the very large body of literature on capillary physiology, and provides a natural framework to incorporate this into descriptions and predictions of peritoneal transport rates. Further, it explicitly predicts that a concentration profile extends a finite depth into the tissue, and tissue penetration is an important consideration if the goal of i.p. therapy is to treat disease in the tissue or disease of finite thickness such as peritoneal carcinomatosis on serosal surfaces. Explicitly, the concentration profile is given by:

$$\frac{C - C_{\mathrm{B}}}{C_{\mathrm{P}} - C_{\mathrm{B}}} = \exp -\sqrt{\frac{(p_{\mathrm{i}}a_{\mathrm{i}})}{D_{\mathrm{i}}}}x \tag{12}$$

where x is the distance from the serosal surface [116]. Equations similar to 9 and 10 can be written for as many types of peritoneal tissue as desirable. Since uptake rates into the various tissue types are parallel processes, they may be summed to provide an estimate of the overall drug transfer.

Concentration Profiles in Normal and Neoplastic Tissue

The profiles from i.p. administration of a small solute (mannitol, 180 Da) and the macromolecule Herceptin (IgG monoclonal antibody to the HER2/neu receptor, ~155,000 Da) are illustrated in Fig. 30.6 for normal abdominal wall (open symbols) and SKOV-3 xenografts (solid symbols) grown in the abdominal wall of athymic rats [163, 169, 177]. The mannitol has higher concentrations deeper within tumor tissue because the density of microvessels in normal tissue is higher than that of the xenograft [169]. On the other hand, despite an increase in i.p. hydrostatic pressure (P_{ip}), the macromolecular agent, Herceptin, is markedly retarded in the tumor in comparison to normal tissue [163]. While tumor interstitial pressure is a factor, the tumor interstitial collagen matrix is a major impediment to penetration of antibodies and other macromolecules [177].

Intraperitoneal Antibody Therapy and the Pharmacokinetic Advantage

An alternative to the typical antineoplastic agent in cancer therapy is the use of i.p.-administered monoclonal antibodies (Mab) in the treatment of intra-abdominal cancers. These antibodies, which are typically linked to some toxic agent, react specifically with antigens on the tumor cell and bind strongly, with subsequent killing of the cell [195]. As outlined in Dedrick and Flessner [196], the general equation for the calculation of the pharmacokinetic advantage is the same as that for small substances (see Eq. 7). The MTAC for immunoglobulin has been estimated from pore theory to be 0.05 mL/min [197]. The total-body clearance of IgG has been estimated to be 0.5–1.0 mL/min [196]. Inserting this into Eq. 7, one may calculate a R_d of 17–33. This suggests a considerable pharmacokinetic advantage in i.p. administration of monoclonal antibody.

The usefulness of this therapy must also be assessed in terms of the ultimate goal. Free ascites cells are readily accessible to MAbs [198]; in this case, the R_d would be the number calculated by Eq. 7. Unlike smaller molecules, however, large proteins do not penetrate tissues readily. Because of their large size (molecular radius = 52 Å), the effective diffusivity in tissue is on the order of 10^{-7}–10^{-9} cm^2/s [129, 199, 200]. Since this is two orders of magnitude less than the diffusivity of small molecules, the diffusive transport of macromolecules such as IgG within normal or neoplastic tissue is very slow. Recent mathematical analyses have also shown that MAbs with high affinity to their antigens are even more severely retarded by the "binding-site barrier" [176, 201–203]. The transport of these molecules is typically dominated by convection, both within the interstitial space [136, 204] and across capillary endothelium [205]. Tissue penetration studies of antibodies administered i.p. in animals [163, 164, 177, 200] have shown that most of the IgG is contained in the initial 300–400 μm of tissue during the first 3 h. These studies also demonstrated that diffusion probably plays only a minor role in the transport of the protein. Studies in tumor-bearing animals confirm these findings, and have not demonstrated large advantages of i.p. MAb administration over i.v. administration [198, 206]. This means that there may be limitations in the treatment of solid tumors and metastases with MAbs or other macromolecules.

Summary

Intraperitoneal chemotherapy should be considered as an alternative to i.v. therapy when the target is contained within the peritoneal cavity or within the adjacent tissue. A compartmental model has been used to formulate a mathematical scheme in order to evaluate the solute transport to specific tissue groups surrounding the cavity. Although the data to fully implement the model do not exist, a simplified version of the model with parameters derived from the literature can be used to solve for the steady-state concentrations in the peritoneal cavity and the plasma. The ratio of these two concentrations defines the regional advantage of i.p. therapy. Several applications of the theory are presented in order to illustrate the method in which i.p. therapy may be evaluated prior to use in patients. Application of the model to treatment of metastatic carcinoma is complicated by major differences in the targeted tissue properties. Recent animal data are discussed to illustrate the challenges of i.p. chemotherapy and immunotherapy for cancer.

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Chapter 31
Peritoneal Dialysis in Developing Countries

G. Abraham, B. Pratap, and A. Gupta

While globalization may be the flavor of the day, it is equally important to look at the social side of economic operations. Trade liberalization by developed countries could boost income prospects in developing economies.

Almost half of the world lives on less than U.S. $2/day, and many countries in the developing world cannot cope with the increasing incidence of chronic kidney disease (CKD). It is believed that nearly 1,016 million people in the world (214 million in East Asia and Pacific, 10 million in Europe and Central Asia, 47 million in Latin America and Caribbean, 5 million in West Asia and North Africa, 437 million in South Asia, 303 million in Sub-Saharan Africa) are living on less than U.S. $1/day. While communicable diseases such as HIV, tuberculosis, gastroenteritis, and malaria are on the rise in some parts, noncommunicable diseases such as diabetes mellitus, hypertension, coronary artery disease, and chronic kidney disease are on the rise in both developed and developing economies throughout the world. Global alliance for combating renal failure and utilization of renal replacement therapy (RRT) such as peritoneal dialysis (PD) are high on the agenda of the International Society of Nephrology and International Society for Peritoneal Dialysis. Worldwide, the average percentage of end stage renal disease (ESRD) patients on PD has increased between 25 and 30%. In particular, an increase in the numbers of patients who survive for longer periods have become a reality as issues of adequacy of dialysis and management of co-morbid conditions and complications are better understood.

Half of all ESRD patients on PD are in emerging economies in Asia, Eastern Europe, the Middle East, and Central and South America [1]. The decrease in the relative use of PD in North America in the past decade is due to the proliferation of hemodialysis (HD) facilities, the combination of an older, frailer incident ESRD population, and a certain degree of disillusionment among nephrologists about the ability of PD as a renal replacement therapy for prolonged periods [2]. An alternative to increasing the dose of PD is to combine PD with HD, and such a combined therapy (bimodal dialysis) has rapidly gained popularity in North America and Japan [2, 3].

Manual intermittent peritoneal dialysis (IPD) is commonly used as a short-term modality for treatment of acute and chronic renal failure in many developing countries, as it is simple and does not require expensive and specialized equipment. In many renal units in developing countries, stylet catheters are being inserted at the bedside to perform acute PD using 1–2 L of fluid in glass bottles or noncollapsible bags, as this is a cheap and effective mode of dialysis therapy. However, repeated punctures have to be made for access to the peritoneal cavity twice a week for IPD. These repeated punctures can lead to complications including abdominal pain, peritonitis, and development of adhesions and obliteration of the peritoneal cavity [4–6]. HD and hemofiltration require highly trained staff, anticoagulant therapy, large volumes of fluids, and access to large veins and are associated with a risk of air embolism. These factors, and uncertainties regarding costs, cast doubt on the practicality, feasibility, and safety of hemofiltration in resource-poor countries, whereas peritoneal dialysis is relatively simple and inexpensive and is more widely available [7–10].

Continuous ambulatory peritoneal dialysis (CAPD) as a modality of treatment in some Asian and South American countries started in the early 1980s. However, its use in most developing countries, including India, began only in the 1990s, and it is gratifying to note that during the past 15 years, the maximum annual growth of CAPD in the world has been reported from Asian countries (Fig. 31.1) [11–14].

There are several problems in starting a CAPD program in the developing world. There is still considerable lack of awareness and information about the benefits of CAPD both among the lay public and the medical community [13]. Even many nephrologists consider CAPD to be inferior to hemodialysis and do not accept the potential advantages of CAPD. They are under the impression that the tropical climate would lead to a greater incidence of peritonitis.

G. Abraham (✉)
Sri Ramachandra Medical College and Research Institute, Chennai, India
e-mail: abraham_georgi@yahoo.com

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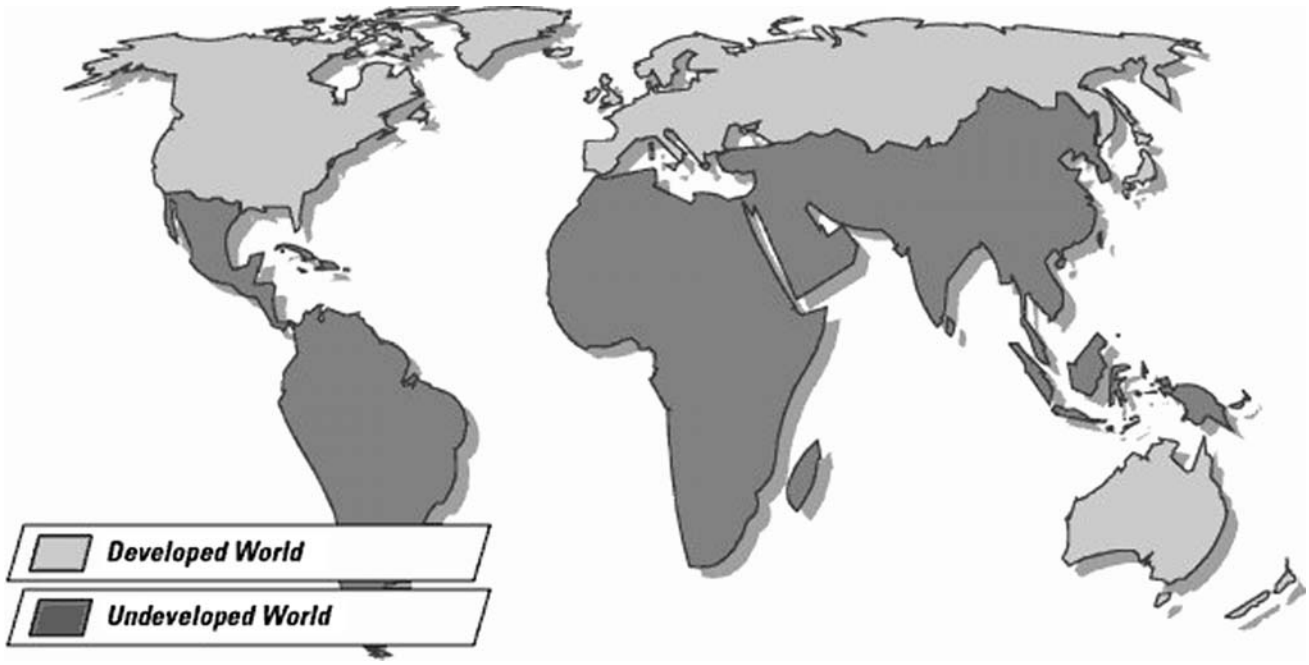

Fig. 31.1 Classification of human development in countries around the world: White – developed; Gray – developing

Patients in developing countries usually report for renal replacement therapy when they have advanced renal failure and significant malnutrition. As a result they are physically incapable of performing self-dialysis and are dependent on other family members. Further, because of prevailing cultural habits, relatives of patients would themselves not agree to patients participating in their own treatment. However since doing three or four exchanges every day is physically demanding, family support tends to wane after a certain period of time because of exhaustion on the part of the caregiver [15, 16]. In a study from South India, CAPD patients used positive coping strategies, which is reinforced by social support from family, friends, and others [15, 16]. There is also a certain inherent fear among people about doing CAPD at home, and they are not very confident about performing the procedure by themselves without supervision.

Most developing countries lack good support systems, which are important if patients develop problems in the course of their treatment. Lack of reliable microbiology laboratories in smaller towns, and communication and transportation facilities are some of these problems. Although these problems appear as minor constraints, they limit the selection of patients to be put on CAPD.

The socioeconomic status of the emerging economies is diverse and the cost of PD, government funding, insurance policies, and the patients' choice influences the decision to put the patient on CAPD. Even today, 75% of the dialysis resources are reserved for only 15% of the world's population, and in many countries, the sole alternative to dialysis or transplantation is death [17].

In the following section of the chapter, we have tried to focus on the penetration of CAPD and associated problems, some of which are unique to the developing countries.

PD Growth in Emerging Economies

As per the World Bank, in China, economic growth is 9.9%, GDP is U.S. $1,700 (per capita), estimated growth of PD is 10–30%, and average PD treatment costs U.S. $6,000–8,000/per year. Reimbursement policies and economic growth are factors contributing to growth to over 10,000 prevalent patients. India, being the second fastest growing major economy in the world, has a growth rate of 9.1%. Wealth distribution in India is fairly uneven, with the top 10% of income groups earning 33% of all income. India's per capita income (PPP) of U.S. $3,400 is ranked 122nd in the world. Cost of PD in India is U.S. $3,913–5,917/per year. Although 5.2% of the GDP is spent on health care, government spending on health care is 0.9% of the GDP, which limits the extent and effectiveness of the coverage it can provide [18]. The health care coverage reaches only less than 15% of the population (Table 31.1).

Table 31.1 Cost of PD in Asian countries

Country	Therapy price (US $)	Usual prescription
Malaysia	5,558	4 exchanges
Singapore	8,889	4 exchanges
Indonesia	4,075	3–4 exchanges
Thailand	6,000	4 exchanges
Philippines	2,650	4 exchanges
South Korea	11,200	4 exchanges
Hong Kong	12,000	4 exchanges
India	3,481	3 exchanges
Japan	50,000	4–5 exchanges

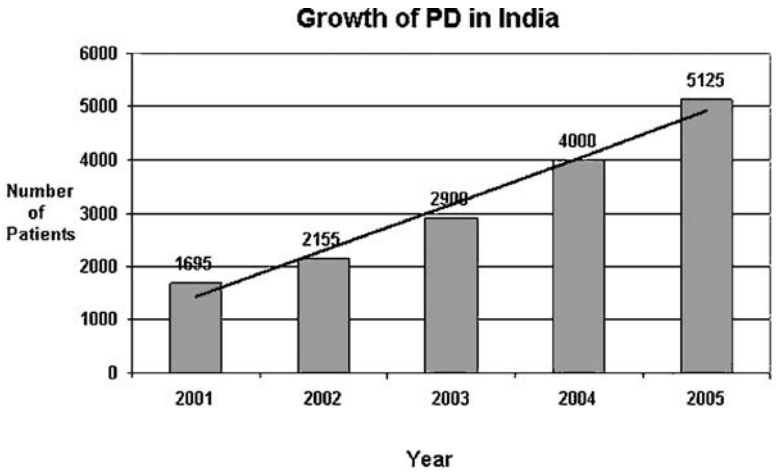

Fig. 31.2 Growth of PD in India

There has been a general increase in the number of ESRD patients on PD in most of the countries in Asia in the last decade. A few countries such as Thailand and Japan have shown a decline in the growth of PD. This decline has also been seen in countries from South America and in Mexico. The exact reason for this negative growth is not clear.

There is also a great deal of variability in growth rate among different countries in the same continent. In Asia, countries including Pakistan, India (Fig. 31.2), Bangladesh, Sri Lanka, Nepal, Indonesia, Vietnam, China, UAE, Brunei, Yemen ,and Iran have shown the maximum growth. African states such as Sudan, South Africa, Egypt, Rwanda, Tunisia, Morocco, and Algeria have active CAPD programs and have increased the utilization of PD in these countries. In China, the PD penetration is 30%, with a prevalence rate of 29.7% of the ESRD patients. Majority of the PD patients are in big cities such as Beijing and Shanghai. The PD penetration is 13% in Brazil, 6% in Chile, 45% in Colombia and 4% in Argentina. There is no government reimbursement in Paraguay, Bolivia and Peru. In some of the developing countries such as those in the South Asian region and in South America, especially Argentina, the negative selection of the patients leads to increased dropout. In Malaysia, there is government support for the PD program.

Since hemodialysis and renal transplantation are not very readily available, CAPD is gaining more popularity. Further, there is now perhaps a greater awareness about this form of treatment in these countries and the manufacturing of the consumables locally have made these products more easily available. The involvement of the clinical coordinators in patient care has led to a reduction in the dropout rate and greater confidence of patients and their relatives in this form of therapy (Fig. 31.3).

Peritoneal Access

Peritoneal dialysis access and a healthy peritoneal membrane contribute immensely to the success of long-term PD. The double-cuff Tenckhoff catheter, developed in1968, is widely used as an access for CAPD and APD. Complications such as catheter tip migration, dialysate leak, perforation of viscera, access-related infections, cuff extrusion, catheter obstruction, and infusion or pressure pain are often related to improper insertion and postimplantation care. The most

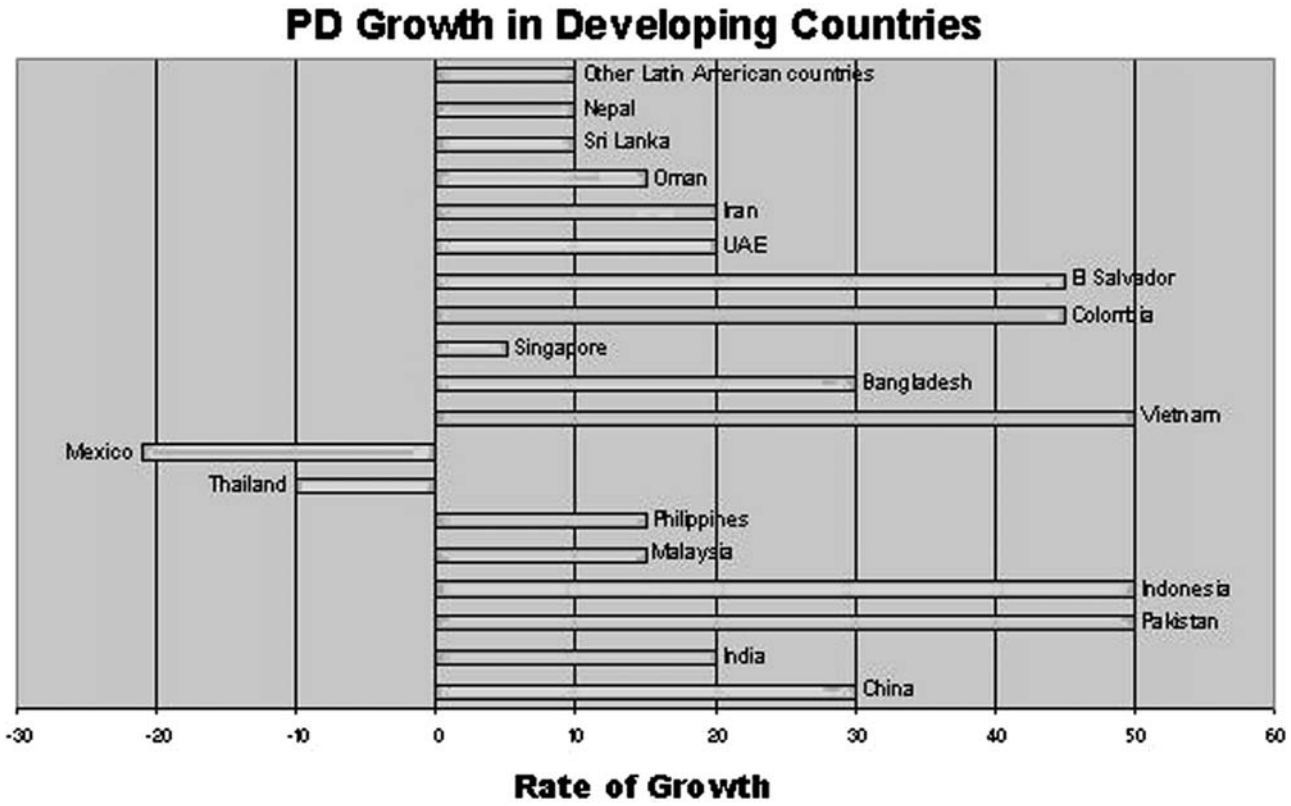

Fig. 31.3 PD growth in developing countries. Courtesy: Ricardo Correa Rotter and Baxter

important factors influencing the healing process are early infections, tissue perfusion, mechanical factors, sinus bacterial colonization, epithelialization, local cleansing agents, exit-site direction, and systemic factors. Single-cuff, double-cuff, or multiple-cuff catheters are used. The most commonly used catheters in developing countries are straight Tenckhoff catheters. The use of swan-neck Tenckhoff catheter with two cuffs is a common practice in India. In our observation, catheter tip migration and outflow block are considerably lessened by the use of swan-neck catheters. Swan-neck catheters have either a straight or coiled intraperitoneal segment. The overall length of adult double-cuff catheter is about 40 cm, with 2 Dacron cuffs 1 cm long separated by about 4–5 cm length. The presence of barium-impregnated radio-opaque strip enables radiological visualization. These catheters are either implanted on a daycare basis using a Tenckhoff trocar or peritoneoscopic equipment by nephrologists, or by a trained surgeon in the setting of an operation theater [19, 20]. This also has an additional advantage of enabling more PD penetration in developing countries.

Catheter malfunction, which is a problem for the nephrologists and the surgeon, is the second-most common complication forcing catheter removal and is seen in up to 20% of the patients [21]. Laparoscopic implantation has the disadvantage of general anesthesia and some complications may develop due to the procedure itself [22]. Laparoscopic repositioning and adhesiolysis without omentectomy are simple and effective procedures that can prolong catheter survival, even in recurrent malfunctions [22] (Fig. 31.4).

The downward exit of the swan-neck catheter prevents the incidence of exit-site infection in PD patients in our experience. PD catheter malfunction may lead to problems of inflow and outflow. In a study, we found that in the first decade of PD, there was an 11% incidence of catheter malfunction [23]. The cause of outflow block was predominantly due to fibrin clots, migration, omental wrapping, a fungal ball, or a kink in the subcutaneous tunnel. This may require catheter removal and reimplantation in certain instances to continue CAPD.

In a small study in a resource-scarce PD facility in India, the total cost of bedside PD catheter implantation was estimated to be about U.S. $90–146 per patient while the total cost of surgical catheter implantation was about U.S. $225–394 [18, 11]. Moreover, there was a decreased incidence of postimplantation peritonitis, pericatheter leak, bloody effluent, and other complications in patients with bedside PD catheter implantation [18]. Therefore, bedside implantation on a daycare basis using Tenckhoff trocar allows early initiation of PD associated with reduced morbidity and mortality [11] (Fig. 31.5).

Fig. 31.4 Tenckhoff catheter malfunction due to intraluminal fibrin clot (Inset shows removed fibrin)

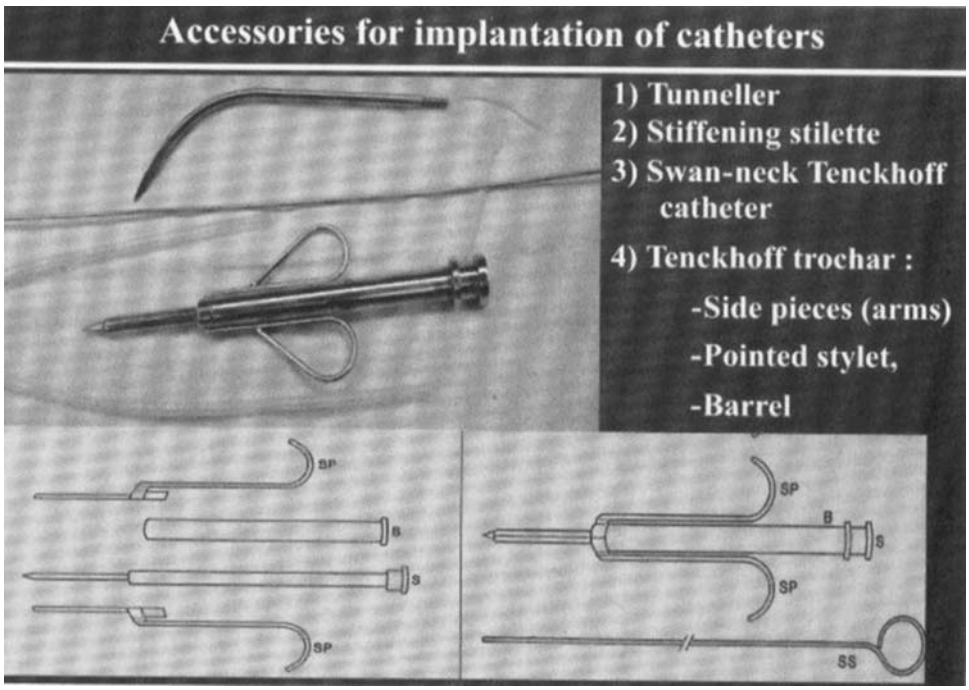

Fig. 31.5 Tenckhoff trocar set

Peritoneal Dialysis Solutions and Systems

Conventional PD solutions are characterized by high concentrations of glucose, by glucose degradation products (GDPs), and by lactate, low pH, and high osmolality. They are thus considered unphysiological or bioincompatible [24, 25]. The recently developed PD solutions, including amino acid–based solutions, icodextrin-based solutions, and

bicarbonate/lactate–based solutions, are unaffordable for the majority of the patients in emerging countries of the world, particularly in countries where the patients have to pay from their own pocket [26, 27].

Icodextrin is a soluble glucose polymer derived from the hydrolysis of cornstarch. It is formulated as a 7.5% aqueous solution (molecular weight 12–20 kDa) with electrolytes [28]. Icodextrin molecules are absorbed primarily with the relatively slow convective fluid movement out of the peritoneal cavity to the peritoneal tissue, and, finally, to blood via lymphatics [29]. During a long dwell with icodextrin, about 40% of the instilled amount is absorbed from the peritoneal cavity in contrast to glucose absorption of 75% after a 6-h dwell with 3.86% glucose-based PD fluid. The absorbed icodextrin is hydrolyzed in the blood by circulating α-amylase, resulting in elevated plasma levels of metabolites of icodextrin, such as maltose, maltotriose and maltotetrose. Chronic use of icodextrin-containing PD fluid results in a decrease in circulating α-amylase activity [29, 30].

The solution is iso-osmotic and ultrafiltration is achieved via colloid osmosis during the long dwell dialysis period (8–16 h). It is used preferentially in patients with high and high-average solute transport characteristics in whom, due to the large effective peritoneal surface area, there is a resultant loss of ultrafiltration. Its main aim is to increase fluid removal and reduce glucose and caloric load. Icodextrin-induced sterile peritonitis is due to an interleukin-6 response with peptidoglycan from thermophilic acidophilic bacteria (*Alicyclobacillus acidocaldarius*) identified as the contaminating proinflammatory substance. The icodextrin-induced sterile peritonitis is usually mild in nature, with the majority of patients being relatively asymptomatic, with dialysis effluent predominantly showing monocytes. Discontinuation of icodextrin leads to rapid resolution of symptoms and clearing of the effluent [28].

Glucose-containing PD solutions produce GDP after heat sterilization in concentrations in the micromolar range. These concentrations are high enough to cause bioincompatible reactions both in vitro and in vivo [31]. The GDPs are believed to inhibit cell proliferation, retard wound healing, induce apoptosis, down-regulate different cytokines, stimulate growth factors (TGF-β, VEGF), and inhibit respiratory burst. The best way to avoid reactive GDP is to have a pH between 2 and 2.6 during sterilization. In clinical studies, low GDP fluids increase level of cancer antigen 125 (a marker of mesothelial cell mass/homeostasis) and decrease hyaluronic acid (reflecting intraperitoneal inflammation). PD fluids with low amounts of GDPs have also been suggested to have a positive effect on systemic parameters, such as circulating advanced glycation end products (AGEs), frequency of peritonitis, decline in RRF, and patient survival [32, 33].

Amino acid–based PD solutions are being sparingly used in developing countries to treat malnutrition. However, there are no reports whether they are effective in prolonging the technique survival [34]. Bioincompatibility of the PD solution plays a major role in overexpression of TGF-β1, which stimulates accumulation of extracellular matrix and finally induces peritoneal membrane dysfunction [35]. The use of bicarbonate containing PD fluid may be helpful in reducing peritoneal fibrosis.

There is a mix of various systems being used in developing countries. While people from the more affluent sections of society have opted for the disconnect systems (such as Y-set, double-bag, etc.) patients coming to government hospitals have opted for the cheaper straight-line systems. This choice would also have an impact on infection rates of the patients.

Peritoneal Membrane Characteristics

The permeability of the peritoneal membrane varies considerably in patients from the developing countries [36–40], as demonstrated by the peritoneal equilibration test (PET) [41–43]. There are no long-term data on the survival of CAPD patients according to peritoneal membrane characteristics from the developing countries. Both high and low transport status has been observed in Indian CAPD patients [44, 45]. In a recently published study, no significant difference in the level of serum CRP between high and low transporters was observed [46]. The CRP correlated positively with age and negatively with serum albumin but did not correlate with other patient characteristics. However, Cueto-Manzano et al. reported that transport type as evaluated by PET was consistent over time in Mexican patients [47] with a D/P creatinine ratio of 0.68 ± 0.10 [47, 48]. Kumar et al. found no statistically significant difference between diabetics and nondiabetics, vegetarians and nonvegetarians, or between females and males [36]. PET results from Pakistan showed low-average and high-average transporters in 46 and 39%, respectively [12].

The CANUSA study has shown higher 2-year mortality in high transporters as compared to low transporters. These high transporters may develop symptomatic fluid retention on CAPD [41, 42]. Thus it could be argued that the higher mortality seen in high transporters may reflect the adverse effect of fluid retention on underlying cardiovascular disease. This volume expansion would also explain some of the association on hypoalbuminemia with high transport status and adverse outcomes. Whether transferring these patients to daytime short-dwell ambulatory peritoneal

dialysis (DAPD) or switching the patients to cycler PD (CCPD) at night would favorably influence the outcome should be looked into in the future. In developing countries such as India, where the cost of CCPD is much higher, it would be advisable to transfer these patients to HD. An alternative approach might be to use a new osmotic agent such as icodextrin in the high transporter group [49].

Adequacy of Dialysis

Only 5–10% of normal renal function can be achieved with dialysis. This is true for both hemodialysis (HD) and PD. The International Society for Peritoneal Dialysis (ISPD) recommendations [50] suggest that residual renal function (measured by renal clearance or urine volume), but not peritoneal clearance, is predictive of survival in prospective observational studies and can account for most of the association between total clearance and survival. Renal clearance and peritoneal clearance have different effects on patient survival. A total Kt/V urea above 1.70 or creatinine clearance above 50 L/week/1.73 m^2 is recommended in CAPD [51, 52]. Knowledge of the transport characteristics of the patient's peritoneal membrane by peritoneal equilibration test (PET) or other tests may help to optimize the prescription to meet this target.

Interventional studies have demonstrated that total $Kt/V < 1.70$ is associated with poorer primary or secondary outcome such as more clinical problems, greater need for erythropoietin therapy, and poorer patient and technique survival. A retrospective study showed that survival was poorer for anuric patients with peritoneal $Kt/V_{urea} < 1.67$ with better outcomes in those with peritoneal Kt/V_{urea} 1.67–1.87. In another study involving a slightly smaller sample of both anuric CAPD and automated peritoneal dialysis (APD) patients, there was a trend of reduced mortality, although not statistically significant, in patients with peritoneal $Kt/V_{urea} > 1.85$.

In 2005, the European Renal Association published the European Best Practice Guidelines (EBPG) for Peritoneal Dialysis [53]. These guidelines suggested that peritoneal dialysis facilities should have a well-articulated, organized structure, incorporating appropriate staff facilities, training and educational programs, and clear protocols to guide the actions of staff and patients. It is essential that the PD program should be supported by a backup HD program and hospital facilities, and preferably by a renal transplantation program. However, there are obviously regional differences in developing countries based on available expertise, socioeconomic factors, access to dialysis fluid, and availability of resources. This is true for certain countries in the Pacific region such as Fiji and remote areas in South Asian countries, where no backup HD facilities are available.

The volume and the number of exchanges used for CAPD vary widely in developing countries. In India and other South Asian countries, 2 L exchanges three times a day is the dialysis prescription for a large majority of the patients, as this is considered to be cost-effective [54]. In developing countries such as China, Malaysia, Thailand, Vietnam, Fiji, Eastern European countries, the Middle East, African countries, and Central and South American regions, 2–2.5 L exchanges four times a day is the usual CAPD prescription [51]. However, dialysis adequacy, as recommended by the recent ISPD guidelines, may not be achievable with low-volume exchanges when the residual renal function declines in prevalent CAPD patients [54]. APD is practiced in a small percentage of patients as per the reimbursement policies and socioeconomic status. A majority of the patients in the South Asian region use 10-L exchanges for 8–10 h during the night and are dry during the daytime. There is a need for low-cost cyclers in developing countries, as a substantial percentage of patients are high-transporters and hence, require APD. The utilization of APD is increasing in developing countries as a result of reimbursement policies by the government and other healthcare organizations.

Ultrafiltration was predictive of survival in anuric APD patients as baseline ultrafiltration below 750 mL/day was associated with poorer survival. Attention should be paid to both urine volume and the amount of ultrafiltration, with the goal of maintaining optimal fluid balance. Bioelectrical impedance is a well-validated method of determining fluid status and its scarce availability may be a limiting factor for monitoring fluid status in PD patients. A small ultrafiltered volume, despite the use of high concentration glucose containing dialysis solutions, should be regarded as a warning sign for the presence of ultrafiltration failure. While Kt/V_{urea} and creatinine clearance are generally closely correlated in patients on CAPD, their relationship is more variable in patients on APD, depending on the dialysis regime and peritoneal transport. There is a significant discrepancy between small solute clearance and middle molecule clearance. Small solute clearance is determined by the frequency and volume of dialysate dwell, while middle molecule clearance is determined by duration of contact of peritoneum to the dialysate.

There is no evidence for a different target Kt/V_{urea} or creatinine clearance between diabetic and non-diabetic patients, or for patients of different sizes. All studies on the effect of Kt/V quoted here used the Watson formula (using actual body weight) for the estimation of V.

Adequacy of dialysis should be interpreted clinically rather than by targeting only solute and fluid removal. Clinical assessment should include clinical and laboratory results, peritoneal and renal clearances, hydration status, appetite and nutritional status, energy level, hemoglobin concentration, responsiveness to erythropoietin therapy, electrolytes and acid-base balance, calcium phosphate homeostasis, and blood pressure control. Residual renal function should be monitored regularly and at an appropriate frequency (every 1–2 months if practicable, otherwise no less frequently than every 4–6 months) so that the PD prescription can be adjusted in a timely manner. For patients with signs and symptoms suggestive of underdialysis, a trial of increasing dialysis should be provided even if Kt/V_{urea} is well above the minimal target.

A Hong Kong study has made certain recommendations specifically for adequacy of CAPD in Asian patients [55]. Their data recommends that 1.7 be the minimal target for total Kt/V in patients on long-term CAPD. Long-term, small-volume (6 L daily) CAPD has been suggested to be safe in Asian patients. Patients with high body mass index, low residual urine volume, and significant cardiovascular disease need close monitoring.

As the cost of PD and the reimbursement policies vary diversely in emerging countries, these guidelines cannot be effectively implemented especially in South Asian countries where PD utilization is increasing [54]. There is no reimbursement by government for PD in Paraguay, Bolivia, and Peru, which has a negative impact on the growth of PD in South America. However, local manufacturing of PD fluid and accessories in India and in China has greatly reduced the cost of PD and enabled increased utilization as a renal replacement therapy.

Pediatric Peritoneal Dialysis

Peritoneal dialysis is being increasingly used as the popular choice of renal replacement therapy in children because of its simplicity, efficiency, and ability to offer a better quality of life [56, 57]. The pediatric nephrologist has to adapt the intraperitoneal volume (IPV) to a wide range of body sizes, from infants to adolescents. The prescribed IPV is scaled for body weight or, more appropriately, for body surface area. Nevertheless, tolerance of the fill volume appears to be a patient-specific parameter. In children, intraperitoneal pressure (IPP) increases when IPV increases. The slope is low until a fill volume of 1,400 mL/m^2 is reached; above this level, IPP jumps, inducing abdominal pain or at least, patient discomfort [58]. In children, as in adults, 18 cm H_2O could be considered the mean of maximum acceptable IPP level. Dialysis effectiveness depends directly on the prescribed IPV. A high IPV will induce high IPP, which is negatively correlated to ultrafiltration capacity. The fill volume, together with dwell time duration and the nature and concentration of the osmotic agent in dialysis fluid, should be taken into account to achieve an optimal peritoneal ultrafiltration capacity [59, 60].

Dialysis prescriptions in Asian pediatric populations have been largely opinion based, following the standard 30–50 mL/kg body weight. To define the adequacy of dialysis, clinical and biochemical parameters such as serum urea and creatinine concentrations have been relied upon. In addition, dialysis prescriptions are mostly limited by the tolerance of the patient for the dialysate volume, as well as the financial constraints.

A study by Iyengar et al. from a South Indian center reported good compliance irrespective of underlying socioeconomic and educational status [61]. A double-cuff Tenckhoff catheter was inserted by a laparotomy with exit site directed downwards. An Ultra Twin bag system was used. However, dialysis adequacy by Kt/V or creatinine clearance was not determined. The volume infused was 30–50 mL/kg/cycle. The PET showed both high average and low average transporters. The cost was borne by out-of-the-pocket payment by 65% of the patients and the rest received reimbursement and donations. The median age of the patients was 9.1 years (9 months–17 years), with a median weight of 20 kg (7–30 kg). There were two episodes of peritonitis – one was culture negative and the other one was fungal peritonitis necessitating catheter removal. Most of the studies in pediatric age group report a peritonitis rate of one episode per 7.1–28.6 patient-months [62–64]. A report from the European Pediatric Peritoneal Dialysis Study Group (EPPS) showed that 23% of the patients or at least one caregiver was identified as a *Staphylococcus aureus* nasal carrier, which is a risk factor for catheter-related infections in children. *S. Aureus* may be transmitted to the catheter either from the patient's nares or from the nares of the caregivers. Piraino et al. noted that a single positive nose culture obtained at any time in the course of CAPD constituted a risk factor for *S. aureus* exit-site infection and peritonitis [65]. This highlights the importance to evaluate the prophylactic potential of mupirocin administered to affected caregivers. The frequency of catheter-related complications ranges from 12 to 73% in literature [62, 66].

A study has been reported from Singapore using a standard dialysis prescription of five exchanges of 1.5 to 2.5% dialysate at 30–50 mL/kg body weight over a period of 10 h without a day dwell on NIPD. The PET showed low average transporters, mean baseline Kt/V and creatinine clearance were 1.89 ± 0.35 and 36.4 ± 11.5 L/1.73 m^4, respectively. A significant increase in peritoneal Kt/V as an increasing trend from 1.89 ± 0.35 at baseline to 2.12 ± 0.54 at 9 months,

despite a decline in residual renal function, was observed [67]. Similarly, an increase in weekly creatinine clearance was also observed [67].

The PET tests were done with 2.5% dianeal dialysate and infused at the patient's usual infusion volume of 50 mL/kg. Dialysate glucose, urea, and creatinine concentrations were measured at 0, 2, and 4 h into the dwell while serum urea and creatinine were measured midway through the dwell. Estimates of nutritional status were assessed from anthropometric measurements, biochemical indices, and body composition. Height was recorded with a Harpenden stadiometer. Weight was recorded when the dialysate fluid was drained. Body mass index was calculated from the formula: weight/height^2 (kg/m^2). The mid-arm circumference (MAC) was measured in centimeters at the midpoint between the tip of the acromion and the olecranon process. Triceps skin fold thickness (TST) was measured in millimeters using a Harpenden skin-fold caliper. The mid-arm muscle circumference (MAMC, in centimeters) was calculated according to the formula: MAMC = MAC − (0.314 × TST). Body composition was measured by bioelectrical impedance.

Nutritional assessment showed an increase in MAC, MAMC, and fat free mass. Children on dialysis are often malnourished with associated poor growth, owing to uremia-associated vomiting, anorexia, and large urinary protein losses. The already poor nutritional state is worsened by peritoneal protein losses because children with ESRD are already at risk for growth failure. Meticulous attention to nutritional issues is imperative to ensure adequate protein and calorie intake to encourage optimal growth [68]. Use of recombinant growth hormone therapy is inaccessible to most of the pediatric patients in the developing world because of the exorbitant costs [61].

Children with CKD are considered at high risk for protein-energy malnutrition. Unrecognized fluid overload, which is common in ESRD, may lead to misinterpretation of most measures of nutritional status. Serial nutritional assessments can be useful in determining trends in nutritional status; however, since volume status may also change over time, the impact of volume overload on nutritional measures must always be borne in mind [69]. Measures should be expressed relative to height or height-age. Moreover, children with CKD should be compared to healthy ones of the same height, race, and stage of pubertal development [69]. Recombinant erythropoietin therapy, 150–250 units/kg body weight on twice weekly basis, can be used as cost-effective, generic forms are available in developing countries such as India [61].

Exit Site Infection and Peritonitis

Technical innovations such as UltraBag, disposable systems, and APD have resulted in large decreases in frequency of peritonitis. Permanent discontinuation of PD, profound malnutrition, and death are major adverse outcomes of PD-related peritonitis [70–73]. The outcome of peritonitis can potentially be affected by several factors, including microbial etiology, host factors, and interventional factors [74] Table 31.2.

Multivariate analysis has shown Gram-negative and fungal peritonitis as risk factors for mortality in PD [74, 75]. The most frequently isolated fungus was *Candida* species. The incidence of fungal peritonitis was 11.3% [75]. The mortality and dropout from CAPD program due to fungal peritonitis was reported to be 83.4% [75]. Two variables – duration of active peritonitis for at least 4 days after institution of proper treatment and long duration of PD – were considered as predictors of adverse outcome [74]. The predictors of persistent peritonitis are advanced age and large decreases of serum potassium and albumin at presentation with peritonitis [76].

Factors that lead to persistence of peritonitis which produce an adverse outcome are co-existent exit site or tunnel infection with the same microbial species and bacteria with a propensity to form biofilm [77]. Exit-site infections and tunnel infections are less common. *S. aureus*, *Staphylococcus epidermidis,* and *Pseudomonas aeruginosa* are responsible for the majority of infections. Nasal carriage of *S. aureus* is a major risk factor for exit site infection. In a cohort of 27 patients with a mean age of 56.1 ± 17.34 years, the prevalence of *S. aureus* nasal carriage was seen in 65% of all patients. However, its presence was not significantly associated with exit-site infection or peritonitis, as 55% of the patients were applying mupirocin to the exit site [78].

The downward direction of the exit site using a swan-neck Tenckhoff catheter and the use of mupirocin and nadifloxacin at the exit site have remarkably reduced the incidence of exit site infection in PD patients in South Asian countries. An exit-site infection that progresses to peritonitis, or a patient who presents with an exit-site infection in conjunction with peritonitis with the same organism, will usually require catheter removal. Relapsing *S. epidermidis* peritonitis suggests colonization of the intra-abdominal portion of the catheter with biofilm and is best treated with replacement of the catheter. Catheter removal should be done promptly rather than submitting the patient to prolonged peritonitis or relapsing peritonitis [79].

Table 31.2 The incidence of peritonitis in some developing countries

Country	Incidence rate of peritonitis
Malaysia – Ong LM, et al. Perit Dial Int 2002; 22 (suppl. 2): Abstract S10	• 1 episode/12.2–34.6 patient-months (Ultra group) • 1 episode/4.9–36.1 patient-months (Carex group)
Tunisia – Hamida BF, et al. Perit Dial Int 2006; 26 (suppl. 2): S45	• 1 episode/45.3 patient-months • GP 39%, GN 17%, FN 5%, CN 40%
Turkey – Afsar, et al. Perit Dial Int 2006; 26 (suppl. 2): S44 – Unsal, et al. Perit Dial Int 2006; 26(suppl. 2): S65	• 1 episode/23.9 patient-months • GP 54%, GN 12%, PM 8%, CN 26%
Thailand – Girivongs D, et al. Perit Dial Int 2006; 26 (suppl. 2): S62	• 1 episode/21.6 patient-months
Singapore – Chionh CY, et al. Perit Dial Int 2006; 26 (suppl. 2): S49	• 1 episode/80.13 patient-months
Serbia – Djurdjevid-Mirkovic DMT, et al. Perit Dial Int 2006; 26 (suppl. 2): S50 – Jovanoci N, et al. Perit Dial Int 2006; 26 (suppl. 2): S55	• 0.44 episodes per patient-year • GP 88.8%, GN 2.7%, FN 2,7%
Brazil – Fernandes NMS, et al. Perit Dial Int 2006; 26 (suppl. 2): S51	• 0.17 episode/patient/year • GP 71%
China – Fang W, et al. Perit Dial Int 2006; 26 (suppl. 2): S51	• 0.146 episodes/patient/year • GP 54.1%, GN 25.5%, PM 7.1%, FN 13.3%
Poland – Liberek T, et al. Perit Dial Int 2006; 26 (suppl. 2): S56	• 1 episode/20.5 patient-months
Chile – Ortiz AM, et al. Perit Dial Int 2006; 26 (suppl. 2): S59	• 0.21 episodes/patient/year • GP 63%, GN 26%, PM 9.6%, FN 1.4%
Venezuela – Ontiveros C, et al. Perit Dial Int 2006; 26 (suppl. 2): S59	• 0.93–1.18 episodes/patient/year • GP 32%, GN 44.3%, PM 4.24%, FN 4.5%, CN 28.9%
Colombia – Mejia CH, et al. Perit Dial Int 2006; 26 (suppl. 2): S58	• 1 episode/24.07 patient-months
India – Nayak KS. Perit Dial Int 2004; 24:422–423 – Prasad N, et al. Perit Dial Int 2003; 23: 400–402	• 1 episode/71 patient-months • 0.63 episodes/patient-year • GP 40%, GN 60%
Pakistan – Hussain R, et al. Ind J Perit Dial 2006; 11: 10–13	• 1 episode/22 patient-months
Sudan – Abu-Aisha H, et al. Ind J Perit Dial 2006; 11: 14–18	• 1 episode/18 patient-months • CN 53%
Greece – Dimitriadis A, et al. Perit Dial Int 2001; 21 (suppl. 1): S40	• 1 episode/14.30 patient-months
Bulgaria – Vazelov ES, et al. Perit Dial Int 2004; 24: 512–517	• 1 episode/13.1 patient-months
Peru – Concepcion L, et al. Perit Dial Int 2001; 21 (suppl. 1): S39	• 1 episode/0.70–0.81 patient-year
Argentina – Barone R, et al. Perit Dial Int 2001; 21 (suppl. 1): S39 – Locatelli A, et al. Perit Dial Int 2001; 21 (suppl. 1): S44	• 1 episode/42.5 patient-months • 1 episode/13–38 patient-months • GP 57%, FN 14%, CN 29%, E.coli 11%
Bangladesh – Samad MA, et al. Ind J Perit Dial 2006; 10: 28–29	• 1 episode every 19.46 patient-months
Kuwait – Al-Hilali N, et al. Perit Dial Int 2002; 22: S42	• 1 episode/18.5 patient-months (Bieffe L3 double bag), 22.5 (ANDY Plus) and 23.7 (NIPD system) patient-months
Nepal – Sharma SK, et al. Perit Dial Int 2006; 26 (suppl. 2): S125	• 0.43 episodes/patient-year

GP – Gram-positive; GN – Gram-negative; CN – culture negative; PN – polymicrobial; FN – fungal.

For those peritonitis episodes in which the PD fluid cell count was >100/μL for more than 5 days, the nonresolution rate was 45.6% compared to 4.2% when the cell count returned to 100/microlitre or less in less than 5 days [74]. The nonresolution rate for those patients that had been on PD for more than 2.4 years was 24.4%, compared to 16.5% for those that had been on PD for less than 2.4 years [74]. Blacks seem to develop less severe peritonitis than Caucasians, and Caucasians have significantly higher nonresolution rates than blacks [74]. Following an episode of peritonitis, over time, dialysis alters the characteristics of the peritoneal membrane and the peritoneal macrophages. The initial systemic WBC count and the initial PD effluent cell count have no independent effect on outcome. Patients with peritonitis episodes due to Gram-positive organisms have a significantly better outcome than episodes due to either polymicrobial or Gram-negative peritonitis. Gram-negative organisms had the worst resolution rate, especially those episodes due to *P. aeruginosa* [74].

Rapid successful treatment of peritonitis is important in order to prevent peritoneal membrane damage and fibrosis. Successful eradication of the pathogen is essential for the prevention of an infection relapse. The Gram-negative organisms such as *Escherichia coli, P. aeruginosa, Acinetobacter* species, and *Klebsiella* species, were successfully treated with once-a-day, intraperitoneal gentamicin 40 mg/2 L single bag in 66.1% of the cases [80]. In developing countries, the use of once-daily administration of a cheap aminoglycoside antibiotic is convenient for the patient, reduces cost, encourages compliance, prevents contamination, and is suitable for outpatient therapy. The main potential benefit of once-daily administration is the possible reduction of nephro- and ototoxicity [81]. The ISPD Committee on Peritonitis feels that the minimum therapy for peritonitis is 2 weeks, although for more severe infections, 3 weeks is recommended. Icodextrin containing dialysis solutions are compatible with vancomycin, cefazolin, ampicillin, cloxacillin, ceftazidime, gentamicin, or amphotericin [82].

Catheter Removal and Reimplantation

Catheter reimplantation following catheter removal after peritonitis may be successfully accomplished. In a study from South India, catheter loss was reported in 9% of the patients with peritonitis [83]. All of them had co-infection with *S. aureus*, fungi (*Candida*), *P. aeruginosa,* and *Mycobacterium tuberculosis*. However, successful reimplantation of the catheter was undertaken in 40% of the patients who lost the catheter. In these patients, laparoscopic examination of the peritoneal cavity permits direct visualization for investigating mechanical dysfunction before catheter implantation [84, 85]. This technique also permits evaluation of pelvic adhesions and lysis of adhesions before implanting the catheter [86]. For refractory peritonitis and fungal peritonitis, simultaneous catheter removal and replacement is not possible. The optimal time period between catheter removal for infection and reinsertion of a new catheter is not known. Empirically, a minimum period of 2–3 weeks between catheter removal and reinsertion of a new catheter is recommended [79]. Catheter replacement as a single procedure can also be done for relapsing peritonitis, if the effluent can first be cleared. This procedure should be done under antibiotic coverage [79].

Fungal Peritonitis

The majority of fungal peritonitis infections are caused by *Candida* (69–85%) [87, 88], but non-*Candida* fungal peritonitis episodes have been reported from India, Brazil, and Hong Kong [89, 90]. *Candida albicans* peritonitis is associated with a worse outcome than non-*C. albicans* peritonitis.

Chan et al. reported that giving treatment with fluconazole therapy alone, without catheter removal, the cure rate was only 9.5%, whereas with fluconazole plus catheter removal the cure rate improved to 66.7% [91]. Addition of intravenous amphotericin B can be performed in patients not responding to fluconazole and catheter removal. Lee et al. successfully used intracatheter amphotericin B and oral flucytosine for a period of 5 weeks for treating fungal peritonitis without catheter removal [92]. Caspofungin, fluconazole, or voriconazole may replace amphotericin B, based on species identification and MIC values. Intraperitoneal use of amphotericin B causes chemical peritonitis and pain; IV use leads to poor peritoneal penetration. Voriconazole is an alternative for amphotericin B when filamentous fungi have been cultured and can be used alone for *Candida* peritonitis (with catheter removal). Catheter removal is indicated immediately after fungi are identified by microscopy or culture. Therapy with these agents should be continued after catheter removal, orally with flucytosine 1,000 mg and fluconazole 100–200 mg daily for an additional 10 days [79].

Mortality due to fungal peritonitis has ranged from 14.3 to 46% [87, 91]. CAPD can be successfully reinstituted after a waiting period of 4–6 weeks. There is a low prevalence of peritoneal adhesions and subsequent CAPD failure. Lo et al. recommended that oral nystatin prophylaxis (500,000 units four times a day) may be given with each antibiotic prescription, since they found that this significantly reduced the rate of *Candida* peritonitis in CAPD patients [93].

Tuberculous Peritonitis

Tuberculous peritonitis is not an infrequent cause of peritonitis in developing countries. The host resistance to tuberculosis is mediated by cell-mediated immunity, which is impaired in chronic renal failure. It is reported with an incidence of 0.3 to 2.5% in CAPD patients [94–97]. Mycobacterial peritonitis can be caused by *M. tuberculosis* or non-tuberculosis mycobacteria. The diagnosis should be considered in any patient with culture-negative peritonitis, nonresolution with conventional antibiotic therapy, and relapsing peritonitis with negative bacterial cultures [95]. Contrary to previous belief, most cases of mycobacterial peritonitis have a predominant polymorphonuclear WBC. Ziehl-Neelsen stain for acid-fast bacillus is usually smear negative. A specific diagnosis can be made by culturing the centrifuged sediment (50–100 mL volume) using a solid medium (Lowenstein Jensen agar) and a fluid medium (Septi-Chek, BACTEC, etc.). The time of detection for growth of mycobacteria is decreased considerably in fluid medium. Repeated examination and culture of multiple dialysis fluid samples will yield better positive results. In our experience, we found that nucleic acid amplification technique (NAAT) using different primers enhanced rapid and early diagnosis of mycobacterium tuberculosis from dialysis effluent, thereby instituting early antituberculous therapy with a four drug regimen, including rifampicin, isoniazid, pyrazinamide, and ofloxacin [98]. Treatment with pyrazinamide and ofloxacin can be stopped after 3 months while continuing the isoniazid and rifampicin. Catheter removal was not necessary as the dialysis effluent cleared up in 7–10 days after institution of antituberculous therapy. In those patients who had early institution of antituberculous therapy, there was no permanent peritoneal membrane damage enabling the patient to continue on PD. However, two of our patients who received treatment for 11 months presented with recurrence of tuberculous peritonitis. The duration of treatment may be prolonged for 15–18 months for a complete cure with no recurrence. The therapeutic level of rifampicin in dialysis fluid is quite low due to its high molecular weight, high protein binding capacity, and lipid solubility. Therefore, for the treatment of tuberculous peritonitis, rifampicin may need to be given intraperitoneally.

Culture-Negative Peritonitis

Culture-negative peritonitis can be due to a variety of reasons, including inappropriate use of prior antibiotics. If there is no growth by 3 days, a repeat cell count with a differential count should be obtained. If the repeat cell count indicates that the infection has not resolved, special culture techniques should be used for identification of lipid dependent yeast, mycobacteria, Legionella, slow-growing bacteria, Campylobacter, fungi, Ureaplasma, Mycoplasma, and enteroviruses. If improvement is inadequate by 5 days of therapy, catheter removal should be strongly considered for culture negative peritonitis except in mycobacterium tuberculous peritonitis.

In case of multiple enteric organisms, particularly in association with anaerobic bacteria, there is a possibility of intra-abdominal pathology, such as gangrenous cholecystitis, ischemic bowel, appendicitis, or diverticulitis. CT scan may help identify intra-abdominal pathology. However, a normal scan does not exclude this. Polymicrobial peritonitis due to contamination during procedure generally resolves with antibiotics without catheter removal.

The correct microbiological culturing of peritoneal effluent is of utmost importance to establish the microorganism. Identification of the organism and subsequent antibiotic sensitivity will not only help guide antibiotic selection but, in addition, the type of organism can indicate the possible source of infection [79]. Centrifugation of 50 mL of peritoneal effluent at 3,000 g for 15 min followed by resuspension of the sediment in 3–5 mL of sterile saline and inoculation of this material both on solid culture media and into a standard blood-culture medium, is the method most likely to identify the causative organisms. With this method, less than 5% will be culture negative. Rapid blood culture techniques (e.g., BACTEC, Septi-Chek, BacT/Alert; Becton Dickinson) may further speed up isolation and identification and are probably the best approach. The majority of cultures will become positive after the first 24 h and, in over 75% of cases, diagnosis can be established in less than 3 days [79]. Culture-negative peritonitis, as high as 53%, was reported from the Sudan PD program [99].

Ultrafiltration Failure

Ultrafiltration failure (UFF) is the most common cause of dropout from CAPD in long-term PD patients. The prevalence of UFF increases from 3% during first year on CAPD to 31% at 6 years [100]. During CAPD, various morphological changes take place in the peritoneum, including mesothelial denudation, interstitial fibrosis, neovascularization, and vascular alterations (replication of basement membrane, fibrosis and hyalinization of the vascular

wall). Recurrent peritonitis is a major cause for these changes. The causative organisms producing these changes are *P. aeruginosa*, *S. aureus*, Mycobacterial infections, and fungal peritonitis. Administration of enalapril has resulted in preserved ultrafiltration by inhibiting TGF-β_1 overexpression. Mesothelial cell regeneration and remodeling can also be maintained [100]. Monitoring of ultrafiltration capacity longitudinally in long-term PD patients is necessary in developing countries to pick up the development of UFF. Changes in solute transport can be linked to peritonitis damage and early exposure to hypertonic glucose changes. Impaired sodium sieving could result from a lack of water channels.

PD in CAPD Patients with HIV Infection

CAPD has been used as a renal replacement therapy for HIV-positive patients in developing countries [101–103]. In Kenya, where there is a high prevalence of HIV infection, McLigeyo reported the use of CAPD with a standard spike connection system [102]. He reported a peritonitis rate of 1/1.5 patient-months in HIV-positive patients as compared to 1/5.7 patient-months in HIV-negative patients. Advances in connectology, technique, nutritional management, and antiretroviral therapy have all improved the survival of HIV patients on CAPD all over the world. In our limited experience, we have documented one episode of peritonitis every 37 patient-months [101]. Steps were taken by health care personnel from contracting HIV by institution of techniques as per universal precautions. Attempts were made to ensure secured connections. Drained fluid was disposed only in toilets flushed well with bleach solution. Empty drain bags were either sent for incineration or were buried in deep underground pits of 10 feet depth. The recommended antiretroviral dosage for HIV positive dialysis patients are zidovudine 100–300 mg BID, lamivudine 25–300 mg OD, didanosine 100–200 mg OD, nevirapine 200–400 mg OD, and nelfinavir 250–1250 mg BD [101].

Hepatitis B Infection

Huang et al. have demonstrated that 75% of CAPD patients were anti-HBsAg-positive as compared to 91.8% of normal controls (no significant difference) [104]. This probably reflects acquisition of HBV infection by CAPD patients before initiation of chronic dialysis therapy in a region hyperendemic for HBV. Patients on HD are more prone to become hepatitis B-positive as compared to patients on CAPD. In a study from Brazil, seroconversion on HD was found to be 0.19/patient-year, while on CAPD it was 0.01/patient-year [105]. The HBV attack rate in HD patients in Brazil has been found to be around 4.5% per year (range 0–6%) and an average 9.4% of HD patients are chronic carriers of hepatitis B virus [106]. Pruritus is another common manifestation of viral hepatitis due to HBV in CAPD patients [107]. HBV infection, unlike HCV infection, did not cause significant serum aminotransferase elevation in CAPD patients; in fact CAPD patients in general were found to have significantly lower alanine amino transferase and aspartate amino transferase levels compared to adult controls who were HBV-positive [108].

Hepatitis C Infection

HCV is an important agent of hepatitis in CAPD patients [109]. The prevalence of hepatitis C infection among patients on CAPD is significantly less than in patients on HD. HCV infection is a significant health hazard as it can lead to chronic active hepatitis, liver cirrhosis and hepatic carcinoma. Patients undergoing hemodialysis treatment are at increased risk of contracting HCV and other viral infections. Transmission of viral hepatitis in particular, HCV in dialysis units, has shown a progressive increase worldwide, ranging between 5% in some developed countries and up to 95% in some developing countries. The annual rate of HCV seroconversion in Saudi Arabia is 7–9%, while its prevalence is variable between 15–90%. The most prevalent genotypes in Saudi Arabia are genotypes 4, 1a, and 1b, whereas genotypes 2a, 2b, 3, 5, and 6 are rare. Genotypes 1 and 4 were associated with different histological grades of liver disease. Mixed infections with more than one genotype were observed in some studies. Interferon-α or pegylated interferon, alone or in combination with ribavirin, have shown great promise for the treatment of chronic HCV in dialysis patients.

The prevalence of anti-HCV has not been found to increase with the duration of CAPD. It has been suggested that CAPD offers better control of HCV infection [109]. A study from Brazil showed that seroconversion from HCV-negative to HCV-positive was 0.15/patient-year for HD patients and 0.03/patient-year for CAPD patients [105]. The hazard ratio for HCV infection in HD patients was 5.7 compared to CAPD patients. The prevalence of

coexisting HBV and HCV infection in CAPD patients depends on the HCV status of the individual [104]. The detection of HCV can be improved by using the second-generation assays in uremic patients [110]. Patients having severe pruritus are more prone to have infection with HCV, and screening for HCV infection should be done in uremic patients on CAPD with unexplained itching. HCV is an important cause of chronic liver disease in CAPD patients and 31% of patients positive for anti-HCV were found to develop liver disease [111]. A recent study from South India reported HCV seroconversion of 1.4% in CAPD patients compared to 18.08% in HD patients, suggesting the advantage of CAPD over HD in developing countries [112].

Hepatitis G Infection

Huang et al. have demonstrated that the prevalence of GBV-C/HGV viremia in CAPD patients was 23.3% compared with 1% in healthy adults ($p < 0.05$) [113]. Patients with GBV-C/HGV infection alone had received more blood transfusions. There are no significant differences between viremic and nonviremic groups with respect to age, gender, duration of previous HD, previous history of surgery and co-infection with HBV or HCV. It is known that GB virus C or hepatitis G virus can be transmitted parenterally, very probably sharing common routes of transmission with HCV. It has been suggested that HGB infection does not seem to be associated with clinically significant hepatitis. The routes of HGV transmission other than transfusion or contamination during the HD procedure should be suspected [114, 115].

Noninfective Complications of Peritoneal Dialysis

Malnutrition in Peritoneal Dialysis

The incidence of malnutrition is high in the PD population, with approximately 50% of patients showing signs of malnutrition [116, 117]. The factors contributing to malnutrition in dialysis patients include catabolic illness, poor dietary intake, and large losses of protein through the peritoneum, often exacerbated by bouts of peritonitis. It has been estimated that 0.5–2.0 g of protein is lost per liter of dialysate [118]. Other causes include underdialysis, financial constraints and, vegetarian dietary habits. Even in nonvegetarians, low protein intake may be a major problem and can contribute significantly to malnutrition [119]. Serum albumin concentration is among the most common primary outcome markers used for nutrition, although it is influenced by many variables. Reduced intake alone rarely results in a lowering of serum albumin levels, not until near starvation is reached. The low serum albumin concentration in PD patients reflect the end result of multiple processes, including reduced intake, dialysis dose, dialysate protein loss, acidosis, and inflammation [120].

Since the cause of malnutrition is multifactorial, its detection is important when patients embark on dialysis. Studies from developing countries reported that more than 80% of patients had a protein intake of less than 1.2 g/kg/day while just 14% had physical evidence of malnutrition, as shown by a BMI of less than 19 and 8% of the patients had a lean body mass of less than 60%. The nutritional status may influence dialysis efficacy, the long-term survival rate, and the quality of life of CAPD patients [117].

Pinlac and Danguclan reported malnutrition with serum albumin of less than 4.0 g/dL in 80% of patients while starting CAPD in the Philippines, which increased mortality and morbidity [121]. In most developing countries, ESRD patients wait until they are very ill before they start renal replacement therapy and strict dietary protein restrictions imposed as part of conservative treatment during the predialysis phase further worsen the malnutrition.

Malnutrition is a major factor affecting patient survival on PD therapy, as this predisposes to peritonitis, worsening of anemia and other complications. In India and certain neighboring countries, a large percentage of CAPD patients are pure vegetarian, and significant malnutrition as assessed by anthropometric and biochemical markers has been encountered in these patients [122]. Jayanthi et al. reported that vegetarians on CAPD showed protein-calorie malnutrition, muscle wasting, low serum albumin, and low hemoglobin and transferrin levels, leading to an increased incidence of peritonitis [122]. Malnutrition is more marked in CAPD patients who are diabetic as compared to nondiabetics [123, 124]. Espinoso et al. reported that diabetes mellitus and female sex were strong predictors for moderate and severe malnutrition [123]. Gamba reported that a low serum albumin was the most powerful predictor of death [125]. CAPD patients are advised to consume a protein intake of 1.2–1.5 g/kg/day. Yuan et al. and Chen et al. have shown that good nutritional management can improve the nutritional status in CAPD patients [126, 127]. The benefit of Chinese traditional medicine in improving the nutritional condition of CAPD patients has also been

reported [128]. Use of parenteral androgenic steroids and oral megestrol acetate has shown positive impact on nutrition in CAPD patients [129].

Subjective global assessment (SGA), along with anthropometry and biochemical parameters, is used for nutritional classification into well-nourished, moderately malnourished or severely malnourished state. Serum albumin levels may be reduced during peritonitis, underlying systemic disease, the presence of inflammation, older age and fluid overload. Peritoneal protein loss (5–15 g/day) may be an important contributing factor for malnutrition in CAPD patients but was not found to be significantly correlated with dietary protein intake and dietary energy intake [130]. Therefore, caution should be exercised in attributing malnutrition in CAPD patients as a direct consequence of increased peritoneal protein loss [130].

Bio-impedance analysis (BIA), Dual energy X-ray absorptiometry (DEXA), and magnetic resonance imaging (MRI) are expensive tools for assessment of malnutrition in developing countries. Ingestion of B-complex vitamins and use of recombinant erythropoietin are increasingly becoming popular in developing countries for treatment of vitamin deficiency and anemia because of the availability of generic preparations at a low cost [131].

As with any other diet, the adequacy of vegetarian diet depends on the individual's food selection. In reviewing a typical menu, nutritionists found that a diet that supplies 2,500 calories would contain 50% more protein than is needed by 98% of the population. It is difficult to find a mixed vegetarian diet that produces a negative nitrogen balance, unless a large part of it consists of sugars, jams, jellies, and other essentially nonprotein foods [132]. In a study on Indian patients, we found that 68.2% of the PD patients and 64.9% of the HD patients had carnitine deficiency, highlighting the importance of carnitine supplementation in these individuals. We found the mean value of carnitine in PD patients to be 38.8 ± 13.66 μmol/L and only 26.3% were vegetarians [133]. Patients on PD also have significant vitamin D deficiency, which is underdiagnosed and, hence, vitamin D supplementation may be necessary in developing countries [134]. As nutritional supplements are available in plenty lately in developing countries in South Asia, these may be used in addition to diet in malnourished CAPD patients.

In a study from Mexico, oral administration of egg albumin-based supplement significantly improved serum albumin, calorie and protein intake, and nPNA, and compared to controls, this maneuver was associated with increased anthropometric parameters and improved SGA evaluation [48]. The prescribed dose was 15 g twice daily for a period of 6 months.

Malnutrition, Inflammation, and Atherosclerosis

Malnutrition, inflammation, and atherosclerosis is an underdiagnosed entity in CAPD patients. Much data show that patients with high peritoneal permeability display the greatest inflammatory status on CAPD; this, in turn, may be associated with the higher mortality of these patients reported in some studies [135]. Several conditions may be implicated in the origin of inflammation in CAPD, including use of bioincompatible dialysis solutions, which may induce IL-6 synthesis by peritoneal mesothelial cells, macrophages, and endothelial cells. Fluid overload has also been associated with inflammation, and a lower total fluid removal has been found related to higher C-reactive protein levels in CAPD patients [136]. Nocturnal intermittent PD (NIPD) significantly decreased serum CRP and displayed a trend toward decreased serum TNF-α and IL-6 concentrations compared with CAPD; whereas CCPD tended to reverse these effects [137].

A study in Mexico evaluated the relationship between extracellular fluid volume (ECFv) expansion, which is commonly seen in PD patients, and inflammation [138]. CRP values positive for inflammation were found in 80.3% of the patients, and those with high CRP (>3.0 mg/L) had higher ECFv/total body water (TBW) ratio, higher serum glucose, lower serum albumin ,and lower ultrafiltration. ECFv/TBW was significantly and independently associated with inflammation, suggesting a correlation between two independent risk factors for mortality, as previously thought. Management of ECFv deserves major attention since some changes in the therapeutic approach, such as diet advice in limiting fluid and sodium intake and the introduction of new osmotic agents, may significantly improve PD as a RRT option.

Associated co-morbid conditions are an important contributing factor for malnutrition in diabetic patients. The most frequent co-morbidity is coronary artery disease in 65% of the patients. The mean serum albumin level at the initiation of CAPD was 2.91 ± 1.42 g/dL with 93% of the patients having a serum albumin of less than 3.5 g/dL at PD initiation [139]. On further analysis, among the diabetics and nondiabetics on CAPD, the serum albumin levels were 2.93 ± 1.42 g/dL. Fifty-one percent of the patients were high transporters and 32% were high average transporters from among a cohort of 350 patients. The mean patient survival was 28 months, with diabetics having poorer survival than

nondiabetics (27 versus 29 months, $p > 0.05$) [139]. Similar results have been shown by investigators from other centers in South East Asian populations, who are relatively more affluent than Indian population [132, 140].

In CAPD patients, nutritional parameters, appetite, and transperitoneal solute movement can be modified by treatment with amino-acid-based dialysis solution (AADS). A study in Poland examined the influence of AADS on serum and dialysate leptin concentrations, as leptin is involved in energy expenditure and appetite regulation [141]. With AADS treatment, there was a significant increase in total body mass, body mass index, and plasma concentrations of total protein and albumin. Administration of AADS in CAPD patients caused a transient decrease in leptinemia and increases in peritoneal excretion and clearance of leptin, as well as dissociation of the physiological relationship between serum leptin level and total fat mass. Nevertheless, patients in developing countries cannot afford the use of AADS because of economic reasons.

Yet another study took a look at polyglucose dialysis solution (PGDS) and its influence on serum indicators of iron status [142]. PGDS administration increased serum transferrin concentration, without enhanced iron binding to transferrin. An increase in transferrin level helps to improve nutritional status. Moreover, the positive effect of PGDS is enhanced especially if prescribed for longer than 6 months. Attention should be given to serum iron parameters to avoid iron deficiency.

Cardiovascular Disease and Peritoneal Dialysis

A major cause of dropout from CAPD in developing countries is death due to cardiovascular disease and its complications. Coronary artery disease (CAD) with cardiac hypertrophy is present in a large number of CKD patients in the developing countries. CAD and diabetes are seen together in epidemic proportions in India and other South Asian countries [143]. Other co-morbid factors like anemia, hypertension, hyperlipidemia, hyperparathyroidism, chronic malnutrition, inflammation, and inadequate dialysis also compound the cardiac problems [144]. All of these factors contribute to the exaggerated atherosclerosis and myocardial, valvular, and coronary calcification seen in patients with CKD. Thus, the exaggerated cardiovascular death seen in CKD and dialysis patients requires prevention and treatment to reduce the morbidity and mortality. The preferred and successful mode of management for CAD patients on dialysis is coronary arteriography followed by revascularization [145].

Locatelli et al. found that dialysis modality had no impact on the development of de novo CAD [146]. There was also no impact on cardiovascular mortality. Ganesh et al. recently found that the initial survival of patients without CAD or myocardial infarction at the start of dialysis was better in PD than in the HD group [147]. They also found a worse outcome in terms of mortality in patients with existing cardiovascular disease. Recent studies showed that many CAPD patients, especially those without residual renal function, were, in reality, fluid overloaded and had a higher frequency of hypertension. It is known that hypervolemia is the most important factor for hypertension and/or left ventricular hypertrophy (LVH). Volume control depends mostly on sodium restriction and daily osmotic ultrafiltration in patients on CAPD. As many patients in developing countries are doing 2 L $\times$ 3 exchanges/day with high and high-average peritoneal transport characteristics, many are volume overloaded and hypertensive. In a study that investigated 24-h ambulatory blood pressure monitoring, 52% were found to be hypertensive, both mean systolic and diastolic BP were significantly increased in high transporters compared to low transporters in both daytime and nighttime BP parameters [148]. Left ventricular mass index was higher in high transporters compared to low transporters. Following an increase in ultrafiltration, mean systolic and diastolic BP decreased and BP levels returned to normotensive levels in 46% of the hypertensive patients requiring discontinuation of antihypertensive drugs [148]. Dialytic ultrafiltration volume was negatively correlated with systolic and diastolic BP.

Prevention of cardiovascular disease by early and aggressive attack of traditional risk factors long before the patient develops ESRD is far more beneficial than the effects of differences induced by dialysis modality choice [149]. For patients already on dialysis, primary and secondary prevention of cardiovascular risk should be analyzed and treated using beta-blockade, aspirin, and angiotensin-converting enzyme inhibitors.

In PD patients, the optimization of fluid balance as an important parameter of adequacy has been neglected, leading to higher prevalence of congestive heart failure and hypertension. Salt restriction, diuretics, and/or icodextrin have all proven to be effective in lowering extracellular body water and reducing blood pressure and LVH in PD patients [30].

In a study of 43 patients with CKD, with 13 (30.2%) on CAPD, the mean coronary artery calcium score (CACS) was 388.6, indicating moderate cardiovascular risk [150]; 92.9% of the patients had CACS more than 400. In those patients who had highly sensitive CRP levels, more than 1 mg/dL, 85.7% had a CACS of over 400. Those patients who were on dialysis for more than 2 years had a CACS of >400 and 43% of the diabetics had scores more than 400. Among the six patients who died, all had a CACS of >400. It is now possible to estimate the atherosclerotic plaque burden in a

noninvasive manner and, thus, predict the chances of developing future coronary events. The presence of any coronary calcium can impact patient management significantly.

In a cross-sectional study among 51 prevalent Chinese patients on CAPD, malnutrition was present in 66.7%, inflammation in 45.1%, and cardiovascular disease in 51%. Malnutrition, inflammation, and atherosclerosis (MIA) syndrome was present in 31.4%. Those patients with MIA and CVD were significantly more fluid overloaded, supporting the possible role of volume overload in the development of malnutrition and MIA syndrome. Overhydration may result in an increased catabolic state for its contribution to inflammation [151]. Chronic fluid retention may lead to gastrointestinal edema and weakens the regional defense capacity against bacteria in bowels. The bacteria, which penetrate into the blood stream, release endotoxins that activate leukocytes, which in turn release cytokines, including IL-1, IL-6, and TNF-α, and provoke and inflammatory cascade [152, 153].

Metabolic Complications and Peritoneal Dialysis

Patients on CAPD are prone to hyperglycemia, dyslipidemia, and hyperhomocysteinemia and have a high risk of cardiovascular death. These metabolic complications can be treated with diet, glycemic control, and lipid-lowering medications. A Chinese study reported 29% of the nondiabetic patients became hyperglycemic after initiation of PD and half of them had elevated glucose levels later than 3 months of PD. Forty and 61% had increased total cholesterol and triglycerides, respectively, and 33% had both hyperglycemia and dyslipidemia. After enforcing strict dietary control, hyperglycemia and hyperlipidemia decreased significantly. This suggests a high prevalence of metabolic complications in PD patients [154]. Sixty-seven patients were enrolled in a study on different combinations of dialysis solution with the first group using only glucose solution, the second group using glucose and amino acid solution, and the third group using glucose and icodextrin. No significant differences in the levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, lipoprotein a, or lipoprotein b were found between the three groups [155].

Statins show beneficial effects on serum lipids and thrombogenesis in various groups of patients [156]. Two interacting processes initiate atherosclerosis: endothelial dysfunction and lipid accumulation. Dysfunctional endothelium promotes atherosclerosis through vasoconstriction, platelet activation, leukocyte adhesion, thrombogenesis, inflammation, smooth muscle cell proliferation, and collagen breakdown. Hypercholesterolemia increases the expression of endothelial adhesion molecules, increased platelet adhesion, and aggregability and augments vasoconstriction. The extrinsic coagulation pathway (tissue factor [TF], tissue factor pathway inhibitor [TFPI]), fibrinolysis (thrombin activatable fibrinolysis inhibitor [TAFI]), and platelet aggregation are upregulated in uremic patients on CAPD. CAPD patients exhibit a more atherogenic lipid profile than hemodialysis patients [157]. Cardiovascular death is a major cause of dropout from PD in both developed and developing countries. HMG-co-enzyme A reductase inhibitors have been proven effective in the treatment of hypercholesterolemia [158, 159]. Statins also have a number of additional pleiotropic effects including improved endothelial function, enhanced fibrinolysis, and antithrombotic action, and it has been suggested that simvastatin is safe, can effectively reduce total and low-density lipoprotein cholesterol, and independently,modulate the blood coagulation cascade, which might reduce the risk of thrombotic complications in CAPD patients [160].

Vitamin D, Calcium, Phosphorous Metabolism, and Bone Disease

Evidence suggests that 25 dihydroxy vitamin D3 and 1,25 dihydroxy vitamin D3 contribute to the bone health of patients with CKD. Bone disease is associated with substantial increase in fracture rate, seen in 5–10% of the population [161, 162]. However, there is a scarcity of data on vitamin D status and parathyroid hormone levels in CAPD patients in developing countries. A study of serum levels of 25 dihydroxy vitamin D3 done in South India has shown that most dialysis patients on CAPD have vitamin D deficiency, as shown by a mild decrease of 15–30 ng/mL in 33.3%, 7–15 ng/mL decrease in 27.7%, and less than 7 ng/mL in 22.2%. The mean iPTH level was 159.7 pg/mL. The mean serum calcium was 8.6 mg/dL, mean phosphorous was 4.5 mg/dL, and mean alkaline phosphatase level was 97 IU [134].

Another study from Slovenia found the highest mean of 25(OH) D in low transporters (12–38 nmol/L), followed by low-average transporters (15–50 nmol/L), high-average transporters (3–66 nmol/L), and high transporters (6–35 nmol/L). The difference in 25(OH) D levels between patients with different peritoneal membrane transport status was not significant. This study showed that 25(OH) D levels in Slovenian patients were low [163]. There is a lower prevalence of hyperphosphatemia in Chinese PD patients, even in the anuric group [164]. Three main methods of

controling hyperphosphatemia are dietary phosphorous restriction, oral administration of phosphorous binders and dialysis. A low phosphorous diet is difficult to achieve if a protein intake of 1.0–1.2 g/kg/day is to be maintained, since protein intake offers a significant load of phosphorous of 18–36 mmol/day. A session of hemodialysis removes 20–40 mmol of phosphorous, and 10–12 mmol/day is removed by peritoneal dialysis [165]. Sevelamer hydrochloride, a drug free of calcium and aluminum, has a high efficacy in lowering serum phosphorus concentration in CAPD patients in addition to improving lipid profile [166].

Markers of bone turnover are iPTH, bone-specific alkaline phosphatase, serum-based immunoassay for bone resorption marker C-terminal cross-linking telopeptide of type I collagen (serum CTX), and the intact collagen I amino-terminal propeptide (PINP) assay [167]. Couttenye et al. recently demonstrated that a low bone alkaline phosphatase (BAP < 27 U/L) and a low iPTH (<150 pg/mL) had good sensitivity and specificity for adynamic bone disease, the most frequent form of low turnover renal osteodystrophy [168].

In a study from Iran involving 47 patients on CAPD for more than 6 months with adequate dialysis of $Kt/V > 2.1$, the mean iPTH level was 102.47 ± 92.64 pg/mL in PD patients. The mean alkaline phosphatase level was 103.30 ± 48.95 mg/dL, mean calcium 9.26 ± 0.47 mg/dL, and mean phosphorous 4.76 ± 1.16 mg/dL [169]. It showed relatively lower serum alkaline phosphatase and serum phosphorous in PD patients, whereas hypercalcemia was more frequent (11.3%) in PD than HD.

A study of bone mineral density (BMD) and serum markers of bone turnover in 65 patients (45 females and 20 males) on PD for a mean of 40.3 ± 23.2 months, with 15 of the women being premenopausal and 30 being postmenopausal, was analyzed [170]. These patients were dialyzed using 1.5–2 L bag exchanges four times a day. The calcium in the PD bath was 3.5 mEq/L in 89.2% of the patients and 2.5 mEq/L in the rest. To control serum phosphorous, 89% of the patients were taking calcium-containing phosphate binders and 37% were taking low doses of vitamin D analogs. Six patients (9.2%) had experienced 11 fractures: 3 at the pelvis, 2 at the femoral neck, 3 at the ribs, 1 metatarsal, 1 metacarpal ,and 1 at the wrist. The total bone mineral content was significantly lower in women than in men ($2{,}066.2 \pm 467.9$ g versus $2{,}664.8 \pm 451$ g, respectively, $p < 0.0001$). The BMD T scores in the osteopenia/osteoporosis range were observed at the lumbar spine in 58.4% and the femoral neck in 78.4% of patients on PD. The mean T score at the lumbar spine and femoral neck were not significantly different between men and women or between pre- and post-menopausal women. Patients with BMD T scores in the osteoporosis range at both regions had increased serum iPTH levels compared to patients in the osteopenic/normal range. Bone mineral content in the whole skeleton correlated negatively with iPTH.

This study found a lack of correlation between markers of bone turnover and bone mass measurements, except for the weak correlation found between serum iPTH levels and total bone mineral content [170]. It seems that measurements of bone mass at sites of pure cortical bone (distal radius) are better sites to determine bone loss and find correlations with bone turnover, than sites of mixed bone – cortical and trabecular – such as the femoral neck or with predominantly trabecular bone, such as the lumbar spine [171].

Anemia

Anemia is considerably less in PD patients compared to HD patients. As malnutrition is very common in PD patients in developing countries, anemia could be an accompaniment to it. In our population of CAPD patients in South India, 33.3% had hemoglobin more than 10 gm/dL, while only 6.5% of the hemodialysis group had similar hemoglobin levels [172]. A Bangladesh study of CAPD patients reported a hemoglobin level of 9.7 ± 1.48 gm/dL [11]. Randomized controlled studies demonstrating a survival benefit or improved cardiovascular outcomes are inconsistent regarding anemia management in PD. Data on peritoneal dialysis patients are limited. A minimum target hemoglobin level of 11 gm/dL, but not exceeding 12 gm/dL, is a rational target.

A proactive approach to anemia management that includes using increased iron supplementation, optimizing dialysis adequacy, and rational prescribing of erythropoietin is recommended to optimize hemoglobin concentration, improve clinical outcome, and reduce the overall costs [173]. As several generic forms of erythropoietin are available in developing countries in South Asia, and although reimbursement is available to a minority, intravenous iron-sucrose along with erythropoietin use is increasingly implemented for treatment of anemia. Occult GI blood loss due to hookworm infestation requires diagnosis and treatment in developing countries. Noncompliance with erythropoietin use is common in PD patients but did not correlate with PD exchange noncompliance. In the developing countries of South Asia, where a sizeable percentage of the patients are vegetarians, folic acid and vitamin B_{12} deficiency should be addressed while managing anemia.

CAPD in Diabetics with ESRD

Diabetic nephropathy is the leading cause of ESRD in the world, and a large number of diabetic ESRD patients are being accepted for renal replacement programs. In India, diabetes is the leading cause of ESRD among CAPD patients in most centers (51 and 78% at two centers) [139, 174]. PD penetration is predominant in patients with diabetes mellitus in Pakistan (57%), Bangladesh (63.77%), and Malaysia (50%) [11, 12]. This is because many of these patients are either elderly or have various co-morbid conditions, particularly coronary artery disease, and therefore are not suitable for renal transplantation. Chan et al. reported in 1987 that although diabetics on CAPD were significantly older than nondiabetics at their center, they had a comparable biochemistry [175]. Most of the diabetics in CAPD in their unit returned to work. They found good glycemic control irrespective of the route of administration of insulin. There was no progressive increase in cholesterol or triglycerides. The cumulative patient survival at 2 years was 86% and technique survival was 100%.

Wei et al. from Singapore reported their experience in 42 type II diabetics with ESRD on CAPD for a period of 18 months [176]. Blood glucose was controlled either by diet and hypoglycemic agents or insulin. The glucose control was similar in the three groups. These workers found no peritoneal membrane failure.

Diabetics on CAPD have been reported to have a greater prevalence of malnutrition than nondiabetics. Espinosa et al. reported that, while 91% of diabetics on CAPD had evidence of malnutrition, only 76% of nondiabetics had a similar problem ($p = 0.02$) [123]. According to these authors, moderate to severe malnutrition was more frequent in diabetics [123].

Lee et al. analyzed their diabetic ESRD patients on CAPD and HD. Diabetic CAPD patients had more hospital admissions, more days of stay in hospital, and higher withdrawal rates from dialysis compared to HD patients [177]. The technique survival was, however, similar in both CAPD and HD. The mortality was lower in CAPD than HD in patients younger than 50 years of age, while it was higher in CAPD than HD in patients more than 50 years of age. An interesting observation by Wu et al. was that diabetic patients on CAPD with poor glycemic control predialysis had increased morbidity and shortened survival [178].

The membrane transport characteristics of diabetics showed high and high-average status. The peritonitis rate was 0.63 episodes/patient-year with Gram-negative organisms being the major cause in a predominantly diabetic CAPD population from India [42]. Most of the patients had significant malnutrition at the initiation of CAPD. The median patient survival was 28 months, with diabetics showing poor survival [139]. CAPD was done predominantly in diabetics in Bangladesh [11]. The patient survival was 63% at 1 year, 48% at 2 years, and 31% at 3 years. The major cause of dropout was death due to cardiovascular and cerebrovascular complications.

Nephrology Manpower in Developing Countries

At present, in several developing countries, a medical doctor may graduate without having entered a dialysis unit or without having seen a hemodialysis machine or PD device. This attitude may exert negative effects: the roles of diabetes and hypertension as causes of renal diseases are probably underestimated by the general physician; patients are often referred late to renal units; and lack of information on renal replacement therapy limits the choice of the less expensive options of self- and home dialysis [119]. The gap between academic and clinical nephrology is one of the causes of the frustrations often described by dialysis doctors. Including renal replacement therapy in medical school curricula may be a useful tool to enhance interest and ensure participation in timely referral to nephrologists and in the choice of dialysis [180].

In a study looking at the attitude of physicians towards establishing and maintaining a PD program, 56.3% believed that follow-up of PD patients should be available in all dialysis centers, 55.2% would like to have a PD clinic at their center, and, in reality, only 13.8% had PD clinic at their centers [181]. Furthermore, 44.6% admitted to have no expertise in managing patients on PD, while 38.1% claimed that they did not have enough space in their dialysis centers to start a PD program. Hence, current practices concerning PD program in Arab countries are modest, and a new strategy is required to expand the PD program in all dialysis centers, including the latest technologies, such as automated PD machines and connectology.

The lack of trained nephrologists in nearly 20 countries in Africa to provide PD as a renal replacement therapy is hampering the growth of PD in Africa. Many countries in Africa have limited accessibility to PD because of the lack of availability of trained personnel, cheap dialysis fluid and accessories [99].

The emergence of clinical coordinators (nurses or dialysis technologists) employed by the dialysis industry in India has largely overcome the difficulties of training and retraining the patients and their relatives in the last decade. These

clinical coordinators are available for advice either in person or through telephone 24-h a day, 365 days a year, on a ratio of 1 coordinator for 40 patients. They are given special structured training for taking care of the chronic PD patients. They substitute for family members for performing dialysis, exit site care, supply of fluid and accessories, early peritonitis treatment, etc.

Future of PD in Developing Countries

The major challenge for developing countries is to make CAPD affordable for ESRD patients. A need for the patients from developing countries to finance their own treatments in the absence of health coverage is a significant hurdle. The use of 2 L $\times$ 3 exchanges/day has been introduced as a cost-saving measure in resource scarce countries. Local manufacturing facilities within developing countries has significantly reduced PD cost. Inclusion of PD in the health care coverage in developing countries will augment the growth of PD further in this globalization era.

Peritonitis incidence has decreased because of the better connectology; however, culture negative peritonitis remains a major hindrance to PD growth. Malnutrition and inflammation and cardiovascular disease require special attention to improve the outcome on PD in developing countries. Cost-effective biocompatible solutions and icodextrin use will improve the peritoneal membrane transport characteristics, which will have a major impact on patient survival. Adequacy is a question of affordability in developing countries and, hence, PD is offered at cheaper rates. Lastly, appropriate training programs for nephrologists, nurses, technologists, and physicians will enhance the growth of PD in developing countries as exemplified by the growth in China, India, Pakistan, Indonesia, Sudan, Bangladesh, the Middle East, and Eastern European countries.

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