Applied Peritoneal Dialysis

Improving Patient Outcomes

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To all my mentors and friends at the University of Santo Tomas, Faculty of Medicine and Surgery in Manila, Philippines, and Northwestern University Feinberg School of Medicine in Chicago, IL, who have, in one way or another, influenced and guided me to become the physician that I am.

To all the medical students, interns, and residents at Advocate Christ Medical Center and MacNeal Hospital, whom I have taught or learned from, especially those who eventually decided to pursue Nephrology as a career. To my parents and my brothers, without whose unwavering love and support through the good and bad times, I would not have persevered and reached my goals in life. Most specially to my two lovely and precious daughters Anastasia Zofia and Isabella Ann, whose smiles and laughter constantly provide me unparalleled joy and happiness, and my very loving and understanding wife Michelle, who has always been supportive of my endeavors both personally and professionally, and who sacrificed a lot of time and exhibited

unwavering patience as I devoted a significant amount of time and effort to this project. Truly, they provide me with motivation and inspiration.

Edgar V. Lerma, MD

This work is dedicated to The Home Peritoneal Dialysis Unit of the University Health Network in Toronto, the Jewel in the Crown of dialysis units, and also my second home. The dedication and expertise of the members of this unit makes my job easy.

I would also like to dedicate this book to my late mentor, Dimitrios Oreopoulos, who took me, someone with no experience or knowledge of peritoneal dialysis, into the Home Peritoneal Dialysis Unit family and taught me the ins and outs of the therapy with uncommon patience and forbearing.

Joanne M. Bargman, MD, FRCPC

Foreword

Having to start on dialysis is a devastating event for anybody with major impacts on lifestyle for both the person affected and for their family and carers. It is therefore not surprising that dialysis at home rather than in a hospital or dialysis centre is chosen by over half of people when given unbiased education and free choice. Peritoneal dialysis is the simplest way for people to have dialysis at home. In addition, there are many economic advantages to peritoneal dialysis in terms of healthcare costs and resources. Peritoneal dialysis, however, is underused in most countries independent of income status. One of the many reasons for this is lack of knowledge about and experience of peritoneal dialysis. This book, *Applied Peritoneal Dialysis*, fully addresses this educational need. The aims of the book are to be practical and enable the reader to deliver person-centred care to the patient on peritoneal dialysis. There is much more to peritoneal dialysis than prescribing different types of fluid. The selection of chapters covers all aspects of caring for someone on peritoneal dialysis – from catheter insertion to selection of dialysate, types of prescription, achieving volume control, and measuring quality of life to mention just a few. No treatment is without complications and there are chapters on specific peritoneal dialysis related complications such as infection and encapsulating peritoneal sclerosis, and chapters on those related to renal failure in general such as anaemia and bone disease. There is a really useful chapter on common questions. Special situations are also considered with chapters on global use of peritoneal dialysis, particularly in low income countries, acute kidney injury, urgent start, and paediatric use.

Peritoneal dialysis is practised globally. The international group of authors ensures that the book is relevant globally. *Applied Peritoneal Dialysis* is therefore an extremely useful addition to the books already available. Its clinical and holistic focus should result in hugely greater confidence in using peritoneal dialysis – and therefore ultimately its availability for and use by people requiring dialysis.

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Chapter 1
History of Peritoneal Dialysis

Ehsan Nobakht, Anita Mkrttchyan, and Niloofar Nobakht

Peritoneal dialysis (PD) is a home-based dialysis modality for patients with end-stage kidney disease (ESKD). For the past several decades, PD has provided flexibility in performing dialysis treatments helping ESKD patients maintain their everyday activities, work, and travel [1]. This flexibility also provides patients with the option to dialyze during sleeping or waking hours and effectively eliminates the need for frequent trips to outpatient dialysis centers. The concept of PD steadily evolved over the centuries through the creativity, dedication, and diligence of several key innovators. By learning about the evolution and history of PD, the reader will gain a more comprehensive understanding of the overall importance of PD and will develop an appreciation for the amount of research, innovation, and perseverance that lead to the current status of PD. This chapter will outline the history of PD and review a number of major scientific breakthroughs that have collectively shaped how PD is currently practiced.

Peritoneal dialysis has its origins in early civilization when the presence of the peritoneum was first discovered. Observations of the peritoneal cavity date back to ancient Egyptian records of animal dissection and are described in the Ebers Papyrus, written in 1552 B.C., as a definitely outlined cavity in which the viscera are somehow suspended [2, 3]. Despite these ancient discoveries, the knowledge and understanding of the explicit structure and functions of the peritoneal membrane remained very limited until the late nineteenth century, when the effect of the discovery of cells began feverishly reverberating throughout medicine and physiology [2]. In early Greek descriptions, physicians like Galen recognized the

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peritoneum in the abdomen of injured gladiators. The word peritoneum is derived from the Greek word *peritonaion*, in which *peri* means "around" and *ton* means "to stretch" [4].

The very first perception of peritoneal dialysis is thought to have occurred in the 1740s from an early surgeon by the name of Christopher Warrick in England who attempted to perform a novel treatment. At that time, Warrick was treating a 50-year-old woman with severe ascites by installing claret wine and Bristol water into her peritoneum with a leather pipe. After the patient recovered successfully, Reverend Stephen Hales wrote about the treatment and proposed that two trochars could be used to allow for in and out lavage of the ascitic fluid [4]. In 1862, Friedrich Daniel von Recklinghausen published information on the peritoneal membrane's cellular components and anatomy for the first time [5]. Later in 1877, a German investigator by the name of G. Wegner explained the idea of peritoneal ultrafiltration. Wegner used animal models to permeate hypertonic solutions made of glycerin and salts to demonstrate increased concentration of the drained peritoneal fluid. Building upon this, he also explained how changing the sugar solution could alter the peritoneal membrane [6].

In 1884, two Englishman, Ernest Henry Starling and Alfred Herbert Tubby, discovered that the peritoneal fluid can be bidirectional and that the removal of fluid from the peritoneum was affected by the quantity of membranal blood vessels. In 1918, Desider Engel, working in Prague, demonstrated that proteins can transport through the peritoneal cavity. A year later, in 1919, M. Rosenberg discovered that the concentration of urea in the blood was equal to that in the peritoneum. This, he concluded, proved that urea could be removed from the body using peritoneal dialysis. Then in 1923, Dr. Tracy J. Putnam used dog models to demonstrate that the peritoneum was a natural "dialyzing membrane" [7].

Simultaneously in 1923, a researcher at the University of Wurzburg named George Ganter was trying to determine how the peritoneum could be effectively utilized to dialyze actual patients in a clinical setting. To implement his idea, Ganter first conducted animal experiments and began by ligating the ureters of guinea pigs. He would inject a saline solution into their peritoneal cavity, where it would dwell for several hours before it was drained. He applied the same technique to treat his first patient, a young woman who presented with ureteral obstruction and uterine cancer. Ganter instilled varying volumes of a saline solution in the patient's peritoneum (1 to 3 liters per fill) until her blood chemistry levels normalized, and she was discharged home [4]. However, the patient subsequently died. Ganter concluded that PD therapy needed to be continued consistently for the patient to survive. Through his comprehensive research efforts, Ganter introduced several impactful concepts and techniques related to the treatment of patients on PD that are still being used today such as the need for sterile solutions, the modification of ultrafiltration by changing the glucose concentration, and the requirements of peritoneal access. In addition, he elaborated that the risk of infection would hinder the procedure and the time and volume of the dwell would determine solute removal. Ganter's research underpinned a foundation of understanding for the future of PD [4].

Despite these early advances, access to the peritoneal cavity remained challenging. In the early 1920s, Stephen Rosenak and P. Sewon created a metal catheter for

the infusion of solution into the peritoneal cavity that helped alleviate some of the existing difficulties maintaining adequate outflow due to the improper position of the previous simple hollow needle being utilized by Ganter. One of the milestones in the history of PD occurred at the Wisconsin General Hospital in 1936. A group of physicians headed by J.B. Wear, I.R. Sisk, and A.J. Tinkle performed PD on a patient who had presented to them with urinary obstruction. For the first time ever documented, consistently performed PD successfully used to treat kidney failure secondary to urinary obstruction. This trial demonstrated that patients can safely and successfully be treated with peritoneal dialysis. After World War I, PD was being used to treat acute kidney failure by German investigators [4].

In the mid-1940s, Dr. P.S.M. Kop, who was an associate of Willem Kolff in Holland working with hemodialysis at the time, quickly turned his attention to the exciting new dialysis modality of PD. Kop built a PD system that integrated gravity, allowing for the dialysis solution to infuse into the peritoneal cavity more easily. There were many different pieces of equipment used for this device, including large glass catheters to infuse the dialysate solution into the peritoneal cavity, latex rubber tubing to transport the dialysate solution to the patient, and large porcelain containers to store the dialysate solution. Kop and his group successfully treated 21 patients using this new integrated system, most of whom survived [4]. During World War II, the battlefield quickly became a lucrative opportunity for advancing dialysis research by treating injured or sick soldiers through PD. This research opportunity first presented itself to two physicians at Beth Israel Hospital in Boston, Massachusetts, in 1945, when Dr. Howard Frank and Dr. Arnold Seligman turned to PD as a potential strategy for treating acute kidney failure on the battlefield. The system that they utilized was like that of Kop and addressed many previously encountered technical issues, such as modifying the solution to best fit each individual patient's clinical needs and optimal flow rates. In addition, they utilized two catheters to reduce the likelihood of obstruction during the outflow portion of the procedure and used large sterile bottles to minimize the chances of contamination and related infections [Figs. 1.1 and 1.2]. That same year, they were able to successfully treat a patient with acute kidney injury caused by an overdose of sulfa drugs using this modified system [8]. This became one of the main turning points in the advancement of peritoneal dialysis.

Even with these improved systems, access to the peritoneal cavity still remained a barrier to achieve optimal outcomes, with the most common approach employing metal trochars left in place for hours at a time. These trochars, though effective, often contributed to intra-abdominal infections, and it was evident that further improvements in peritoneal access were required. In 1952, Arthur Grollman from the Southwestern Medical School in Dallas, Texas, described a new approach that he had researched. This new approach utilized 1-liter containers attached to a plastic tube; this plastic tube was then connected to a polyethylene catheter. The polyethylene catheter was groundbreaking for two main reasons: first, the tube was more flexible and could safely be left in place for longer periods of time, and second, Grollman had installed tiny holes at the intraperitoneal portion of the catheter, which kept the patient's body tissue from hindering the drainage. Overall, this

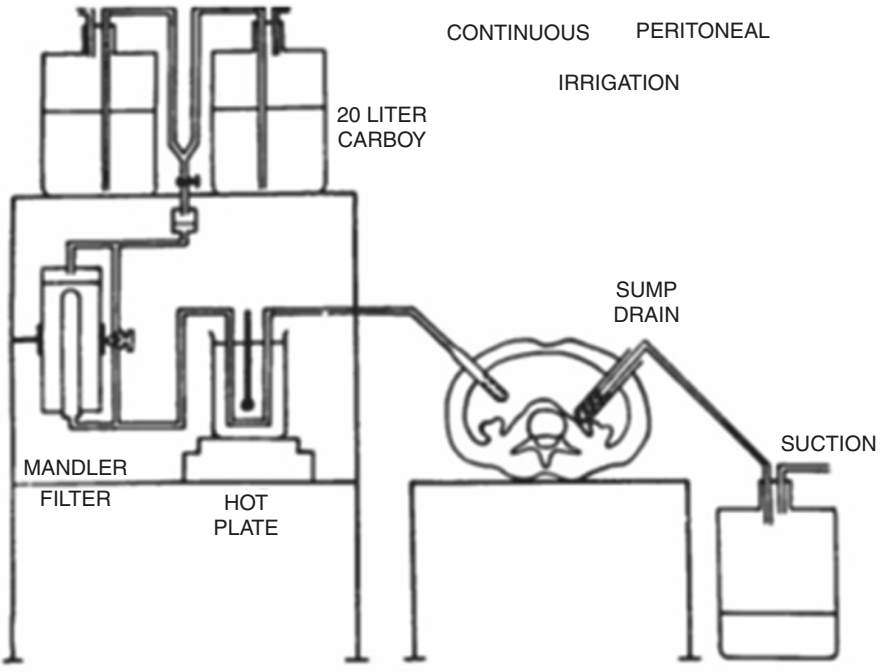

Fig. 1.1 Continuous open peritoneal irrigation by Frank, Seligman and Fine

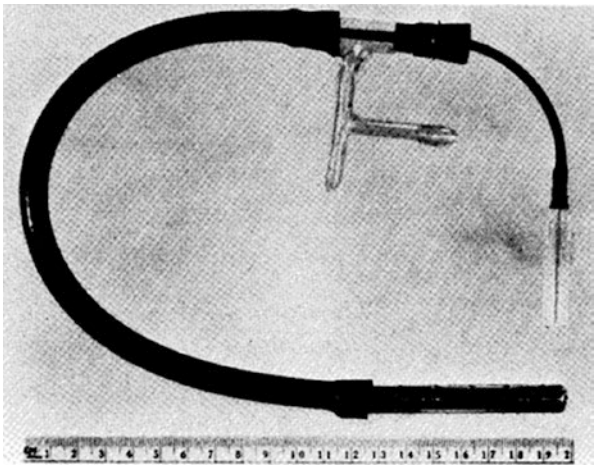

Fig. 1.2 The flexible sump-drain of Frank, Seligman and Fine, composed of ordinary rubber glass and stainless steel

allowed for better inflow and outflow of the fluid throughout the abdomen and peritoneum [9]. Furthermore, Grollman proposed that the fluid should remain in the abdomen for 30 minutes and then be drained into the sterile storage container [4].

In 1959 at the Naval Hospital in San Francisco, California, a research team led by Paul Doolan was also looking into PD under battlefield conditions. Doolan and

his group created a modified version of Grollman's groundbreaking polyethylene catheter. This new catheter allowed for long-term usage while maintaining its flexibility. In addition, it had several side holes and grooves that provided improved drainage and further minimized drain hole blockage. Around this same time, Richard Ruben, who also worked at the Naval Hospital and was finishing his tour of duty, was asked to treat a woman with kidney failure. Ruben decided to initiate this patient on PD with Doolan's new and improved catheter. After the patient received dialysis, her condition dramatically improved, but once it was stopped, she would begin to deteriorate again. After examining this pattern, Ruben suggested that the patient could go home for the week but should return to the center on weekends to receive dialysis. They continued this pattern of treatment for 7 months and only had to replace the catheter once during this period [10].

In 1959, Dr. Morton Maxwell at the Wadsworth VA Hospital in Los Angeles, California, analyzed the research already conducted on PD by Frank, Seligman, and Grollman and wanted to build a more simplistic system for treating acute kidney failure. He wanted to create a system that was easy to connect, utilize, and disconnect by medical professionals. Also, with the goal of minimizing infection risk, he used fewer tubing connections [11]. Maxwell reached out to a local intravenous solution manufacturer and commissioned them to design a customized glass container that would hold the PD dialysate and would be attached to a plastic tubing and a polyethylene catheter. This new system consisted of instilling 2 liters of peritoneal solution into the peritoneal cavity, leaving the solution to dwell for 30 minutes and then draining the peritoneal solution back into the original container, repeating these exchanges as necessary [4]. These exchanges were done continuously until the patient's blood chemistry levels were normalized. Using his method, Maxwell was able to successfully treat many patients. His work was published in the "Peritoneal Dialysis: 1. Technique and Applications" article in 1959, demonstrating the medical importance and simplicity of his procedure, which became known as the "Maxwell technique." This was a tremendous accomplishment in the field of PD, as dialysis was no longer limited to specific hospitals that already had the necessary, specialized equipment in place. PD could now be done in any hospital which had the required basic supplies [4].

In late 1959, Fred S.T. Boen published a thesis on PD in Holland. In his thesis, he discussed the advantages of PD, highlighting the simplicity of the procedure and emphasizing that the PD minimized the likelihood of sudden blood volume changes, allowed for altering the procedure by adjusting the dialysate for better management of volume and electrolytes, and had the potential to be safely utilized as a long-term dialysis modality. He described the influence of glucose concentration on the ultrafiltration [4]. Boen was invited by Dr. Belding Scribner to continue his research at the Northwest Kidney Centers in Seattle, Washington. Accepting the offer, Boen relocated to Seattle in 1962, where he developed an automatic peritoneal dialysis system that operated overnight without requiring the supervision of a physician [12]. His system included 20- to 40-liter bottles for the dialysate, a capped latex catheter, sump drainage that held more fluid, larger infusion bottles for repeated infusions, and a drainage monitor to measure the amount of fluid being pulled out

from the patient. Even with these new developments, Boen still had serious concerns about peritonitis. The new catheter he created was an open system that could significantly increase the patient's risk of infection, so he abandoned this technique and went back to the earlier system of removing the catheter at the end of each procedure. Boen is considered as one of the founding fathers in the field of PD [4].

In 1963, Dr. Henry Tenckhoff working at the University of Washington joined Boen's group and expressed his concerns about the difficulty of transporting 40-liter dialysate bottles to the patient's home for treatments [4]. He was able to eliminate this arduous requirement by installing a water still inside the patient's home to get sterile water. The sterile water was then mixed with the dialysate concentrate, which was cycled in and out of the peritoneum by a controller unit. Although this simplified the procedure, the catheter still needed further modifications. Tenckhoff improved his design by customizing the catheter that was previously designed by Wayne Quinton and Dr. Russell Palmer. He shortened their siliconized catheter and suggested that there can be a straight and curled design to it. Additionally, he added Dacron felt cuffs to assist in sealing the openings through the peritoneum. Lastly, he designed and added a metal trochar to help place and position the catheter more easily [13]. Following these modifications, Tenckhoff's new system was complete and ready to be used for performing PD on patients.

Norman Lasker, the acting director of the Renal Division at the Seton Hall College of Medicine in New Jersey, had visited the Seattle group to gain better insight of the new automated systems that had been created by Tenckhoff. After seeing his system, Lasker was concerned about the difficulty of managing a system like this at his own group. To address this, he started working to create a simpler system that utilized 2-liter sterile glass bottles, a device to warm the dialysate solutions, a device to measure the volume of infused dialysate, and a drainage bag. He soon began treating patients in their homes with his new automated cycler device with great success [4]. Shortly after Lasker had created and tested his new automated cycler, Dimitrios Oreopoulos, who had recently been tasked with running a four-bed intermittent PD program at the Toronto Western Hospital, ordered several "Lasker's cyclers" for his home patients, as he had been very impressed with Lasker's design. Oreopoulos's program quickly became very successful, thanks to these cyclers, and his program expanded to more than 70 patients on intermittent dialysis, making it one of the largest PD programs in the world at that time [4].

In 1975, Dr. Jack Moncrief established an in-center hemodialysis program in Austin, Texas, where a patient by the name of Peter Pilcher was admitted to begin his hemodialysis treatments. After Peter's fistula would not function, it became clear that he was not a viable candidate for hemodialysis. Moncrief suggested that the patient move to Dallas, where he could transition to PD. When the patient refused, Moncrief decided to join forces with Robert Popovich, a biomedical engineer, to develop a PD system to save the patient's life. Their system included a 2-liter bottle with tubing and a Tenckhoff catheter attached. In addition, Popovich recommended that five 2-liter exchanges should be performed to normalize the patient's blood chemistry levels. Therefore, the fluid would need to remain in the peritoneum for a total of 4 hours and then be drained. This process, hypothesized

and tested by Moncrief, Popovich, and another researcher named K. D. Nolph, became known as "continuous ambulatory peritoneal dialysis" (CAPD) [14]. Eventually, Dr. Oreopoulos adopted this new technique and started a CAPD program at his practice in Toronto as well, with a few minor modifications. He changed the sterile glass dialysate bottle to a sterile plastic polyvinyl chloride (PVC) bag for easy transport, which resulted in an overall decrease in infections, and was met with positive feedback from patients [15]. Furthermore, Oreopoulos collaborated with Baxter to design a PVC bag with a spike at the end for a more sterile, secure, and easier way to attach the bag to the tubing [4].

Continuing to improve upon their original design, Moncrief and Popovich created an ultraviolet exposure system located at the spike of the bag to help decrease the chances of infection even further. In Italy, Dr. Umberto Buoncristiani created the flush-before-fill mechanism, known as the "Y-system." This system allowed for bacteria to be rinsed away before the new dialysate was instilled into the patient, significantly reducing the chances of peritonitis [16]. This "Y-system" was eventually changed to a double-bag system for the purpose of requiring only one connection. In 1978, the Food and Drug Administration (FDA) approved the CAPD procedure, and in the following year, Baxter brought to the market the CAPD system, which included an antiseptic solution for the maintenance of the bag and spike, a Luer lock made out of titanium for catheter connection, tubing with a one-sided spike at the end, and solution bags [4]. In 1981, Dr. Jose Diaz-Buxo and Dr. D. Nakayama developed a hybrid system called "continuous cyclic peritoneal dialysis" (CCPD). This system utilized a cycler device that instilled and drained dialysate on a continuous basis at night with a 1- to 2-liter dwell during the day. It allowed for the peritoneum to be in continuous contact with dialysate fluid for 24 hours [4].

In 1983, Medicare legislation permitted PD to be reimbursed at a rate indistinguishable from that of in-center hemodialysis. As news of this legislation spread, PD symposiums began to be held worldwide, giving clinicians and researchers opportunities to present PD clinical research, to share and discuss physician and patient experiences with PD, and the benefits of PD [4]. At the end of the 1980s, PD cyclers continued to expand and improve in their hardware components and layout, making them less bulky, quieter, and most importantly safer. Cyclers such as PCS 2000 produced by Fresenius, Pac-X and Pac-XTRA by Baxter, and PD T by Gambro all incorporated these changes [17]. The machines allowed for utilization of disposable materials and personalization of dwell time and volume to fit the patient's needs.

Patients could dialyze with a wide range of treatment schedules such as intermittent PD (IPD), nightly intermittent PD (NIPD), CCPD, and tidal volume prescription (TPD). Then in 1994, HomeChoice was produced by Baxter. This machine was portable and weighed 12 kg, which was lighter than the previous machines. Also, its new volumetric pumps allowed for accurate exchanges [17]. The next edition, HomeChoice Pro, allowed for a 60-day treatment recording and storage on a 2 Mb data card. This helped healthcare providers better manage patients' therapy, by utilizing the card to retrieve historical data on patients' treatments and assess the adherence to therapy. As other companies witnessed the success of these features, they started to adopt similar features on machines such as Serena, Sleep Safe, PD

100 T, PD 101, and PD 200. The latest edition of these machines incorporated a 60- to 180-day treatment recording period and the opportunity to prescribe exchange fill volume, total dialysate volume, and tidal time [17].

Machines like Serena and Sleep Safe allowed for decision-making on the number of cycles and dwell time. In addition, Sleep Safe had the ability to detect the usage of wrong solution bags and displayed the percentage of glucose per cycle. They had different ways of moving and measuring volume. Serena utilized pressure chambers which had a gravity-based system and allowed for prescription in breakpoint modality, preventing spending a large amount of time at the end of the exchange and its enhanced drainage [17]. Sleep Safe and HomeChoice Pro utilized hydraulic and pneumatic pumps and used a volumetric system. All machines that were being produced came with a built-in battery that allowed for treatment suspension and data storage in case of a power outage. With the enhancement of software technology, cyclers were beginning to get programmed based on patient's treatment and personal data [17].

Recent cyclers such as HomeChoice Claria, Amia, Kaguya, and Sleep Safe consist of bidirectional communication properties and new treatment schedules. The great transformation of PD happened with the bidirectional communication between the patient's cycler at home and the medical care team at a given facility. This feature can be utilized with the HomeChoice Claria cycler [17]. It has the Sharesource portal, in which medical professionals can adjust dialysis prescriptions, obtain treatment data, and resolve problems by simply logging into the portal. Lastly, Sharesource provides opportunities for remote patient management (RPM), which enhances the quality of treatment, reduces in-center patient visits and costs, and decreases technique failure and patient dropout rates [17].

The demand for pursuing and utilizing PD as a dialysis modality continues to grow rapidly, and PD is now universally recognized as a very safe and cost-efficient dialysis modality. As PD continues to advance and flourish, it is important to understand the history of PD and to appreciate all the innovations, trials, and tribulations that took place in order for PD to progress to the current status. Thanks to the dedication, perseverance, and creativity of many individuals throughout history, PD has become a mainstay of modern home dialysis therapy and has given ESKD patients a safe, convenient, and effective way to receive life-saving dialysis treatments in the comfort of their own home.

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Chapter 2
Physiology of Peritoneal Dialysis

Chang Huei Chen and Isaac Teitelbaum

Peritoneal Anatomy

The peritoneum is the serosal membrane that lines the peritoneal cavity. It has a surface area similar to that of body surface area, ranging 1–2 m^2 in adults. It consists of two parts: the parietal peritoneum which covers the abdominal wall and the diaphragm and the visceral peritoneum which covers the intra-abdominal organs. The parietal peritoneum accounts for 20% of the total peritoneal surface area. It receives blood supply from the lumbar, intercostal, and epigastric arteries and drains into the inferior vena cava. The visceral peritoneum accounts for 80% of the total peritoneal surface area. It receives blood supply from the mesenteric artery and drains into the portal system. The total peritoneal blood flow is estimated to range from 50 to 100 mL/min [1].

Peritoneal Membrane Histology

The peritoneal cavity is lined by a monolayer of mesothelial cells equipped with microvilli and covered by a thin layer of peritoneal fluid. The peritoneal fluid provides lubrication and allows free movement of visceral organs during respiration and peristalsis [2]. The mesothelial cells modulate the peritoneal microcirculation

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by secretion of vasodilators, e.g., prostaglandins, nitric oxide, and the vasoconstrictor endothelin. The mesothelial cells play an important role in the initiation of the local immune response through secretion of chemokines that regulates leukocyte infiltration [3]. Underneath the mesothelium is the interstitium, which is comprised of a gel-like matrix containing adipocytes, fibroblasts, collagen fibers, capillaries, nerves, and lymphatic vessels [2, 4].

Models of Peritoneal Transport

As solute and water move across the peritoneum from blood into the peritoneal cavity, they encounter six resistance barriers: the unstirred fluid layer overlying the endothelium of the peritoneal capillaries, the capillary endothelium, the endothelial basement membrane, the interstitial space, the mesothelium, and the unstirred fluid layer overlying the mesothelium [5]. Of these barriers, the two unstirred fluid layers and the mesothelium are thought to offer negligible resistance to solute and water transport; the major transport barrier is the capillary endothelium [6]. Several models have been proposed to explain the physiology of peritoneal transport, which we will discuss in details below.

The Three-Pore Model

Based on his observations regarding the nature of the transcapillary movement of solutes and water into the peritoneum, late Bengt Rippe postulated the existence of three pores of different sizes in the capillary endothelium. The "large pores" with a functional radius of 200–300 Å (20–30 nm) refer to wide interendothelial clefts. They allow transport of macromolecules such as albumin and other proteins and account for approximately 5–8% of the total pore area. The "small pores" with a functional radius of 40–60 Å (4–6 nm) refer to smaller clefts between endothelial cells. They allow transport of water and small solutes such as sodium, potassium, urea, and creatinine. Approximately 90–93% of the total pore area consists of the small pores, and they are responsible for the majority of fluid transport. Finally, Rippe postulated the existence of "ultrapores" with a functional radius of 2–4 Å (0.2–0.4 nm) which allow transport of water only. This prediction, made entirely of the basis of physiological observations, predated the discovery of aquaporins. The ultrasmall pore has since been demonstrated to be aquaporin 1 (AQP1) [7]. The ultrapores account for about 2% of the total pore area but can contribute up to 40% of the total capillary ultrafiltrate [6, 8, 9].

The Pore-Matrix Model

As noted above, the large and small pores are both interendothelial cell clefts. The pore-matrix model states that it is the density of the glycoprotein matrix on the luminal side of the cleft that determines whether a particular cleft functions as a large or small pore. At clefts endowed with a dense glycoprotein matrix, only small solutes can pass through the interendothelial space; these clefts function as "small pores." In contrast, clefts endowed with only a loose glycoprotein matrix allow both small solutes and macromolecules to pass through the interendothelial space; these clefts function as "large pores" (Fig. 2.1). Thus, in this model, there are no defined "small pores" or "large pores"; the difference in transport characteristics depends on the density of the glycoprotein matrix that fills the interendothelial space [10].

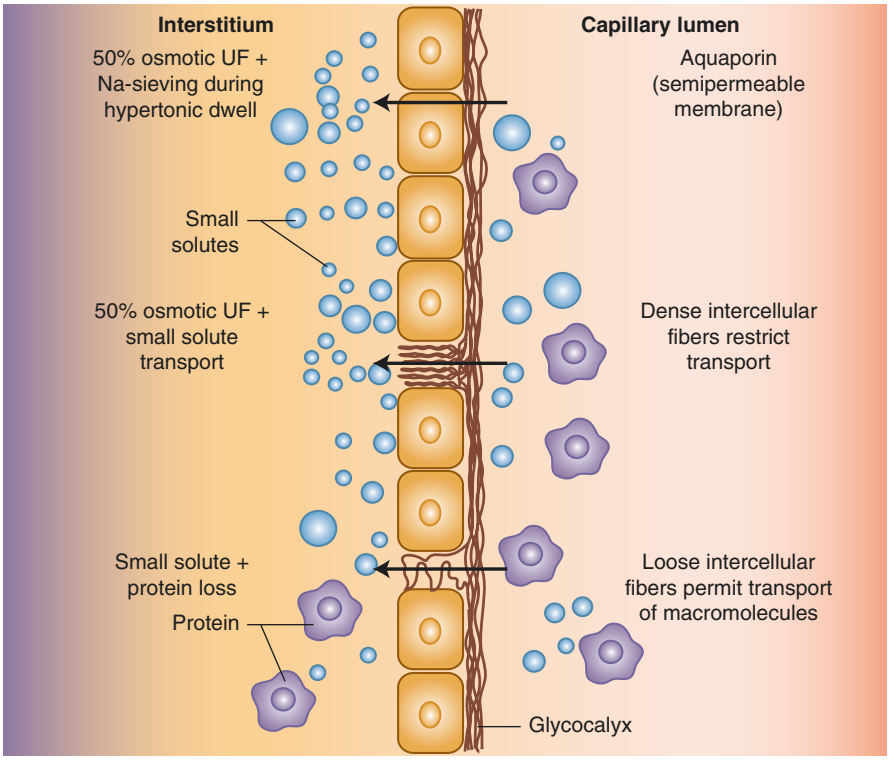

Fig. 2.1 Pore-matrix model. (Modified from Flessner [10])

The Distributed Model

In the distributed model, capillaries are assumed to be distributed uniformly throughout the interstitium at variable distances from the mesothelium. Solute transport is affected by the distance of each capillary from the mesothelium and the overall density of the peritoneal capillaries. The distance of each capillary from the mesothelium determines its relative contribution. The collective contribution of all the peritoneal capillaries determines the effective surface area for solute transport (Fig. 2.2). Therefore, two patients with the same anatomical peritoneal surface area could have different peritoneal vascularity and thus different effective peritoneal surface areas for solute transport. Within a given patient, the effective peritoneal surface area could vary depending on the clinical scenario. For example, inflammation, as seen in peritonitis or after prolonged exposure to high dextrose-containing fluid, increases vascularity and leads to increased effective peritoneal surface area. In this model, the degree of vascularity within the peritoneal membrane is the major

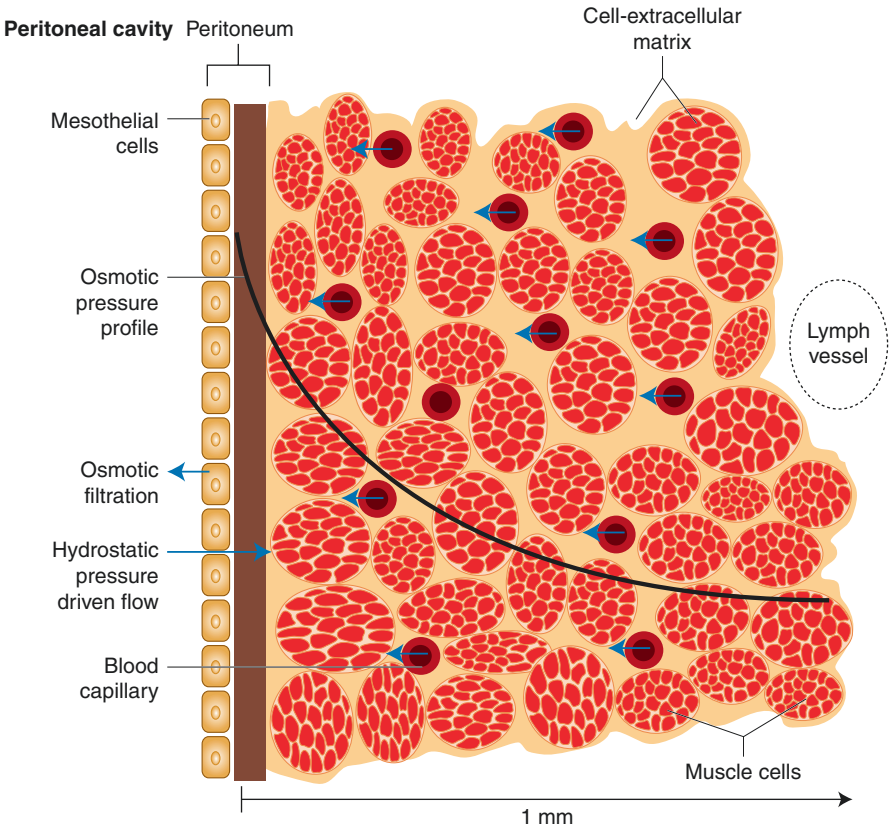

Fig. 2.2 Distributed model. (Modified from Flessner [10])

determinant of solute transport [9, 11, 12]. It must be emphasized that these three models of peritoneal transport are not mutually exclusive. Rather, they should be viewed as complementary with one another, forming a cohesive whole.

Physiology of Peritoneal Transport

Solute Transport

During peritoneal dialysis (PD), solutes are transported bidirectionally between the peritoneal capillary blood and the peritoneal cavity, mainly by diffusion and to a lesser extent by convection. Diffusion refers to the movement of solutes from a region of high concentration to a region of low concentration. For example, diffusion of urea from capillary blood to the peritoneal cavity is at its maximum at the start of a PD dwell, when the concentration of urea in the dialysate is zero. With ongoing diffusion, the concentration gradient across the peritoneal membrane diminishes. In addition to the concentration gradient, other factors affecting diffusion of solutes during PD include the total peritoneal surface area that is in contact with the dialysate, peritoneal vascularity, molecular weight of the solute, and intrinsic permeability of the peritoneal membrane. In clinical practice, increasing the fill volume recruits more peritoneal membrane to be in contact with dialysate, which then improves solute clearance. Keshaviah and colleagues studied the relationships between dialysate fill volume and the peritoneal transport constant (KoA) of small solutes in patients on chronic dialysis. They found that the KoA of urea, creatinine, and glucose increase in an almost linear fashion with fill volumes between 0.5 L and 2.0 L [13]. The authors attributed the increase in KoA to recruitment of more peritoneal surface area with larger fill volume.

Vasodilatory agents augment peritoneal solute clearance by increasing peritoneal capillary surface area and vascular permeability. Administration of intravenous dopamine or intraperitoneal nitroprusside has been shown to improve creatinine and urea clearances in animal models [14, 15]. Acute peritonitis is associated with an increase in small-solute transport, as a result of inflammation-induced increases in peritoneal capillary surface area and vascular permeability [16–18]. Permeability of the peritoneal membrane is an intrinsic property dependent on the number of pores per unit surface area, the density of the peritoneal capillaries, and the distance between capillaries and the mesothelium [1, 19]. It is different in each individual patient and can be characterized by using the peritoneal equilibration test.

Convective transport refers to the movement of solutes as a direct result of fluid movement into the peritoneal cavity (i.e., solvent drag). The magnitude of convective transport of a given solute is determined by transperitoneal ultrafiltration (UF) and the sieving coefficient of that solute [19]. The sieving coefficient is the fraction of the solute which passes through the membrane with the water flow, ranging between 0 and 1. Because no solutes pass through the aquaporins, there is no

convective transport at these sites. On the other hand, small solutes do move through the small and large pores resulting in significant convective transport.

Ultrafiltration

Ultrafiltration in PD is achieved either by creation of an osmotic gradient across the peritoneal membrane using crystalloid agents (e.g., dextrose, amino acids) or by inducing water flow with a colloidal agent (e.g., icodextrin). When using a crystalloid agent, the osmotic gradient is maximal at the start of a PD dwell; it diminishes with time due to dilution of the dialysate osmotic agent concentration and the absorption of the osmotic agent into lymphatics and tissues. This gradient can be maximized by using dialysate with a higher concentration of the osmotic agent (i.e., a higher dextrose concentration). Using 1.36%, 2.27%, and 3.86% anhydrous glucose dialysis solutions (equivalent to 1.5%, 2.5%, 4.25% dextrose solutions, respectively) for 6-hour dwells in patients on continuous ambulatory peritoneal dialysis (CAPD), Heimbürger and colleagues demonstrated a positive relationship between net UF rate and glucose concentration in the dialysis solution [20]. If icodextrin, a large molecule with a molecular weight (MW) of 13,000–19,000 Da, is used as the osmotic agent, the absorption is much slower compared to glucose (MW 180 Da), resulting in a more sustained osmotic gradient and UF.

In addition to the osmotic gradient, other factors affecting UF include the hydraulic conductance of the peritoneal membrane, the effective peritoneal surface area, the reflection coefficient of the osmotic agent, the hydrostatic pressure gradient, and the oncotic pressure gradient [1, 2]. The hydraulic conductance of the peritoneal membrane differs between patients and likely reflects the density of aquaporins versus small and large pores and the distribution of capillaries in the interstitium [1]. The reflection coefficient (σ) of a given solute at a particular pore, which ranges between 0 and 1, refers to the extent to which that solute is prevented from traversing that pore. A value of $\sigma = 1$ indicates that 100% of the solute gets reflected back from the membrane, i.e., that the membrane is completely impermeable to that solute [21]. In contrast, a value of $\sigma = 0$ suggests that the membrane is completely permeable to that solute. One would ideally wish to use an osmotic agent with a high reflection coefficient at the small pores. However, glucose has a low reflection coefficient of only 0.03 at the small pores; therefore, large concentrations are needed to achieve ultrafiltration [22]. In contrast, icodextrin has a hydrodynamic radius greater than the functional radius of the interendothelial cell clefts (the small pores) and consequently a high reflection coefficient [23]. Therefore, with prolonged dwell time, icodextrin is more effective in sustaining the osmotic gradient than glucose.

Under normal conditions, peritoneal capillary pressure is higher than the intraperitoneal pressure, creating a hydrostatic pressure gradient that favors movement of fluid from capillary blood into the peritoneal cavity. This gradient may be greater in a volume-expanded patient and lower in a volume-depleted patient [1]. Oncotic pressure acts to keep fluid in the blood and therefore counterbalances the

hydrostatic pressure and opposes UF. If the oncotic pressure is low, such as in hypoalbuminemic patients, UF may be greater than expected [1]. An increase in intraperitoneal pressure reduces the hydrostatic gradient and may lead to decreased UF. Wang and colleagues investigated the effect of increased dialysate fill volume on peritoneal fluid and solute transport in Sprague Dawley rats and found that an increase in dialysate fill volume resulted in higher intraperitoneal hydrostatic pressure and lower net UF [24]. Intraperitoneal pressure rises from the supine to the upright position and is highest when patients are seated. This is demonstrated in the study by Twardowski and colleagues, measuring the intra-abdominal pressure in 18 patients on CAPD in the supine, sitting, and upright positions [25].

Sodium Sieving

Heimburger and colleagues observed a decrease in dialysate sodium concentration during the initial period of a 6-hour PD dwell which is most prominent when using 3.86% anhydrous glucose solution [22]. Simultaneously, plasma sodium concentration increases slightly. This is due to the fact that aquaporins, which generate up to half of the total ultrafiltrate in response to glucose, are totally impermeable to sodium. Therefore, free water entering the peritoneal cavity dilutes the intraperitoneal sodium and decreases its concentration (lower D/P_{Na}), while the sodium reflected by the aquaporins remains in the blood. As seen in Fig. 2.3, this "dip" in dialysate sodium concentration is most marked at 60–90 minutes. Over time, as sodium begins to enter the dialysate via diffusion through the small pores, the dialysate sodium again rises [26]. This is clinically relevant, as repeated short dwell times with very hypertonic dialysate may result in hypernatremia and increased

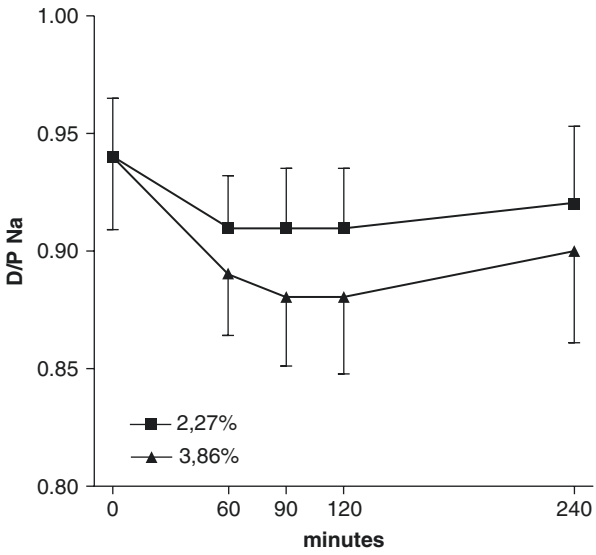

Fig. 2.3 The ratio of dialysate sodium concentration to plasma sodium concentration (D/P Na) in 2.27% and 3.86% dextrose solutions. The dialysate sodium concentration is the lowest (i.e., lowest D/P Na) at 60–90 minutes. Afterward, sodium then enters the dialysate via diffusion through the small pores, and dialysate sodium concentration rises gradually with time. (From Gomes et al. [26]. Reprinted with permission of Oxford University Press)

thirst sensation. Note that while this phenomenon has become known as sodium sieving, it is physiologically due to the *reflection* of sodium at the aquaporin.

Fluid Absorption

During PD, fluid is lost continuously from the peritoneal cavity via the lymphatic vessels and by absorption into the surrounding tissues of the abdominal wall. It is subsequently taken up by local lymphatics and peritoneal capillaries due to Starling forces [19, 27]. Lymphatic absorption mainly occurs through the lymphatic stomata in the diaphragm, which return peritoneal lymphatic drainage through the right lymphatic duct (70–80%) and the thoracic duct (20–30%) [28]. Lymphatic absorption is dependent on diaphragmatic movement, intraperitoneal pressure, and posture. In the setting of hyperventilation, lymphatic absorption increases. A rise in intraperitoneal pressure, such as with increased intraperitoneal volume, results in increased lymphatic absorption [28]. Upright posture is associated with a lower rate of lymphatic flow, presumable due to decreased contact of dialysate with the diaphragm [28, 29].

Studies have shown that the rate of macromolecular marker appearance in plasma is only approximately 10–20% of its disappearance rate from the peritoneal dialysate [30, 31]. Heimbürger and colleagues investigated the relative contributions of direct lymphatic absorption and absorption into tissues to the total peritoneal fluid absorption in CAPD patients with UF failure [31]. Using radioiodinated human serum albumin (RISA), they compared the disappearance rate of RISA from the dialysate with its appearance in the plasma, assuming that the rate of appearance of RISA in the plasma correlates with the lymphatic absorption rate. They found that the appearance rate of RISA in the plasma is much lower than its disappearance rate from the dialysate. In addition, the plasma RISA concentration continued to rise in an almost linear fashion for up to 16 hours after termination of the study dwell. Based on these findings, the authors concluded that direct lymphatic absorption is of only minor importance for the total fluid absorption in PD patients and that the interstitial compartment serves as a reservoir of macromolecules, which are then absorbed by local lymphatics. It is estimated that total fluid absorption from the peritoneal cavity in man occurs at a rate of 60–90 mL/hr, with 10–20 mL/hr flowing into lymphatics and 50–80 mL/hr flowing into the surrounding tissues [27, 32]. It should be recognized that this “bulk” fluid absorption results in loss of both UF and solute clearance, as the reabsorbed fluid had previously been equilibrated with solute.

Kinetic of a Single Peritoneal Dialysis Dwell

Taking into account both transcapillary UF of fluid *into* the peritoneal cavity and lymphatic reabsorption of fluid *from* the peritoneal cavity (so at any point in time, *net* UF represents the algebraic sum of transcapillary UF and lymphatic

reabsorption), the kinetics of a dwell may be summarized as follows: At the start of a PD dwell, transcapillary UF rate is at its maximum, and intraperitoneal volume increases quickly. Over time, the UF rate declines, as the osmotic gradient diminishes due to dialysate glucose being absorbed from the peritoneal cavity. Intraperitoneal volume continues to increase as fluid moves from the peritoneal capillaries into the peritoneal cavity, until the rate of lymphatic reabsorption equals the UF rate. Thus, to capture maximum net UF, one would ideally wish to drain the abdomen at this time. Once the rate of transcapillary UF falls below the rate of lymphatic reaborption, intraperitoneal volume begins to decline. When osmotic equilibrium between the blood and the dialysate is reached, UF ceases entirely; intraperitoneal volume continues to fall by virtue of lymphatic reabsorption.

Peritoneal Equilibration Test

The peritoneal equilibration test (PET) is used in clinical practice to evaluate the transport characteristics of the peritoneal membrane in an individual patient. It was first standardized by Twardowski and colleagues in the 1980s with regard to the sampling procedure, duration of the dwell, and evaluation of the results [33]. The test is done by instilling 2 L of 2.5% dextrose dialysate into an empty abdomen while the patient is supine, dwelling for 4 hours, with the drain volume recorded at the end. Dialysate samples are taken at 0, 2, and 4 hours, and a plasma sample is drawn at 2 hours. As illustrated in Fig. 2.4 and summarized in Table 2.1, patients are categorized into one of four transporter groups based on the dialysate to plasma creatinine ratio (D/P Cr): high, high average, low average, and low [33]. The ratio of dialysate glucose at 4 hours to dialysate glucose at time 0 (D/D_0 G) is used as a control to assess the accuracy of the PET. If D/P Cr and D/D_0 G differ by more than one transport category, the PET is likely inaccurate [33].

Patients who are high (rapid) transporters have the most rapid equilibration of creatinine because of high intrinsic membrane permeability. Similarly, dialysate glucose diffuses rapidly into the blood through the highly permeable membrane. Thus, these patients rapidly dissipate the glucose-induced osmotic gradient and have low ultrafiltration (Fig. 2.4). In contrast, low (slow) transporters have the slowest equilibration of creatinine, due to low membrane permeability. Dialysate glucose diffuses into blood slowly, they maintain the glucose-induced osmotic gradient longer, and they, therefore, have higher net UF. In the clinical setting, rapid transporters tend to have good small-solute clearance but may have suboptimal UF, while slow transporters tend to have good UF but may be deficient in small-solute clearance. Theoretically, rapid transporters would benefit from frequent short-duration dwells such that UF is maximized. In contrast, slow transporters would be better served with long-duration large-volume dwells, to maximize solute diffusion.

The net UF is calculated as the difference between the drain volume and the instilled volume and is used to evaluate UF capacity during the PET. The use of 4.25% dextrose solution instead of 2.5% dextrose solution – known as the modified

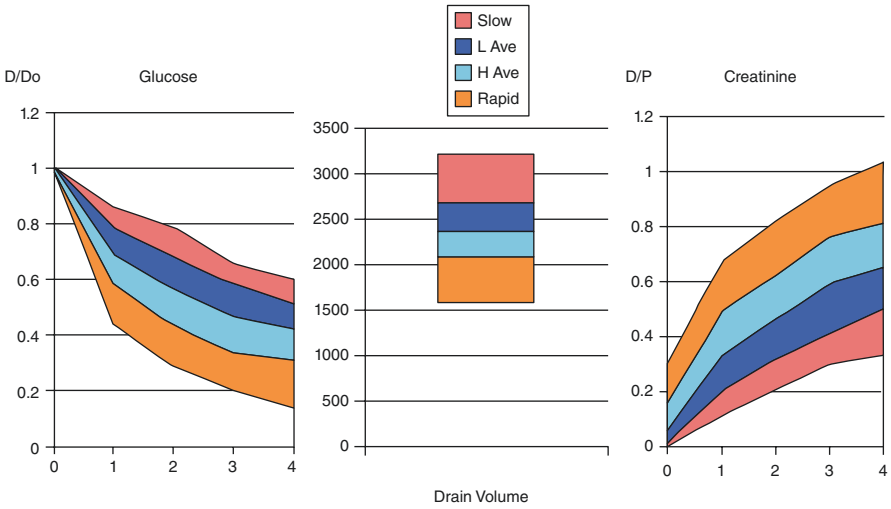

Fig. 2.4 Peritoneal equilibration test. (Adapted from Twardowski et al. [47])

Table 2.1 Classification of transporter groups

Transporter group	Standard PET with 2.5% dextrose D/P Cr	Standard PET with 2.5% dextrose D/D_0 G
High	> 0.81	< 0.26
High average	0.65–0.81	0.26–0.38
Low average	0.5–0.65	0.38–0.49
Low	< 0.5	> 0.49

PET peritoneal equilibration test, *D/P Cr* ratio of dialysate creatinine to plasma creatinine, D/D_0 *G* ratio of dialysate glucose at 4 hours to dialysate glucose at time 0

PET – is more sensitive in capturing patients with UF failure, because the change in UF volume is more pronounced when using a more hypertonic solution [34–36]. Solute transport characteristics do not differ between the standard and modified PETs [36]. However, using computer simulated modeling, Rippe demonstrated that the difference in UF volume over a 4-hour period between patients with normal UF capacity and those with UF failure is about 400 mL when using 4.25% dextrose solution compared to 200 mL with 2.5% dextrose solution [35]. Clinically, ultrafiltration failure is commonly defined as net UF < 400 mL after a 4-hour dwell using 4.25% dextrose solution, and the routine use of the modified PET rather than the standard test is therefore recommended by many PD experts [37].

A 1-hour "mini-PET" using 4.25% dextrose solution has been proposed by La Milia and colleagues to be a simple and fast method to evaluate solute transport and free water transport in patients on PD [38]. The authors performed standard and mini-PETs in 52 patients on PD using 4.25% dextrose solution. They found that

results of net UF and categorization of transport groups using the mini-PET correlate well with those obtained using the standard PET.

Changes in the Peritoneal Membrane with Time on Peritoneal Dialysis

Over time, morphological changes occur in the peritoneal membrane in patients on long-term PD. Prolonged exposure to glucose and glucose degradation products (GDP) leads to production of various proinflammatory and angiogenic factors, including nitric oxide (NO), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF). These then lead to neo-angiogenesis of peritoneal capillaries, which in turn increases the effective peritoneal surface area with resultant augmentation of small-solute transport [39]. Comparing peritoneal biopsies obtained from healthy subjects (control), uremic patients not yet on PD, patients on short-term PD (< 18 months), and patients on long-term PD (> 18 months), Combet and colleagues demonstrated that nitric oxide synthase (NOS) activity and upregulation of VEGF are positively correlated with the duration of PD. Moreover, patients on long-term PD had a 2.5-fold increase in the density of peritoneal capillaries, compared to the control subjects [40].

Davies and colleagues examined the effects of dialysis on longitudinal changes in peritoneal kinetics using serial PETs to quantify changes in small-solute transport (D/P Cr) and UF over a period of 5 years. They found a significant increase in D/P Cr during the first 6 months of PD therapy, and there was a further increase over the next 4 years [41]. With increased small-solute transport across the peritoneal membrane, glucose diffuses into the peritoneal capillaries more rapidly, resulting in rapid loss of the osmotic gradient and a decline in net UF. Accordingly, Heimbürger and colleagues found significant correlations between time on PD and increasing D/P Cr as well as decreasing drained volume and D/D_0 G [42]. In a separate study, Heimburger and colleagues compared solute and fluid transport characteristics in CAPD patients with loss of UF capacity to that in patients with intact UF capacity. They found that there is a higher diffusive mass transport coefficient for small solutes (sodium, creatinine, urea, etc.) in patients who lost UF capacity, resulting in rapid absorption of glucose and loss of the osmotic driving force [43].

Long-term exposure to dialysis solution that is hyperosmotic, hyperglycemic, and acidic often causes chronic inflammation and injury to the peritoneal membrane. Yanez-Mo and colleagues demonstrated that peritoneal mesothelial cells undergo a transition from an epithelial phenotype to a mesenchymal phenotype, when they are subjected to peritoneal dialysis solution [44]. This process – referred to as epithelial to mesenchymal transition (EMT) – leads to mesothelial denudation, submesothelial fibrosis, and reduction of vascular permeability [45, 46]. This culminates in reduced permeability of the peritoneal membrane, leading to a decline in solute and fluid transport.

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Chapter 3
Peritoneal Dialysis Patient Selection

Ephantus Njue, Sinan Yaqoob, and Niloofar Nobakht

Peritoneal dialysis (PD) is highly underutilized worldwide with wide regional variation. In the United States, only 9% of ESRD patients are on PD compared to rates as high as 79% in other countries. This exceptionally low rate is a worrying statistic for a developed country such as the United States and requires immediate attention. A recent NKF-KDOQI conference identified clinical, operational, societal, and policy-related factors that prevent access to PD as a modality of choice [1]. When educated about their options, most patients would choose home dialysis as their preferred modality [6]. Clinical studies and research from around the world have consistently shown that as a home-based dialysis therapy, PD is associated with improved patient survival, better preservation of residual kidney function, lower risk of infection, and increased patient satisfaction all while reducing financial stress to governments [5]. According to Devoe et al. (2016), there is a strong association between patient-targeted dialysis modality education and selecting and receiving PD [7]. Despite significant and widely accepted benefits of home dialysis, its utilization rate has remained unacceptably low in the United States (<2% for home hemodialysis (HHD) and < 10% for PD), rates far below that of other industrialized nations [1].

The viability of PD and its place in kidney replacement therapy has evolved over time. PD is now much safer due to improvements in peritoneal access and catheter design, dialysate solutions, connectology, exit site management, peritonitis prevention strategies, and more. The growing use of automated PD has also led to

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improved patient- and technique-related outcomes over recent decades [2]. Most ESRD patients are eligible to pursue and select PD as their dialysis modality; in some studies, up to 85% of the ESRD population were deemed suitable candidates for PD. The low utilization of PD in the United States, therefore, most likely points to many factors and barriers within our healthcare system.

Patient selection is a shared decision between an empowered patient and a knowledgeable provider. A shared decision is a process in which clinicians and patients work together to make decisions and select tests, treatments, and care plans based on clinical evidence that balances risks and expected outcomes with patient preferences and values. Patient selection for home dialysis starts with education in the early stages of CKD. The initiation of modality education early in the disease process results in higher uptake of home dialysis [6]. Of particular interest, patients who selected PD over hemodialysis (HD) were more likely to have progressed further in the educational system, be physically independent, have been seen by a nephrologist earlier in the pre-ESRD period, and be more autonomous in the decision-making process before ESRD onset [4].

The inherent benefits of PD compared to HD should compel providers to offer PD first. Unfortunately, barriers exist in the form of physicians and nurses who have had minimal exposure to the PD modality in medical and nursing schools, respectively. The myths, misinformation, and inherent biases from a poorly informed provider play a critical role in PD selection. Most patients trust their physicians to choose the best option for them; unfortunately, most physicians are not comfortable offering PD due to an overall lack of exposure to the therapy. According to Ghaffari et al. [3], most nephrologists are uncomfortable with recommending PD as a viable modality option due to the lack of exposure. Successful home dialysis programs should include a medical director who is a champion of home dialysis and has the support of physicians, social workers, dieticians, and experienced nurses who are all strong proponents of home dialysis and are effective educators.

Essential qualifications for pursuing the PD modality are motivation, desire for autonomy, and flexibility. There are few absolute contraindications for PD other than the lack of a functional peritoneal membrane. Active inflammatory bowel disease and recently inserted ostomies are medical reasons to withhold PD, given that they are commonly associated with increased risk for PD-related peritonitis and leakage, respectively [2]. Old ostomies are not outright contraindications to PD, and catheters should be placed on the opposite side or presternal to minimize the likelihood of complications. Active inflammatory bowel pathologies such as diverticulitis may increase the risk of developing potential polymicrobial peritonitis. Other potential barriers include extensive abdominal adhesions due to prior surgeries or previous infective processes such as peritonitis or pelvic abscess. Cognitive disorders such as dementia, Alzheimer's, or developmental disorders are relative contraindications as caregivers could be utilized to assist the patient in PD-related procedures.

Severe dexterity or physical weakness in the absence of supportive caregivers may be a barrier to PD due to safety issues. Vision-related problems such as blindness, frailty, and upper extremity amputations in the absence of caregivers are other

barriers to PD. Homelessness and lack of storage spaces may be modifiable barriers as well. Comprehensive health assessments are imperative in modality selection. A thorough home environmental assessment is critical for long-term success in utilizing the PD modality; a clean living environment with adequate storage space for PD supplies is required. A pet assessment is equally important, especially if indoor pets, such as dogs and cats, are present in the patient's home. Different programs have unique policies regarding pets, but the general rules are that pets should not be present during the critical PD connections due to the risk of infection and that generally more than two pets are considered to be too many.

Conditions that increase intra-abdominal pressure (IAP) such as large polycystic kidneys, pregnancy, and space-occupying tumors may limit PD's viability as a modality. The risk of hernias, hemorrhoids, and other conditions that may result from IAP should be addressed and may require strategies to minimize those risks. Constipation should be avoided, and dialysis in the supine position is strongly encouraged. Careful surgical assessment before the placement of PD catheters is essential for the identification of potential risk factors. Hernias should be repaired before or during the PD catheter placement procedure to avoid related complications after PD has been initiated.

Many CKD patients will choose PD if adequate, effective, and timely modality education is provided. An increase in PD uptake will require a concerted effort to educate and empower providers on the benefits of PD. A comprehensive educational program in nursing schools and nephrology fellowships should be mandated to allow a balanced, shared decision process. All relevant stakeholders should acknowledge and address the existing barriers to increase home dialysis awareness and knowledge. Evidence-based protocols and procedures on PD practice should be standardized to make PD the dialysis modality of choice in all eligible individuals.

Home modalities should always be offered to ESRD patients as the first dialysis modality option in the absence of absolute or non-modifiable contraindications. In particular, patients on the transplant list should be encouraged to select and utilize PD as a bridge therapy. CKD patients should be referred to in-center HD only after all reasonable options for home dialysis have been exhausted. There are no known criteria or litmus test for choosing an ideal PD candidate. Careful assessment with an open mind is essential in empowering patients for optimal shared decision-making. Exploring the roles of caregivers and family members should always be discussed in detail, especially for patients with significant physical or cognitive challenges to self-care.

There are a few tools available to guide educators and other providers in the determination of ideal or eligible PD patients. The MATCH-D tool is designed to guide clinicians through the home dialysis evaluation process, as well as to educate them on the key issues to consider when offering home dialysis to their ESRD patients. The tool is color-coded by viability and choice of home dialysis. Green represents characteristics that are highly recommended, yellow represents significant barriers that could be eliminated, and red represents PD not being recommended in the absence of a caregiver (Fig. 3.1).

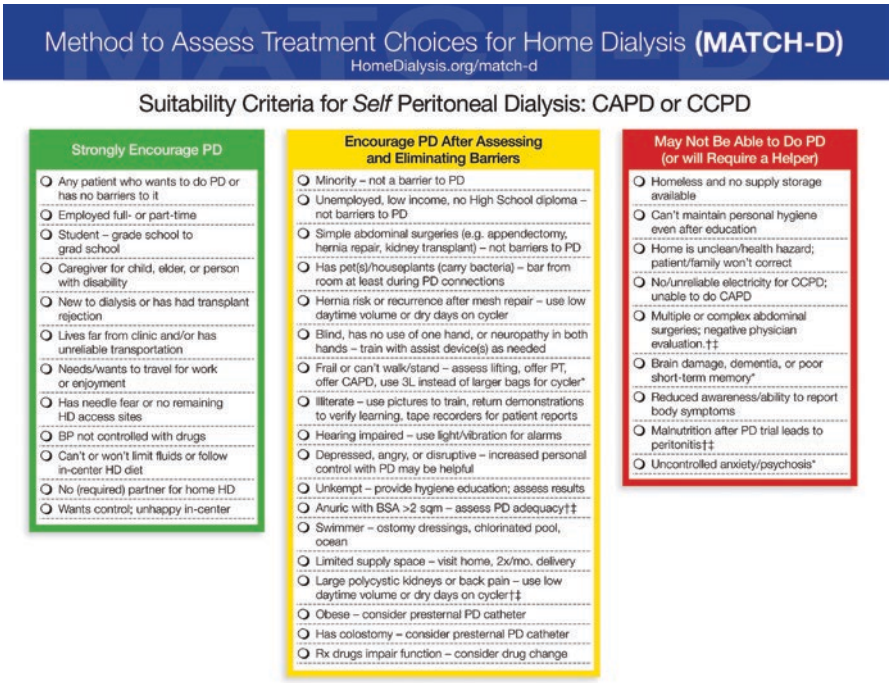

Fig. 3.1 MATCH-D tool. (Courtesy of homedialysis.org)

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Chapter 4
Epidemiology of Peritoneal Dialysis

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Introduction

In 2016, in the United States, the prevalence of end-stage kidney disease (ESKD) patients was 726,331, and the number of prevalent ESKD patients has typically risen by 20,000 per year [1]. The adjusted annual number of incident ESKD cases in the United States had a sharp rise between the 1980s and 1990s, and the rate leveled off in early 2000 and had declined since its peak in 2006. Incident cases of ESKD have been stable in the last decade in the United States with an incident count of 124,675 patients in 2016 compared to 115,921 patients in 2010. The ESKD crude incidence rate is projected to rise by 11–18% between 2015 and 2030, and the number of prevalent ESKD patients is estimated to rise to 971,000–1,259,000 between 2015 and 2030 [2]. In 2016, in the United States, peritoneal dialysis (PD) was used as the modality of kidney replacement by 50,552 patients. The number of incident ESKD patients choosing PD has increased by 85% from 2007 to 2016 [3]. Understanding why patients ultimately utilize one mode of kidney replacement therapy over another is critical. In this chapter, we discuss the epidemiology of PD in the United States, common characteristics among countries with high PD prevalence rates, factors affecting PD utilization, relevant clinical outcomes in PD, and potential solutions for overcoming underutilization of PD.

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Incidence of Peritoneal Dialysis

Among incident ESKD patients in the United States in 2016, 9.7% used peritoneal dialysis, while the percentage of patients undergoing preemptive kidney transplant and hemodialysis (HD) was 2.8% and 87.3%, respectively. In the United States, the number of incident PD patients peaked in the mid-1990s, then declined for more than a decade, but has increased by 60.2% since 2000. Additionally, PD continues to remain the most common form of home-based dialysis (overall use of incident home HD was 3.1% compared to 9.7% of PD among incident ESKD patients receiving dialysis in 2016) [1].

The maximum percentage of incident ESKD patients receiving peritoneal dialysis is in the pediatric age group from 0 to 21 years, and among adults, the age group with the highest rate of peritoneal dialysis use is the age group between 45 and 64 years [1]. Peritoneal dialysis incidence is more in males; the most common cause of ESKD is diabetes, followed by hypertension. The number of incident African-Americans on peritoneal dialysis was 2547 patients/year compared to 8475 Caucasians/year, and patients of non-Hispanic ethnicity were more likely to be placed on PD compared to Hispanics [1]. An area of future research is to understand the causes of low utilization of PD among different racial/ethnic minorities and develop interventions to overcome barriers that may be present in these groups.

Prevalence of Peritoneal Dialysis

In the United States in 2016, approximately 7.1% (50,552 patients) of all ESKD patients were prevalent PD, while the prevalence of kidney transplant was 29.4%, and hemodialysis was 63.2%. The prevalent PD population in the United States increased by 87.2% from 2000 to 2016. The percentage of prevalent ESKD patients receiving PD was most common in the age group between 22 and 44 years (8.8%) and among females (7.4%). The most common cause of ESKD was diabetes (19,205 patients), followed by hypertension (14,174 patients). The number of prevalent African-Americans on peritoneal dialysis was 12,391 patients compared to 33,928 Caucasians in 2016. The percentage of prevalent ESKD patients on PD that are Hispanic is 6.3% compared to non-Hispanic (7.4%) [1].

As mentioned above, since 2000, the *prevalent* PD population in the United States has increased by 87.2% compared to a 60.2% rise in the *incident* PD population as the prevalence of PD usage is determined not only by incidence rates but also by technique survival on PD and patient survival which is improving [1].

There is a variable distribution of the global prevalence of PD compared to the United States (7.1%), with PD usage ranging from 2% in Jordan, Lithuania, Macedonia, and Slovakia to 71% in Hong Kong [1].

Common Characteristics of Countries with High PD Prevalence Rates

In 2016, the highest utilization of PD occurred in Hong Kong (71%), the Jalisco region of Mexico (61%), Guatemala (57%), New Zealand (30%), Thailand (28%), and Qatar (27%); for the remaining countries, PD utilization was less than 22% of the total population of dialysis patients [1]. Important lessons can be learned from the countries with high PD prevalence.

Healthcare policies, practices, and reforms can increase the utilization of PD. One such effective strategy is the "PD-first policy" that has been in place since 1985 in Hong Kong where all patients with ESKD are offered PD as the kidney replacement modality of choice unless there is a medical contraindication. In the mid-1980s, Hong Kong was reaching full capacity for in-center hemodialysis and thereby instituted the "PD-first policy" primarily because of economic and resource considerations. The government reimburses for hemodialysis only if a contraindication exists for PD. If the patient chooses to perform in-center hemodialysis, he or she would have to be supported by a not-for-profit, charitable organization or a private hemodialysis center [4]. The outcome of this policy is that Hong Kong has the highest PD utilization rate (71%) in the world [5]. Additionally, a "PD-first policy" has been implemented in Thailand [6]. The government of Thailand introduced a universal health coverage scheme (UCS) in 2002. The inclusion of kidney replacement therapy for ESKD in UCS coverage occurred in 2008. The "PD-first policy" was a part of the universal health system scheme to address the shortage of dialysis facilities and medical personnel and to improve education among trainees as well as access to care, with the understanding that PD is a more economical and efficient modality of kidney replacement therapy compared to hemodialysis. According to the policy, PD would be offered first, with hemodialysis as a second-line treatment for patients unsuitable for PD. Additionally, nephrologists were incentivized with a fixed fee for incident and prevalent PD patients. The effect of the "PD-first policy" has increased PD utilization in Thailand from 5.5% in 2007 to 28% in 2016 [1, 4].

"PD-favored policies" have been encouraged in China, Canada, Mexico, Guatemala, and India. The government encourages PD use as a primary modality of kidney replacement therapy while removing any disincentives. The reasons for "PD-favored policies" include the need for cost containment, empowering patients and caregivers, advancing PD treatment, and improving access to care. In China, healthcare system reforms were established in 2011 resulting in expansion of primary medical insurance covering more than 95% of the population [7]. Additionally, in 2012, the Chinese social security system included coverage of uremia or ESKD to reduce the financial burden on individual patients. As a result of this expanded health insurance coverage, the number of patients utilizing PD as a proportion of all dialysis use in China increased from 16% in 2012 to 20% in 2014 [8]. In Canada, the geographical variability in PD utilization between provinces is due to limitations in access to care as well as differences in reimbursement structure. The Ontario PD initiative of 2010 targeted to achieve a 30% PD prevalence and to improve dialysis

access to rural patients. The Canadian government, in 2012, also developed ESKD patient care targets in terms of dialysis care plan, education, patient engagement, and modality choice to promote PD uptake. The percentage of prevalent PD patients in Canada has slightly improved to 19.9% in 2016 compared to 18.1% in 2011 [1]. In Mexico, more than 80% of patients are covered by the Mexican social security system. The "PD-favored policy" is supported by the Mexican social security system and the public sector institutions as a resource-conscious and cost-effective measure to provide dialysis access to more patients with ESKD with the same budget [9].

A "PD-favored policy" can be integrated into a larger "home dialysis-first policy" as adopted by Australia and New Zealand. The reason for implementing the "home dialysis-first policy" was the perceived clinical and economic benefit of home dialysis (PD and home HD) compared to in-center HD as well as to address the shortage of healthcare professionals in Oceania. Australia and New Zealand (NZ) introduced a range of national health reforms in 2008–2012. In Australia, the reforms included maintaining national quality control and safety standards, improving cost-effectiveness, and activity-based funding (whereby hospitals get paid for the number and the mix of complex patients they treat). In 2015, PD percentage prevalence compared to all dialysis modalities in Australia was 15% and 29% in NZ [10]. In NZ, the reforms established a policy of shifting to home dialysis modalities [11]. The overall proportion percentage of peritoneal dialysis of all home dialysis modalities in Australia is 68% in 2015. The government in Australia has set a 50% target of home dialysis usage. In New Zealand, both proportion percentages of peritoneal dialysis and home hemodialysis of all home dialysis modalities are markedly elevated at 62% and 47% in 2015 [10].

Lessons learned from countries with a high PD prevalence are that government policies and incentives are critical in determining the particular mix of kidney replacement modalities. For example, a "PD-first" policy is an effective way to increase PD uptake and expand access to kidney replacement therapy in a cost-effective way while empowering patients and their family members. Other patient factors, dialysis factors, industry factors, and health system-related factors affecting utilization of PD are discussed below (see Fig. 4.1).

Epidemiological Factors Affecting Utilization of PD

Patient Factors

Age

Even though the elderly, age 65 years or greater, are the largest growing age group of patients with ESKD, the use of PD is less prevalent in the elderly in the United States. The percent prevalent ESRD patients on PD between 65 and 74 years is 6.6% and over 75 years is 5.8% [1]. The concerns of higher comorbidities such as

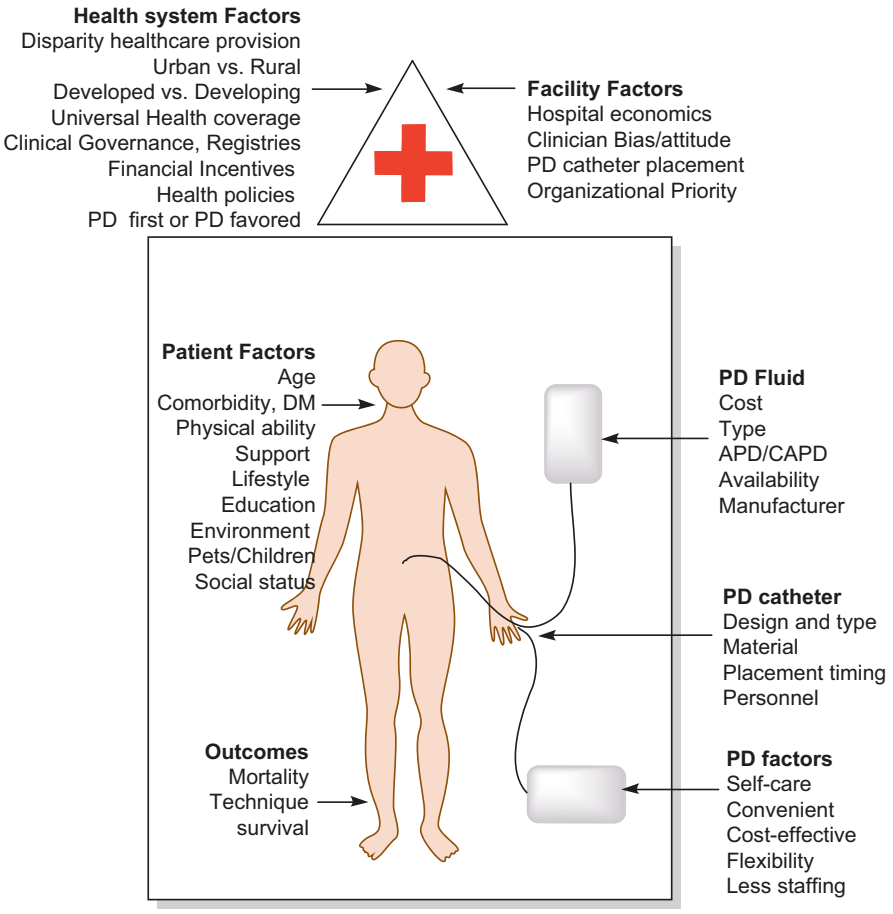

Fig. 4.1 Factors affecting PD utilization

cardiovascular disease, malnutrition, physical limitations (such as impaired visual acuity, hearing impairments, and dexterity issues), residing in a skilled nursing facility, a less robust support system, and other psychosocial limitations may create anti-PD biases among providers and possibly explain the low prevalence among the elderly, even though data suggests that PD is a reasonable choice in this population [12, 13]. For example, in France, the PD prevalence among elderly (over 70 years of age) is 54% in men and 59% in women [14]. In France and Denmark, there are assisted PD programs that are publicly funded to improve the utilization of PD among the elderly. The cost of assisted PD is equivalent to in-center HD. Assisted PD is an evolving concept and may improve utilization of PD in the elderly [15].

Comorbid Conditions: Diabetes Mellitus (DM)

In the United States, percentage prevalence of DM is 37% compared to all PD patients [3]. Many diabetic patients who have severe comorbidities such as peripheral arterial disease, advanced neuropathy, amputation of the digits, advanced retinopathy resulting in hampered manual dexterity, and visual acuity are therefore consigned to in-center hemodialysis rather than PD. A large study analyzing 398,940 incident ESKD Medicare patients from 1995 to 2000 demonstrated that patients with diabetes without comorbidity had a lower risk of death on PD compared to HD among younger patients, while the risk of death was lower on HD compared to PD among the elderly [16]. Caution should be used with the generalizability of data from registry studies as effect sizes were not large. A recent systematic review of 25 observational studies had inconsistent and variable results on patient survival across study design and subgroups of patients with different forms of kidney replacement therapy, suggesting that either PD or HD could be the initial modality of choice in ESKD patients with diabetes [17]. Registry survival studies are expensive and consistently show similar results. Survival of PD patients is improving over time, survival of HD patients is unchanged, and so survival between the two modalities is essentially the same [18]. Understanding the reasons for the low use of PD in patients with diabetes is critical to allow for targeting education and care pathways to increase PD utilization.

Physical Ability and Support System

Dexterity and visual acuity may hinder the patient's ability to utilize PD and may lead to biased decisions by providers to not offer PD. With the advent of assisted PD programs and improved connection assist devices, these physical barriers may be successfully addressed but require dedicated care teams with expertise in assisting these patients and families.

Patient Awareness of PD

An important factor influencing the growth of PD includes the implementation of education programs for patients with advanced CKD [19]. Most patients with CKD have limited awareness of the various modalities for management of ESKD. In a study by Finkelstein et al., when asked about the level of "perceived knowledge" concerning kidney disease, only 23% of patients reported having extensive knowledge about kidney disease, while 35% of patients reported little or no knowledge of kidney disease. In terms of awareness of different ESKD modalities, more than 50% of the patients did not have knowledge of the different peritoneal dialysis modalities. Also, knowledge of peritoneal dialysis was less compared to hemodialysis in patients with CKD stage 4 (42% compared to 54.9%) [20]. A pre-dialysis education program helps create awareness about management options. The likelihood of opting for home dialysis, having an arteriovenous (AV) fistula access, and lower

mortality risk during the first 90 days was noted among attendees of a pre-dialysis option class [19].

In 2012, a survey of 1365 dialysis patients demonstrated that approximately 50% of the patients reported receiving less than 30 minutes of pre-dialysis education and 6–10% reported no time or do not remember receiving such education [21]. Strategies to improve pre-ESKD care education include developing enhanced educational tools such as websites, courses, and other teaching materials [22].

Financial Considerations

Incremental cost-effectiveness ratio (ICER) is an economic measure to understand therapeutic interventional strategies or treatments. ICER is the ratio of change in costs to incremental effectiveness of treatments (e.g., treatment effect difference between different kidney replacement modalities). Additive costs of a dialysis modality would include capital cost (infrastructure), human resource cost (full time or part time), overhead cost (e.g., administration, maintenance), and dialysis consumable costs (medical supplies and office consumables). The effectiveness of a dialysis modality can be measured by survival and quality-adjusted life years (QALY) gained. QALY is a function of the length of time and the quality of life lived, and a value of one assumes that 1 year of life is lived in perfect health [23]:

$$\text{ICER} = \frac{\text{Incremental costs between treatments}}{\text{Survival and QALY gained between treatments}}$$

The long-term survival outcomes and QALY gained between PD and HD are similar (with perhaps a better QALY for PD). Since the denominator is nearly equal between treatments, the ICER is directly proportional to incremental costs of different dialysis modalities. Cost data analysis between PD and HD has several methodological flaws and limitations which can be minimized by HD/PD cost ratio. A global comparison of HD/PD cost ratio by Nayak et al. revealed that hemodialysis was 1.25 times higher in cost than PD in 22 out of 46 countries suggesting that PD is a more cost-effective dialysis modality [24]. Additionally, in the United States in 2016, the average cost on a per-patient basis is $76,177 for PD and $90,971 for HD [1].

Also, socioeconomic status (SES) is a part of a larger framework of determinants in modality selection. PD prevalence was lower in patients treated in the private sector compared to public sector (hospitals or health system) [25].

Other Patient-Related Factors

Absolute contraindications to the use of PD tend to be infrequent but include a nonfunctioning peritoneal membrane. All other patient-related factors are “relative” barriers, which can be overcome by a motivated patient and clinician experience in the PD center. Lifestyle preferences play an important role in choosing

PD. Peritoneal dialysis empowers patients and caregivers with more freedom with "self-care" and gives them the convenience of adjusting PD into their lifestyle (such as time management concerning work, travel, and duration of sleep). Additionally, one has to consider a suitable environment (adequate space for doing PD, storing supplies, barring pets from PD room), history of abdominal surgery, intact cognitive ability, attitude, coping skills, and the amount of inherent residual kidney function.

Facility Factors

Clinician Attitude and/or Bias

Clinician bias and attitude can strongly influence the options offered to a patient. Clinicians need to be comfortable and have clarity in understanding PD as well as the indications and relative contraindications for the use of PD. Traditionally, PD programs have had a selection bias for younger patients with fewer comorbidities [26]. These biases are likely unfounded, and numerous strategies have been successfully utilized to increase access to PD [27]. For instance, Canada has developed assisted PD programs with improved outcomes to support elderly patients with functional limitations that would otherwise be on in-center dialysis [28]. The use of telemedicine and remote monitoring are other strategies that can be used to support patients and their families in the home environment [29, 30].

Professional societies are increasingly developing educational tools to ensure that trainees in nephrology have strong foundations in home dialysis modalities. However, there remains a need to develop standardized home dialysis training curricula.

PD Catheter Placement

PD catheter placement is a rate-limiting step for incident PD start rates and prevalence rates on PD (as a successful PD catheter placement also affects technique survival). The issues related to PD catheter placement are the ideal design of the catheter, placement technique and timing, and the availability of skilled operators able to successfully place PD catheters. It is essential to identify a skilled operator who can place PD catheters with a high success rate. There is variability in the use of surgeons, interventional radiologists, interventional nephrologists, and general nephrologists placing PD catheters. There is evidence that the placement of PD catheters by nephrologists can improve PD utilization by reducing wait times for patients [31, 32] (see Chap. 7).

Dialysis Organizational Priorities

The reasons for the low prevalence of peritoneal dialysis in the United States (7%) compared to high PD prevalence countries (e.g., Hong Kong, China, Thailand, Australia) may be partially accounted for by the predominance of private dialysis providers and the overwhelming use of in-center hemodialysis. The density of community-based dialysis facilities owned by large dialysis organizations has increased faster than the general population making in-center hemodialysis readily available for the public. Additionally, the operational priorities of for-profit dialysis organizations also influence modality distribution. An observational study on incident dialysis patients over 4 years demonstrated underutilization of PD in three out of five large dialysis organizations and was associated with a higher risk of death. These findings also suggest a correlation exists between the use of PD and outcomes [33].

Clinical Governance/Registry Data

National registries (ANZDATA, PDOPPS, CNRDS, ERA-EDA, and USRDS) can help audit and provide feedback to PD centers to improve PD practices and outcomes as there are variations in peritonitis rates and outcomes between different centers worldwide [34–36]. Audits and feedback from national registries would improve retention of patients with better technique and patient survival (quality of dialysis) and hence the overall prevalence of PD.

Industry Factors

Several industry factors may affect the utilization of peritoneal dialysis. The PD fluid manufacturer, import duties on PD fluids, ability to match the demand and supply of PD fluid, cost of PD fluid, use of newer technologies in automated PD, and priorities of the dialysis organization are all factors that may play a role in the use of PD.

In 2015, the United States had a temporary PD fluid supply constraint that decreased the utilization of PD [4]. In contrast, the Thai government in 2007 reduced the import duty on PD fluids after implementing the PD-first policy which led to a marked rise in PD prevalence [37]. Health system factors and industry factors are intertwined to affect PD prevalence.

Technological advancements in PD have led to increased growth of PD in parts of the world. For instance, automated PD (APD) has been an essential determinant for increasing prevalence of PD in America. Eighty percent of patients in the United States choose APD as their initial modality [38]. Further technological advances

such as voice recognition commands and remote monitoring of therapies through telemedicine are areas of technological advancements with the potential to increase PD utilization by reducing the burden on the patient of traveling long distances to the PD center [39].

Dialysis Factors

Peritoneal dialysis requires certain patient and social characteristics to be successful. For instance, there is a need to have adequate storage space for supplies, a clean place to perform exchanges, and ideally a quiet and well-lit space for self-care. Facilities at home such as space, drain access, privacy, and hygiene are essential.

In addition, due to the unique characteristics of PD, patients may transition from HD to PD to achieve better hemodynamic stability, improved volume control, and more dietary choices. In some cases, loss of vascular access options may necessitate a switch from HD to PD.

Healthcare System Factors

Health system and governmental factors that include financial incentives, clinical reimbursement, availability of universal health coverage, healthcare policies (PD-first, PD-favored, and home HD-favored), and disparities in healthcare access affect PD utilization patterns.

Universal Healthcare Coverage

Universal health coverage can positively impact the prevalence of PD depending upon the incentives and regulations. We have learned from high PD-prevalent countries such as China and Thailand that inclusion of ESKD in the universal health system plan has resulted in a rapid rise of PD [40]. In Thailand, universal health coverage and peritoneal dialysis-first policy were implemented in 2007, along with reduced import duty for PD fluids which reduced cost for PD. In China, over 95% of residents were eligible for insurance with the policy reform. Also, PD is a more cost-effective modality compared to HD in China which could have increased PD uptake [4]. In the United States, expedited health insurance coverage for home dialysis was implemented by the Centers for Medicare & Medicaid Services (CMS), whereby the 90-day waiting period is waived for the uninsured incident Medicare eligible patients starting home dialysis.

Financial Incentives and Clinical Reimbursement

As mentioned earlier, PD is a more cost-effective treatment compared to HD. Additionally, physician reimbursement has been suggested to affect trends and usage of PD. In the United States, the bundled payment system, introduced in 2011 by the Centers for Medicare & Medicaid Services (CMS), which combines the payment for dialysis care as well as injectable drug or oral equivalents had led to a shift in momentum toward the use of PD as compared to in-center HD [41]. Additional incentives to healthcare providers exist in the United States for supervising training of patients for home dialysis, as well as equal reimbursement for seeing a home dialysis patient once a month compared to two to three in-center hemodialysis visits a month. These changing dynamics in healthcare policies and physician reimbursement have led to year-by-year rise in incident ESKD patients on peritoneal dialysis in the United States from 2012 to 2016. Since 2011, the growth of incident peritoneal dialysis therapies has increased by 44% to 12,095 patients in 2016 [1].

Healthcare Policies (PD-First and PD-Favored)

Hong Kong has the highest PD utilization rate with the PD-first policy implemented in the mid-1980s, and PD-favored policies have been established in China and Thailand since 2008–2012 [5]. The details of these policies and their impact on PD prevalence have been addressed previously. Additionally, a rapid rise in PD uptake was seen in the United States when the fee-for-service payment system was replaced by the prospective payment system (PPS) by the Centers for Medicare & Medicaid Services (CMS) in 2011 which included specific PD incentives [41].

Healthcare Disparities

About one-fifth of the US population lives in rural areas, and the resources to provide home dialysis therapies are less developed in these areas. For instance, travel to monthly visits at central dialysis centers may be excessively far and expensive. Provision of peritoneal dialysis can increase access to care in resource-limited settings in remote rural areas. In fact, an interesting observation has been that patients on PD in a rural setting are under the care of an urban PD training center [42]. Advances in telemedicine are addressing these barriers to increase utilization of PD in rural settings [29]. On the other hand, PD does afford access to kidney replacement therapy in areas where infrastructure to support HD centers may be limited or poorly developed.

Another disparity is between economic factors between developed and developing nations. In developing nations, PD remains a more resource-conscious and cost-effective therapy compared to HD which makes it a more desired economical option

[42]. In developed nations, if the private sector is dominant, then momentum to maximally utilize in-center hemodialysis units and fixed costs exists [4]. The Thailand government reduced import duty on PD fluids as a part of the PD-first policy which reduced cost of PD and improved PD uptake [4].

Epidemiology of Infection-Related Complications in PD Patients

Infection-related complications in peritoneal dialysis patients are one of the reasons for transfer to hemodialysis. These include peritonitis (61%) and exit site infections or catheter tunnel infections (23%) [43]. Peritonitis is a leading cause of hospitalization among PD patients.

Peritonitis is a preventable major complication of PD and an important determinant of technique and patient survival [44, 45]. Patient risk factors for PD-related peritonitis that are well established include diabetes mellitus, ethnicity, and malnutrition [46]. Certain modifiable risk factors identified include being overweight, smoking, depression, hypokalemia, hypoalbuminemia, invasive interventions (e.g., colonoscopy), low socioeconomic status, and psychosocial factors [46, 47]. Miscellaneous risk factors associated with peritonitis are dialysis-related (training, biocompatible fluids, wet contamination), infection-related (nasal *Staphylococcus* carrier status, and previous exit site infection), and social (living distance from PD unit and owning pets) [48].

Prevention of peritonitis is crucial for good outcomes. The goal peritonitis rate described is less than 0.5 episodes per year at risk depending on the patient population. Observational studies and multinational studies have demonstrated a decreasing trend in peritonitis rates (gram-positive organisms more than gram-negative) over the last two decades [49–51]. These trends are explained by adherence to evidence-based international guidelines. In Australia, peritonitis rates significantly fell (37%) after regular audits and feedback by national registries and also promoting peritonitis prevention trials by Australian Kidney Trials Network [52]. Although fewer than 5% of episodes with peritonitis are fatal, peritonitis is a major contributor to mortality in around 16% of PD patients [53, 54] (see Chap. 13).

Epidemiology of Mortality in PD Compared to HD

Technique survival and mortality are essential determinants of the prevalence of PD. PD catheter-related problems account for 12% of PD patients who transfer to HD in the first year of therapy [55] and was the second most common cause of technique failure. It is crucial to ensure proper placement of a PD catheter for the best outcomes. Poor technique survival is inversely associated with the prevalence of

PD. Examples of continuous quality improvement processes to improve technique survival and mortality have been implemented in Australia (with Australian Kidney Trial Network) and Turkey (Turkey Multicenter PD group). The Australian Kidney Trial Network conducts original high-quality, investigator-initiated, randomized controlled trials to improve practices, technique survival, as well as patient survival. Such collaborative research groups also help connect with leading researchers from other countries [56]. In Turkey, since the multicenter PD study group was established, prevalent PD patients have increased fivefold.

Non-modifiable factors associated with mortality and technique survival include genetics, diet, cultural practices, lifestyles, and socioeconomic status. Certain modifiable risk factors include dialysis prescriptions, adherence to treatment, comorbid illnesses, body size, peritoneal membrane transport, and dialysis practices.

Mortality has been correlated with the type of therapy that is offered in the dialysis unit. In Rio de Janeiro, the mortality rate for patients with ESKD was higher at in-center hemodialysis units that did not offer peritoneal dialysis therapy. Interestingly, mortality rates were lower in centers where both automated peritoneal dialysis and continuous ambulatory peritoneal dialysis were offered than in centers that only offered continuous ambulatory peritoneal dialysis [57]. In the United States, the large dialysis organizations with lower PD-prevalent patients had worse mortality outcomes. Additionally, in European registry data, there has been a strong correlation with a prevalence of peritoneal dialysis in the treating center as well as the likelihood of receiving a kidney transplant in the first year of kidney replacement therapy [33].

There are no randomized controlled trials addressing the mortality difference between PD and HD. Most of the data are from registries controlled for propensity-matched mortality scores and marginal structural analysis. The survival of PD patients is improving over time, and the survival on HD is unchanged. In the initial studies, there was an apparent survival advantage on peritoneal dialysis compared to thrice weekly hemodialysis, which could be due to preservation of residual kidney function in patients transitioning to PD or the early disadvantage of "unplanned" starts or complications of tunneled catheter use in hemodialysis. A study comparing PD with HD in planned starts did not demonstrate the early survival advantage for PD and no change over time to a late survival disadvantage for PD, even in diabetics [18]. The bottom line is outcomes in PD, if not superior, are at least comparable to HD.

There is variability in mortality data worldwide. Improvements in survival on PD versus HD have been reported in the past decade from North America (the United States and Canada), Asia (Republic of Korea, Hong Kong, Japan), and Oceania (Australia and New Zealand) [4, 5, 58, 59]. More contemporary era studies have shown equal outcomes comparing PD with hemodialysis [60, 61]. Since there is no difference in mortality outcomes between HD and PD, the patients should ultimately choose a dialysis therapy based on lifestyle, personal preference, and guidance from the healthcare team.

Proposed Solutions to Overcome Underutilization of PD

As learned from the countries of Hong Kong and Thailand, one effective strategy for improving uptake of PD would be a "PD-first policy," whereby PD should be offered to all patients with ESKD unless a contraindication for PD exists. Reimbursement structures favoring PD would have to be prioritized in the policy. Other solutions for growing PD could be improving pre-ESKD care, reforming current education strategies for patients and providers, and remodeling delivery of dialysis care to suit patient goals (through urgent start PD protocols, telemedicine services, assisted PD and PD as respite). Respite PD is supportive therapy at home prior to transition to hospice.

Improving pre-ESKD care is crucial to equip patients and their families with knowledge of kidney disease (including prognosis) and treatment options available (kidney replacement therapy, kidney transplantation, and conservative management) and understand the advantages and disadvantages of treatment options to better plan their "life goals." Restructuring the current continuity clinic model to integrate education, anemia management, nutrition services, as well as a dialysis access coordinator into an "advanced CKD clinic" will address the complexity of care provided to patients with kidney failure and provide a "one-stop shop" model to improve patient satisfaction, convenience, and outcomes.

Education should focus on patients as well as healthcare providers (including primary care providers, nephrologists, and nephrology trainees). Education of primary care providers in the community about awareness of the burden of kidney disease and treatment options available. (e.g., early referral of patients to a CKD clinic). Also, one has to focus on developing a standardized PD education curriculum as well as use innovative teaching methods to improve nephrology trainee experience.

Remodeling delivery of dialysis focuses on the unmet needs of resource-limited areas (such as lack of infrastructure, remote location of patients), patients without pre-ESRD care who are "unplanned starts," and expanding care to the elderly. Urgent start PD protocols allow patients to receive expedited education about dialysis modalities and offer "urgent start" PD to interested patients in a hospital or outpatient setting within 48–72 hours of placement of a PD catheter. A small nonrandomized study demonstrated the safety and feasibility of urgent start PD as an option for late-referred patients presenting without a plan for dialysis modality [31, 32]. Additionally, "transitional start units (TSU)" are being used in the United States to offset the home dialysis versus in-center HD imbalance [62]. Patients qualifying for TSU could be motivated incident dialysis patients, as well as patients at various transition points in the kidney disease continuum (such as failed renal allograft transitioning to RRT) who are naïve in their understanding of kidney disease, treatment choices, and the risk/benefit of dialysis modalities. A dedicated team of healthcare professionals (comprising nephrologists, nurse practitioners, social workers, dieticians, and nurses) frequently meets with patients to improve clarity about treatment choices. TSU empower patients to find the best kidney replacement

therapy based on personal life goals. Other ways to improve access to care is through innovative technologies such as telemedicine in PD and remote patient monitoring [29, 30]. Also, assisted PD services (entail supporting patients who are unable to perform PD) and respite PD are ways to overcome underutilization of PD in elderly nursing home patients. Assisted PD services are available in Canada and France [15, 63]. Assisted PD is not reimbursed in the United States yet, and the costs are borne by family members.

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Chapter 5
The Evolution of Peritoneal Dialysis Solutions

Ephantus Njue, Lewis Simon, and Mohammad Kamgar

The use of peritoneal dialysis (PD) solutions was first described by Wegner, a German investigator in the late nineteenth century. He injected hypertonic and hypotonic solutions into the peritoneal cavity of a guinea pig and observed that hypertonic solutions increased the volume in the cavity and hypotonic solutions decreased the volume. Wegner's findings triggered interest in the use of solutions for the treatment of uremia. Several scientists followed suit; Ganter used saline to treat uremia, and Heusser added dextrose to increase ultrafiltration (UF). Rhoads added lactate in PD solutions as a buffer to correct acidosis in 1938. The use of PD solutions has continued to evolve to the present day in the quest for formulating an optimal dialysate. The durability of PD as a dialysis modality depends on the type of solution utilized and its long-term effects on the peritoneal membrane. Many have argued that biocompatible solutions are ideal because they are proposed to limit the long-term degradation of the peritoneal membrane.

PD solutions are used as osmotic agents to regulate UF by increasing or decreasing the tonicity as needed. The fluid is used to treat uremia through diffusion and convective transport across the membrane. The commercially used solution in the United States is the traditional dextrose-based solution composed of water, osmotic agents (glucose), electrolytes, and minerals. In addition, they have low PH for the purposes of preservation and prolonging shelf life. There has been a slow uptake for neutral or biocompatible solutions worldwide; the reasons for this will be explored later in this chapter. Ideal PD solutions would promote and position PD on an equal footing with other kidney replacement modalities in terms of longevity.

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According to Vanholder [6], an ideal PD solution must possess the following characteristics:

- Have a sustained and predictable solute clearance with minimal absorption of the osmotic agents.
- Supply deficient electrolytes and nutrients if required.
- Correct acid-base problems without interacting with other solutes in the PD fluid.
- Be free of and inhibit the growth of pyrogens and microorganisms.
- Be free of toxic metals.
- Be inert to the peritoneum.

Unfortunately, the most commonly utilized PD solutions are far from ideal. They are highly acidic, are glucose-based, are easily absorbed, contain glucose degradation products (GDPs), wash out local antibodies, and are difficult to add buffers due to crystallization. The solutions also contain dextrose in varying concentrations, which generates GDPs during the sterilization process. The systemic effects of GDPs include myocardial toxicity; locally, they cause mesothelial cell proliferation, increased production of advanced glycation end products (AGES), and vascular endothelial growth factor (VEGF). Topley [5] opined that the structural or "fibrotic" changes within the peritoneal membrane result in the alteration of its transport characteristics. The aggregate effects of these by-products include inflammation, fibrosis, vascular proliferation, and ultimately UF failure.

Composition of PD Solutions

Osmotic Agents

Ultrafiltration (UF) is a critical component of dialysis in order to avoid extracellular fluid volume overload. By creating an osmotic gradient, UF is achieved by a glucose concentration gradient in PD solutions versus the plasma glucose levels. The degree of UF is dependent on the concentration gradient wherein higher glucose concentration creates a higher gradient leading to flux of water from the vascular compartment into the peritoneal cavity. This gradient for UF dissipates as glucose is absorbed in the opposite direction along its own concentration gradient. Blood glucose control is a critical factor for UF; hyperglycemia can lead to increased fluid absorption leading to fluid overload. Osmotic gradient can be increased by using solutions with higher osmolarity. Glucose, therefore, is not an ideal osmotic agent because it is rapidly absorbed, worsens metabolic effects, and is difficult to utilize in labile diabetic patients. An ideal osmotic agent should be metabolized easily with nontoxic degradation products, poorly absorbed, inert and non-toxic to the peritoneal membrane, and inexpensive. In addition, such a product must be effective at low concentrations with no metabolic consequences of absorption and must be of nutritional value if absorbed. Several osmotic agents have been used throughout the history of PD including glucose, saline, amino acids, mannitol, polyglucose, and sorbitol.

Glucose is the most commonly used osmotic agent in PD and is available in North America in three different dextrose concentrations: 1.5, 2.5, and 4.25 percent. It is not an ideal osmotic agent due to it being easily absorbed (hence rapidly dissipating the osmotic gradient for UF) and the associated metabolic complications from its absorption including hyperglycemia, hyperlipidemia, and weight gain. These high glucose concentration solutions, low pH, and GDP production can affect peritoneal host defense mechanisms by inhibiting phagocytosis and bactericidal activities. These "unphysiologic" characteristics of PD fluids have been associated with significant loss of peritoneal mesothelial cell viability and function, compromised peritoneal immune system components, and promotion of fibrosis [1].

The advantages of traditional dextrose-based PD solutions are primarily associated with its cost-effectiveness, safety, and availability. The long-term effects of these solutions on the peritoneal membranes are consequential; some studies have associated them with terminal membrane failure including encapsulating peritoneal sclerosis. The use of conventional PD fluids, characterized by acidic pH (5.0–5.8), high lactate concentrations (30–40 mmol/L), high osmolality (320–520 mOsm/kg), high glucose concentrations (75.5 to 214 mmol/L), and contamination by GDPs, may contribute to these adverse outcomes [1]. However, cost and availability have remained impediments for use of biocompatible PD solutions.

Fluid removal with PD is mainly achieved via convection, and water removal from plasma exceeds sodium removal in the first few hours of a dwell, often leading to hypernatremia. Therefore, the relatively low sodium level in PD solutions helps offset the tendency for hypernatremia. Relatively low calcium concentrations can aid in the treatment of hyperphosphatemia by allowing the patient to use calcium-containing phosphorus binders without the risk of systemic hypercalcemia. However, hypocalcemia may develop in some patients, particularly in those with poor compliance in taking calcium-containing phosphorus binders as prescribed. The use of a lower concentration of magnesium is designed to prevent hypermagnesemia and bone disease. Lactate is commonly used to control acidosis by supplying an absorbed buffer that is quickly converted to bicarbonate in the liver.

The constituents of these solutions are listed in Table 5.1.

Two common commercially available solutions in North America are Dianeal by Baxter and Delflex by Fresenius. For CAPD, they are available in 1-liter, 2-liter, 2.5-liter, and 3-liter sizes, and for APD, they are available in 3-liter, 5-liter, and 6-liter sizes.

Table 5.1 Constituents of PD solutions

Dextrose (%)	1.5, 2.5, 4.25
Sodium (mEq/L)	132
Chloride (mEq/L)	2.6
Magnesium (mEq/L)	0.5, 1.5
Lactate (mEq/L)	35, 40
Calcium mEq/L	2.5, 3.5
pH	5.2, 5.6

Adapted from Guest [3]

Neutral pH solutions (biocompatible solutions) are not commonly used in North America, and many are not even available for use. They produce lower levels of GDPs, and it is postulated that they effect minimal mesothelial cell damage. This may suggest that patients could stay longer on PD with these solutions, but this is unproven. Indeed, in studies of technique failure in PD, problems with the integrity of the peritoneal membrane rank very low on the list of causes. Theoretically, biocompatible solutions should have better outcomes than traditional glucose-based solutions. In addition to utilizing lactate as a buffer, sodium bicarbonate is added in a separate chamber within the solution bag to prevent calcium and magnesium carbonate precipitation. The chamber is broken just before starting dialysis. Examples of these products are Physioneal, Balance, bicaVera, and Gambrosol Trio.

The amino acid-based solutions contain the same electrolytes as glucose-based solutions and have the same lactate buffer. They come in 0.5 to 2 percent concentrations. Since they are colloids, they have relatively strong osmotic properties compared to crystalloids. They are designed for patients at high risk for protein loss, such as high transporters, and also help with blood glucose control and reduce overall insulin demand. The primary disadvantage of amino acid-based solutions is uremia due to increased amino acid absorption, which can potentially lead to metabolic acidosis. These products are most often used as a nutritional supplement and are utilized in addition to a standard glucose-based PD solution. There is controversy surrounding the use of amino acid-based solutions and whether they contribute in any way to nutritional status, and because of this, most practices do not utilize these products. The current commercially available amino acid-based solution is Nutrineal through Baxter.

The polyglucose solutions are made up of glucose polymers, and due to their molecular size, they are not able to cross the peritoneal membrane. These solutions act as colloids and have an osmolarity of 285–286 mOsm/L. For this reason, polyglucose solutions are able to sustain an oncotic gradient leading to sustained UF. These solutions require a long dwell time because of the sustained oncotic gradient. Thus, the pressure created by these solutions will decline only slowly during the dwell, and a positive net UF is therefore sustained throughout the long dwell [2]. The current commercially available polyglucose solution is Extraneal (icodextrin) supplied by Baxter. It is traditionally used as a last fill or a single manual exchange for a long dwell. Despite its impressive UF characteristics, it has somewhat restricted use due to cost. Recently, as more physicians have become aware of its unique characteristics and potential benefits to PD patients, there has been an increase in utilization. In most organizations, it requires a non-formulary exception request to be approved before it can successfully be prescribed. Icodextrin is slowly absorbed though the lymphatic system and degraded by serum amylase into glucose. In the event of suspected pancreatitis in this patient population, evaluation of serum lipase instead of serum amylase is recommended. This is because serum amylase may not increase in patients on icodextrin, thus making the evaluation of serum amylase levels an ineffective means of diagnosing pancreatitis in these patients. Icodextrin has a black label from the US Food and Drug Administration (FDA) due to its potential for producing false glucose readings with GDHPQQ

glucose monitors. It is critical that patients on icodextrin ask their endocrinologist for an appropriate glucose monitor to avoid these false readings. While in the hospital, blood sugar should be checked using peripheral blood draws unless the ward glucometers are compatible with icodextrin. After the discontinuation of icodextrin, its effects on serum glucose can persist for up to 2 weeks. Patients using icodextrin need to always have a safety warning device with them that can alert providers about the potential artifactual elevation of serum glucose secondary to icodextrin metabolites in systemic circulation.

Conclusion

Peritoneal dialysis (PD) is a widely accepted dialysis modality with superior health outcomes compared to hemodialysis in the short term. The sterilization process of glucose-based solutions leads to increased production of GDPs and AGES, potentially leading to peritoneal membrane damage. The earliest symptom of PD failure is a reduction in UF. The use of biocompatible solutions, theoretically, should increase the duration of integrity of the peritoneal membrane and make PD a feasible choice as a long-term dialysis modality. William et al. [7] demonstrated that a new PD solution delivered to the peritoneum at neutral pH, and containing significantly lower levels of GDP, may significantly improve the homeostasis of the peritoneal cavity. However, recent clinical trials by Schaefer et al. [4] report a different story from the remarkable peritoneal biopsy study carried out in multiple pediatric nephrology centers across Europe. The study concluded that neutral-pH, low-GDP PD fluids induce early inflammation, epithelial-to-mesenchymal transition (EMT), and marked vascularization of the peritoneum, all of which are associated with peritoneal membrane transport function. Although the study was carried out in a pediatric population and the same factors might not necessarily apply to the adult population, its findings still create doubts regarding the negative effects that biocompatible solutions may have on peritoneal membrane's long-term integrity and function. Further clinical trials on biocompatible solutions will ultimately determine the future use of these products.

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Chapter 6
Automated Cyclers for Peritoneal Dialysis

Ephantus Njue, Anita Mkrttchyan, and Sou Tang

Peritoneal dialysis (PD) has evolved remarkably over the decades proving itself to be a competitive alternate to hemodialysis (HD). In 1962, Norman Lasker designed the first PD cycler featuring four 2-liter glass containers of PD solution to obtain a reservoir of 8 liters, connected to pre-sterilized disposable tubing and bags [6]. The concept of the semiautomatic machine was applied to many other cyclers, and most were modeled after Lasker's, the forerunner of all modern cyclers. Starting toward the end of the 1980s, PD cyclers underwent progressive improvement in terms of hardware components and layout, making continuous cycler peritoneal dialysis (CCPD), also known as automated peritoneal dialysis (APD), safer, quieter, and less bulky. Continuous progress in the hardware component of cyclers led to the availability of portable cyclers suitable for home treatment.

In 1994, Baxter launched HomeChoice, which abandoned the gravity control of flows using volumetric pumps and allowed for delivery of higher accuracy of dialytic exchanges [3]. This generation of cyclers utilized disposable materials and allowed individualization of PD treatments via personalized dialysis prescriptions. Additionally, these cyclers have contributed to the optimized management of ultrafiltration (UF) failure, the achievement of adequate dialytic clearances in anuric patients and more effective avoidance of poor patient compliance, and also increased the overall convenience of performing PD at home [5]. APD has greatly increased in popularity in the past decade and has become the preferred dialysis modality of choice for those with an active lifestyle.

Baxter and Fresenius are the two major companies that manufacture and supply the PD cyclers in North America. Current cycler technology delivers solution and

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removes dialysate from the patient through fills, dwells, and drains. The goals of the cyclic PD is to provide safe and effective dialysis in an automated manner while the patient is sleeping, making it a more convenient option with minimal lifestyle interruptions or changes.

APD allows a patient to have more freedom during the day, especially for patients who require a family member to be a caregiver. This grants the patient the freedom to enjoy regular activities and travel and also aids those with work commitments or school-age children, allowing the day to appear more normal without disruptions [2]. In addition, APD causes less significant increases in intra-abdominal pressure (IAP) compared to CAPD because APD is performed at night while the patient is asleep. Increased IAP can lead to the formation of abdominal wall hernias, genital edema, hydrothorax, and other serious complications. IAP should be monitored using simple unit-specific techniques, and pressures above 18 cm of water should be addressed by reducing the fill volume and factoring the UF per cycle. Disadvantages of APD may include increased UF which can lead to decreased residual kidney function and frequent machine alarms, which can pose challenges for patients and caregivers. Additionally, although the APD machine is theoretically portable, it is heavy and difficult to transport and can easily break down. The APD machine also requires an outlet power supply, meaning that the cyclers will not be able to run on a generator. According to Domoto and Weindel (2020), machine noise, restricted range from machine while undergoing dialysis, and feelings of less well-being likely related to UF were factors which limited the long-term success of CCPD [4].

Available modes offered by the APD machine include:

- CCPD
- Intermittent peritoneal dialysis (IPD)
- Nocturnal intermittent peritoneal dialysis (NIPD)
- Tidal peritoneal dialysis (TPD)
- High-dose CCPD
- High-dose TPD

CCPD is a process that utilizes a cycler to perform several exchanges automatically at night. The continuous cyclic process can increase dialytic efficacy and fluid removal, allowing greater clearance to be achieved with this modality compared to CAPD. It allows for better flexibility with the number and volume of exchanges during the night without taxing the patient. Increased fill volumes are better tolerated in the supine position; this position also helps minimize increases in IAP. Setup of the cycler usually takes place at bedtime or may be set up earlier during the day. Unlike HD, CCPD typically does not cause patients to experience posttreatment fatigue because there are no major fluid shifts. There are also fewer connection and disconnection procedures within a 24-hour time period, leading to a significant reduction in the risk of touch contamination. A typical CCPD prescription consists of 3 to 4 exchanges during the night with fill volumes ranging between 2 and 3 liters each and a long day dwell with fill volumes ranging from 1.5 to 2 liters each [1].

In IPD, patients generally dialyze for a few days per week. Treatments consist of short cycles with 2–3-liter fill volumes (in children 3–40 mL/kg) performed over

8–10 hours per session, with the peritoneal cavity being drained completely. The patient remains dry in between sessions. This mode of treatment is usually for patients with significant residual kidney function, allowing the patient to achieve adequate clearance with a smaller overall dose of dialysis. A main disadvantage of IPD is limited solute removal, especially of large solutes. This mode of treatment is also quite costly due to its utilization of large volumes of PD solution. This treatment modality is referred to as nocturnal IPD if it is performed nightly with dry days. NIPD is mostly reserved for patients with high solute transport and limited UF. Due to its shorter dwell times, NIPD can allow one to achieve better UF than the longer dwell times utilized in CAPD. The total dialysis volume per treatment typically varies between 8 and 12 liters.

TPD has a constant reserve volume of dialysate that remains in place throughout the entire treatment. The dwell time for TPD varies, and the initial fill is usually in the range of 2.0–2.5 liters. The peritoneal cavity is partially drained, leaving a reserve volume, and is then refilled. This process is repeated until the end of the treatment when the peritoneal cavity is completely drained. If necessary, the peritoneal cavity can be refilled for a daytime exchange. The reserve volume of dialysate provides continuous contact with the peritoneal membrane. The drain time in TPD is flow-regulated: once the programmed inflow and drain volumes are achieved, the cycler will automatically move into the next phase of the exchange. The purpose of TPD is to enhance the clearance of small solutes by reducing the normal loss of dialytic time that is associated with the inflow and drainage of solution of the intermittent technique. TPD may be useful for patients with inflow and outflow pain, as well as those with slow drainage or frequent machine alarms due to drainage-related problems. Like IPD, the main disadvantage of TPD is its increased cost due to the large volume of dialysate being utilized during treatments.

High-dose CCPD and high-dose TPD consist of adding additional daytime cycles, typically during the late afternoon or evening, to a patient's nightly CCPD or TPD therapy. The long daytime dwell is divided into two shorter exchanges that may be performed manually or cycler-assisted. The divided daytime dwells can improve both clearance and UF. High-dose CCPD tends to mimic the three-pore model by allowing short cycles at night for UF, midrange cycles for small solutes, and long dwells for large solute clearance. High-dose CCPD also enhances patient comfort by allowing larger volumes while sleeping and smaller volumes for first pause and last fill. By allowing large volumes in supine position, the risks associated with elevated IAP pressures such as hernia, genital edema, hydrothorax, and others are drastically minimized.

Peritoneal dialysis cyclers available through Fresenius are listed below:

Newton IQ System Cycler (Fig. 6.1).

Made by Fresenius Medical Care. It drains by gravity, minimizes drain pain, and requires perfect balance of the PD solution bags. It has different modes available to meet specific patient therapy needs.

Freedom Cycler (Fig. 6.2).

Made by Fresenius Medical Care. It is mainly utilized for pediatric patients and requires four-wheel stand for portability.

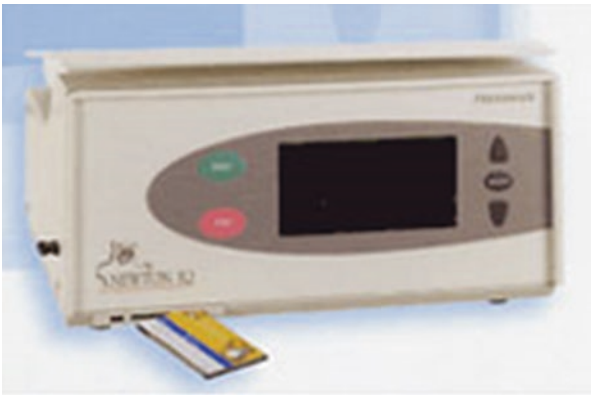

Fig. 6.1 Newton IQ System Cycler. (Used with permission from Fresenius Medical Care)

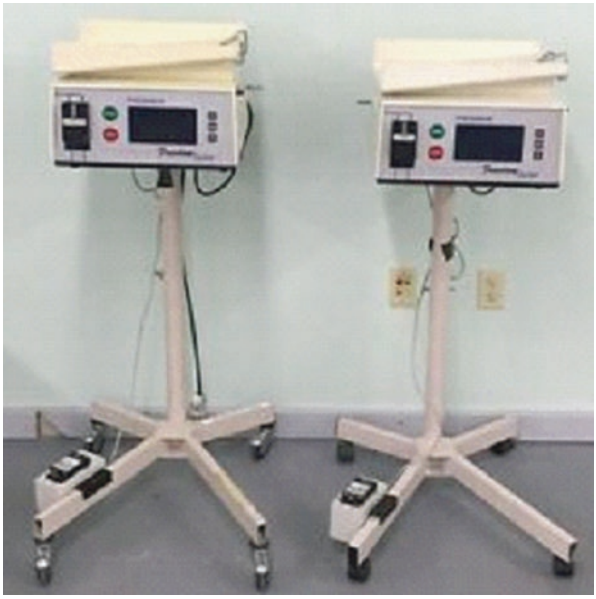

Fig. 6.2 Freedom Cycler. (Used with permission from Fresenius Medical Care)

Liberty Cycler (Fig. 6.3).

Made by Fresenius Medical Care. This cycler has a large color display screen with touch screen compatibility. It has an integrated stay•safe® and PIN system which decreases the risk of touch contamination. It has a modem capability for data communication with providers.

Peritoneal dialysis cyclers available through Baxter are listed below:

HomeChoice (Fig. 6.4).

Made by Baxter Healthcare Corporation. It is easy to troubleshoot without interrupting the treatment and has simple programming.

HomeChoice Pro (Fig. 6.5).

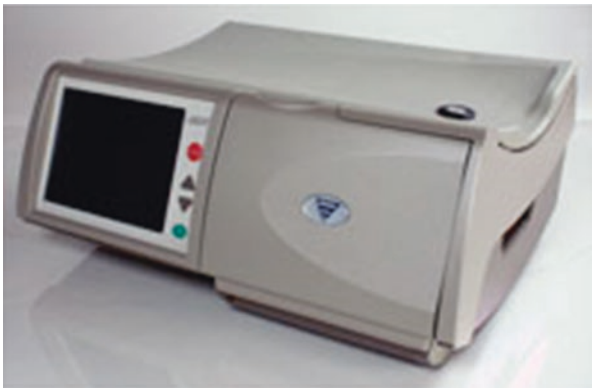

Fig. 6.3 Liberty Cycler. (Used with permission from Fresenius Medical Care)

Fig. 6.4 HomeChoice. (Used with permission from Baxter Healthcare Corporation)

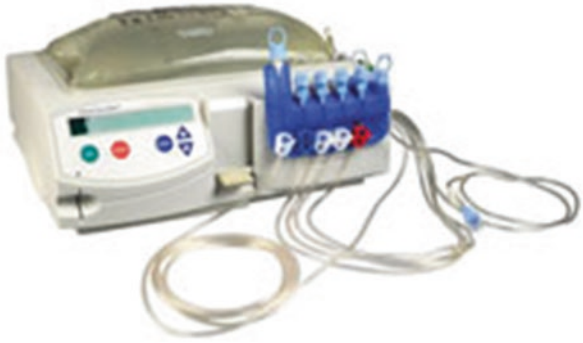

Fig. 6.5 HomeChoice Pro. (Used with permission from Baxter Healthcare Corporation)

Made by Baxter Healthcare Corporation. The operating system is similar to that of the HomeChoice but has an added slot for a ProCard. The ProCard requires a special program to access its feature and allows for comprehensive data programming and uploading. It is mainly for the pediatric population due to its ability to perform low-volume treatments.

Amia (Fig. 6.6).

Fig. 6.6 Amia. (Used with permission from Baxter Healthcare Corporation)

Made by Baxter Healthcare Corporation. The newest cycler on the market with innovative and futuristic features, the Amia cycler is portable, voice-guided, and user-friendly (provides step-by-step directions and full color animations), and remote monitoring is available through Baxter's ShareSource platform.

Conclusion

Over the decades, many milestones have occurred for the PD cycler to evolve. These improved cyclers and specialized PD techniques have been instrumental in providing PD patients with greater flexibility, more significant lifestyle advantages, and increased PD treatment efficacy and efficiency. Collectively, these improvements and advantages have shown PD to be a competitive alternative to HD. With patient interest in PD consistently rising year after year, an executive order has been issued to increase the use of home dialysis modalities by 25% by the year 2025.

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Chapter 7
Continuous Ambulatory Peritoneal Dialysis Versus Automated Peritoneal Dialysis – Are There Differences in Outcomes?

Scott D. Bieber

Peritoneal dialysis (PD) can be performed either manually, as with continuous ambulatory PD (CAPD), or with the use of a machine to assist dialysate exchanges, best termed automated PD (APD). Historically, the choice of PD modality was driven by peritoneal membrane characteristics of an individual patient. APD was largely reserved for use among patients who were rapid or high transporters and was considered inappropriate for slow or low transporters. However, over the years, clinical experience has revealed that APD can be used effectively in patients of all transport types. As a result, patient and physician choice spurred by the availability of convenient automated devices for the delivery of PD has recently skewed the selection of sub-modality in favor of APD, irrespective of peritoneal membrane characteristics. The utilization of APD has increased over recent years in both developing and developed countries, with significantly higher rates of APD use relative to CAPD use in developed countries [1]. In the United States, PD is becoming increasingly synonymous with APD as over 70% of patients are treated with the sub-modality [2]. In Canada, the proportion of PD patients treated with APD exceeds 60% [3]. With the rate of kidney failure worldwide on the rise and the PD population in many parts of the world positioned to expand rapidly, the number of patients treated with APD is expected to become even larger. This chapter attempts to answer the question of CAPD vs. APD: Are there differences in outcomes? The outcomes assessed will include residual kidney function, peritonitis, attainment of volume balance, technique survival, mortality, and health-related quality of life. The reader should not infer that these are the only outcomes of interest when comparing sub-modalities of PD. Rather, these outcomes are highlighted in this chapter because, at the time of writing, they are the most thoroughly studied.

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Residual Kidney Function

Studies of individuals undergoing maintenance dialysis have consistently associated greater residual kidney function with lower mortality risk [4]. Moreover, individuals with a more rapid loss of kidney function after the initiation of peritoneal dialysis have a significantly higher risk for death [5]. The lower mortality with higher residual kidney function may be explained by differences in solute removal or volume balance. In dialysis-dependent patients, removal of uremic solutes in the middle molecular weight range and protein-bound solutes is dependent to a larger extent on the residual kidney function [6–8]. Furthermore, euvolemia is easier to attain in individuals with residual urine output [9]. Another plausible explanation could be that the amount of residual kidney function is a surrogate for the presence of metabolically active kidney tissue, which may have a systemic protective effect. Many factors have been implicated in the rate of decline of residual kidney function in individuals undergoing maintenance dialysis, including baseline kidney function at the start of dialysis, ultrafiltration strategy, systemic blood pressure, presence of diabetes and/or congestive heart failure, use of renin-angiotensin aldosterone system blockers, and type of dialysate utilized [10–17]. Table 7.1 summarizes studies performed to examine the association of outcome and residual kidney function [10, 11, 14, 18–30].

With the importance of residual kidney function noted and inherent differences in fluid shifts, glucose burden, and volume control existing by PD submodality, the question is raised about whether or not there is a difference in residual kidney function between APD and CAPD. As indicated in Table 7.1, a handful of observational studies have demonstrated a faster loss of residual kidney function in individuals undergoing APD [19, 20, 23–25, 30]. Most of these studies have been small single-center studies with limited adjustment for confounding factors, and most subjects were not treated with renin-angiotensin-aldosterone system blockers. Similarly, two studies reported that the likelihood of complete loss of kidney function in the first year of PD was higher in individuals undergoing APD compared with CAPD [29, 30]. The majority of these studies do not consider the influence of variations in APD prescription on the rate of decline in residual kidney function. In summary, the existing information available is conflicting with some reports associating a faster decline in residual kidney function in individuals treated with APD and some not confirming this finding. The majority of the studies do not show a convincing difference by modality (Table 7.1). It appears reasonable to conclude that the evidence that APD leads to more rapid decline in residual kidney function is not persuasive. It has yet to be proven whether or not modality-specific effects on residual kidney function are clinically relevant.

Table 7.1 Summary of data from studies that have compared rate of loss of residual kidney function in end-stage kidney disease treated with continuous ambulatory peritoneal dialysis and automated peritoneal dialysis

First author (year)	Study type	Period/ country	Data source	Sample size (CAPD, APD)	Follow-up duration	Measure of GFR	Outcome
De Fijter (1994) [18]	Randomized controlled trial	1988–1991 Netherlands	Single center	82 (41, 41)	24 month	24-hour urine CrCl ml/min/1.73 m^2	No significant difference in change in the two groups (CAPD, 4.0 to 2.8 ml/min/1.73 m^2; APD, 5.4 to 2.1 ml/min/1.73 m^2)
Hiroshige (1996) [19]	Prospective cohort study	1992–1994 Japan	Single center	18 (5, 13)	6 month	24-hour urine CrCl ml/min/1.73m^2	Approximately 0.3 ml/min/month decline of residual kidney function in APD group compared with no significant change in CAPD group ($p < 0.01$)
Hufnagel (1999) [20]	Prospective cohort study	1995–1997 France	Single center	36 (18, 18)	12 month	24-hour urine CrCl ml/min/1.73m^2	Significantly greater decrease in APD group (−0.28 ml/min/month) vs. the CAPD group (−0.1 ml/min/month) at 6 months ($p = 0.04$). At 1 year, −0.26 ml/min/month with APD vs. −0.13 ml/min/month with CAPD ($p = 0.005$)
Bro (1999) [21]	Randomized controlled trial	1995–1999 Denmark	Multicenter	34 (17,17)	6 month	24-hour urine CrCl ml/min	No significant difference in decline in residual kidney function; mean clearances at the end of 6 months: APD, 3.0 ml/min; CAPD, 3.5 ml/min
Gallar (2000) [22]	Prospective cohort study	Spain	Single center	20 (11, 9)	12 month	Unclear ml/min	No difference in kidney function between groups at baseline or at 1 year. Change in CAPD, 6.11 to 4.9 ml/min; change in APD, 7.1 to 5.5 ml/min

(continued)

Table 7.1 (continued)

First author (year)	Study type	Period/ country	Data source	Sample size (CAPD, APD)	Follow-up duration	Measure of GFR	Outcome
Hamada (2000) [23]	Prospective cohort study	Japan	Single center	34 (17, 17)	24 month	Daily urine volume, ml/d	Daily urine volume declined significantly more in the CAPD group (381 ml to 147 ml) compared to the APD (223 ml to 157 ml), ($p < 0.01$)
Moist (2000) [10]	National Registry Data	1997 United States	Dialysis Morbidity and Mortality Wave 2 Study of United States Renal Data System	1032 (722, 310)	8–18month	Time to anuria (<200 ml/24 hours)	No significant difference in time to anuria in individuals treated with CAPD and APD
Singhal (2000) [11]	Prospective cohort study	1994–1997 Canada	Single center	242 (211, 31)	27 ± 14 month	Mean of 24-hour urine urea and creatinine clearances, L/week	PD modality a significant predictor of decline in kidney function only when the volume of PD fluid used daily was not included in analysis
Hidaka (2003) [24]	Prospective cohort study	1995–2001 Japan	Single center	34 (27, 7)	12–48 month	Mean of 24-hour urine urea and creatinine clearances, L/week	More rapid loss in kidney function in APD group (22 months vs. 28 months to a 50% reduction in glomerular filtration rate) $p < 0.001$
Johnson (2003) [14]	Prospective cohort study	1995–2001 Australia	Single center	146 (134, 12)	21 ± 15month	Mean of timed urine urea and creatinine clearances, ml/ min/ 1.73m^2	No difference in rate of decline in kidney function in individuals treated with CAPD and APD
Rodriguez-Carmona (2004) [25]	Prospective cohort study	1998–2002 Spain	Single center	104 (53, 51)	12–24 month	Mean of 24-hour urine urea and creatinine clearances, ml/min	Independent significant association of treatment with APD to lower residual kidney function at 1 year

Liao (2008) [26]	Retrospective study	1996–2005 Taiwan	Single center	270 (188, 82)	39.4 ± 24	Mean of 24-hour urine urea and creatinine clearances ml/min/1.73m^2	No difference in rate of decline in kidney function in individuals treated with CAPD and APD
Balasubramanian (2011) [27]	Retrospective study	2003–2008 United Kingdom	Single center	277 (130, 147)	5 years	Mean of 24-hour urine urea and creatinine clearances L/week	No differences in the rate of decline of kidney function between the two groups (CAPD, 15.4 L/week/ysear; APD, 15.7 L/week/year)
Cnossen (2011) [28]	Retrospective study	2001–2008 United States	Multicenter Renal Research Institute	620 (179, 441)	450 days	Unclear ml/min	No difference in time-averaged residual kidney function between the two groups
Michels (2011) [29]	Prospective cohort study	1997–2006 Netherlands	The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)	583 (505, 78)	3 month–3 year	Mean of 24-hour urine urea and creatinine clearances ml/min/1.73m^2	No significant difference in the rate of decline of kidney function in individuals treated with CAPD or APD. Individuals started on APD had a two times higher risk of achieving anuria in the first year compared with CAPD
Perez (2014) [30]	Prospective cohort study	2000–2010	Multicenter, Spain	439 (368, 125)	24 month	Mean of 24-hour urea and creatinine clearances ml/min/1.73m^2	Patients with lower baseline residual kidney function had an increased risk for faster decline in residual kidney function when treated with APD Probability of developing anuria was higher in patients starting on APD

APD automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis, *CrCl* creatinine clearance

Peritonitis

CAPD and APD differ significantly in the frequency and method of making the connections and disconnections between the PD catheter and the dialysis bags. This difference raises the question of whether or not one technique predisposes to, or decreases the risk of, the patient acquiring a peritoneal infection. The method of making connections for CAPD has significantly changed over the years from manual spiking of bags with a separate connection and disconnection with the dialysate bag and drain bag for each exchange to the twin bag systems. Twin bag systems consist of a dialysate and drain bag pre-attached to a Y-set which allows each exchange to consist of a single connection and disconnection along with technology that precludes the need for manually spiking the dialysate bag and routinely consists of "flush before fill." The twin bag system is the only CAPD setup available today in most parts of the world and is the dominant reason for the reduction in the risk for peritonitis in individuals undergoing PD [31]. Historically, improvements in connection systems for APD lagged behind those for CAPD.

An understanding of this differential evolution of connection systems for CAPD and APD is critical when interpreting studies comparing peritonitis rates for CAPD and APD patients during different time periods (Table 7.2) [18, 21, 27, 32–39]. Most of the published studies do not include description of the connection systems used by subjects undergoing CAPD and APD included in the comparisons. Nevertheless, it is possible to make some broad assessment of these comparative data. In the early days of the therapy, the number of connections and disconnections for performing PD was the single most important determinant of peritonitis rates; since APD required fewer connections and disconnections than CAPD, peritonitis rates with the former were often reportedly lower than with CAPD. Improvements in connection systems for CAPD, however, occurred before that for APD. This, in turn, may have been the reason for some studies from this intervening period to show a higher risk for peritonitis for individuals undergoing APD. Since then, the APD connection systems have improved as well, and in many contemporary studies, there is no significant difference in risk for peritonitis with the two therapies. In summary, the PD modality is likely to have little impact on an individual patient's risk of peritonitis.

Volume Management

During peritoneal dialysis, there is a disproportionately larger movement of water from capillaries to the peritoneal space across aquaporins early during the course of the dwell [40, 41]. This results in the dissociation between salt and water removal also known as "sodium sieving." With longer dwells, there is continued diffusive movement of sodium across the peritoneal capillaries, and hence, if the dwell is long enough, the dialysate to plasma ratio for sodium will approach unity. This

Table 7.2 Summary of data from studies that have compared risk of peritonitis in end-stage kidney disease treated with continuous ambulatory peritoneal dialysis and automated peritoneal dialysis

First author, et al. (publication year)	Study type	Period/ country	Data source	Sample size (CAPD, APD)	Follow-up duration	Outcome
De Fijjter (1994) [18]	Randomized controlled trial	1988–1991 Netherlands	Single center	82 (41, 41)	24 month	Overall rate (episodes per patient year) was 0.94 for CAPD and 0.54 for APD, difference of 0.43 episodes per patient year ($p = 0.03$). Median time to first episode of peritonitis was 18 months for APD and 11 months for CAPD ($p = 0.06$)
Bro (1999) [21]	Randomized controlled trial	1995–1999 Denmark	Multicenter	34 (17,17)	6 month	2 cases of peritonitis in CAPD group and 1 case in APD group
Oo (2005) [32]	National Registry Data	1994–1997 United States	Multicenter	11,975 (9190, 2785)	6 month–2 years	Average time to first peritonitis longer with CAPD compared to APD (17.1 vs. 16.1 months (0.70 vs. 0.74 episodes per patient-year, respectively) $p = 0.008$)
Davenport (2009) [33]	Retrospective study	2002–2003 United Kingdom	Multicenter	863 (538, 325)	2 years	Average number of months between peritonitis episodes 14.7 for CAPD and 18.1 for APD (0.81 vs. 0.66 episodes per patient year, respectively) ($p < 0.05$). Significant variation in peritonitis rates between facilities
Nessim (2009) [35]	Retrospective study	1996–2005 Canada	Multicenter	3180 (unclear)		No difference in peritonitis rate ratio between CAPD and APD (RR = 1.03, 95% CI 0.91–1.16, $p = 0.65$). CAPD was not associated with shorter time to peritonitis than APD (HR 1.02, 95% CI 0.92–1.13, $p = 0.69$)
Balasubramanian (2011) [27]	Retrospective study	2003–2008 United Kingdom	Single center	372 (178, 194)	5 years	CAPD peritonitis rate 1:29 patient months, APD peritonitis rate 1:37 (0.41 vs. 0.32 episodes per patient year, respectively). Odds ratio 0.78 in favor of APD (95% CI 0.63–0.98)

(continued)

Table 7.2 (continued)

First author, et al. (publication year)	Study type	Period/ country	Data source	Sample size (CAPD, APD)	Follow-up duration	Outcome
Ruger (2011) [36]	Retrospective study	1993–2007 Netherlands	Single center	205 (112, 93)	Review of all cases of peritonitis, 14-year period	Peritonitis frequency in CAPD 1:18.6 patient months and 1:19.4 patient months in APD (0.65 vs. 0.62 episodes per patient year, respectively), difference not statistically significant
Lan (2014) [38]	Prospective cohort	2003–2011 Australia, New Zealand	Multicenter	6959 (2761,4198)	1.9 years	PD modality was not associated with a higher likelihood of developing peritonitis. APD was associated with a borderline reduction in the likelihood of a first episode of Gram-positive peritonitis and with lower rates of culture-negative peritonitis and higher rates of Gram-negative peritonitis. Peritonitis outcomes were comparable between both modalities
Beduschi (2015) [39]	Prospective cohort	2004–2011 Brazil	Multicenter	2890 (1445, 1445) Propensity score matched	60 months	No difference in time to first peritonitis between groups (HR 1.04; CI95% 0.90 to 1.20). No difference in peritonitis rates between groups: CAPD 0.23 vs. APD 0.26 episodes per patient year
El-Reshaid (2016) [37]	Retrospective study	2005–2014 Kuwait	Single center	208 (180, 128)	Variable	The peritonitis rates were 1 in 29 months in CAPD and 1 in 38 months in APD ($p < 0.05$). Percentages of peritonitis-free patients over 10-year period in CAPD and APD were 49 and 60%, respectively ($p < 0.05$). Time to develop peritonitis was 10.25 ± 3.1 months in CAPD compared to 16.1 ± 4 months in APD ($p < 0.001$). Relapse and recurrence rates were similar in both groups

APD automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis

peritoneal physiology implies that frequent short dwells with APD may result in greater removal of hypotonic fluid during cycling, and this could result in reduced net sodium removal, which would put patients at risk for hypertension and volume overload.

Table 7.3 lists the studies that have examined 24-hour sodium and water removal as well as those that have examined clinically relevant measures of volume status in individuals treated with CAPD and APD [18, 21, 25, 34, 42–47]. Many studies reveal superior sodium removal with CAPD as compared to APD. However, these studies should be considered with two important caveats: Firstly, the "flush-before-fill" process prior to each exchange has impact on the total volume that is used for each exchange. The flush fluid goes directly into the effluent bag without ever having participated in the exchange. Failure to account for the flush volume – a limitation of many studies that have examined this question – can result in erroneously attributing sodium and water in the flush to what was achieved with the PD modality. CAPD done with four exchanges per day uses a cumulatively larger total flush volume over the 24-hour period that of a typical APD prescription. Thus, some studies have overestimated sodium and water removal with CAPD. Secondly, APD prescriptions are heterogeneous; the prescriptions with longer dwell times, with diurnal exchanges, and with icodextrin for long diurnal dwells are associated with significantly higher sodium and water removal [45, 46, 48]. Given these considerations, it is difficult to support the notion that sodium and water removal with APD is systematically less than with CAPD. Our current understanding indicates that individualized and careful prescription management can result in equivalent removal of salt and water, achievement of target weight, and blood pressure control in individuals treated with CAPD or APD.

Technique Survival

When patients transfer from PD to HD, it is considered "technique failure." Reasons for this transition are complex and can be minimized in the right setting with appropriate resources and experienced care providers [39, 49–55]. Inherent differences exist in burden of therapy between sub-modalities of PD that may have impact on the ability of patients to remain on the therapy. Additionally, provider practice patterns can complicate technique survival studies, including the ones comparing CAPD to APD. Table 7.4 lists available evidence documenting technique survival rates between CAPD and APD [18, 28, 54, 56–61]. Analysis of data from one randomized controlled trial was unable to demonstrate a significant difference in technique survival in individuals treated with the two therapies. However, the trial was underpowered to detect an effect of PD sub-modality on technique survival [18]. Subsequent observational data are split. Given these data, it is difficult to conclude that the PD modality has a meaningful effect on technique survival.

Table 7.3 Summary of studies comparing surrogate measures of volume management in individuals treated with continuous ambulatory peritoneal dialysis or automated peritoneal dialysis

First author, et al. (publication year)	Study type	Period/ country	Data source	Sample size (CAPD, APD)	Follow-up duration	Outcome
De Fiijter (1994) [18]	Randomized controlled trial	1988–1991 Netherlands	Single center	82 (41, 41)	24 month	No difference in mean arterial pressure or mean dry weight over time. Antihypertensive meds were used in 60% of individuals undergoing CAPD and 74% undergoing APD
Bro (1999) [21]	Randomized controlled trial	1995–1999 Denmark	Multicenter	34 (17,17)	6 month	No episodes of weight > 2 kg above dry weight in CAPD group, two cases in APD group. Mean systolic blood pressure similar in both groups
Frankenfield (1999) [34]	Retrospective study	1995–1997 United States	Multicenter	(~700, 500)	Three different 2-month time periods	No significant difference in proportion of individuals with hypertension by modality
Ortega (2001) [42]	Prospective cohort study	2001 Spain	Single center	36 (16, 20)	24-hour (sodium balance studies)	In CAPD group, daily peritoneal sodium removal and net ultrafiltration volume were significantly higher and systolic blood pressure lower
Rodriguez-Carmona (2002) [43]	Baseline cross-sectional data and prospective cohort study	2002 Spain		141 (63, 78) 32 individuals before and after change from CAPD to APD	3-month, 24-hour collections for sodium balance	Sodium removal was significantly greater in the CAPD group, independent of ultrafiltration volume. Sodium removal decreased significantly after switching from CAPD to APD

Rodriguez-Carmona (2004) [25]	Prospective cohort study	1998–2002 Spain	Single center	104 (53, 51)	12–24 month	Ultrafiltration and sodium removal rates were consistently and significantly lower in APD group. Better control of systolic blood pressure in CAPD group
Bavbek (2007) [44]	Cross-sectional study	2007 Turkey	Two centers	62 (32, 30)	–	APD group with significantly lower daily ultrafiltration volume, higher serum brain natriuretic peptide, and left ventricular mass index but no significant difference in blood pressure, compared to CAPD group
Davison (2009) [45]	Cross-sectional study	2004–2006 Canada	Single center	158 (90, 68)	–	No significant difference in sodium removal, ultrafiltration, or blood pressure between groups. Liberal use of icodextrin, limited number of nocturnal exchanges, and supplemental daytime exchange in APD group
Van Biesen (2011) [46]	Cross-sectional study	Europe	Multicenter	661 (53% APD)		Individuals without access to icodextrin were excluded. PD modality was not associated with extracellular volume excess as measured by bioimpedance
Cnossen (2012) [47]	Cross-sectional study	Netherlands	Multicenter	44 (24, 20)	~21–30 month	Total sodium removal lower in APD compared with CAPD but no statistically significant difference in systolic blood pressure, ultrafiltration volumes, or brain natriuretic peptide UF

APD automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis

Table 7.4 Summary of studies comparing technique survival and all-cause mortality in individuals treated with continuous ambulatory peritoneal dialysis or automated peritoneal dialysis

First author, et al. (publication year)	Study type	Period/country	Data source	Sample size (CAPD, APD)	Follow-up duration	Outcome
De Fijter (1994) [18]	Randomized controlled trial	1988–1991 Netherlands	Single center	82 (41, 41)	24 month	No significant difference in technique survival or all-cause mortality
Mujais (2006) [56]	Post hoc analysis of prospectively collected data	2000–2003 United States	Multicenter Baxter Healthcare Corporation On-Call™ system	40,869		Better technique survival in APD (mostly concentrated in the first year of therapy); no difference in all-cause mortality
Badve (2008) [57]	National Registry Data	1999–2004 Australia and New Zealand	Multicenter Australia and New Zealand Dialysis and Transplant (ANZDATA)	4128 (2393, 1735)	5 year	No significant difference in technique survival or all-cause mortality
Sanchez (2008) [58]	Retrospective study	2003–2005 Mexico	Single center	237 (139, 98)	2 year	Technique survival significantly better and all-cause mortality lower in individuals undergoing APD
Mehrotra (2009) [54]	National Registry Data	1996–2004 United States	Multicenter United States Renal Data System (USRDS)	66,381 (42,942, 23,439)	2–10 years	No significant difference in technique survival or all-cause mortality
Michels (2009) [59]	Retrospective study	1997–2006 Netherlands	Multicenter The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)	649 (562, 87)	5 year	No significant difference in technique survival or all-cause mortality

Johnson (2010) [60]	National Registry Data	1999–2004 Australia and New Zealand	Multicenter Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry	High transporters (142, 486) Low transporters (n = 196)	3 month–10 years	Compared APD vs. CAPD in high transporters and APD vs. CAPD in low transporters. No significant difference in technique survival between groups, lower death risk in high transporters treated with APD and higher death risk in low transporters treated with APD
Cnossen (2011) [28]	Retrospective study	2001–2008 United States	Multicenter Renal Research Institute	620 (179, 441)	3 month–7 years	Significantly better technique survival in individuals undergoing APD, no significant difference in all-cause mortality
Sun (2011) [61]	Retrospective study	1997–2008 Taiwan	Single center	282 (121, 161)	3 month–10 years	Technique survival higher in APD group and lower all-cause mortality in APD group as a whole. For individuals older than 65, APD was associated with higher mortality
Beduschi (2015) [39]	Prospective cohort	2004–2011 Brazil	Multicenter	2890 (1445, 1445) Propensity score matched	60 months	CAPD patients had a higher risk for overall and cardiovascular mortality. No significant differences were seen in technique failure
Tang (2016) [55]	Retrospective study	1999–2011	Multicenter	4574 (2287, 2287) Propensity score matched	10 years	Differences were observed in various time sub-periods, but over the entire study, there were no differences in technique failure or mortality
Li (2018) [62]	Retrospective study	2005–2015 China (Baxter Data)	Multicenter	100,351 (99,983, 368)	10 years	APD associated with overall lower risk of death compared with CAPD. Benefit observed only up to 4 years of follow-up, after that risk of death similar

APD automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis

Mortality

Mortality data available comparing APD to CAPD is also mostly observational (Table 7.4) [18, 28, 39, 54–62]. Attributing differences in mortality to any therapy is difficult and confounded by measured and unmeasured patient- and facility-specific factors. Studies have suggested that at least two potential causal physiologic mechanisms may be differentially affected by the two PD sub-modalities: residual kidney function and serum albumin level. In the only randomized prospective trial to have examined the outcome of mortality, there was no difference in patient survival; however, the clinical trial was significantly underpowered to detect a difference [18]. Similarly, the majority of large observational studies available have not reported any differences in mortality in individuals treated with either CAPD or APD. However, there are three exceptions to this general theme of equivalency. One single-center study revealed lower death risk in patients <65 years of age treated with APD, while elderly patients had similar outcome on CAPD and APD [61]. Another single-center study from Mexico reported a lower mortality for individuals treated with APD, particularly in the first year of dialysis [58]. In the analysis of the Australian and New Zealand dialysis registry, there was lower death risk in fast or high transporters treated with APD compared with CAPD but higher death risk in slow or low transporters [60]. It is important to note that the overwhelming majority of patients have an "average" peritoneal transport type. Thus, based upon the available data and these considerations, it appears that the selection of PD modality is not likely to be an important determinant of death risk for the majority of PD patients.

Health-Related Quality of Life

APD prescriptions are seemingly beneficial for patients to maintain their current lifestyle since the bulk of the dialysis treatment is performed while sleeping. Conversely, if done incorrectly and without proper support from dialysis providers, APD may be complicated by frequent machine alarms and drain pain which can alter sleep patterns and lead to patient frustration and burnout. Patients who are light sleepers, night wanderers, or get up frequently to go to the bathroom at night may prefer not to be connected to a cycler. Patients or partners may be hesitant to "medicalize" their bedroom. Thus, it is conceivable that there may be differences in the health-related quality of life in individuals treated with the two PD sub-modalities (Table 7.5) [21, 27, 29, 63–66]. A small prospective study found that individuals undergoing APD reported more time available for work, family, and social activities but reported a greater incidence of sleep disturbances compared to CAPD patients [21]. Another cross-sectional survey suggested better mental health in APD patients and higher rates of anxiety in individuals undergoing CAPD [63]. Notwithstanding these two studies, none of the other studies were able to demonstrate a significant difference in health-related quality of life between the two PD modalities. Thus, it

Table 7.5 Summary of studies comparing health-related quality of life in individuals treated with continuous ambulatory peritoneal dialysis or automated peritoneal dialysis

First author, et al. (publication year)	Study type	Period/ country	Data source	Sample size (CAPD, APD)	Follow-up duration	Outcome
Bro (1999) [21]	Randomized controlled trial	1995–1999 Denmark	Multicenter	34 (17,17)	6 month	Significantly more time for work, family, and social activities but greater problems with sleep disturbances in APD group
de Wit (2001) [63]	Cross-sectional study	1993–2001 Netherlands	Multicenter The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)	96 (59, 37)		Mental health better in APD group: less depression and anxiety. No difference in physical functioning.
Sunder (2008) [64]	Prospective observational study (fixed crossover design)	India	Single center	18 (all high or high average transporters)	All individuals underwent 6 month CAPD followed by 6 month APD	No significant difference in parameters of physical or mental quality of life
Guney (2010) [65]	Cross-sectional study	Turkey	Single center	68 (48, 20)		No significant difference in health-related quality of life, sleep quality, or depression
Balasubramanian (2011) [27]	Retrospective study	2003–2008 United Kingdom	Single center	372 (178, 194)	5 years	No significant difference in health status, physical or mental health scores by SF-36 questionnaire
Michels (2011) [29]	Prospective cohort study	1997–2006 Netherlands	The Netherlands cooperative study on the adequacy of Dialysis (NECOSAD)	550 (486, 64)	3 month–3 year	No significant differences in quality-of-life scores between groups
Yang (2018) [66]	Cross-sectional study	2009–2013	Singapore Multicenter	266 (145,121)	2 surveys	No significant difference in quality-of-life scores between groups

APD automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis

is premature to attribute a better health-related quality of life to selection of APD or CAPD.

In conclusion, inherent differences exist when comparing APD with CAPD. There are likely to be significant differences in individual patients and healthcare systems that will impact the choice of sub-modality. Existing medical literature does not support the superiority of one modality over the other when comparing outcomes of residual kidney function, peritonitis, technique survival, mortality, or quality of life. Given these findings, it is most prudent for providers to focus on educating the patient about their options and assist them in selecting a modality that will best suit their individual interests and lifestyle.

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Chapter 8
Peritoneal Dialysis Access: Catheters and Placement

John H. Crabtree

Being able to use peritoneal dialysis (PD) successfully as a mode of kidney replacement therapy requires a functional and durable access to the peritoneal cavity. Access is provided by a catheter device that bridges the abdominal wall to serve as a conduit for infusion and drainage of dialysis solutions. This chapter will focus on current practices, describing the most commonly used catheter types, patient-specific catheter selection, and catheter placement methods.

Catheters

The majority of catheters are constructed from silicone rubber, a material well-recognized for its biocompatibility and biodurability. Erosion of silicone catheters due to the use of topical antibiotics at the exit site has been reported but appears to be a rare complication [1]. The most commonly used PD catheter types are illustrated in Fig. 8.1. The standard double Dacron (polyester) cuff, straight- and coiled-tip catheters with straight or preformed arc bend intercuff segments constitute the core of PD access devices used around the world (Fig. 8.1a, b). Two-piece extended catheters were originally designed to provide a presternal exit site (Fig. 8.1c) [2]. The extended catheter system is comprised of a one-cuff abdominal catheter segment that attaches to a two-cuff subcutaneous extension segment using a double-barbed titanium connector. Extended catheters permit remote location of the exit site away from the usual lower abdominal sites to the upper abdomen, presternal area, and back regions [2–4]. This placement of the exit site away from the abdomen can be helpful for patients with an ostomy or rolls of pannus.

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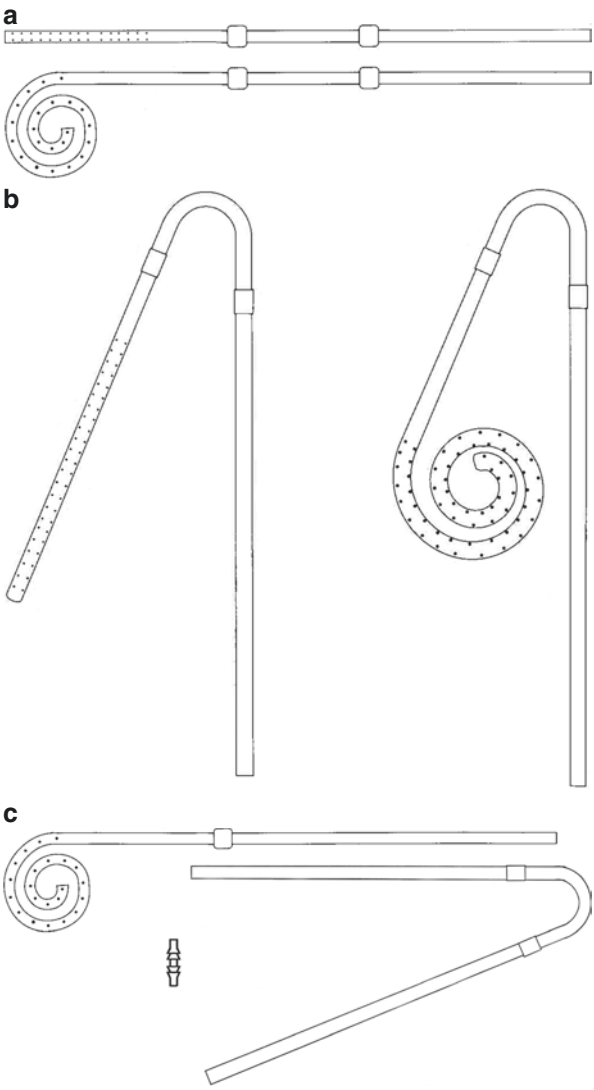

Fig. 8.1 Shown are commonly used peritoneal catheters. (**a**) Catheters with straight intercuff segment, two cuffs, and straight or coiled tips. (**b**) Catheters with preformed intercuff arc bend, two cuffs, and straight or coiled tips. (**c**) Extended catheter with one cuff, coiled-tip abdominal catheter, two-cuff extension catheter with preformed intercuff arc bend, and titanium double-barbed connector. (Reprinted from Crabtree et al. [42] with permission from Multimed, Inc.)

A number of adaptations of the standard catheter designs have been made in an attempt to address the common mechanical problems of tip migration, pericatheter leaks, and tissue attachment. However, none of these other configurations has convincingly proven beneficial over the standard catheter designs shown in Fig. 8.1 but increases device cost, adds difficulty to insertion and removal, and is not globally available.

Catheter Selection

Patients present with a range of body sizes and shapes, medical conditions, and other special needs that make it unrealistic to expect that one catheter type can serve all. The choice of catheter type should take into consideration the patient's belt line, obesity, skin creases and folds, chronic skin conditions, intestinal stomas, gastrostomy tubes, incontinence, physical limitations, bathing habits, and occupation. This requires that the peritoneal dialysis access team be familiar with a basic inventory of catheter types to enable patient-specific customization of the peritoneal access and provides optimal pelvic position of the catheter tip and flexibility in exit site location. Poor catheter choice can result in flow dysfunction, flow pain, and exit site locations prone to infection, making inaccessible to the patient [5, 6]. Practical applications of a basic catheter inventory are illustrated in Fig. 8.2.

The most suitable choice of catheter is the one that produces the best balance of pelvic location of the catheter tip, exit site in a low infection-risk zone easily visible and manageable by the patient, and permits insertion through the abdominal wall with the least amount of tubing stress. This choice must take into consideration not only the patient's physical characteristics and clinical conditions but also the dimensions of the catheter device.

The catheter insertion site and the length of intraperitoneal tubing determine the pelvic position of the catheter tip. Overly deep placement of tubing in the pelvis can be attributed frequently to using the umbilicus as a landmark for catheter insertion and not taking into account the dimensions of the catheter tubing. Excessively deep pelvic placement of the catheter, wedging the tip between the rectum and bladder or uterus, can lead to extrinsic compression of the catheter side holes by these structures resulting in flow dysfunction and pain at the end of effluent drain, especially in combination with the hydraulic suction of automated peritoneal dialysis [6]. To avoid this mistake, the pubic symphysis is recommended as the reference point for optimal position of the catheter tip in the upper part of the true pelvis [7]. With the patient supine and the catheter tubing placed in the paramedian plane, the upper extent of the catheter tip end that is to rest in the upper portion of the true pelvic bowl is aligned with the upper border of the pubic symphysis bone (Fig. 8.3). For straight-tip catheters, preferably a design with 15 cm of tubing length beyond the deep cuff, a point 5 cm from the tip of the catheter is aligned with the pubic symphysis upper border. With coiled-tip catheters, the upper border of the coil is aligned with the upper border of the pubic symphysis. The insertion incision is indicated by marking the upper border of the deep cuff of the catheter in the paramedian plane. This skin incision site will intercept the musculofascial layer at the proper distance above the true pelvis [7].

The incision site will also determine what exit sites can be achieved by the device in question. Catheters with a preformed swan neck bend in the intramural segment must precisely follow the arc configuration, selecting an exit site location 2–4 cm

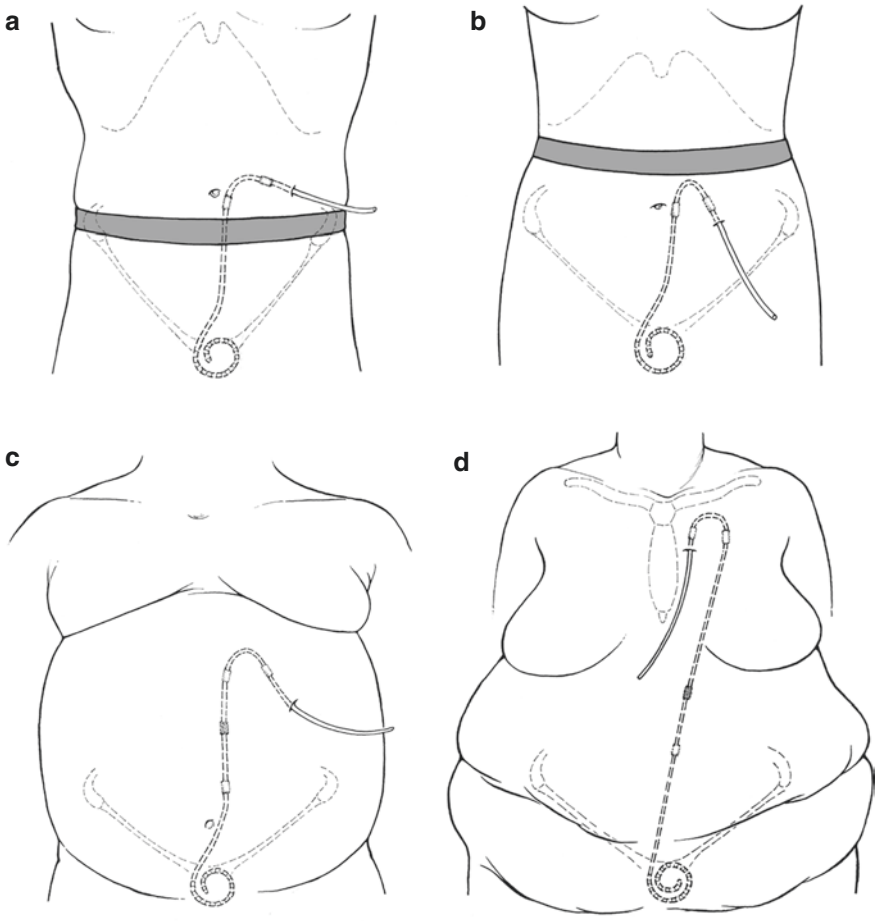

Fig. 8.2 Practical applications of a basic catheter inventory. (**a**) Straight intercuff segment catheter with laterally directed exit site emerging above a low-lying belt line. (**b**) Preformed swan neck intercuff arc bend catheter with downwardly directed exit site emerging below a high-lying belt line. (**c**) Extended catheter with upper abdominal exit site for an obese rotund abdomen, lower abdominal skin folds, or incontinence. (**d**) Extended catheter with presternal exit site for severe obesity, multiple abdominal skin folds, intestinal stomas, or incontinence. (Reprinted from Crabtree and Chow [43] with permission from Elsevier)

beyond the superficial cuff in line with the external limb of the catheter. Catheters with straight intramural segments are best limited to a gentle laterally directed subcutaneous arc in order to avoid inducing excessive forces disrupting tensile memory that can potentially lead to catheter tip migration or superficial cuff extrusion [7]. The exit site is selected 2–4 cm beyond the superficial cuff. A prospective cohort study demonstrated no difference between downward and laterally directed exit

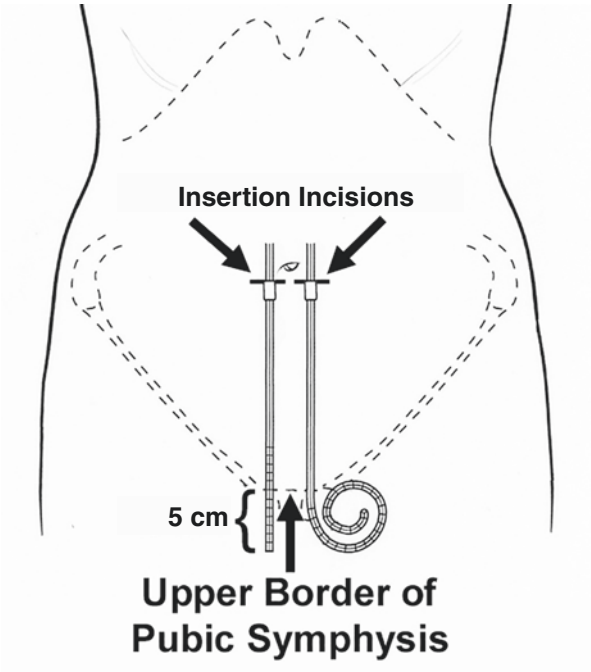

Fig. 8.3 Schematic of a supine patient showing the method in which the catheter insertion site and deep cuff location are determined in order to achieve proper pelvic position of the catheter tip. For straight-tip catheters, ideally a design with 15 cm of tubing length beyond the deep cuff, a point 5 cm from the tip of the catheter is aligned with the pubic symphysis upper border. With coiled-tip catheters, the upper border of the coil is aligned with the upper border of the pubic symphysis. (Reprinted from Crabtree et al. [42] with permission from Multimed, Inc.)

sites with regard to rates of exit site and tunnel infections, peritonitis, and catheter loss [8].

After determining the insertion site to achieve optimal pelvic position of the catheter tip and the exit site that can be reached from this location, the patient is examined in a sitting position. The selected exit site of the catheter being tested must be in a location easily visible to the patient, not within the belt line, inside a skin crease, or on the blind side or apex of an obese skin fold. If the available inventory of single-piece catheters cannot produce both satisfactory pelvic position and exit site location, device selection shifts to a two-piece extended catheter to remotely locate the exit site away from the lower abdominal region to the upper abdomen or upper chest while retaining optimal position of the catheter tip [9, 10].

Instead of the cumbersome use of sample catheters to determine the insertion site that produces optimal catheter tip position and exit site location, a process of stencil-based preoperative mapping is emerging, using marking stencils to provide a reliable and reproducible method of catheter selection [11]. Marking stencils are provided by some dialysis catheter manufacturers for their most commonly used coiled-tip catheter designs. Stencils permit accurate and reproducible association of the catheter design elements to anatomical landmarks to assist in determining the best catheter style and insertion site that will produce optimal pelvic position of the

catheter tip and ideal exit site location. In addition to the preoperative evaluation for catheter selection, the marking stencil is used again at the time of the catheter placement procedure to retrace the previously determined insertion incision, tunnel configuration, and exit site location [12].

The PD access team of each center should agree on a basic catheter inventory and confirm that these specific items are made available for the peritoneal access procedure. A protocol for preoperative mapping should be developed to assure that the patient receives the most appropriate catheter type from this inventory.

Catheter Insertion

Implantation procedures for PD catheters include percutaneous needle-guidewire, open surgical dissection, peritoneoscopy, and surgical laparoscopy. Add-on techniques of extended catheter placement and catheter embedment can be incorporated into any of these procedures. Each method will be summarized followed by a description of completion steps in the placement procedure that are common to all approaches. Regardless of the approach used, observance of a number of details is required to assure the best opportunity for creating a successful long-term peritoneal access. A best practice checklist for preoperative preparation and peritoneal catheter placement is provided in Table 8.1.

Percutaneous Needle-Guidewire Technique

Placement of catheters by blind percutaneous puncture is performed using a modification of the Seldinger technique. The convenience of this approach is that it can be performed at the bedside under local anesthesia using prepackaged self-contained kits that include the dialysis catheter. Often, the technique includes prefilling the abdomen with dialysis or saline solution instilled through an introducer needle inserted through an infraumbilical or paramedian incision [13, 14]. Alternatively, a Veress needle may be used to perform the prefill, or the prefill step may be skipped altogether [15]. A guidewire is passed through the needle into the peritoneal cavity and directed toward the pelvis. The needle is withdrawn. A dilator with overlying peel-away sheath is advanced through the fascia over the guidewire. The guidewire and dilator are withdrawn from the sheath. Optionally, to facilitate insertion, the catheter can be straightened and stiffened by insertion of an internal stylet. If a long guidewire is used, it can be left in the peel-away sheath, and the catheter is threaded over the guidewire. The dialysis catheter is directed through the sheath toward the pelvis. As the deep catheter cuff advances, the sheath is peeled away. The deep cuff is advanced to the level of the fascia.

The addition of ultrasound and fluoroscopic guidance to the percutaneous approach has greatly increased its safety and utility. Comprehensive preprocedural

Table 8.1 Checklist for patient preparation and peritoneal catheter implantation

Preoperative assessment performed by a multidisciplinary PD access team to select the most appropriate catheter type, insertion site, exit site location, and implantation technique
Implement bowel program to prevent perioperative constipation
Shower on the day of procedure with chlorhexidine soap wash of the planned surgical site
If hair removal is necessary, use electric clippers
Empty the bladder before procedure; otherwise, Foley catheter should be inserted
Single preoperative dose of prophylactic antibiotic to provide antistaphylococcal coverage
Operative personnel are attired in cap, mask, sterile gown, and gloves
Surgical site is prepped with chlorhexidine-gluconate scrub, povidone-iodine (gel or scrub), or other suitable antiseptic agent and sterile drapes applied around the surgical field
Peritoneal catheter is rinsed and flushed with saline and air squeezed out of the Dacron cuffs by rolling the submerged cuffs between fingers
Paramedian insertion of the catheter through the body of the rectus muscle with deep catheter cuff within or below rectus muscle
Pelvic location of the catheter tip
Placement of purse-string suture(s) around the catheter at the level of the peritoneum and posterior rectus sheath and/or the anterior rectus sheath
Catheter flow test performed to confirm acceptable function
Subcutaneous tunneling instrument should not exceed the diameter of the catheter
Exit site located ≥2 cm beyond superficial cuff
Skin exit site directed lateral or downward
Exit site should be smallest skin hole possible that allows passage of the catheter
No catheter-anchoring sutures at the exit site
Attach dialysis unit's preferred catheter adapter and transfer set at time of procedure
Exit site protected and catheter immobilized by nonocclusive dressing

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assessment utilizing ultrasound may permit objective case selection for safe percutaneous insertion of catheters in patients who may have otherwise been excluded because of prior abdominal surgery or obesity [16]. During the course of the access procedure, ultrasonography can be used to identify and avoid injury to the inferior epigastric vessels and bowel loops. Fluoroscopy permits confirmation of needle entry into the peritoneal cavity by observing the flow of injected contrast solution around bowel loops [17]. The use of imaging techniques eliminates the need to perform a prefill. The retrovesical space is identified by contrast pooling in this dependent location. The guidewire and catheter are advanced to this site. The remainder of the procedure proceeds as described for blind placement. Although the radiopaque tubing stripe permits fluoroscopic imaging of the final catheter configuration, the proximity of adhesions or omentum cannot be assessed. Practitioners of percutaneous guidewire placement techniques often leave the deep catheter cuff external to the fascia to avoid having to dissect the cuff from the rectus sheath and muscle if subsequent catheter removal is required. After testing flow function, the catheter is then tunneled subcutaneously to the selected exit site.

Open Surgical Dissection

Placement of the PD catheter by open surgical dissection can be performed under local, regional, or general anesthesia [18]. A transverse or vertical paramedian incision is made through the skin, subcutaneous tissues, and anterior rectus sheath. The underlying muscle fibers are split to expose the posterior rectus sheath. A small hole is made through the posterior sheath and peritoneum to enter the peritoneal cavity. A purse-string suture is placed around the opening. The catheter, usually straightened over an internal stylet, is advanced through the peritoneal incision toward the pelvis. The stylet is partially withdrawn as the catheter is advanced until the deep cuff abuts the posterior fascia. After satisfactory placement has been achieved, the stylet is completely withdrawn, and the purse-string suture is tied. (The purse-string suture helps to secure the catheter and prevent leakage of dialysis fluid.) The catheter tubing emerges through the anterior rectus sheath incision or through a separate puncture in the anterior sheath. The fascia is sutured, and the catheter is tunneled subcutaneously to the selected exit site following a satisfactory test of flow function.

Peritoneoscopic Procedure

The peritoneoscopic approach is a proprietary laparoscopic-assisted technique of peritoneal catheter placement (Y-TEC, Merit Medical, South Jordan, UT, USA). Although peritoneoscopy and laparoscopy are synonymous terms, the word peritoneoscopic has been retained by interventional nephrologists to indicate the Y-TEC approach [19]. The procedure is typically performed in a treatment room under local anesthesia. A 2.5-mm trocar with an overlying plastic sleeve is inserted percutaneously into the peritoneal cavity through a paramedian incision. The obturator of the trocar is removed, permitting insertion of a 2.2-mm laparoscope to confirm peritoneal entry. The scope is withdrawn, and 0.6–1.5 L of room air is pumped into the abdomen with a syringe. The scope is reinserted, and the overlying cannula and plastic sleeve are visually directed into an identified clear area within the peritoneal cavity. The scope and cannula are withdrawn, leaving the expandable plastic sleeve to serve as a conduit for insertion of the catheter straightened over a stylet toward the previously identified clear area. The plastic sleeve is withdrawn and the deep cuff is pushed into the rectus sheath. After testing flow function, the catheter is tunneled subcutaneously to the selected exit site.

Surgical Laparoscopy

Laparoscopy provides a minimally invasive approach with complete visualization of the peritoneal cavity during the catheter implantation procedure. Laparoscopic

procedures are performed under general anesthesia in an operating room environment. Surgical laparoscopy uses either a basic or advanced approach to providing PD access. Basic laparoscopic catheter placement is defined as using the laparoscope to merely witness the positioning of the catheter tip within the peritoneal cavity in real time [20, 21], whereas advanced laparoscopic implantation utilizes additional preemptive procedures to minimize the risk of mechanical catheter complications [22–24]. With either approach, a pneumoperitoneum is created by insufflating CO_2 gas through an abdominal wall puncture site using a Veress needle or optical trocar device placed at a location separate from the point of intended catheter insertion. Alternatively, especially when patients have had previous midline abdominal surgery or peritonitis, initial port placement and gas insufflation can be performed by open dissection cutdown to the peritoneal cavity. The laparoscope is inserted at this remote location to guide placement of the PD catheter into the pelvis through a second port device placed at the designated catheter insertion incision. Completion of catheter positioning is the endpoint of basic laparoscopy.

Advanced laparoscopic catheter placement employs proactive adjunctive techniques. Laparoscopically guided tunneling of a port device through the rectus sheath permits placement of the catheter in a long musculofascial tunnel directed toward the pelvis and effectively prevents catheter tip migration, reducing the risk of pericatheter hernias and pericatheter leaks [22–24]. Observed redundant omentum that lies in proximity of the catheter tip can be displaced from the pelvis into the upper abdomen and fixed to the abdominal wall or falciform ligament or folded upon itself (omentopexy) [25–27]. Intraperitoneal adhesions that may affect completeness of dialysate drainage can be divided. Intraperitoneal structures that siphon up to the catheter tip during the intraoperative irrigation test can be laparoscopically resected, e.g., *appendices epiploicae* of the sigmoid colon and Fallopian tubes [25, 28]. Redundant and bulky rectosigmoid colon blocking the pelvic inlet can be suspended along the lateral abdominal wall (colopexy) [25]. Previously unsuspected abdominal wall hernias and patent *processus vaginalis* can be identified and repaired at the time of the catheter placement procedure [24, 25].

The deep cuff of the catheter is positioned in the rectus muscle just below its point of entry through the anterior fascial sheath. A purse-string fascial suture around the catheter at the level of the anterior sheath is recommended to further reduce the risk of pericatheter leak [25]. The pneumoperitoneum is released, but laparoscopic ports are left in place until a test irrigation of the catheter demonstrates successful flow function. After any indicated adjunctive procedures are completed, the catheter is tunneled subcutaneously to the selected exit site.

Extended Two-Piece Catheter Insertion

The abdominal segment of the extended catheter (Fig. 8.1c) can be implanted by any of the above-described insertion techniques [9, 10, 29, 30]. A secondary

incision is made in the vicinity of the planned upper abdominal, presternal, or back exit site. The measured distance between the abdominal insertion incision and the secondary incision is used to determine how much tubing length will be trimmed from one or both of the catheter segments in order to correctly span the distance. The trimmed catheters are joined with a supplied double-barbed titanium connector, and the linked catheter segments are tunneled on the surface of the fascia from the abdominal insertion site to the remote secondary incision with a tunneling rod. The extension catheter is then tunneled from the secondary incision to the exit site using a stylet to complete the procedure.

Catheter Embedding

Commonly described as the Moncrief-Popovich technique [31], catheter embedding consists of implanting a PD catheter far in advance of anticipated need. Instead of leaving the external limb of the catheter exteriorized through the skin, it is embedded in a subcutaneous track. When kidney function declines to the point of needing to initiate dialysis, the external limb of the catheter is retrieved through a small skin incision that can be performed at the bedside or in the office.

Because the catheter has been allowed extended healing time within the abdominal wall, the patient is able to proceed directly to full volume peritoneal dialysis without the necessity of a break-in period. Catheter embedment can serve as a strategy for growing PD programs by achieving early patient commitment to their modality choice. The need for insertion of vascular catheters and temporary hemodialysis can be avoided in patients previously implanted with an embedded catheter. The embedding technique permits more efficient surgical scheduling of catheter placement as an elective nonurgent procedure and helps to reduce stress on operating room access. Disadvantages of the catheter embedding strategy include the need for two procedures (implantation and externalization) as opposed to one and the possibility of futile placement in the event of an adverse change in the patient's condition during the time period that the catheter is embedded or the patient undergoes a preemptive kidney transplant and the catheter is never used [32, 33].

Catheter embedding can be incorporated into any of the implantation approaches using any catheter type. The catheter is temporarily externalized through the future skin exit site prior to embedment. The exit site scar serves as a landmark to know where to come back to for externalization. After acceptable flow function of the catheter is confirmed, the tubing is infused with heparin, plugged, and embedded in the subcutaneous tissue. To minimize the risk of hematoma or seroma and to facilitate later retrieval, the catheter should be embedded in a linear or curvilinear subcutaneous track using a tunneling stylet as opposed to curling the tubing into a subcutaneous pocket [34]. Embedding should not be performed if anticipated need

for dialysis is <4 weeks or if the patient has had previous major abdominal surgery or peritonitis where adhesiolysis may likely leave blood in the peritoneal cavity. Externalization of embedded catheters is easily accommodated in the clinic provided that a suitable procedure room is available. Catheters have been embedded for months to years with an 85–93% immediate function rate upon externalization [32, 34–36]. Catheter dysfunction is usually due to adhesions or intraluminal fibrin clots. Overall, 94–99% are successfully used for dialysis after radiologic or laparoscopic revision of nonfunctioning catheters [32, 34, 36].

Procedure Elements Common to All Approaches

Following catheter insertion by one of the four approaches, it is important to test catheter patency and flow function before accepting placement. A variety of clinical practices exist for testing hydraulic function. A limited approach is syringe irrigation of the catheter with a small volume of saline. Easy return of some of this fluid and changes in the level of an air-fluid interface in the catheter during respiration confirms that the catheter is located in the peritoneum and has no kinks. A more complete test of flow function consists of infusing 500–1000 ml of saline or dialysate and observing for unimpeded inflow and outflow, allowing a 100–200-ml residual volume to avoid leaving peritoneal structures siphoned up to the catheter side holes. Larger irrigation volumes may permit an opportunity for redundant omentum, *appendices epiploicae*, or uterine tubes to drift up to the catheter tip and manifest as a cause for slow or low-volume drainage. Repositioning the catheter may resolve the flow dysfunction, whereas laparoscopic techniques can definitively deal with these identified sources of obstruction and reduce the risk for future mechanical complications. The larger irrigation volume also provides an assessment of hemostasis and washes out any accumulation of blood from the procedure.

After demonstrating satisfactory hydraulic function, the catheter is tunneled to the exit site using a stylet device that does not exceed the diameter of the catheter. Available from most major catheter manufacturers, the Faller stylet is specifically designed for subcutaneous tunneling of catheters and can be advanced through the skin without making a prior incision. The use of hemostat clamps is to be avoided. Patency of the catheter should be checked following tunneling with a syringe flush of saline to demonstrate that the tubing was not kinked during its subcutaneous passage.

The PD unit's preferred catheter adapter and transfer set should be attached at the time of the catheter placement procedure. Although a plastic adapter is provided with the catheter, some PD units prefer a separately supplied titanium adapter. Attaching the preferred adapter and transfer set at the time of the procedure spares

the PD nursing staff from having to go through meticulous sterile preparation procedures to make these necessary connections and risk iatrogenic peritonitis. A final flush of the catheter and attachments with heparin solution may help to minimize the risk of postoperative fibrin plugs.

At the conclusion of the procedure, the catheter and transfer set must be adequately immobilized to prevent traction at the exit site. Catheter-anchoring sutures should not be used. Instead, the catheter can be effectively immobilized with medical adhesive tincture and sterile adhesive strips and a nonocclusive gauze dressing sufficient in size to further secure the catheter.

Similar to hydraulic testing, there is a wide range of postoperative catheter flushing policies among PD centers, if performed at all [37]. The most common practices include flushing with saline or dialysis solution, using 500- to 1000-ml volumes with added heparin, 1000 units/L. The primary reason for flushing is to prevent fibrin or blood clot obstruction of the catheter. A flexible approach can be taken based upon patient conditions at the time of the catheter placement procedure. If bloody effluent is recognized during hydraulic testing and/or the patient undergoes multiple interventions during catheter placement that increases the risk of bleeding, it is advisable to flush the catheter within 24 hours, repeating the lavage until clearing of blood is demonstrated. Unless there is persistence of blood in the effluent, flushes can be extended to weekly intervals until PD is started. If catheter placement is uneventful with negligible blood in the test irrigant, initial flush is performed at 1 week, and then weekly until dialysis is initiated.

Choosing a Catheter Implantation Approach

Operator performance aside, when catheter placement by percutaneous needle-guidewire with/without image guidance, open surgical dissection, peritoneoscopy, and basic laparoscopy are compared with identical study populations, the reported outcomes are not that different [15, 20, 21, 38–40]. However, a recent meta-analysis comparing open dissection, basic, and advanced laparoscopic catheter implantation procedures demonstrated significantly superior outcomes for advanced laparoscopy over the other two approaches with regard to catheter tip migration, flow obstruction, and catheter survival [41]. The strength of advanced laparoscopic implantation is the adjunctive procedures that are enabled by this approach. Nevertheless, the chosen implantation technique must take into consideration patient factors, e.g., anesthetic risk and magnitude of any previous abdominal surgery. Other aspects that influence choice include facility resources supporting the procedure and the expertise and availability of the operating team. Table 8.2 offers guidelines for selecting a PD catheter insertion approach.

Table 8.2 Suggested guidelines for selecting a peritoneal dialysis catheter insertion approach

	Previous major surgery or peritonitis (order of suggested technique)	No previous major surgery or peritonitis (order of suggested technique)
Patient suitable for general anesthesia	Advanced laparoscopic Open surgical dissection	Advanced laparoscopic Image-guided percutaneous Open surgical dissection or peritoneoscopic Percutaneous without image guidance
Patient only suitable for local anesthesia/sedation	Open surgical dissection	Image-guided percutaneous Open surgical dissection or peritoneoscopic Percutaneous without image guidance

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Chapter 9
Peritoneal Dialysis Catheter Insertion by the Nephrologist

Claire Kennedy and Rory McQuillan

Introduction

Timely, quality peritoneal dialysis (PD) catheter placement is the key to PD technique survival and a successful PD program. There are several PD catheter insertion techniques. A surgical approach (open or laparoscopic) under general anesthetic is most commonly used worldwide. Alternatively, percutaneous PD catheter insertion can be performed under local anesthetic by an interventional nephrologist or radiologist. This procedure can be done under ultrasound, fluoroscopic, or peritoneoscopic guidance to improve visibility and safety.

The major advantage of percutaneous PD catheter insertion is related to its simplicity in terms of logistics and staff resources. This approach eliminates the need for an operating room, surgeon, and surgical assistants. It is performed under conscious sedation with local anesthesia, thereby eliminating the need for an anesthetist and avoiding the risks of general anesthesia in these patients with often high anesthetic risk.

These advantages are particularly important in low-resource settings [1]. A successful PD catheter insertion program for Aboriginal and Torres Strait Islanders (ATSI) in Queensland, Australia, was described [2]. The ATSI live remotely and have limited access to and interactions with large hospitals and dialysis units. An outreach PD program, centered on nephrologist-led PD catheter insertions and close involvement with dedicated PD nurses, facilitated the provision of timely and safe PD, despite geographic limitations [2].

The percutaneous approach facilitates immediate catheter use if necessary, as no large surgical incisions are made. Percutaneous PD catheter insertion facilitated a short break-in period for 245 studied patients in India [1]. The mean break-in period was 2.68 (± 2.6) days, with low mechanical and infective complication rates [1].

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Table 9.1 Advantages and disadvantages of percutaneous PD catheter insertion

Advantages	Disadvantages
Avoid anesthesia	Risk of catheter malposition
Less-resource utilization	Risk of damage to intra-abdominal structures
Shorter catheter break-in period	Unable to add-on procedures (e.g., omentopexy)
Shorter patient recovery time	Not all patients are candidates
Careful planning of exit site	

Other advantages of the percutaneous approach include shorter patient recovery time and increased control over the exit site position.

However, the percutaneous approach also has some disadvantages when compared to the surgical approach (Table 9.1). The reduced visibility increases the risk of catheter malposition. Reduced visibility also increases the risk of damage to intra-abdominal viscera. Add-on procedures such as adhesiolysis, omentopexy, hernia repair, and catheter fixation can be employed during surgery and may improve catheter position or function. These add-on procedures are not possible with the percutaneous approach. Meticulous patient selection and preparation are therefore critical to the success of percutaneous PD catheter insertion.

Patient Selection

Careful patient selection is the cornerstone of safe percutaneous PD catheter insertion. It must be clarified that the patient is able to comfortably lie flat for 1 hour. The patient should be reviewed in person by the interventional nephrologist. The medical comorbidities, surgical history, and medications should be considered. A methodical abdominal examination and a bedside ultrasound examination should be performed [3]. The following issues determine suitability for percutaneous PD catheter insertion:

- *Medical History*: Patients with large polycystic kidneys abutting the anterior abdominal wall are not candidates for percutaneous catheter insertion. Adhesions are more likely if there was previous severe PD peritonitis, and so a surgical approach should be considered in this context [4]. A surgical approach is also preferred if an unusual exit site is requested or mandated.
- *Surgical History*: Those patients with a history of major abdominal surgery (particularly if there was a previous midline laparotomy) or multiple abdominal surgeries are not candidates for percutaneous PD catheter insertion due to the risk of adhesions [4]. Minor previous abdominal surgery is not necessarily a contraindication [3].
- *Medications* and allergies should be reviewed. Medications of particular interest are anticoagulants and antiplatelet agents. Suggested dosing of these drugs is

Table 9.2 Utility of ultrasound in the context of percutaneous PD catheter insertion

Patient selection	Visceral slide test
	Subcutaneous tissue depth
	Polycystic kidney disease
	Venous collaterals
Catheter insertion	Empty bladder
	Epigastric artery location
	Bowel loops
	Needle and catheter positioning

outlined in the "Patient Preparation" section. Other pertinent medications are those that delay wound healing and increase the risk of pericatheter leaks, such as corticosteroids and sirolimus [5].

- *Abdominal examination* should be performed with specific attention to the presence of abdominal wall hernias (inguinal, umbilical, or incisional). Those patients who have hernias are best served in the operative setting where the hernia can be repaired at the same time as the catheter is inserted. Patients with extremes of body size carry increased risk with the percutaneous approach.
- *Ultrasound examination* can facilitate patient selection [3] (Table 9.2). In those with polycystic kidneys, kidney proximity to the anterior abdominal wall can be ascertained. The visceral slide test can help identify those with adhesions. Visceral and parietal peritoneal surfaces normally move freely against each other. Adhesions may be present if visceral sliding is <2 cm on deep inspiration and are highly likely if there is absence of visceral slide.

Patient Preparation

There are a number of preparatory steps that should be undertaken in an organized fashion. A series of thorough checklists and protocols (such as for patient preparation, preoperative preparation of the surgical field, and postoperative care), as well as detailed patient information, will help avoid missing any of the following important steps [6]:

- *Patient Education*: Patients should be given basic catheter care and dialysis education prior to consenting for the procedure. It is important to be consistent and thorough with this education as deviations lead to complications and reduced patient satisfaction [7]. Training prior to the catheter insertion should be considered for the most vulnerable patients.
- *Bowel Preparation*: Calcium, oral iron supplements, and any other constipating medications should be held for 1 week prior to catheter insertion to prevent constipation. Patients should fast from midnight prior to the procedure. We administer laxatives for 3 days prior to PD catheter insertion. This is to empty

the bowel, improve the operative field, and reduce the risk of peritoneal contamination in case of bowel injury. However, not all groups advocate bowel preparation as it also has the potential for patient discomfort and electrolyte abnormalities.

- *Anticoagulation*: If the patient is on anticoagulation, decisions regarding periprocedural anticoagulation should be made on a case-by-case basis and occasionally require input from cardiology or hematology colleagues. Ideally, warfarin or other anticoagulant should be held for 5 days prior to the procedure. In some cases, bridging with low-molecular-weight heparin is required; it too should be held for 48 hours prior to the procedure. Antiplatelet drugs (aspirin, clopidogrel, prasugrel) and nonsteroidal anti-inflammatory drugs should ideally be held for 5 to 7 days prior to the procedure. All can be restarted the day after uncomplicated catheter insertion.
- *Skin Preparation*: The patient should wash well with antiseptic soap the night before PD catheter insertion. The operator should carefully mark the skin with a marker pen prior to the procedure and check this site in both sitting and standing positions. The proposed exit site should be visible to the seated patient to facilitate exit site and catheter care, and not coincide with the beltline. Abdominal hair should be clipped, ideally prior to the patient's shower.
- *Diabetic medications* should be adjusted as per local policy.
- *Microbiological Screening*: Although screening for methicillin-resistant *Staphylococcus aureus* (MRSA) and endonasal carriage of *Staphylococcus aureus* is recommended in the International Society for Peritoneal Dialysis (ISPD) guidelines [6], the ISPD also acknowledges that no data exist regarding the effectiveness of screening and eradication of *Staphylococcus aureus* nasal carriage (e.g., intranasal mupirocin) prior to PD catheter insertion [8]. There is some evidence to suggest that prophylactic nasal antibiotics reduce the risk of exit-site infections (but not peritonitis) compared to placebo [9].
- *Antibiotic Prophylaxis*: Single-dose, intravenous antibiotic prophylaxis should be administered to help prevent early-onset peritonitis. A first-generation cephalosporin is most frequently used. A randomized controlled trial from Florida reported reduced early peritonitis with single-dose vancomycin (1 g) compared to single-dose cefazolin (1 g) or no antimicrobial prophylaxis [10]. These benefits should be considered in light of local microbiological patterns and the risks of emerging resistance.
- *Catheter Size*: For an in-depth discussion regarding catheter types and selection, please refer to Chap. 6 of this book. Regardless of catheter choice, an appropriate length should be selected for the patient to optimize patient comfort and catheter function [11]. The catheter tip should sit in the deep pelvis; the pubic symphysis corresponds to this location externally. The planned exit site and the pubic symphysis should be used as the landmarks to guide catheter length and, therefore, planned position of the deep cuff (Fig. 9.1). We have most experience with double-cuff, curled-tip catheters and describe insertion of these catheters below.

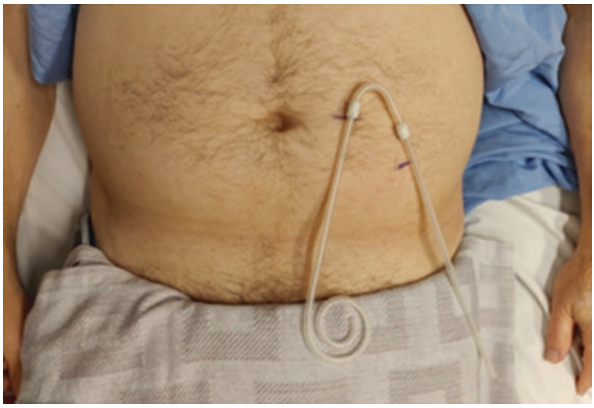

Fig. 9.1 The pubic symphysis is used as an anatomical landmark to help plan catheter length and cuff positioning (using a dummy catheter). This patient's beltline is below the umbilicus. The deep cuff and exit site positions were chosen above the umbilicus and checked in sitting, standing, and lying positions

Resources and Equipment

International guidelines suggest that a dedicated PD access team, comprised of invested nurses, nephrologists, interventional radiologists, and surgeons, is important to streamline catheter insertions and improve catheter outcomes [6, 12]. A nephrologist-led percutaneous PD catheter insertion program needs the support of local surgeons and interventional radiologists, as occasionally backup will be required.

The procedure can be scheduled as an elective outpatient day case for well outpatients. Catheters inserted as an outpatient have comparable outcomes to those inserted during elective inpatient admissions, at almost half of the cost [13]. At the other end of the spectrum, this procedure also facilitates urgent start PD in unwell inpatients, including those in the intensive care unit.

The procedure is performed in a prepared room, with an oxygen supply, suction, and adequate lighting, space, and equipment. Table 9.3 summarizes the equipment and supplies needed to insert a PD catheter safely. Ideally two assistants are present (one scrubbed and one not scrubbed). The patient should have intravenous access secured for antibiotic administration and also in case of emergency or major bleeding.

Peritoneal Dialysis Catheter Insertion Technique

The patient should urinate prior to positioning for the procedure.

A modified Seldinger approach, under ultrasound guidance, is our preferred technique.

Before the procedure, an ultrasound is performed. The bladder is confirmed to be empty, thereby reducing the risk of bladder perforation [14]. A urinary catheter can be inserted if there are voiding dysfunction and incomplete bladder emptying. Color

Table 9.3 Peritoneal dialysis catheter insertion equipment

Patient monitoring	Automated blood pressure cuff
	Oxygen saturation monitor
Imaging	Ultrasound machine
	Sterile ultrasound probe cover and gel
General supplies	Mask
	Sterile gloves
	Sterile gown
	Cleaning solution and scrub brush
	Variety of needles
	Variety of syringes
	Sutures
	Scalpel
	Dressing
Specific supplies	Peritoneal dialysis catheter insertion tray
	Curved Kelly forceps for blunt dissection
	Double-cuff PD catheter kit
	Rigid introducer
	IV pole with Y-tube PD administration set
	2-liter drain bag
	2-liter bag of dialysis solution
	1-liter 0.9% sodium chloride irrigation solution
Medications	Local anesthetic agent
	Midazolam
	Fentanyl
	Heparin
	Metoclopramide
	Intravenous antibiotic

Doppler can identify the inferior epigastric and hypogastric vessels and help the operator to avoid them (aim 2–3-cm distance between insertion point and vessel). Ultrasound can also help to identify a site with maximal separation between the abdominal wall and bowel loops, thereby reducing the risk of bowel injury (Fig. 9.2).

We insert the catheter in a paramedian location, away from the linea alba, for a number of reasons. The linea alba is anatomically weak, and so a PD fluid leak is more likely if the catheter is inserted through it rather than through the rectus abdominis muscle. There is a pre-peritoneal space behind the linea alba which can lead to catheter malposition (Fig. 9.3). Finally, insertion through the rectus muscle, but not the linea alba, allows one to direct the catheter caudally through this muscle belly, thus making migration less likely.

The site should be cleaned thoroughly and the cleaning solution allowed to dry. Sterile drapes are placed. Local anesthetic is infiltrated 2–5 cm below and lateral to the umbilicus, and a small paramedian incision is made. Obese patients will require a larger incision to gain adequate access and visibility. Blunt dissection to the rectus

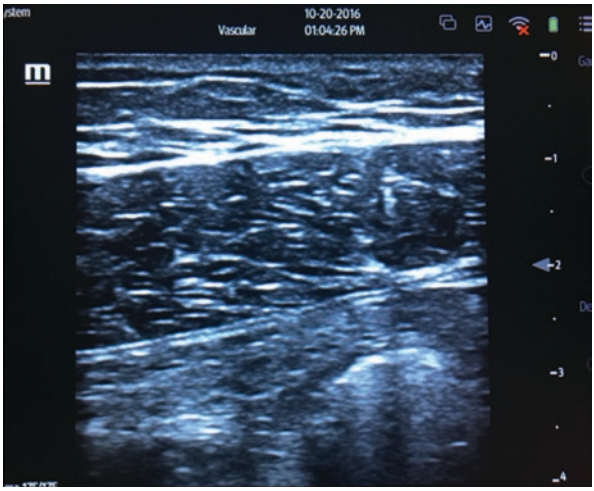

Fig. 9.2 Clear ultrasound visualization of the paramedian abdominal wall layers using the vascular ultrasound probe

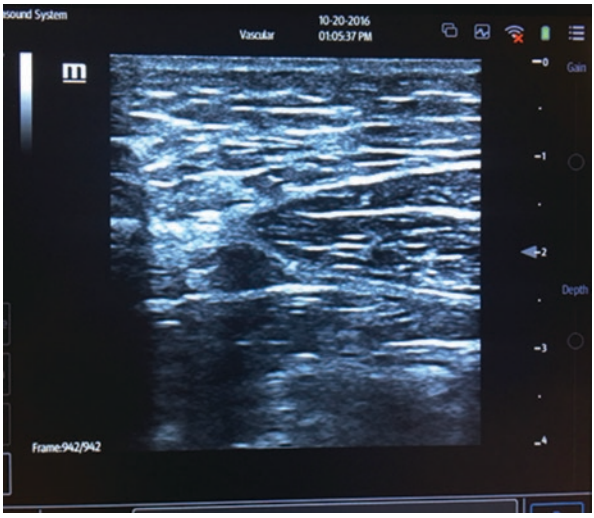

Fig. 9.3 Clear ultrasound visualization of the abdominal wall layers using the vascular ultrasound probe. The thin, anatomically weak linea alba and its pre-peritoneal space are visualized. Catheter insertion through the linea alba has a higher risk of PD fluid leak and malposition compared to insertion through the rectus abdominis muscle

sheath is performed (Fig. 9.4). An 18-gauge needle is inserted into the peritoneal cavity at a 45-degree angle, directed toward the pelvis. This should be done under real-time ultrasound guidance. Upon entry to the peritoneal cavity, there will be reduced resistance, and a "pop" sensation may be felt. Correct needle position is confirmed by painless filling with 500 ml–1000 ml of saline. Ultrasound during fluid infusion demonstrates increased separation of bowel loops.

A 1-mm guidewire is inserted through the introducer needle lumen, and the needle is removed, leaving the guidewire in place. A transverse incision is made on the

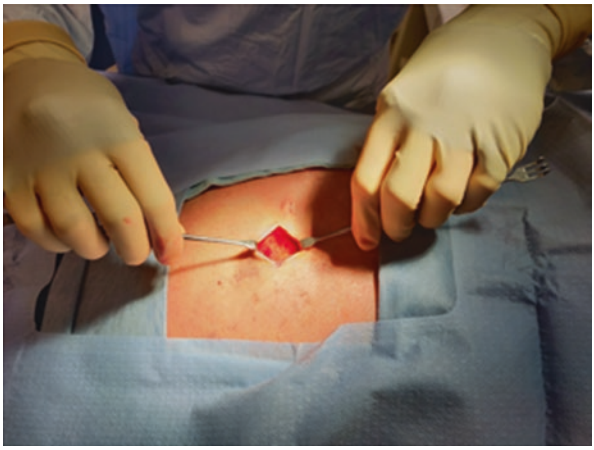

Fig. 9.4 Blunt dissection is performed to the level of the anterior rectus sheath

rectus sheath, and a pocket for the deep cuff is made in the rectus muscle. A 16-French blunt plastic dilator and a peel-away sheath are together threaded over the guidewire into the abdominal cavity. The dilator and guidewire are removed, leaving the peel-away sheath in place. The soft PD catheter, straightened by a rigid introducer, is inserted through the peel-away sheath into the peritoneal cavity, usually aiming for a midline or left lower quadrant position so that normal peristalsis will help keep the catheter in place. The intraperitoneal segment is advanced and the peel-away sheath divided, until the deep cuff is buried in the rectus muscle. The rigid introducer is removed.

The catheter coil position is checked by ultrasound. Infusion and drainage of dialysate confirm catheter position and function. In a well-functioning catheter, 1-liter inflow takes approximately 5 minutes, and outflow takes approximately 10 minutes.

An exit site is created in the pre-planned site with a single stab of the scalpel, which is essentially the exact size of the catheter. The catheter is tunneled to the exit site using the tunneling stylet (Fig. 9.5), and the superficial cuff is placed approximately 2 cm from the exit site. No sutures should be placed at the exit site. The paramedian incision is closed in layers and dressed with a nonocclusive dressing. The adaptor is attached to the catheter, and the catheter is capped with heparin. Erect and supine abdominal radiographs can be performed at this point to confirm catheter position and rule out bowel perforation [15]. Some advocate the use of a lateral abdominal radiograph to visualize the catheter tip in relation to the pelvic brim [16]. Patients are monitored for several hours after the procedure.

Table 9.4 provides a summary of PD insertion technique.

Technique variants may be used. A Veress needle may be used to gain access to the peritoneal space and infuse saline instead of the earlier steps outlined above (Fig. 9.6). The Veress needle has a retractable blunted point as well as a cutting point. The blunted point retracts against high resistance (muscle) exposing the cutting point, whereas the blunted point stays in place against low resistance (bowel).

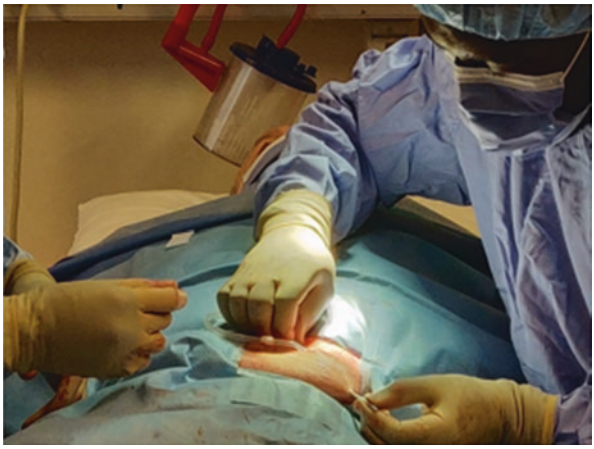

Fig. 9.5 The catheter is tunneled to the exit site using a tunneling stylet

Table 9.4 Summary of PD catheter insertion technique

Bedside ultrasound	Empty bladder
	Identify safe insertion point
Location	Paramedian, through rectus abdominis muscle
Site preparation	Cleaning solution, sterile drapes
	Local anesthetic
	Blunt dissection to rectus sheath
Access peritoneal cavity	18-gauge needle, confirm with saline
	Guidewire, remove needle
	Dilator and peel-away sheath, remove guidewire and dilator
Insert PD catheter	PD catheter and rigid introducer, peel-away sheath removed simultaneously
	Rigid introducer removed
Check position	Ultrasound
	Dialysate infusion and drainage
Exit site	Single stab of scalpel
	Tunneling stylet
Final steps	Suture paramedian incision (*not* exit site)
	Attach transfer set, cap with heparin
	Monitor patient for several hours

The "trochar method" utilizes a large bore trochar with a sharp-pointed stylet, which is inserted through the linea alba. The tract and insertion sites are larger, and so leaks are more common [17]. The modified Seldinger approach described above is generally considered simpler and safer.

Fluoroscopic guidance incorporates intraperitoneal contrast to identify peritoneal structures and confirm correct positioning of the catheter. Radiocontrast is injected following entry into the peritoneum. The spider-like movement of contrast

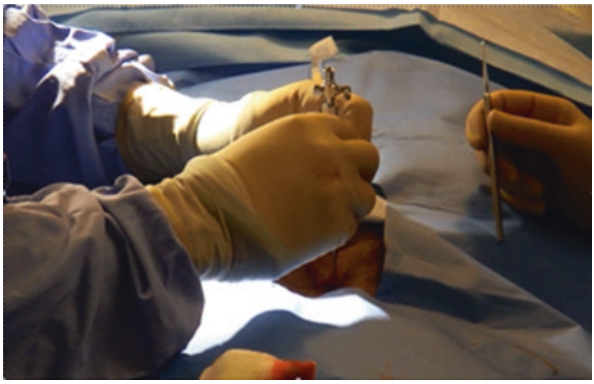

Fig. 9.6 Insertion of the Veress needle through the linea alba

into the spaces between peritoneal layers confirms correct needle position. If the needle is incorrectly positioned, the pattern of contrast movement is different. For example, if the needle is positioned in the bowel, the contrast will spread and fill the bowel loop. If the needle is positioned in visceral fat, the injected contrast forms a round shape. The course of the guidewire can also be tracked. When the catheter is placed, contrast injection can confirm final position. It is important to note that the quality of the images is often poor and may not identify omentum or adhesions.

Peritoneoscopic guidance utilizes a small peritoneoscope/laparoscope to enable direct visualization of the peritoneal cavity (although introduction of the peritoneoscope is blind) [18]. This is performed by the nephrologist (or interventional radiologist) under local anesthetic, in contrast to laparoscopic PD catheter insertion, which is performed by a surgeon in the operating room under general anesthetic.

Peritoneoscopy involves insertion of a 2.5-mm trochar with a plastic sleeve into the peritoneal cavity through a paramedian incision. The trochar obturator is removed, a 2.2-mm peritoneoscope inserted, and correct positioning within the peritoneal cavity is confirmed. The peritoneoscope is withdrawn, and room air is insufflated into the abdomen using a hand pump. The peritoneoscope is re-inserted, and a clear area within the peritoneal cavity, suitable for catheter placement, is identified and the equipment guided there. The peritoneoscope and cannula are withdrawn, leaving the plastic sleeve behind. This serves as a guide for insertion of the PD catheter over a stylet. The plastic sleeve is withdrawn leaving the PD catheter in place. The catheter is secured and tunneled as was described for the Seldinger approach.

Complications

A small amount of ooze at the exit site is normal. Blood-tinged dialysate, which clears on subsequent flushing, is also considered normal after catheter insertion. The major procedural complications, which may require urgent surgical intervention, are organ perforation, major bleeding, or catheter malposition (Table 9.5).

Table 9.5 Potential complications of percutaneous PD catheter insertion

Minor
Minor bleeding
Blood-tinged dialysate
Major
Catheter malposition
Bowel perforation
Bladder perforation
Major bleeding

Table 9.6 Early PD catheter care

Do not disturb the dressing (unless heavily soiled with blood)
Do not bathe/shower until exit site healed
Take analgesia for the pain; the pain should improve daily
Ooze may occur and should be managed by applying additional dressings over the original dressing (do not remove the original dressing)
Extensive bleeding mandates hospital attendance
Regular laxatives to encourage daily bowel movements
No driving for 1 week
No heavy lifting for 6 weeks

Bowel perforation occurs in less than 1% of procedures. It usually occurs at the time of entry into the abdominal cavity or when the catheter is advanced into the pelvis. It may present with sudden abdominal pain, a hissing sound, foul smell from gas release, watery stool with dialysate inflow, or cloudy/feculent dialysis effluent. Bladder perforation may present with sudden pain, extreme urinary urgency, and massive "urine" volume with dialysate inflow. Dipstick analysis of the feces or urine respectively shows high glucose due to the presence of dialysate.

Inflow through a malpositioned catheter (e.g., pre-peritoneal position) may be painful. Drainage may be minimal and may be clear initially and later blood-tinged. Major bleeding is seen in <1% of procedures. It may be evident externally at the catheter site or with hemoperitoneum that does not clear with flushing.

Early Peritoneal Dialysis Catheter Care

A dry, nonocclusive dressing should be applied at the time of catheter insertion. The catheter should be separately immobilized to the abdominal wall with fixing tape (so that it can be accessed without disturbing the exit site dressing).

The patient should be given detailed advice about early catheter care, as summarized in Table 9.6. Laxatives are typically given to avoid straining with constipation, which can increase the intra-abdominal pressure and increase the chance of dialysate leaks.

Approximately 7 days post-catheter insertion, the patient should attend for a dressing change by a PD nurse using sterile technique. The catheter should be flushed at this time; we use 1 liter of heparinized dialysate with a heparin lock. If the effluent is bloody after the first flush, additional flushes should be performed until the effluent clears.

Dressing changes and catheter flushes are typically performed weekly for 3 weeks. At this time, the exit site should be fully healed, the patient can assume exit site care, and the catheter can be used for PD training. Centers differ with respect to the use of topical antibiotic cream at the exit site. Regardless of local policy, topical antibiotic cream is not recommended until the catheter exit site has fully healed.

Patient Outcomes

The careful patient selection described above, with exclusion of higher-risk candidates, leads to difficulty comparing outcome data for the various catheter insertion techniques. Additionally, there are few prospective or randomized trials to guide practice.

Surgical and percutaneous approaches have been compared in a number of published reports. A systematic review summarized 13 heterogeneous studies ($n = 2681$ patients). The compiled results suggested that outcomes with the percutaneous approach were similar to outcomes with the surgical approach (open, laparoscopic, or peritoneoscopic) in terms of 1-year catheter survival, catheter dysfunction, and PD fluid leaks. A lower incidence of peritonitis was observed at 1 year in those who underwent percutaneous placement (incidence rate ratio 0.77, $p = 0.02$) [19].

As mentioned, selection bias is unavoidable. One group attempted to account for this by retrospectively comparing outcomes in patients with no history of prior abdominal surgery who underwent first PD catheter insertion (i.e., all eligible for percutaneous approach). 63 patients underwent percutaneous PD catheter insertion, and 64 underwent surgical PD catheter insertion over a 7-year period. There were no significant differences between groups with respect to peritonitis, exit site leak drainage failure, and catheter survival at 3 and 12 months [20].

Program Outcomes

A successful percutaneous PD catheter insertion program has been shown to have a positive impact on PD utilization. A review of PD uptake in three centers in Florida was undertaken [21]. The proportion of patients with incident end-stage kidney disease choosing PD was relatively stable over several years at 16%, 17%, and 18%. A peritoneoscopic PD catheter insertion program was rolled out and PD uptake rose to 32%, 22%, and 27%, respectively. The nephrologist-led catheter insertion program was discontinued some years later, and the overall uptake across the three sites fell

to 6%. The authors credited the percutaneous catheter insertion program with the positive trend in PD uptake [21].

A Canadian population-based cohort study reviewed 3886 patients with advanced chronic kidney disease who underwent open surgical, laparoscopic, nephrology-percutaneous, or radiology-percutaneous catheter insertion [22]. 83% of all patients ultimately received PD. After adjustment, PD utilization was shown to be highest in the nephrology-percutaneous group, compared to other three groups. It was suggested that this was related to optimized catheter insertion timing, excellent technique, and greater nephrologist commitment to PD success [22].

Interesting variations in PD uptake were demonstrated in the 2013 UK Renal Registry review [23]. 20.1% of incident dialysis patients started PD. 68% of those centers with nephrologist-led catheter insertion programs (13 of 19 centers) reported over 20% of incident dialysis patients starting PD. 50% of those centers with surgeon-led catheter insertion programs (7 of 14 centers) had over 20% of incident dialysis patients starting PD [23].

Financial Considerations

As percutaneous PD catheter insertion may be performed as an outpatient, without the need for anesthesia, surgeon, or other operating room resources, the costs are substantially less than those associated with surgical catheter insertion [13]. Formal cost-effectiveness analysis of a percutaneous PD catheter insertion has not been performed to date.

Dialysis reimbursement policies vary worldwide and can impact on the uptake of the home dialysis modalities including PD. There has been a recent switch to a "bundled" prospective payment system of reimbursement for Medicare-covered dialysis patients in the United Sates, which has incentivized home dialysis provision. Increased reimbursement for percutaneous PD catheter insertion has also incentivized this procedure by interventional nephrologists or radiologists. The authors feel that in order to ensure growth of PD as a modality, incentives aimed at promoting PD catheter insertion should be attached to the patient successfully performing PD at home rather than to the catheter insertion per se. Incentivizing the insertion itself may lead to an increase in poorly placed catheters.

Quality Improvement

It is incumbent on all interventional nephrologists to review their catheter outcomes in a transparent way and continually strive for quality improvement. Several international recommendations regarding PD catheter insertion quality improvement have been made.

Operator Training

Operator experience is paramount to the success of the technique. Each operator should have adequate training and supervision prior to independent catheter insertion, as outlined by the American Society of Diagnostic and Interventional Nephrology [24]. It is recommended that these skills be gradually built by observing a catheter insertion, assisting with a catheter insertion, supervised catheter insertions (six in a 1-year period), and independent catheter insertions (ten in a 6-month period to consolidate skills, with a logbook record). Following review of the logbook procedures and catheter outcomes with an experienced operator, additional supervision or training may be deemed necessary.

The operator is most often a nephrologist or interventional radiologist but may also be a specialist nurse or a physician assistant. The operator skillset may extend to PD catheter removal, buried PD catheter exteriorization, and PD catheter manipulation. PD catheter insertion training courses are available in various high-volume centers internationally and provide anatomy teaching, ultrasound instruction, and hands-on simulation experience.

A quality control tool such as a cumulative summation chart may help plan and track training. The use of this tool for peritoneoscopic PD catheter insertions was described [25]. The chart followed the trainees' learning curves and demonstrated curve flattening as training advanced and the trainees became more skillful. Technical proficiency was observed after 23 procedures [25].

Ultrasound skills are invaluable as outlined above and increase safety with minimal additional resource utilization. The use of fluoroscopic or peritoneoscopic guidance necessitates significant additional resources and training [26].

Local Audit

The ISPD recommends that each program perform continuous audit of catheter insertions and outcomes, with a multidisciplinary review of the results at least annually [6]. Suggested audit outcomes of interest with their corresponding targets are outlined in Table 9.7. The primary marker of successful outcome is >80% catheter patency at 1 year.

Table 9.7 Audit outcomes

	Target
Number of insertions	
Waiting time	
Bowel perforation	< 1%
Significant hemorrhage	< 1%
Early exit site infection (14 days)	< 5%
Early peritonitis (14 days)	< 5%
Functional catheter problem requiring manipulation/replacement/modality change (1 year)	< 20%

Program Collaboration

Collaboration among centers is also crucial to foster operator training, standardize access to PD, and benchmark outcomes. The UK Renal Registry, for example, coordinates a regular multicenter PD access audit across England, Wales, and Northern Ireland.

Conclusions

The success of a PD program depends on timely access to high-quality PD access. We suggest that a PD access program with dedicated staff and resources for both percutaneous and surgical PD catheter insertions offers exactly this.

Given the reduced visibility with the percutaneous approach and therefore increased risk of catheter malposition and organ perforation, patients should be carefully selected for this procedure and meticulously prepared. Several technique variations exist, all of which are followed by fastidious early catheter care. Where available, ultrasonography, fluoroscopy, and peritoneoscopy can increase the safety of the procedure by increasing visibility. A percutaneous catheter insertion program can impact positively on patient and program outcomes in high- and low-resource settings alike.

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Chapter 10
Peritoneal Dialysis Adequacy

Ali Z. Ibrahim and Joanne M. Bargman

The Importance of Time Compared to Small Solute Clearance

In discussing how adequacy has been considered throughout the history of peritoneal dialysis (PD), one must first understand the concept of uremia and how its treatment evolved. Principally, the ideas that ultimately led to interventions such as the Giovannetti diet stemmed from the notion of by-products of protein metabolism being causative of the uremic syndrome [1]. This diet, which consisted of protein restriction to minimize production of urea, demonstrated the emphasis placed on plasma chemistry in shaping how dialysis adequacy was measured.

In subsequent years, Scribner and others noted that chronic PD patients experienced improvement or stabilization of uremic symptoms, such as neuropathy, compared to their hemodialysis (HD) counterparts, despite the observation that PD had less reduction of plasma creatinine and urea [2]. They hypothesized that the peritoneum was more permeable and effective at removing higher molecular weight uremic solutes than was HD [2]. Such solutes, by virtue of their size, were removed at a slower rate than urea and were less effectively removed by cellulose HD membranes, particularly during treatments that lasted only a few hours. What followed was the idea that removal of such higher weight solutes in the HD patient necessitated a minimum number of hours of dialysis per week, rather than on specific plasma chemistries of urea and creatinine. This formed the basis of the "square meter per hour" hypothesis, which suggested that inadequate removal of middle

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molecules was responsible for uremic complications and that in HD their removal was proportional to time on dialysis (more specifically the product of dialysis hours and the useable surface area of the dialyzer measured in square meters) rather than measured conventional solute chemistry (urea and creatinine) [3]. In essence, this emphasis of improving patient symptoms by focusing on dialysis time over specific solute concentrations formed some of the understanding of PD adequacy and its effect on the understanding of symptomatic uremia.

A Solute Shift

While understanding the complexity of uremia was made difficult by the inability to measure non-urea middle molecular weight uremic toxins, some efforts were made in later years to determine dialysis timing and dosing effects on patient outcomes. A landmark work in this respect, the National Cooperative Dialysis Study (NCDS), sought to explore this relationship in hemodialysis patients [4]. Designed as a two-by-two randomized controlled trial, the groups were divided into low vs. high time-averaged urea concentrations and long vs. short dialysis time. The main outcome of interest was hospitalization rates for nonaccess-related problems. In this design, urea concentration changes could be seen as a surrogate for small molecular weight uremic toxin clearance, with dialysis time representing a surrogate for clearance of middle molecular weight uremic toxins [5]. Interestingly, overall both low urea concentration and longer dialysis time were associated with lower hospitalization rates. The dialysis time variable, however, was just shy of statistical significance ($p = 0.06$). A distinction needs to be made here regarding such results that may have clinical validity but are erroneously discarded as irrelevant for not reaching the appropriate p value [6]. It is important also to note that certain exclusion criteria limit the external validity of the NCDS. For instance, patients with diabetes, uncontrolled hypertension, systemic disease, and cancer were excluded. These populations, of course, form the bulk of dialysis patients currently.

Regardless, these findings led to a shift in focus from dialysis time to urea concentration as the basis to measure dialysis dose and outcome. What followed was an attempt by Sargent and Gotch to adopt a pharmacokinetic model relating treatment and blood urea concentrations; this led to formulation of Kt/V urea [7]. A secondary analysis of NCDS data using Kt/V urea led to solidification of this relationship as a "step" function, where a value less than 0.8 was associated with greater morbidity, and a value greater than 0.8 was associated with lower morbidity [8]. There was no gradation of association, no causation identified, and most importantly, no randomized controlled trial to validate Kt/V as a suitable predictor of meaningful patient outcomes. Furthermore, the acceptance of a step function was unique, as little in biology or physiology relates outcome as behaving via this kind of function.

Despite the lack of validation, Kt/V urea became a standard for dialysis dosing thereafter. Accordingly, with no other established metric, the utility of Kt/V urea as

a predictor of clinical outcomes was readily applied to continuous ambulatory peritoneal dialysis (CAPD) by Teehan et al. [9]

Putting Solute Clearance to the Test

The question of solute clearance as it related to peritoneal dialysis adequacy led to another landmark work on the subject, the CANUSA study [10]. The purpose of this study was to examine the relationship among dialysis adequacy, nutrition, and clinical outcomes. 680 incident peritoneal dialysis patients, the majority of whom (98%) were undergoing CAPD, with the remainder on continuous cycling peritoneal dialysis, were studied. The study utilized Cox proportional hazards modeling with dialysis adequacy and nutritional status as time-dependent covariates, with the main outcomes being mortality, technique failure, and hospitalization.

Overall, there was an increase in the relative risk of death with age, presence of diabetes, presence of cardiovascular disease, and lower Subjective Global Assessment of nutrition. Interestingly, there was an association between increased mortality and lower creatinine clearance, which at this stage was defined as the sum of renal and peritoneal clearances, with no distinction between the two. It is worth noting that out of the 680 study patients, only 90 had died within the study period, with the majority of other included patients being administratively censored at the end of the study period. Accordingly, the mortality results are mostly based on interpolated data and modeled curves rather than actual survival data [10].

Despite its limitations, the CANUSA study results reinforced the notion that with greater total small solute clearance, PD patients achieved better outcomes. This, in turn, led to a trend toward increased dose of PD, measured by Kt/V urea. This was so prevalent that it led to further reinforcement by the Dialysis Outcomes Quality Initiative (DOQI) guidelines in 1997, which suggested a weekly target Kt/V of 2 for CAPD, 2.1 for CCPD, and 2.2 for intermitted PD (IPD), with a creatinine clearance target of 60 liters per week [11]. However, due to the observation in CANUSA that low (slow) transporters who had lower creatinine clearances had better survival, the Canadian Society of Nephrology then decreased the target clearance in low and low-average transporters to 50 liters per week.

The axiom of higher clearance translating to a mortality benefit for PD patients was prevalent in North America in light of these recommendations, despite no randomized controlled trial evidence. A challenge to this concept came in the form of the ADEMEX study, a Mexican-based prospective randomized controlled trial examining the effects of increased peritoneal clearance thresholds on mortality rates in PD patients [12]. In short, ADEMEX investigators randomized 960 patients into a control group receiving 8 liters of dialysate a day, and an intervention group receiving 10–12 liters per day to a weekly creatinine clearance of 60 liters per week, consistent with DOQI guidelines. Despite a difference in Kt/V between the control and intervention group (average peritoneal Kt/V urea 1.62 vs. 2.13), survival rates

between the two groups were equal. This held true even with stratification by factors such as age, diabetes status, and serum albumin.

ADEMEX marked a departure from the reliance on small solute clearance in PD patients as a predictor of improved mortality. Lo et al. also examined Kt/V targets and clinical outcomes in a randomized prospective study in Hong Kong, randomizing CAPD patients to Kt/V thresholds of 1.5–1.7, 1.7–2, and greater than 2 [13]. No survival benefit was found with higher Kt/V than 1.7, but interestingly, patients maintained at lower Kt/V of 1.7 were deemed by their physicians to have "inadequate dialysis and ultrafiltration." Nutritional indices and hospitalization were similar across groups. The authors concluded that a Kt/V of less than 1.7 was therefore associated with more "clinical problems." With that in mind, there is no clearly defined and evidence-based lower limit for Kt/V in peritoneal dialysis.

This wave of critically examining the reliance on small solute clearance touched on the hemodialysis world as well, as exemplified by the HEMO study [14]. In this study, hemodialysis patients were randomized to low- vs. high-dose hemodialysis (Kt/V 1.2 vs. 1.6), again with no difference in clinical outcomes. These studies suggested no survival advantage with higher Kt/V urea or creatinine clearance, meaning high-dose dialysis regimens were onerous without significant benefit. The results from these trials posed an important question: What else can then be considered in predicting clinical outcomes for PD patients if we cannot rely on small solute clearance, namely, Kt/V urea or creatinine clearance?

The Role of Residual Kidney Function

The answer to effective PD adequacy may be a multipronged approach of maximizing peritoneal uremic toxin clearance while maintaining residual native kidney function and urine volume. This is in contrast to a strict focus on small solute clearance. In a reanalysis of the CANUSA data by Bargman et al., the investigators sought to separate the effects of residual renal clearance from that of peritoneal clearance which were simply added together in the original CANUSA report. In doing so, we were able to demonstrate that the signal for improved survival was driven exclusively by renal clearance. The scale of renal clearance needed for a clinically significant reduction in mortality was impressive; just 0.5 mL/min of glomerular filtration rate was associated with a 12% survival advantage. In addition, every 250-mL increment in daily urine volume was associated with a 36% reduction in the relative risk of death [15]. This association between residual kidney function and improved survival has been demonstrated in several other studies [16–18].

There are no clear established reasons why residual kidney function confers such mortality benefit for PD patients. It may be an epiphenomenon representative of a healthier patient overall, and so such a patient would naturally have a lower mortality. Inflammation, as a possible comorbid condition affecting both residual kidney function and mortality, has been explored as an important factor [19–21].

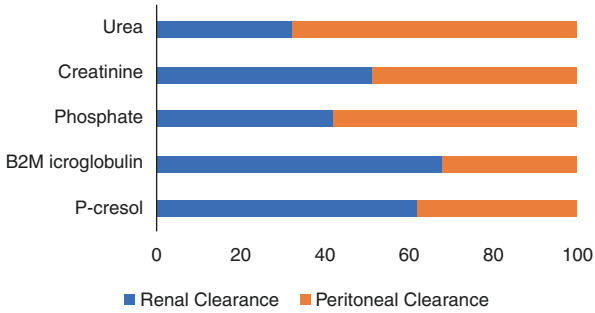

Fig. 10.1 Percentage of peritoneal and renal clearance of uremic molecules

Pecoits-Filho et al. have shown an association between loss of residual kidney function and a rise in inflammatory markers such as IL-6 and CRP [22]. Improved total sodium and water removal and maintenance of volume status may also explain the mortality benefit of residual kidney function in PD patients [23, 24]. This is particularly important knowing that volume overload with hypertension and left ventricular hypertrophy is a frequent problem in PD patients [25]. Lastly, Bammens et al. also demonstrated that renal clearance may play a larger role in clearance of middle molecular weight uremic toxins (e.g., beta-2 microglobulin and p-cresol) (see Fig. 10.1 adapted from original paper) [26].

Adding to the concept of residual kidney function aiding in clearance of uremic toxins, beyond small molecules such as urea, Leong et al. demonstrated a similar effect in hemodialysis patients. Particularly, they showed that patients without residual kidney function undergoing hemodialysis thrice weekly accumulated more toxic levels of uremic secreted middle molecular solutes than patients dialyzing twice weekly but with residual kidney function. It is worth noting that the difference was not compensated by the additional hemodialysis treatment despite the consequent increased weekly Kt/V urea [27].

Euvolemia as an Adequacy Measure

In addition to improvement in clearance of middle molecular weight uremic toxins, achieving volume control with adequate ultrafiltration is an important parameter to consider in PD adequacy. This concept was elucidated in the European APD Outcome Study (EAPOS) which sought to identify baseline predictors survival in anuric PD patients [28]. In this prospective cohort, the authors found that among other predictors (diabetes, poor nutritional status, advanced age), baseline ultrafiltration of less than 750 mL/24 h was associated with poor survival. Interestingly, baseline creatinine clearance was not found to have an effect on either patient or technique survival.

This result may agree with that seen in the previously mentioned ADEMEX study [12], in which increased solute clearance was not found to be associated with mortality benefit, with the knowledge that almost half of the study patients were anuric. A corollary to consider is that poor ultrafiltration may have possibly contributed to some of the mortality in the study patients.

Volume maintenance through adequate ultrafiltration, while important for patient outcomes, needs to be balanced against the risk of over-ultrafiltration and volume depletion, which may result in reduction in residual kidney function [29].

Maintenance of Residual Kidney Function

Maintaining residual kidney function in PD patients utilizes similar strategies to those used in pre-dialysis chronic kidney disease patients (Table 10.1). First and foremost, avoidance of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) is encouraged. The use of intravenous contrast is discouraged unless absolutely necessary, and in such cases, ensuring the patient is well hydrated is recommended [30]. Some centers recommend the use of N-acetylcysteine (NAC) to mitigate the risk of contrast-induced nephropathy, but evidence for this is lacking [31].

Despite the trepidation of some clinicians in using angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) in kidney patients, evidence actually shows a correlation with preserved residual kidney function with the use of these drugs in PD patients [32, 33]. Efforts should be made particularly to increase their utilization in patients who were taken off these medications due to hyperkalemia in the pre-dialysis end-stage kidney disease treatment phase.

With regard to kidney transplant patients with failing allografts transitioning to PD, there is some evidence to suggest continuing immunosuppression if the glomerular filtration rate is greater than 1 mL/min [34, 35]. This is extrapolating a similar mortality benefit as had been seen in the CANUSA reanalysis [15]. The choice of medication for immunosuppression has not been well studied, but minimizing calcineurin inhibitors (CNI) due to their known risk of nephrotoxicity is suggested.

Table 10.1 Strategies to preserve residual kidney function in PD patients

Strategies to preserve residual kidney function
Avoiding NSAIDs
Discouraging IV contrast use, but if needed, ensuring euvolemia and considering NAC
Increasing use of ACEi and ARBs
Maintaining immune suppression for functioning allografts, minimizing CNI exposure
Avoiding extracellular fluid volume depletion

Table 10.2 Strategies to increase PD dose

Strategies to increase PD dose
Increasing dialysate fill volume
Increasing number of exchanges
Using night cycler to increase exchanges while decreasing cycle length
Adding icodextrin day dwell

Practical Ways to Increase Adequacy

As mentioned previously, maintaining PD adequacy is a multipronged approach that includes maximizing peritoneal clearance with the dialysis prescription while maintaining residual kidney function as discussed above. The upcoming International Society for Peritoneal Dialysis Practice Recommendations will focus on a prescription in the context of the patient and his/her goals rather than targeting small solute clearance parameters [38].

If a patient is clinically and biochemically suspected to be under-dialyzed, several changes to the PD prescription can help increase the adequacy of peritoneal clearance (Table 10.2). The first change would be a total increase in the volume of dialysate used, by way of fill volume and number of exchanges. Increasing fill volumes increases volume of diffusion as well as the recruitment of peritoneal membrane surface area. This enhances solute clearance and ultrafiltration [36]. Additional exchanges may also enhance overall adequacy but can become onerous requiring additional therapy time in patients on automated peritoneal dialysis (APD). A large number of exchanges can also be onerous to those patients on CAPD. Such patients who undergo nightly exchanges via an automated cycler are best served by adding a day dwell of icodextrin solution which enhances solute clearance and ultrafiltration while maintaining a reasonable therapy time overnight [37]. This day dwell can be maximized in volume as well keeping in mind patient comfort and activity.

Summary

In considering the evolution in understanding of PD adequacy, we can appreciate that small solute kinetics have not been proven to fully capture how PD treats and ameliorates symptoms of kidney failure. The clearance of middle molecular weight toxins and the importance of volume control and preservation of residual kidney function are all important concepts that need further attention and understanding. Above all, emphasis needs to be placed on patient-important outcomes such as morbidity, mortality, and quality of life.

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Chapter 11
Techniques in Peritoneal Dialysis

Vikram Aggarwal and Martin J. Schreiber Jr.

Introduction

Understanding peritoneal physiology and technical innovations in peritoneal dialysis has led to a significant reduction in therapy-related complications over the last four decades. Technology and techniques to perform peritoneal dialysis (PD) have evolved and, in its current form, are reliable, easy to use, and come at an acceptable cost. Also, various regimens and modes of PD allow for social interaction and optimizing PD efficiency in terms of solute clearance and fluid removal. Overall, the successful advances in PD techniques have prompted broader utilization and served as the foundation for major ESKD healthcare reform initiatives in the USA to support further growth of home-based dialysis [1]. We will outline procedural principles and details of variations of flow techniques (tidal, intermittent, or continuous), regimens [intermittent PD (IPD or continuous PD (CPD)], and modes of PD (manual or automated). These strategies allow for using tidal PD (TPD), continuous flow peritoneal dialysis (CFPD), assisted peritoneal dialysis, urgent-start PD, incremental PD, and remote patient monitoring (RPM) in clinical practice [2]. We will also outline various approaches that can further enhance the scope of PD usage in specific clinical situations.

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PD Technique and Related Glossary

PD Exchange

The PD technique involves stepwise procedures to connect the PD catheter and perform PD exchange. Maintenance of standard aseptic precautions during PD exchanges to prevent PD-related infectious complications is an integral part of PD technique. The success and longevity of PD largely depend on the quality of initial training and how the patient follows the appropriate technique to the last detail.

A typical manual PD exchange consists of several steps [Fig. 11.1]:

- *Drain* (outflow): In this initial step, the indwelling fluid from the previous exchange is allowed to flow into an empty bag. Draining typically takes 10–20 minutes. The amount of fluid drained during each exchange is referred to as drain volume.
- *Fill* (inflow): After the initial "flush before fill," the PD solution is allowed to flow into the peritoneal cavity via the afferent limb of the Y-shaped tubing. This phase usually takes about 10 minutes. PD solutions are usually warmed to body temperature before use. The amount of PD solution used to fill the peritoneal cavity is referred to as fill volume.
- *Dwell*: After filling peritoneal cavity, the PD solution stays for specific dwell time to allow for the solute exchange and ultrafiltration.

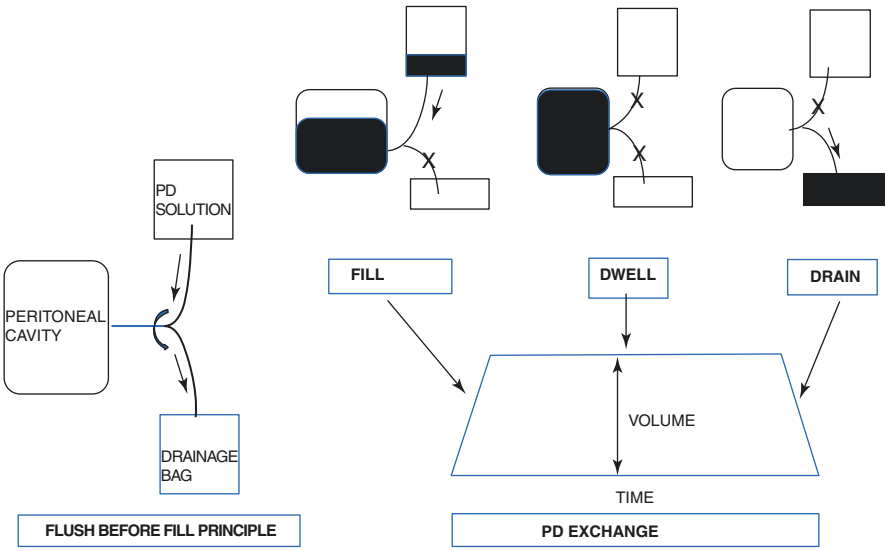

Fig. 11.1 Typical PD exchange demonstrating fill, dwell, and drain phase with relation to intraperitoneal fluid volume and time

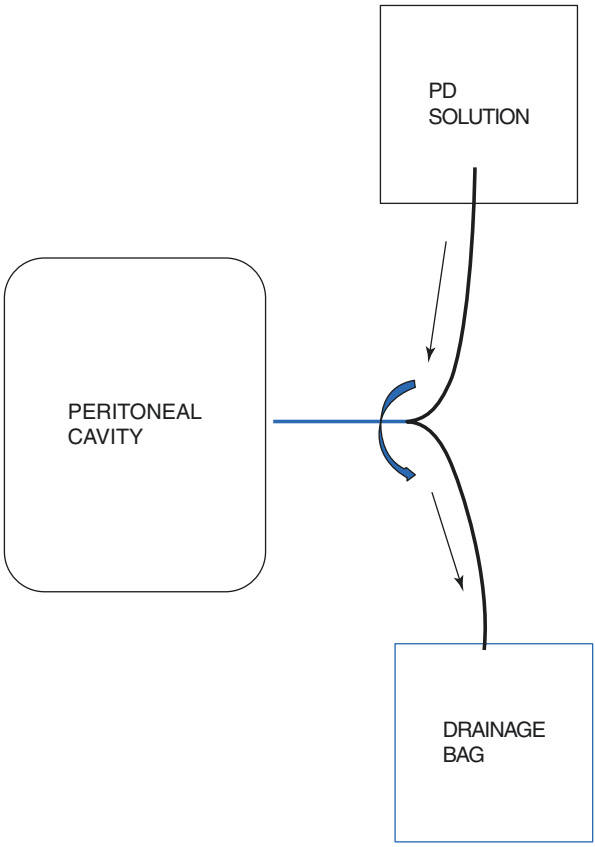

Fig. 11.2 Flush-before-fill principle: PD solution is allowed to flow into the peritoneal cavity via the afferent limb of the Y-shaped tubing before the start of the fill phase of the exchange

At the start of the PD exchange procedure, the "Y tubing set" is connected to the PD catheter via a transfer set and extension tube. The Y-set tube has an afferent limb which is connected with a fresh dialysate bag and an efferent limb with a drainage container attached. The Y system connectology applies the "flush-before-fill" principle [Fig. 11.2]. This approach allows for lines to be flushed free of possible bacterial contamination before each dialysate infusion without opening the system to the outside air (the drain, flush, instill method). First, after connection, a small amount of fresh dialysate (100 ml) is flushed into the drainage bag, and then the peritoneal cavity is drained so that any contaminants introduced during the connection procedures are flushed into the drainage bag and not into the peritoneal cavity. After drainage, the fresh dialysate is infused. This "drain first-infuse later" principle has markedly decreased peritonitis incidence in people doing manual or automated exchanges [3, 4].

PD Technique

PD technique, in its simplest form, relates to the flow pattern of PD fluid during PD exchanges. The intermittent flow and tidal flow patterns are routinely used. Continuous flow peritoneal dialysis (CFPD) has not been adopted into clinical practice despite having mechanistic advantages [2] [Fig. 11.3].

In *intermittent flow PD*, the peritoneal cavity is completely drained before fresh dialysis fluid is instilled. Most currently used PD prescriptions such as CAPD, nocturnal intermittent peritoneal dialysis (NIPD), and continuous cyclic peritoneal dialysis (CCPD) are performed with intermittent flow technique.

In *tidal peritoneal dialysis* (TPD), only a portion of the initial fill volume is drained and replaced by fresh dialysis fluid during each exchange. TPD is a common strategy applied for patients who experience "drain pain" [5, 6]. Drain pain is discomfort in the abdominal/rectal region due to the catheter irritating or exerting a hydraulic suction effect on adjacent visceral organs or parietal peritoneum during the drain period as intraperitoneal volume decreases. This sensation generally diminishes over time but maybe problematic early in the course of PD, particularly in patients on automated peritoneal dialysis. In TPD, a residual volume (usually 15%–25%) is kept in the abdomen at the end of each dwell as a cushion to prevent the catheter from irritating the visceral organs. For example, for a 2-liter fill volume, 80% tidal exchanges would imply that 1600 ml is drained at the end of the dwell, followed by a 1600-ml infusion. The reservoir of fluid left in the peritoneal cavity is finally drained out with the final exchange.

TPD is also used in situations where catheter function is suboptimal and where full drainage takes too much time leading to frequent drain alarms that can interrupt sleep during CCPD/NIPD regimens [5, 6]. Automated cyclers can be programmed to deliver TPD. Tidal PD can also be used in patients who experience pain or discomfort during the fill phase.

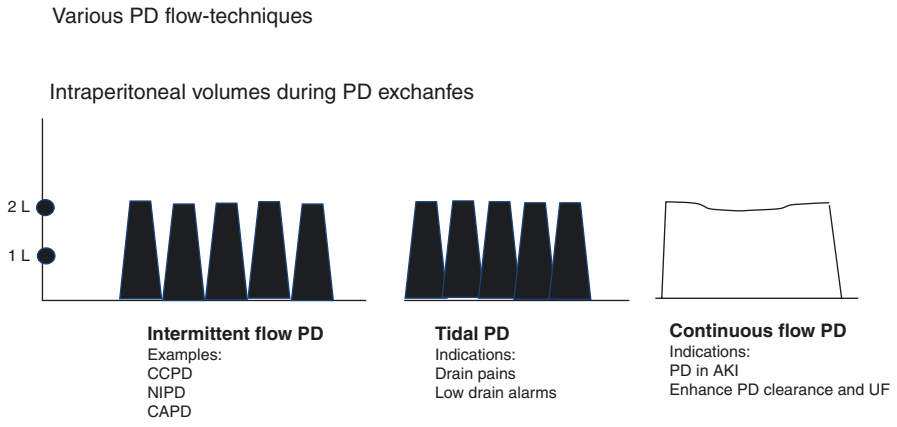

Fig. 11.3 Various PD flow techniques

Continuous Flow Peritoneal Dialysis (CFPD)

In CFPD, a continuous flow of dialysis fluid is instilled, and at the same time, spent dialysate is drained via a separate catheter or lumen. CFPD is a potential strategy to enhance peritoneal clearance and ultrafiltration by achieving a larger concentration gradient between the dialysate and plasma for solute and glucose, respectively [7]. Nourse et al. demonstrated similar outcomes with CFPD compared to conventional PD in pediatric patients with AKI [8]. This concept can theoretically be applied in chronic PD patients with failing membrane function. However, CFPD is rarely used due to challenges associated with the use of double- or dual-lumen catheters, the technical limitations of achieving predictable and real-time ultrafiltration rates, and the requirement of large amounts of dialysate fluid to achieve higher flow volumes. Besides, there is no proven advantage of increasing small solute clearance in terms of survival [9].

Regimen and Modes of Performing PD Exchanges [Fig. 11.4]

A PD regimen entails a systematic plan of how PD exchanges will be performed. PD exchanges can be conducted intermittently (IPD) or continuously (CPD). In IPD regimens, there are periods when the peritoneal cavity is not filled and left dry, while with CPD regimens, the peritoneal dialysate is always present in the peritoneal cavity.

The mode or the methods by which PD exchanges are attained depend on patients' choice, lifestyle, and medical necessity in some situations. Three modes of PD regimens/exchanges are manual (mPD), automated (aPD), and assisted. In some

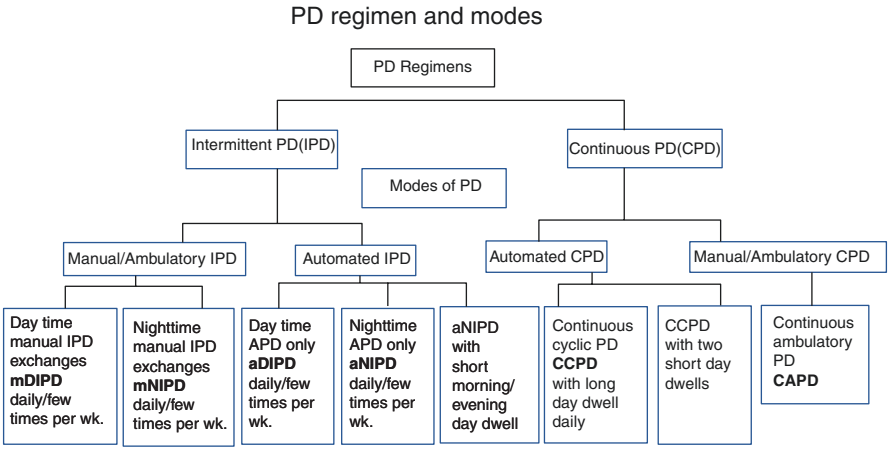

Fig. 11.4 PD regimen and modes

cases, people use both automated and manual methods. On rare occasions, *assisted PD* is a means of supporting people unable to perform their PD, with trained staff or family members assisting with all or part of the dialysis procedure [10].

The PD prescription for an individual incorporates details of PD regimen, mode, fill volume, number of exchanges, and dwell times..

Intermittent PD Regimens

PD exchanges are performed periodically, several times per week. IPD regimens can be done manually (mIPD) or with an automated cycler (aIPD). aIPD regimens allow for patient convenience as the exchanges can be conducted automatically during nights (sleep period) instead of time-consuming frequent manual exchanges. CPD regimens provide better peritoneal small- and middle-molecule clearance compared to IPD regimens as there are many hours in the day where no dialysis is taking place in the latter regimen.

Automated Cycler-Assisted IPD Regimens (aIPD): (Nighttime or Daytime)

Automated nocturnal intermittent peritoneal dialysis (aNIPD) is done with an automated cycler at night only with dry daytime periods. aNIPD is the most preferred combination of PD method and regimen by the patients as it frees up their daytime and avoids the feeling of discomfort while ambulating with daytime dwells. By its nature, aNIPD is performed in a supine position. On rare occasions, daytime IPD (aDIPD) with cycler can also be offered if patients have discomfort with being tethered to the machine during sleep.

Most of the daily IPD regimes are accomplished with automated mode (cycler), and the patients have to be connected to machine for short periods (6–10 hours). Thus, the commonly prescribed aNIPD involves performing machine-assisted IPD regimen at night. In addition, details such as total nightly volume of 8 liters, dwell volume of 2 liters, 4 exchanges over 8 hours, and concentration of PD solutions are specified in aNIPD prescription [Table 11.1].

Manual IPD Regimens (mIPD): (Daytime or Nighttime)

Manual daytime ambulatory PD (mDIPD), i.e., 1–2 daytime exchanges with 2–3-L dwell volumes, nighttime use of single manual PD exchanges most often with icodextrin solution (mNIPD) only, or a hybrid of manual daytime and nighttime

Table 11.1 Typical PD prescriptions

Intermittent PD	Typical daily prescription
Machine-assisted: aIPD (aNIPD or aDIPD)	Total dwell time = 6–10 hours Number of exchanges = 3–5 exchanges Dwell volume per exchange = 2–2.5 liters PD solution: dextrose-based
Manual: mDIPD or mNIPD	Total dwell time = 6–12 hours Number of exchanges = 1–3 exchanges Dwell volume per exchange = 2–3 liters PD solution: Dextrose or icodextrin
Continuous PD	Prescription
CAPD (manual)	Total dwell time = 24 hours Number of exchanges = 3–5 exchanges Dwell volume per exchange = 1.5–3 liters PD solution: dextrose of icodextrin
CCPD (machine-assisted)	Total dwell time = 24 hours aNIPD as above + machine-assisted single daytime exchange of 1–3 liters with either dextrose or icodextrin solution
Enhanced CCPD (hybrid of machine and manual mode)	Total dwell time = 24 hours aNIPD as above followed by the last fill and another exchange some time during the day with a 1–2 liter dextrose or icodextrin solution

exchanges are used such that patients avoid the inconvenience of being connected with an automated cycler [Table 11.1]. These mIPD regimens are often incorporated to facilitate an incremental PD approach (as described below).

Intermittent PD regimens have patient-centered and medical advantages in terms of the following:

- Can be safely prescribed in patients with residual kidney function (RKF). The ADEMEX trial and reanalysis of the CANUSA study have established that peritoneal small solute clearance is not associated with survival on PD [11, 12].
- In patients with residual kidney function (RKF), an incremental PD regimen safely allows patients to do infrequent and shorter PD regimens at their homes. Incremental PD is more acceptable to the patients initiating kidney replacement therapy and attracts them to PD. Incremental PD refers to the practice of incorporating RKF to achieve the total desired solute removal and initially prescribing only a modest dose of IPD, typically 6 L/day or less [13, 14].
- IPD regimens done in a supine position, with low fill volumes, minimize mechanical complications of leaks and hernia associated with continuous elevation of the intra-abdominal pressure [15–17]. If patients at risk for, or with established leaks and hernia, have minimal RKF, then these IPD strategies can allow patients to initiate RRT with PD within 2 weeks of catheter placement (urgent-start PD) and avoid HD [18, 19]. While urgent-start peritoneal dialysis is usually performed with an automated cycler, manual exchanges can be performed if no cycler is available [20].

- Allows for rapid and small-volume exchanges (cycler-assisted). Thus, beneficial in patients with rapid transport status.

These advantages and variations of IPD have allowed prescribers to individualize PD prescriptions based on challenging clinical situations and expand the use of PD as outlined in Table 11.2 and Table 11.3.

Table 11.2 IPD strategies during initiation or early phase of PD start

Potential application	IPD strategy	Advantage
Urgent-start peritoneal dialysis During training period During initial home self-care or assisted treatments	mDIPD aDIPD aNIPD mNIPD (nighttime icodextrin)	Patients often have residual kidney function during this phase Allows for small-volume exchanges and in supine position: Avoids risk of elevated intra-abdominal pressure and thus minimizes the risk of leak
Incremental peritoneal dialysis	mNIPD (night icodextrin) aNIPD mDIPD (1–3-day exchanges) Hybrid of above All of the above can be performed daily or few times a week	Patients often have residual kidney function during this phase
Assisted peritoneal dialysis Increase in uptake of PD in patients with barriers related to self-care PD	aNIPD/aDIPD mNIPD/NDIPD	Easier for relatives or staff to perform 1/2 visits for connection and disconnection
Remote-patient monitoring	aNIPD/aDIPD	Can monitor adherence to therapy and catheter dysfunction

Table 11.3 IPD strategies during long-term maintenance phase of PD

Potential application	IPD strategy	Advantage
Patients with fluid overload-rapid transport status	aIPD: aNIPD, aDIPD	Allows for rapid exchanges to optimize ultrafiltration
Mechanical issues: Post-abdominal surgery, i.e., hernia repair Preexisting hernia not requiring surgery	aIPD: aNIPD, aDIPD	Avoids increased intra-abdominal pressure by using the supine position
Assisted peritoneal dialysis Change in medical condition which is a barrier to self-care PD and at risk for transfer to in-center HD	aNIPD/ aDIPD mNIPD/ NDIPD	Easier for relatives or staff to perform one to two visits for connection and disconnection
Remote patient monitoring	aNIPD, aDIPD	Can monitor adherence to therapy and catheter dysfunction

Continuous Peritoneal Dialysis (CPD) Regimens

Manual CPD, i.e. CAPD

In CAPD, 1.5 to 2.5 liters of dialysis fluid is manually instilled into the peritoneal cavity three to five times daily. Each exchange involves drain, fill, and dwell phases, as described above [Table 11.1]. During the dwell phase, the patient goes about a regular routine until it is time for the next exchange. Even though CAPD involves frequent manual exchanges, it appeals to patients who do not want to be continuously tethered to a cycler or who have issues operating and dealing with machines and alarms. CAPD is also useful when there are flow problems of the dialysis fluid through the catheter. Also, it offers a cheaper option to provide PD in developing countries.

Machine-Assisted CPD, i.e., CCPD

Automated peritoneal dialysis is usually performed using an automated cycler which is programed to deliver three to four exchanges overnight for 6–10 hours, depending on the patient's preference and sleep pattern. During the daytime, the APD patient has the option of either an extended last fill/dwell, usually with icodextrin, or to perform two long (6- to 8-hour) daily dwells (referred to as last fill and midday exchange) [Table 11.1]. At bedtime, the patient connects to the cycler, which drains the day fill, followed by automated night exchange initiation and instillation of the last fill which the patient then carries during the day. In the morning, the patient with last dwell remaining in the abdomen disconnects from the cycler and is free to go about daily activities until bedtime. Most cyclers can be programmed to vary inflow volume, inflow time, dwell time, and drain time. Cyclers also monitor outflow volume and excess drainage (UF volume). Current APD machines have alarms for inflow failure, overheating, and poor drainage.

Continuous peritoneal dialysis regimens are employed to enhance small and middle molecular weight solute clearance and hence used in patients with low or low-average transport status or those with uremic symptoms or with minimal or absent residual kidney function. CCPD with daytime exchange with icodextrin can augment ultrafiltration in patients with rapid transport status.

Aseptic Precautions

During the performance of PD, patients are expected to follow certain aseptic practices under carefully controlled conditions to minimize contamination by pathogens. Practices include hand hygiene, using a mask, and maintaining a safe environment in the area where the exchanges are being carried out.

Excellent hand hygiene by the patient, family members, and members of the healthcare team is essential before initiating the PD exchange procedure. 70% alcohol-based hand rubs for at least 15 seconds is the most preferred method [21]. Handwashing for 15 seconds with antimicrobial soap (4% chlorhexidine) is the most effective method for hand cleansing. Visibly dirty hands require handwashing with soap. Wearing a face mask during a dialysis exchange is recommended. All injection ports should be scrubbed with chlorhexidine and alcohol before injections, and the use of multiple-dose vials (e.g., heparin or potassium chloride) for dialysate supplements should be avoided to decrease the risk of introducing microorganisms [21].

ISPD guidelines recommend that PD patients apply topical antibiotic (mupirocin or gentamicin) cream or ointment to the catheter exit site daily. As mentioned above, space where PD is performed should be kept clean, dry, well-lit, and pet-free [21].

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Chapter 12
Peritoneal Dialysis in Acute Kidney Injury: Prescribing Acute PD

Daniela Ponce and André Luís Balbi

Prescribing Acute PD

In the 1970s, acute PD was widely accepted for the treatment of acute kidney injury (AKI), but this practice has declined in favor of HD [1–5]. PD is frequently used in developing countries because of its lower cost and minimal infrastructural requirements [4–7]. However, in developing countries, the infrastructure for quality research is often lacking, meaning that there has been limited evidence on standardized treatment regimens such as indications, dosing and technical failure, and mortality.

Technical Aspects and Controversies

The use of PD in AKI is facilitated by placement of a Tenckhoff catheter which can be safely performed at the bedside by a nephrologist, radiologist, or surgeon. PD offers several advantages over HD, namely, technical simplicity and a lower risk of bleeding. The gradual and continuous nature of PD ensures that disequilibrium syndrome is prevented and that cardiovascular stress is minimal, which reduces the risk of renal ischemia and fluid-electrolyte imbalance [1–8].

Besides the classical indications (volume overload, electrolyte disorders, uremic symptoms, or acid-base disturbances), PD can also be used to maintain volume

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control in patients with congestive heart failure (functional Class IV) and control hyperthermia and hypothermia. In the setting of natural disasters, when patients are at risk for AKI and damage to infrastructure makes access to electricity, clean water, and facilities for water treatment unavailable, PD has been described as an important and lifesaving RRT modality [8–12].

The technique of fluid delivery in acute PD can increase the risk of peritonitis because there are significantly more connections and disconnections compared with the three to four exchanges in chronic continuous ambulatory PD. Using an automated cycler PD could minimize the number of connections, which reduces the risk of complications, including contamination. Nursing time is also reduced because all cycles occur automatically. Cyclers also offer tidal PD in which a small volume of fluid is left in the abdomen at all times, which may reduce mechanical complications and discomfort. Tidal PD also has the theoretical benefit of increased solute clearance because fluid continuously dwells in the peritoneal space, including during the fill and drain portion of the cycle. Automated cyclers have been used extensively for PD in AKI, but they may prove to be too expensive in low-resource settings.

The use of commercially produced PD solutions is recommended [13]. Although dialysate solutions are manufactured in a number of developing countries, their availability continues to be limited in many regions of the world. Because they are too heavy to be delivered by air, they often need to pass through several countries before they reach their final destination. As a result, a number of PD units produce their own solutions using a mixture of modified Ringer's lactate and glucose, both of which are readily available in most hospitals. The potential risks are contamination and infection.

There has been much interest in the composition of dialysate or replacement fluid used for RRT in critically ill patients, in particular because patients with shock or liver failure may not be able to convert lactate to bicarbonate. In RCTs that compare lactate-based replacement fluids versus bicarbonate-based replacement fluids for CRRT, patients randomized to bicarbonate-buffered solutions had more rapid correction of acidosis and less cardiovascular instability [14]. In PD, the evidence is limited to one small RCT that also showed that acidosis in patients with shock or liver failure was corrected significantly faster if bicarbonate-containing solutions were used rather than lactate-based fluids [15].

Standard PD solutions do not contain any potassium. As a result, a significant number of chronic PD patients develop hypokalemia (potassium <3.5 mmol/L) or require potassium supplementation, especially because hypokalemia is a risk factor for peritonitis and death in chronic PD patients [16]. In acute PD, potassium loss can be particularly high because each 2-L exchange has the potential to remove up to two times the serum potassium concentration. Such rapid potassium loss can be prevented or corrected by adding potassium to the dialysis solution [17].

We [1, 10, 17] demonstrated that control of serum potassium was obtained after a 1-day session of high-volume PD. If the serum potassium fell to <4 mmol/L, potassium 3.5–5 mmol/L was added to the dialysis solutions. Strict adherence to an aseptic technique and attention to detail are important when adding fluids or drugs to the dialysis solution.

It is also true that PD is not as efficient as extracorporeal therapy with respect to small solute removal per unit time. Lower efficiency can be observed in large and severely hypercatabolic patients, fluid removal can be unpredictable, there is always the risk of infection, and there are possible issues with mechanical ventilation [5]. PD is absolutely contraindicated in patients with recent abdominal surgery and relatively contraindicated in patients with abdominal hernia, adynamic ileus, intra-abdominal adhesions, peritoneal fibrosis, or peritonitis. Table 12.1 shows the advantages and disadvantages of PD.

Since volume and solute removal is slow and unpredictable, PD is not as efficient as extracorporeal blood purification techniques for the treatment of emergencies such as acute pulmonary edema or life-threatening hyperkalemia [9–12, 18–21]. Another possible limitation of PD in AKI is that of associated protein losses which may aggravate malnutrition. Protein losses as high as 48 g/day have been reported, but some reports document maintenance of serum albumin levels [22–25]. Protein supplementation, either enteral or parenteral (1.5 g/kg/day), is recommended for AKI patients on PD [26, 27].

The high glucose concentrations in peritoneal dialysate may cause hyperglycemia, even in nondiabetic patients. This is easily correctable through intravenous or intraperitoneal administration of insulin. Peritonitis occurring in patients with AKI using PD as a modality of RRT can lead to very poor outcomes, and older studies report a frequency as high as 40% [2, 3, 6]. With better catheter implantation techniques and automated methods, the incidence of peritonitis has been reduced, and the risk of infection in PD is similar to other forms of extracorporeal blood purification for AKI [2, 3].

Previous studies have reported that PD can increase intra-abdominal pressure (IAP), which leads to impaired diaphragm mobilization and decreased pulmonary compliance and ventilation, which may cause or worsen respiratory failure [26, 28]. However, PD is seldom the cause of ventilation impairment in patients without pulmonary disease. Results from our group suggest increases in the pulmonary compliance without changes in IAP in AKI patients treated with PD [29]. Recently, the

Table 12.1 Advantages and disadvantages of peritoneal dialysis (PD) in acute kidney injury (AKI)

Advantages	Disadvantages
Technically simple	It requires intact peritoneal cavity with adequate membrane function
No need for expensive equipment	It may not be adequate for severe acute pulmonary edema or life-threatening hyperkalemia
It avoids vascular access	Infection (peritonitis) can occur
It ensures minimum blood loss	Ultrafiltration and clearance cannot be exactly predicted
Biocompatible	It can cause protein losses
Useful in all types of AKI	It can cause hyperglycemia and hypernatremia
More rapid renal recovery	It may impair respiratory mechanics
It provides continuous RRT and cardiovascular stability Beneficial in select patient population (children, heart failure, cirrhosis, bleeding diathesis)	Lactate buffer

same group performed a prospective cohort study that evaluated 154 patients, 37 on continuous PD and 94 on HD [30]. Respiratory mechanic parameters such as pulmonary static compliance (Psc), resistance of the respiratory system (Rsr), and oxygenation index (OI) were assessed for 3 days (pre- and post-dialysis moments). The initial clinical parameters were similar in the two groups, except for the older age in continuous PD group. In both groups, Psc increased significantly post-dialysis, with no difference between the two groups. Rsr remained stable among patients on continuous PD and decreased among HD patients. There was difference in Rsr between the two groups at the post-dialysis moments in days 1 and 2 ($p = 0.03$). OI increased in both groups, although there was no difference between them. IAP was evaluated only in patients treated by PD, and there was no increase during the treatment. We concluded that AKI patients undergoing IMV and HD or PD had statistical significant improvement in the mechanical ventilation and oxygenation, with no difference between the two groups.

Evidence and Guidelines

Recently, interest in using PD to manage patients with AKI has been increasing. The first question that must be asked is whether PD can provide adequate clearance in the treatment of AKI patients. Our study group, from the Botucatu School of Medicine, Brazil, demonstrated that with careful thought and planning, critically ill AKI patients can be successfully treated with PD [2, 10, 17, 31–33].

We assessed the efficacy of high-volume peritoneal dialysis (HVPD) in a prospective study of 30 consecutive AKI patients [10]. PD was performed using a Tenckhoff catheter, 2-L exchanges, and 35–50-minute dwell times. The prescribed Kt/V value was 0.65 per session, the duration of each session was 24 hours, and a total dialysate volume of 36–44 L/day was used. HVPD was effective in the correction of blood urea nitrogen (BUN), creatinine, bicarbonate, and fluid overload. Weekly Kt/V was 3.8 ± 0.6, and the mortality was 57%. Five years later, we performed another prospective study on 204 AKI patients treated with HVPD (prescribed Kt/V = 0.60/session). Sepsis was the main cause of AKI (54.7%) followed by heart failure (24.7%). BUN and creatinine levels stabilized after four sessions to approximately 50 mg/dL and 4 mg/dL, respectively. Weekly delivered Kt/V was 3.5 ± 0.68 and the mortality rate was 57.3%. Older age and sepsis were identified as risk factors for death. Persistence of urine output, increases of 1 g/day in nitrogen balance (NB), and achieving 500 mL/day were associated with better prognosis [32].

UF after three sessions were identified as favorable prognostic factors. We concluded that HVPD is effective in selected patients. However, if after three sessions UF is low or NB is negative, substitution or addition of HD should be considered. There were mechanical complications in 7.3% of AKI patients treated with HVPD, and 12% of patients had developed peritonitis. Change of the dialysis method occurred in 13.3% of patients because of refractory peritonitis or mechanical complications (leakage or UF failure).

Dialysis dose adequacy in AKI is a controversial subject, and there are very limited data on the effect of PD dose on AKI. Solute clearance in PD is limited by dialysate flow, membrane permeability, and surface area in contact with dialysate. Exchanges of 2 L lasting approximately 1 hour can achieve a saturation of the spent dialysate in the range of 50%. This means that over 24 hours, a daily Kt/V of 0.5 can be achieved in a patient with a body weight between 60 and 65 kg [2, 8–10].

We performed a trial involving 61 septic AKI patients randomized to receive higher-intensity ($n = 31$) or lower-intensity ($n = 30$) PD therapy (prescribed Kt/V of 0.8/session versus 0.5/session). The two groups had similar mortality after 30 days (55% versus 53%, $p = 0.83$). We demonstrated that increasing the intensity of continuous HVPD therapy does not reduce mortality and does not improve control of urea, potassium, and bicarbonate levels [27].

According to the International Society for Peritoneal Dialysis (ISPD) guidelines for PD for AKI, where resources permit, targeting a weekly Kt/V urea of 3.5 provides outcomes comparable to that of daily HD; targeting higher doses does not improve outcomes. This dose may not be necessary for many AKI patients, and targeting a weekly Kt/V of 2.1 may be acceptable [13].

Recently, Parapiboon et al. [34] performed a study whereby 80 critically ill patients with AKI underwent PD. This was a randomized controlled trial comparing the two regimens recommended in the ISPD guidelines, aimed at achieving target weekly Kt/V of 3.5 and 2.1, respectively. Patients were randomized 1:1 to receive 1.5 L of PD fluid using manual PD and a single-bag open system delivered either hourly (36 L/24 hours) or every 2 hours (18 L/24 h) for the first 48 hours. Following this, they could perform exchanges less often, based on metabolic parameters and fluid balance. Catheters were inserted by the nephrologist at the bedside and used immediately. Patients were excluded if they had severe hyperkalemia (> 6.5 mmol/L), were hypercatabolic, had CKD stage 5, were HIV-positive, or had had recent abdominal surgery or had a midline scar. Fluid balance and delivered dose were calculated on a daily basis. The primary endpoint was 30-day mortality, and secondary endpoints were dialysis dependence, metabolic control, peritonitis rate, and length of hospital stay.

The primary hypothesis was that intensive treatment would result in a 10% reduction in mortality. However, the number of patients needed to power this study was >700, and as such, it was underpowered for the primary endpoint. Mortality, however, was compared using Kaplan-Meier survival analysis.

The dropout rate was low, with one patient in the low-intensity arm changing to HD and two of the high-intensity patients being transferred to low intensity due to either hyperglycemia or hypokalemia.

Baseline characteristics were not significantly different between the two groups. However, it must be noted that as this study was performed in Asia, the mean body weight was low (60.1 kg ± 11.1) compared with that seen in other countries and the dwell volumes were low because of this. The patients were similar to those in the study by Ponce-Gabriel et al., with 88% on mechanical ventilation, 69% on inotropic support, and a mean APACHE II score of 26 (10).

Seventy-five patients were included in the analysis. The achieved weekly Kt/V was 2.26 in the low-intensity group and 3.3 in the high-intensity group. There was

no significant difference in metabolic control although ultrafiltration was higher in the high-intensity group. The average glucose concentration in the PD fluid was not reported, making interpretation of the ultrafiltration results difficult. Peritonitis rates were similar between the two groups, and despite the use of an open PD system, the overall peritonitis rate was similar to that in the Brazilian study (10). The mortality was 72% in the high-intensity and 63% in the low-intensity groups ($p = 0.18$), suggesting no advantage to the higher-intensity treatment. These results suggest there is unlikely to be any advantage in achieving a weekly Kt/V > 2.2.

The conclusion from these studies is that there is now objective evidence that the lower target and recommended dwell times published in the ISPD guidelines are sufficient for treating AKI with PD and do not lead to inferior outcomes. This has significant implications for those low- and middle-income countries setting up acute PD centers, giving them the reassurance that large volumes of fluid are not necessary and, as such, acute PD is affordable and lifesaving [35]. Future studies should address whether different ways of assessing the adequacy of PD treatment for AKI would be useful. The goal would be to better understand how best to ensure adequate dialysis and use this to base recommendations for treatment to maximize outcomes and minimize costs.

Another important question to consider is whether PD is comparable to other dialysis methods as it applies to AKI patients. The answer to this question is not straightforward. Current available modalities present advantages and disadvantages under specific circumstances, and these therapies should therefore be considered more of as a continuum rather than a series of modalities to be compared [13, 31–37]. Few studies have compared PD with other dialysis methods in AKI patients, and there are conflicting findings with regard to efficacy and cost. An older study by Phu et al. [20] compared intermittent PD with continuous RRT and demonstrated a worse outcome in patients treated with PD. However, specific factors such as the use of rigid catheters, manual exchanges, too short dwell time (15 minutes), and no dialysis dose quantification likely were confounding factors.

A randomized study performed by our group in 120 AKI patients compared HVPD versus daily intermittent HD [31]. Baseline characteristics were similar in both groups, which included older patients (mean age >60 years), patients with a high APACHE II score, and patients using vasoactive drugs (>60%). Both RRT modalities achieved metabolic and acid-base control. Mortality did not differ significantly between the two groups (58% versus 53%). Renal recovery was similar for both modalities, but HVPD was associated with a significantly shorter time to recovery (7.2 ± 2.6 versus 10.6 ± 4.7 days).

George et al. [36] performed a randomized study to compare continuous venovenous hemodiafiltration (CVVHDF) and PD in critically ill patients. No difference was observed in correction of metabolic parameters and fluid overload. Urea and creatinine clearances were higher, and fluid correction was faster with CVVHDF. The mortality rates in the two study groups were similar. Unfortunately, the procedures were performed at different technological levels to the detriment of PD, in which rigid catheters, locally available PD fluids, and manual exchanges were used.

In another prospective study, we compared the effect of HVPD against prolonged HD (PHD) on AKI patients' outcome [38]. The PHD and HVPD groups were similar in gender, severity, and etiology of AKI. There was a trend toward statistical difference regarding the presence of sepsis (62.3% in PHD group versus 44.9% in

HVPD group, $p = 0.054$). Delivered Kt/V and UF were higher in PHD group, and there was no difference between the two groups in mortality and recovery of kidney function or need for chronic dialysis.

In 2013, a systematic review published by Chionh et al. [39] included 24 observational cohorts or randomized adult population studies ($n = 1556$ patients) on PD and in the setting of AKI. The primary outcome of interest was mortality. According to the authors, the overall methodological quality was low, and they concluded that there is currently no evidence to suggest significant differences in mortality between PD and extracorporeal blood purification in AKI and that there is a need for high-quality evidence in this important area.

In the most recent trial [40], Al-Hwiesh et al. compared 120 AKI patients randomized to treatment with tidal PD or CVVHDF. It is important to note that high-volume tidal PD (25 L per session) and a more biocompatible PD solution were used in this study. The survival at 28 days was significantly better in the patients treated with tidal PD when compared to CVVHDF (69.8% vs. 46.8%, $p < 0.01$). Recovery of kidney function was also in favor of tidal PD (60.3% vs. 35.5%, $p < 0.01$).

We published the largest cohort study providing patient characteristics, clinical practice, patterns, and their relationship to outcomes in a developing country [41]. Its objective was to describe the main determinants of patient and technique survival, including trends over time of PD treatment in AKI patients.

For comparison purposes, patients were divided into two groups according to the year of treatment: 2004–2008 and 2009–2014. A total of 301 patients were included, though 51 were transferred to HD (16.9%) during the study period. The main cause of technique failure (TF) was mechanical complication (47%) followed by peritonitis (41.2%). There was a change in TF during the study period; patients treated during 2009–2014 had a relative risk (RR) reduction of 0.86 (95% CI, 0.77–0.96) compared with patients treated between 2004 and 2008, and three independent risk factors were identified: period of treatment at 2009 and 2014, sepsis, and age >65 years.

During the study, there were 180 deaths (59.8%). Death was the leading cause of dropout (77.9% of all cases), mainly due to sepsis (58.3%), followed by cardiovascular disease (36.1%). The overall patient survival rate was 41% at 30 days and patient survival improved along study periods. Compared with patients treated from 2004 to 2008, patients treated at 2009–2014 had a RR reduction of 0.87 (95% CI, 0.79–0.98). The independent risk factors for mortality were sepsis, age >70 years, Acute Tubular Necrosis Individual Severity Score (ATN-ISS) >0.65, and positive fluid balance. In conclusion, we observed an improvement in patient survival and TF between the two time periods, even after correction for several confounders and using a competing risk approach.

Table 12.2 shows the dialysis protocol technique, prescription, adequacy parameters, adverse events, and outcome in different and recent studies (last 12 years) on PD in AKI.

Practical Aspects of Prescribing, Delivering, and Monitoring PD

We have prepared a flowchart of the practical aspects of prescribing, delivering, and monitoring the PD in AKI patients (Fig. 12.1).

Table 12.2 Dialysis protocol technique, prescription, adequacy parameters, adverse events, and outcome in different and recent studies on peritoneal dialysis (PD) in acute kidney injury (AKI)

Study	Time period	Patients	PD prescription	Weekly Kt/V	UF (l/session)	Adverse events	Outcome
Ponce-Gabriel et al. [10] Prospective study	2007	$N = 30$ 59 ± 8 years 60% septic	Flexible catheter 36–44 L HVPD	3.8 ± 0.6	1.8 ± 0.6	17% Infectious: 17% Mechanical: 7%	Mortality = 57% Not recovery of kidney function =13%
Ponce-Gabriel et al. [31] Randomized trial PD × dHD	2008	$N = 120$ 64 ± 20 vs. 62 ± 21 42 vs. 47% septic	Flexible catheter 36–44 l HVPD	3.6 ± 0.6 vs. 5.8 ± 1.9 $p < 0.01$	2.1 ± 0.7 vs. 2.4 ± 0.7 $p = 0.39$	23 vs. 24% $p = 0.21$ Infectious: 18 vs. 13% Mechanical: 5 vs. 13% $p > 0.05$	Mortality = 58 vs. 53% ($p = 0.71$) Not recovery of kidney function =17% vs. 23% ($p = 0.61$)
George et al. [36] Randomized trial CVVHF vs. CPD	2011	$N = 50$ 45 ± 17 vs. 44 ± 16 48 vs. 28% septic $p > 0.05$	Flexible catheter 24–48 L CPD	NR	2.9 ± 2.4 vs. 2.8 ± 4.1 $p > 0.05$	24 vs. 12% $p > 0.05$ Infectious: NR Mechanical: 24 vs. 8% $p > 0.05$	Mortality = 84 vs. 72% ($p = 0.71$) Not recovery of kidney function = NR
Ponce et al. [33] Prospective study	2012	$N = 150$ 64 ± 16 years 55% septic	Flexible catheter 36–44 L HVPD	3.6 ± 0.6	1.2 ± 0.7	18% Infectious: 12% Mechanical: 7.3%	Mortality = 57.3% Not recovery of kidney function =6.6%

Ponce et al. [38] Randomized trial PD × dHD	2013	$N = 143$ 57 ± 21 vs. 68 ± 24 $p > 0.05$ 45 vs. 51% septic $p > 0.05$	Flexible catheter 36–44 L HVPD	5.8 ± 1.6 vs. 3.6 ± 0.4 $p < 0.01$	2.5 ± 0.7 vs. 1.4 ± 0.7 $p = 0.039$	23 vs. 24% $p = 0.21$ Infectious: 19 vs. 16% Mechanical: 15 vs. 13% $p > 0.05$	Mortality = 63.3 vs. 63.9% ($p = 0.91$) Not recovery of kidney function = 9.6% vs.6.5% ($p = 0.67$)
Parapiboon et al. [34] Randomized trial HVPD vs. low-volume PD	2017	$N = 75$ 59 ± 21 vs. 60 ± 24 $p > 0.05$ 65 vs. 61% septic $p > 0.05$	Flexible catheter 18–36 L HVPD	3.3 ± 0.6 vs. 2.2 ± 0.4 $p < 0.05$	2.5 ± 0.7 vs. 2.6 ± 0.4 $p = 0.39$	15 vs. 8% $p = 0.21$ Infectious: 15 vs. 8% $p > 0.05$ Mechanical: NR	Mortality = 72 vs. 63.9% ($p = 0.81$) Not recovery of kidney function = NR
Al-Hwiesh et al. [40] Randomized trial CVVHDF vs. TPD	2018	$N = 120$ 44 ± 12 vs. 45 ± 44 $p > 0.05$ 60.3 vs. 35.5% septic $p > 0.05$	Flexible catheter 25 L TPD	NR	1.9 ± 0.7 vs. 1.4 ± 0.4 $p = 0.39$	17 vs. 9% $p = 0.21$ Infectious: 17 vs. 9% $p < 0.05$ Mechanical: NR	Mortality = 69.8 vs. 46.8% ($p = 0.04$) Not recovery of kidney function = 60.3 vs. 35.5% ($p = 0.03$)

NC not calculated, *NR* not reported, *CPD* continuous peritoneal dialysis, *HVPD* high-volume PD, *TPD* tidal PD, *dHD* daily hemodialysis, *CVVHDF* continuous venovenous hemodiafiltration, *PHD* prolonged

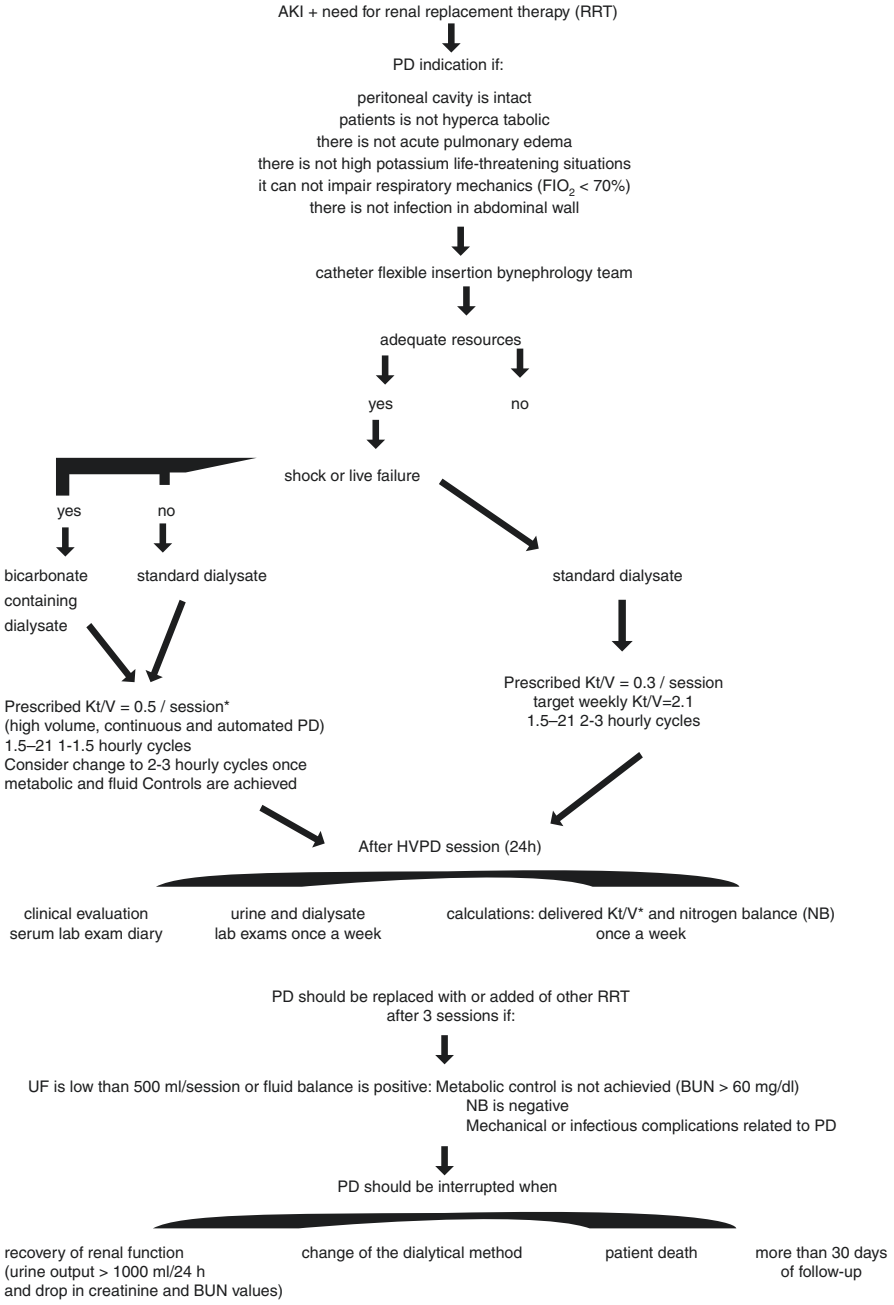

Fig. 12.1 Practical aspects of prescribing, delivering, and monitoring the PD in AKI patients

Conclusion

This chapter provided information not only supporting PD as an alternative to extracorporeal therapy for AKI but also discussing the targets to be addressed when using PD including adequate dose and metabolic and fluid control.

In conclusion, PD is a simple, safe, and efficient way to correct metabolic, electrolytic, acid-base, and volume disturbances generated by AKI; it can be used as an RRT modality to treat AKI in developing and developed countries, either in or out of the intensive care unit setting. Furthermore, we have observed an improvement in patient and technique survival over the years even after correction for several confounders.

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Chapter 13
Prescribing Chronic Peritoneal Dialysis Therapy

Anjali Bhatt Saxena

Introduction

Peritoneal dialysis (PD) is an effective and flexible modality of kidney replacement therapy. Many variations in the PD prescription exist, thus allowing patients to have individualized treatments based upon their lifestyle, residual kidney function, and clinical condition. In this chapter, we will review the different types of PD, how to prescribe an initial PD regimen, and the mainstays of PD prescription modification for prevalent patients. When prescribing PD, it is important to remember that patients may need several prescription modifications over their PD lifetime. Initially, most patients have residual kidney function and will do well with many prescriptions. As dialysis vintage increases, the prescription must be refined to meet both solute clearance and ultrafiltration goals.

Peritoneal Dialysis Modalities

There are two main types of peritoneal dialysis: continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). The main distinction between the two modalities is that the former utilizes only manual exchanges, whereas the latter incorporates the PD cycler in the regimen. In both CAPD and APD, several prescription variations exist (Table 13.1).

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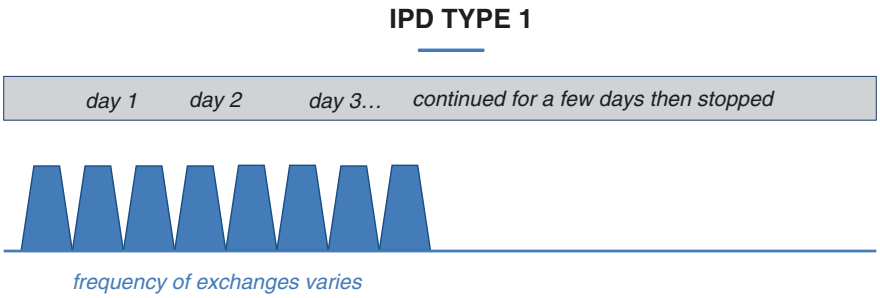
Table 13.1 PD prescription variations

Continuous ambulatory PD (CAPD)
Intermittent PD
PD exchanges during all or part of the day, dry night
PD exchanges on some days of the week, with certain days off of PD
Nocturnal intermittent PD (NIPD)
Nightly PD dwells, dry day
Automated PD (APD)
Nocturnal intermittent PD (NIPD)
PD at night with the cycler, dry day
Intermittent PD (IPD)
PD only some days of the week
Nightly cycler treatment with only part of the day on PD, some portion of the day dwell-free
Continuous cyclic PD (CCPD)
Cycler at night with a last fill at the end of the cycler regimen, all day dwell until nighttime connection to cycler
High-dose CCPD or CCPD+
Cycler at night, with one or more daytime exchange (either manually or using the cycler)
Tidal PD
Cycler at night, each cycler drains an incomplete and designated portion of the fill volume in order to leave a "buffer" amount of PD fluid in the peritoneum; the last drain is usually complete
Can be used as an NIPD, CCPD, or CCPD+ regimen

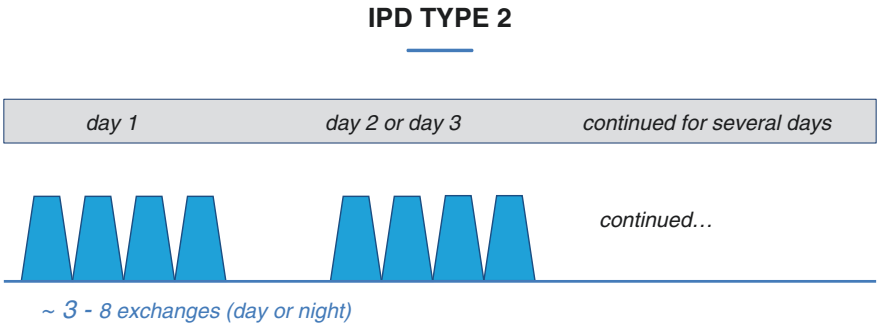
The first main variation on the PD prescription is called intermittent PD (IPD). IPD can be performed using CAPD or APD, *i.e.*, it can be done with all manual exchanges or by using the cycler for exchanges. IPD should usually be reserved for patients with residual kidney function. Three types of IPD can be described, what we will term IPD types 1, 2, and 3. In IPD type 1, the patient receives continuous exchanges for a period of several days, followed by a time of rest (Fig. 13.1). IPD type 1 is uncommon, but it can be useful in the following settings: a hospitalized patient, patients needing dialysis but not yet trained for home, or patients with acute kidney injury (AKI), particularly in resource-poor settings where hemodialysis is not readily available. IPD type 2 can be described as multiple exchanges per day (either manually or via cycler) with a dry period of at least several hours during each 24-hour period; the dry period can be at night or during the day (Fig. 13.2). One example of IPD type 2 is nocturnal intermittent PD (NIPD), a PD regimen that involves nighttime dwell(s) with a dry day. NIPD can be performed manually (one manual exchange at bedtime followed by a drain in the morning) or using the cycler (connection to the cycler at bedtime, with several cycler exchanges during the night followed by cycler drain in the morning without a last fill) (Figs. 13.3 and 13.4). NIPD is useful not only in patients with residual kidney function but also in those



uses:

- *hospitalized patient, needing dialysis but not yet trained for home*
- *inability to do PD at home (older era, developing areas)*
- *AKI*
- *can be manual or cycler based*

Fig. 13.1 IPD type 1



uses:

- *new patient, needing dialysis but not yet trained*
- *urgent start PD*
- *post – abdominal surgery*
- *incremental PD*
- *manual or cycler based*

Fig. 13.2 IPD type 2

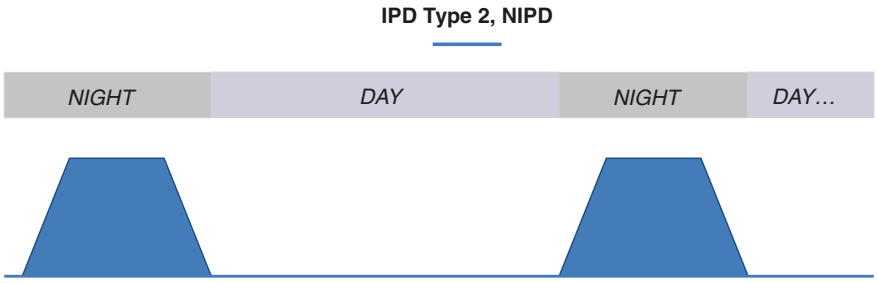


Fig. 13.3 IPD type 2, NIPD

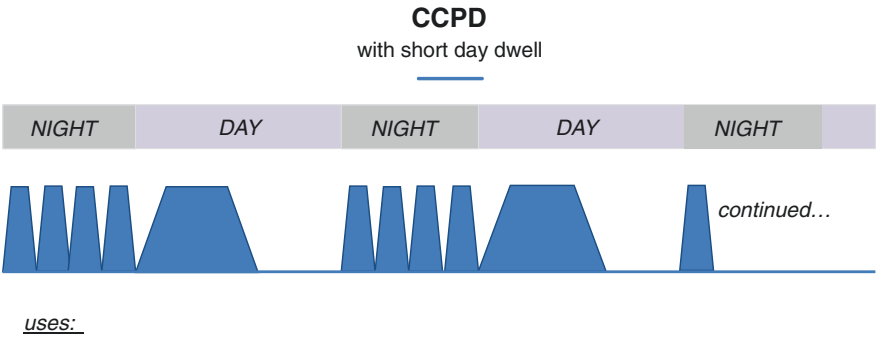


Fig. 13.4 CCPD with short day dwell

with a small hernia, particularly while awaiting surgical repair of the hernia. Another example of IPD type 2 is in urgent-start PD or postabdominal surgery, situations in which a patient undergoes multiple supine exchanges, either at night at home or during the day in the clinic, followed by a dry period. Low-volume supine PD in the postoperative period reduces the risk for peri-catheter leaks [1, 2]. The urgent-start

PD/postabdominal surgery PD regimen is described in more details below. Finally, IPD type 3 can be described as PD performed all or part of the day, either CAPD or APD, for fewer than 7 days a week. As noted above, all of the IPD prescriptions are best suited for patients who have residual kidney function. The presence of residual kidney function allows PD patients to undergo what is called incremental PD, described below.

The second main variation on the PD prescription is continuous PD, a term that essentially refers to the point that the peritoneum is continuously in contact with PD fluid 24 hours a day, 7 days a week. Continuous PD can be done with CAPD (three to five manual exchanges every day) or APD (nighttime cycler with last fill in the morning, with or without a daytime exchange) (Figs. 13.5, 13.6, and 13.7). Most patients worldwide start PD with a continuous regimen although the incremental or IPD prescriptions are gaining popularity of late in those incident patients who have residual kidney function. Patients without residual kidney function should be on continuous PD prescriptions because middle-molecule clearance is highly dwell time-dependent and these patients need a long dwell sometime throughout the 24-hour day for this purpose once their native kidneys can no longer perform this function [3].

Tidal PD is another variation on the PD regimen. Tidal PD is typically used with APD (cycler) therapy. Its main use is to alleviate drain pain in those patients on APD who experience pain during peritoneal drainage with the cycler. The idea of tidal PD is to leave a small buffer of PD fluid constantly in the peritoneum during the cycler therapy, therefore allowing the catheter to "float" in the PD fluid to avoid the catheter moving adjacent to intraperitoneal organs and causing pain during drains. A pictorial description of tidal PD is shown in Fig. 13.8. With tidal PD, the patient

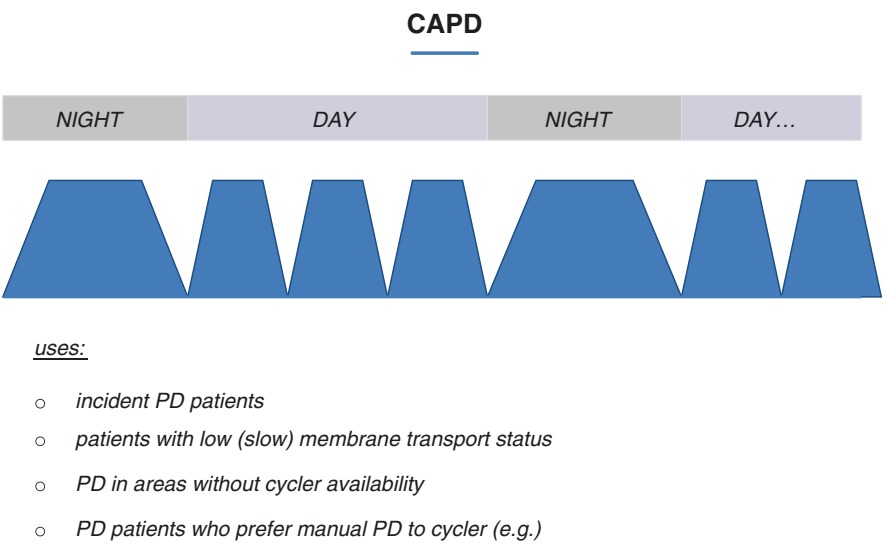
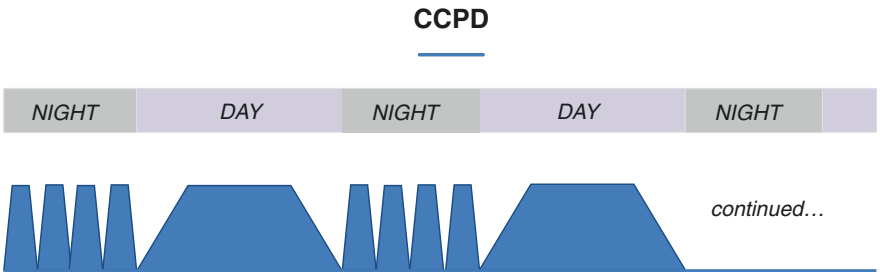


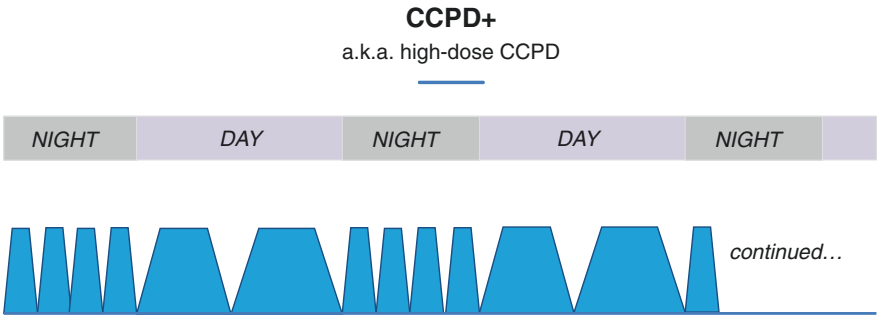
Fig. 13.5 CAPD



uses:

- *maintenance (chronic)PD*

Fig. 13.6 CCPD



uses:

- *maintenance (chronic)PD*
- *patients with high (fast) membrane transport status who need shorter day dwells*
- *patients requiring higher PD volumes to achieve adequate solute clearance*

Fig. 13.7 CCPD +, aka high-dose CCPD

connects to the cycler at the initiation of PD as usual. The full inflow volume is instilled for the first inflow. Thereafter, for each drain period, only a portion of the initial inflow volume is drained, and the same volume is instilled for the next inflow. Typically tidal PD prescriptions will allow 5–20% of the initial inflow volume to remain intraperitoneally between each exchange. In other words, after the initial inflow, the subsequent drains will drain between 80 and 95% of the initial inflow volume (and the subsequent inflow volumes will be of the same volume). At the end

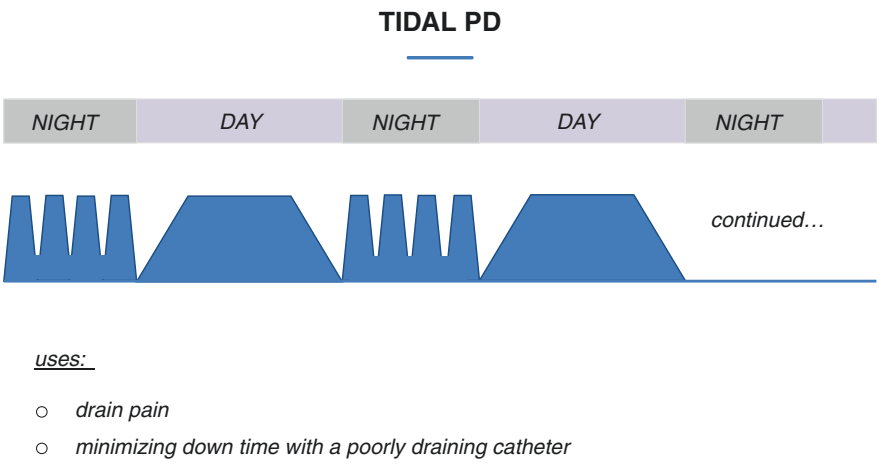


Fig. 13.8 Tidal PD

of the cycler therapy, in the morning, a full drain will usually occur. It is not recommended to prescribe less than 80% drain volume with tidal PD due to the risk of increased intraperitoneal volume in the case of incomplete drains during the nighttime.

Basics of the PD Prescription

There are two main goals of PD: solute clearance and fluid removal. Diffusion is the mechanism responsible for the majority of small solute transport from the blood into the peritoneum, although convection plays a smaller role in small solute clearance and may contribute more to middle-molecule clearance. Fluid removal occurs via osmosis due to the osmotic gradient between the blood and the peritoneal fluid in the peritoneal cavity. Both diffusion and fluid removal (or ultrafiltration) require time to occur, termed the dwell time. A review of the physiology of PD can be found in Chap. 2, Physiology of Peritoneal Dialysis. Dwell time is part of the PD prescription, as is the type of PD fluid to be used, i.e., what percent dextrose solution (1.5%, 2.5%, or 4.25% dextrose or icodextrin) in order to optimize ultrafiltration for a particular patient. Typically the dwell time will not change on a day-to-day basis, but the PD fluid type might change depending on the fluid status of the patient.

Initial Prescription

The initial PD prescription should take into account several factors: lifestyle preferences, patient size, residual kidney function, type of PD desired, and fluid status, among others. One of the most important factors to consider when deciding upon an

initial PD prescription is the patient's lifestyle. One of the main benefits of PD over in-center hemodialysis (HD) is that it affords the patient a more flexible schedule and also can disrupt their daily schedule to a lesser degree than in-center HD. Therefore, it is of upmost importance that a full interview is conducted with patients prior to PD initiation, in order to determine what type of PD schedule would suit them best. For example, a mother of young children who needs to get up multiple times during the night to attend to her children might fare better on CAPD than APD, since with the latter she would be tethered to the dialysis cycler throughout the night. Alternatively, a patient who wishes to continue working during the day would fare better on APD, so that she can receive her dialysis at night and be free of the need for midday exchanges.

Patient size is also a main determinant of the PD prescription. The total volume of dialysate required per day can, in part, describe the total dialysis dose. Smaller patients will need less total dialysate volume per day to adequately remove uremic toxins than larger patients. The following equation can be used to estimate the total daily dialysate volume a patient needs to meet the minimum desired peritoneal Kt/V_{urea} target:

$$Kt/V_{urea} = \left(24\,\text{h drain volume} * D/P_{urea}\right) * \text{time}/V \tag{13.1}$$

In this equation, drain volume (DV) is the summation of the total number of liters of dialysis instilled per day plus the daily ultrafiltration volume. D/P_{urea} refers to the dialysate to plasma ratio of urea at the end of a typical dwell time or, in other words, how much of the dialysate is saturated with urea. In most patients, D/P_{urea} after a 4-hour dwell is at least 90% or 0.9. Time is 7 days since, by convention, Kt/V_{urea} is reported as a weekly number. Finally, V refers to the volume of distribution of urea, which is considered equivalent to the total body water (TBW) volume. It can be determined by using standard TBW formulae such as the Watson formula [4]:

For males:

$$\text{Total Body Water}\left(\text{TBW}\right) = 2.447 - 0.09156 \times \text{age} + 0.1074 \times \text{height} + 0.3362 \times \text{weight}$$

For females:

$$\text{TBW} = 2.097 + 0.1069 \times \text{height} + 0.2466 \times \text{weight}$$

Numerous online calculators are available to help determine volume distribution of water or urea. An example of how to use Eq. 13.1 above in determining an initial prescription can be found in Table 13.2.

A note should be made that the Watson formula for TBW can yield inaccurate results when used in obese patients. Fat mass does not contain much water and is unlikely to be a source of body-mass producing toxins; therefore, the estimation of the volume of distribution of urea (V_{urea}) in obese patients would be overestimated

Table 13.2 Sample PD prescription

49 years old male: 70 kg, height 163 cm, anuric
V = 39 L (using the Watson formula)
Goal *weekly* peritoneal Kt/V_{urea} = 1.7
Goal *daily* peritoneal Kt/V_{urea} = 1.7 ÷ 7 = 0.24
Daily Kt/V_{urea} = [(24 h drain volume * D/P_{urea}) * time] ÷ V
0.24 = [(24 h DV * D/P_{urea}) * time] ÷ V
0.24 = [(24 h DV * 0.9) * 1 day] ÷ 39 L
24 h DV * 0.9 = 0.24 * 39 L
24 h DV = (0.24 * 39 L) ÷ 0.9
24 h DV = 10.4 L daily
The patient needs 10.4 L daily of combined inflow volume and UF per day
Assuming he needs at least 1 L daily UF to stay euvolemic, he would need 9.4 L daily of inflow volume divided throughout the day

when using the Watson formula (which includes body weight in its calculation). When V (or TBW) is overestimated, the dialysis dose must be higher than when V is not overestimated to meet set Kt/V_{urea} targets, and this can lead to the following consequences: (1) increased amount of daily dialysate needed to meet targets, leading to (2) increased glucose exposure to the peritoneum, (3) increased burden of therapy due to increased fill volumes or increased number of exchanges per day, and (4) increased cost of therapy. An alternative to using the actual body weight is the use of the ideal (standard) body weight or a compromise between the two. Unfortunately, little data exists to support this practice, and there are no data yet comparing outcome and Kt/V_{urea} using actual vs. ideal body weight. A second alternative for determination of TBW is the use of bioimpedance spectroscopy. A discussion of the use of actual vs. ideal body weight or the use of bioimpedance is out of the scope of the current review.

Residual kidney function can and should be accounted for in the initial PD prescription. The amount of PD fluid needed to meet solute clearance targets can be reduced in a patient with significant residual kidney function, with the benefit of less exposure of bioincompatible dialysate with the peritoneal membrane, and achievement of clearance targets while receiving less onerous and less costly lower clearance prescriptions. Additionally, studies have suggested that incremental PD can help maintain nutritional health, increase the amount of free time off of PD, and perhaps lead to slower decline in residual kidney function over time [5–7]. A full discussion of incremental PD can be found in Chap. 21.

The other component of the PD prescription aside from solute clearance involves ultrafiltration. The PD dialysate can be prescribed at different osmotic strengths (i.e., 1.5%, 2.5%, or 4.25% dextrose) in order to obtain optimal ultrafiltration volumes. As described in the chapter on PD physiology, the higher the dextrose concentration in the PD fluid, the higher the osmotic gradient, which in turn leads to more ultrafiltration. In general, a good practice is to prescribe or teach patients to use the lowest dextrose concentration needed to achieve desired ultrafiltration

targets because higher dextrose concentration fluids are associated with a greater risk for long-term failure of the PD membrane [8]. Icodextrin is a colloid solution that creates a slow and sustained ultrafiltration profile; it should only be used for long dwells (8+ hours), particularly in those patients who are high (rapid) transporters based on the PET or 4-hour D/P_{creat} test.

Prescription Modification

As described in the introduction, most incident PD patients will do well with most all PD prescriptions, mostly because they have residual kidney function to assist with solute and water clearance. Nevertheless, the initial prescription should be evaluated approximately 4 weeks after the initiation of PD, and the initial evaluation should include an assessment of solute clearance (Kt/V_{urea}, ultrafiltration volume, 24-hour urine volume, and residual kidney function including weekly renal Kt/V_{urea}). The International Society for Peritoneal Dialysis (ISPD) guidelines have recommended a target total weekly Kt/V (urine + peritoneal) of 1.7 [9]. Additionally, the initial Peritoneal Equilibration Test (PET) should be performed at this time to determine the membrane transport type of the patient. As long as a patient is meeting solute targets due to a combination of peritoneal and renal Kt/V_{urea} clearances, the patient should have regular 24-hour urine collections to determine the renal Kt/V_{urea} component to their total Kt/V_{urea}. We recommend urine testing at the minimum of every 4 months but preferably every 3 months in these cases. Once the daily urine volume is less than 100 mL, 24-hour urine collections can cease, and solute targets can be measured with peritoneal Kt/V_{urea} only.

PD patients should be seen regularly to evaluate clinical parameters such as clinical signs of uremia and volume disturbance. The necessary frequency of visits will vary based upon patient's dialysis vintage (incident patients may benefit from more frequent visits until they are deemed to be clinically stable), dialysis efficacy and clinical stability, and local- or country-specific requirements regarding dialysis patient care. Regarding inadequate solute clearance, the most efficient method of increasing solute clearance is to increase inflow volumes. Increasing contact between the peritoneal membrane and the peritoneal fluid has been shown to be more effective in increasing solute clearance than increasing the frequency of exchanges. With both CAPD and APD, it is possible to gradually increase inflow volumes in quantities of 200–250 mL per exchange per week, until the required inflow volume is achieved.

Ultrafiltration targets are patient-dependent and based upon the patient's fluid status as well as their peritoneal membrane transport status. Having PET data available greatly enhances the ability to prescribe the correct dwell time duration as well as the percent dextrose solution (or icodextrin) needed for the patient. As a general rule, high transporters will need shorter dwells in order to optimize ultrafiltration volumes, whereas low transporters can ultrafilter quite well with longer (e.g., 4 hours) exchanges. There is no hard and fast rule that a low transporter needs to be

on CAPD – it is quite possible to have a low transporter use the cycler for two to three exchanges during the night, followed by either no last fill (if they have significant residual kidney function) or a last fill, as needed. On the other hand, most high transporters will fare better with cycler therapy overnight and either a dry day (if they have significant residual kidney function) or if they don't have significant residual kidney function a last fill with either icodextrin for the long day dwell or a last fill with dextrose and a midday exchange in order to avoid fluid absorption.

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Chapter 14
Urgent-Start Peritoneal Dialysis

Arshia Ghaffari and Win Win Hlaing

Background

Peritoneal dialysis (PD) and hemodialysis (HD) are considered complementary therapies that provide similar clinical outcomes for patients with end-stage kidney disease (ESKD) [1–7]. PD has several advantages over in-center HD including preservation of vascular access sites, maintenance of residual kidney function, increased likelihood to maintain employment, and lower therapy cost [8]. Yet, while in countries with a "PD-first" policy up to 80% of ESRD patients are on PD, only about 10% of the worldwide dialysis population is on PD [9, 10].

This variability in PD utilization is multifactorial and involves complicated infrastructural, financial, policy, and resource issues. However, a common problem in places with low PD penetration is that most patients (up to 75%) start dialysis suboptimally without established dialysis access [11–13]. While there have been efforts to optimize pre-dialysis education, promote preemptive dialysis access creation, and improve planning for transition to kidney replacement therapy (KRT), these efforts have largely been unsuccessful. In the United States, despite CMS (Centers for Medicare & Medicaid Services) incentives to provide pre-dialysis education when patients have chronic kidney disease (CKD) stage 4, the percentage of patients initiating dialysis with a central venous catheter (CVC) has not changed in the past 20 years [11].

Historically, before HD was readily available, PD was commonly used as an acute dialysis modality in hospitalized patients (see chapter on acute PD). Moreover, emergent PD for acute and chronic dialysis needs remains commonplace in

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pediatrics as well as in countries with limited access to HD [14]. Yet, even if expertise exists, there remain many barriers to PD initiation in patients with an unplanned start. The advent of modern HD technology and ability to obtain rapid dependable temporary HD access has resulted in HD winning out as the favored therapy in the urgent or emergent setting. Consequently, the infrastructural requirements and expertise to directly place patients without an established plan onto PD does not readily exist in most centers. Furthermore, when patients "crash" into dialysis and are started on in-center HD, often without choice, the likelihood of transitioning to PD later in the course of their care is unlikely [15].

It is abundantly clear that patients starting dialysis with a CVC have significantly worse outcomes as compared to patients starting dialysis with an established arteriovenous fistula, graft, or PD catheter (PDC) [16]. CVCs are associated with a high risk of infectious, cardiovascular, and access-related complications. The overall mortality rate is considerably higher (up to 40%) in the first 3 months after starting HD with a CVC, and a higher mortality rate persists even after transition to a permanent access [17–20].

Over the past 20 years, in an effort to avoid CVCs while increasing patient choice, multiple investigators have demonstrated that early initiation of PD after PD catheter implantation is a safe, effective, and feasible in unplanned patient starts [21–25]. As part of a movement to implement urgent-start PD programs, protocols have been developed to safely transition late-presenting patients onto PD without having to wait 2–4 weeks after PD catheter implantation [26]. In this chapter, we will define urgent-start PD, discuss how urgent-start PD is completed and outcomes, and provide information about establishing urgent-start PD programs.

Urgent-Start PD: Definition and Candidacy

There are varying definitions of urgent-start PD in the literature. The predominant definition is initiation of PD exchanges less than 2 weeks after PD catheter insertion in patients with newly diagnosed ESRD who do not have a plan for kidney replacement therapy [26]. The 2-week timeline is based on the historical surgical recommendation not to utilize the PD catheters prior to 2 weeks after implantation [27]. In practice, most urgent-start PD patients are initiated on PD exchanges within 4–5 days after PD catheter insertion, with some studies reporting emergent-start PD immediately after PD catheter placement. Some investigators have suggested limiting the term "urgent-start PD" to those needing dialysis in less than 72 hours while utilizing the term "early-start PD" for those needing dialysis between 72 hours and 14 days [28]. Conversely, in our experience, if a patient has an emergent indication for dialysis (severe hyperkalemia, pulmonary edema, overt uremia), we utilize HD or continuous renal replacement therapy (CRRT) with a temporary CVC. Once stable, we then evaluate for PD candidacy and allow for transition to urgent-start PD and removal of CVC to limit exposure to CVCs [26].

Potential candidates for urgent-start PD include patients with GFR 3–10 ml/min/1.73 m^2 with no absolute contraindications or unresolvable barriers to PD and with no emergent need for dialysis. Absolute contraindications are similar to conventional start. When contraindications are correctable, we make sure to address them to allow patients the opportunity for PD.

Identifying appropriate urgent-start PD candidates increases the likelihood of both short-term and long-term PD technique success [29, 30]. Although patients in urgent need of dialysis may have a difficult time making decisions about complicated dialysis options, focused options education, with family involvement helps facilitate understanding and decision-making. Education can be provided by the nephrologist, renal case worker, dialysis nurse, social worker, or dedicated renal educator. Education should be unbiased and provided at a grade school level.

PD candidacy evaluation should be incorporated into the education. A checklist of questions to screen candidacy helps identify potential barriers [26]. The two main areas to screen include social barriers (home condition/cleanliness, space for dialysis supplies, access to toilet and sink, family support) and medical barriers (functional capability/disability, abdominal surgeries, psychiatric disorder, memory problems, hearing and vision impairment). Although the patient has the ultimate choice in modality of dialysis, a provider recommendation about what dialysis option is helpful in guiding decision-making.

Urgent-Start PD: How Is It Accomplished?

Once a patient presents with advanced CKD in need of urgent dialysis initiation, urgent-start PD involves having a process to evaluate the patient for PD candidacy, establish rapid PD access, and assist with the transition of patient onto PD in a safe manner (Fig. 14.1).

Depending on surgical expertise and patient comorbidities, PD catheter placement can be arranged as an either inpatient or outpatient. The preferred method for PD catheter placement in conventional-start PD has been laparoscopic placement with concomitant correction of hernias, redundant omentum, epiploic appendages, or adhesions [31, 32]. However, in the setting of urgent-start PD, while this approach may provide the best long-term catheter outcomes, it may be challenging as it requires a skilled surgeon and an available operating room with the appropriate equipment. Additionally, common comorbidities in ESRD patients may result in the need for anesthesia (and sometimes cardiac) clearance which may delay the procedure.

Surgical techniques utilizing local anesthesia or percutaneous approaches to PD catheter placement have been well studied and deemed to have similar short-term outcomes to laparoscopic PD catheter placement [33–39]. Interventional nephrologists and radiologists with appropriate expertise can place dual-cuff PD catheters without requirement for general anesthesia and therefore do not require pre-procedure anesthesia or cardiac clearance. The disadvantage of the percutaneous

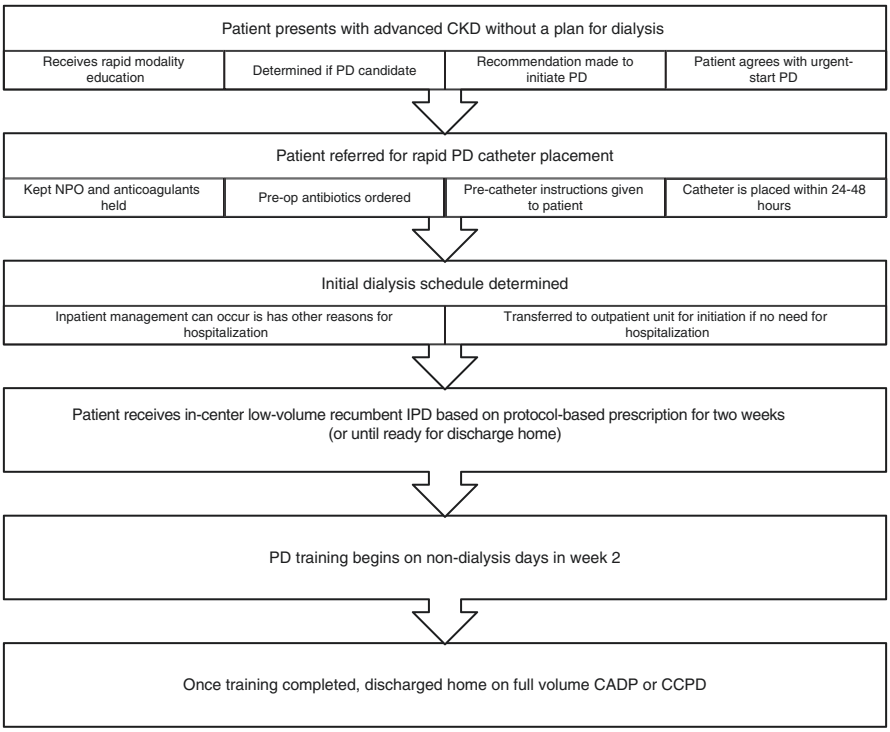

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Fig. 14.1 Urgent-start PD flow demonstrating steps from patient presentation until discharge home

approach is that it is difficult to perform in the very obese and in patients with prior major abdominal surgeries.

Once the catheter is placed and deemed functional, the decision needs to be made how soon the patient can start nurse-assisted exchanges [26]. If the patient requires immediate dialysis initiation, low-volume recumbent PD exchanges either manually or via a cycler in the inpatient setting are initiated with the assistance of a nurse (depending on center expertise and equipment availability). If there is no immediate need, the patient can be discharged with follow-up in the PD clinic within 24–48 hours. Upon arrival to the PD clinic, the PD nursing staff complete an assessment as to the need for urgent-start PD [26]. If the patient meets the criteria for dialysis initiation, the physician is informed, and nurse-assisted, supine, low-volume exchanges are initiated at the peritoneal dialysis clinic.

The specific prescription for urgent-start PD depends on the degree of residual kidney function, patient size, and other clinical parameters such as uremia, volume status, and degree of hyperkalemia and acid-base derangements. If the patient is not overtly uremic, intermittent PD (alternating days), with dry days in between, are started to theoretically allow tissue ingrowth into the catheter cuffs. However, if the

patient has more overt uremia or volume overload, daily therapy can be implemented. Most protocols involve four to eight cycles of low-volume exchanges (usually 750–1250 ml) over a 6–8-hour period. Fill volume can be increased by 250–500 ml per exchange per week [26, 40].

All exchanges should be performed with the patient in the supine or semi-supine position to minimize increase in intra-abdominal pressure and pericatheter leaks. The abdomen should be left dry during the ambulatory period in the initial 2 weeks. While urgent-start PD can be accomplished by manual exchanges, automated PD minimizes the work burden on the nursing staff and catheter manipulation.

During the first week of therapy, videos are utilized to provide patients with passive learning while receiving PD treatments. During the second week, training is started and usually completed in the third to fourth week. When training is nearing completion, a home visit is done to make sure the home is ready for PD therapy. If deemed appropriate, supplies are ordered, and patients are sent home on self-care home PD at full volume, much like a conventional-start PD patient.

It should be noted that during the urgent-start period, the prescribed regimen is focused on controlling uremic symptoms and achieving volume and electrolyte control. The aim is not to achieve a specific Kt/V target. Specific clearance targets can be considered once the patient is on a home PD regimen.

Establishing an Urgent-Start Program

Establishing the infrastructure prior to attempting to initiate patients on urgent-start PD is essential to program success [40]. Urgent-start PD requires coordinated care among multiple disciplines. Aside from patient education and selection, the abilities to achieve rapid PD catheter placement, cultivate nursing support, and secure administrative backing are critical parts of any program.

Rapid PD catheter placement is the rate-limiting step in any urgent-start program. Regardless of the method of catheter placement, there must be a commitment by the surgical team to place catheters within 24–48 hours of request and to manage catheter complications as needed in a timely manner.

Experienced nurses are preferred to manage medically challenging patients. Nurses should become familiarized with urgent-start concepts of low-volume recumbent PD as well as potential complications. Specific protocols in managing patients and complications in the urgent-start period are helpful in standardizing practice.

Administrative support, both at the hospital and clinic levels, should include provision of adequate PD expertise, supplies (catheters, cyclers, solutions, and chairs), space, and staffing. Training of nurses and ancillary staff on concepts of urgent-start PD is imperative to program success.

Studies to Support Early PD Initiation

Before the advent of formal urgent-start PD programs, multiple studies evaluated the effect of initiating PD exchanges prior to 2 weeks after PD catheter placements (Table 14.1) [21–25]. Immediate full-volume PD exchanges after PD catheter placement was demonstrated to be feasible without increased risk for pericatheter leak or migration if a purse-string suture was placed at the internal cuff [21]. This was further supported in another study demonstrating less than 5% incidence of pericatheter leak or outflow failure with early initiation of PD (within 6 days of catheter placement) [22].

The first report that resembled modern urgent-start PD was by Povlsen and Ivarsen in which automated PD was started in a protocol-driven manner less than 24 hours after open surgical PDC placement [23]. Fill volumes were 1200–1500 ml based on body weight (<60 kg or >60 kg). This retrospective study demonstrated that as compared to planned start patients, the urgent-start PD group had similar 3-month technique survival, no difference in infectious complications, but had a significantly higher mechanical complication rate (28.9% versus 7.7%, $P < 0.02$).

Lobbedez et al. in an observational study compared hospitalizations and patient survival for 34 unplanned start PD patients as compared to 24 unplanned start HD patients with follow-up out to 1 year [24]. The median time to PD initiation was 4 days. Initial hospitalization duration, survival-free of hospitalization at 6 and 12 months, mean duration of hospitalization, and adjusted 1-year survival were no different between the two groups.

In the largest study, Yang reviewed early start of incremental PD in 226 patients with 84 late-start PD patients with regard to catheter-related complications within 6 months of catheter insertion [25]. In the early group, PD was started in 2.0 ± 2.7 days, whereas in the late group, PD was started 41 ± 43 days. Overall complications were no different between the two groups.

However, it should be noted that these studies were hospital-based without a distinct urgent-start PD structure. Therefore, although they provided data that early initiation of PD is feasible without overt complications, they were considerably different compared to how we define and apply urgent-start PD currently.

Contemporary Urgent-Start PD Studies

Since 2010, multiple newly formed urgent-start PD programs worldwide have published their experiences (Table 14.2). Unfortunately, these studies are predominantly observational, lack satisfactory control groups, and are mostly single-center. Nonetheless, the overall trend of results allows understanding of potential outcomes.

In 2012, as part of a quality improvement report, we shared our initial experience with urgent-start PD [26]. In this report, we compared 90-day outcomes of our urgent-start PD population to conventional-start PD patients comparing

Table 14.1 Studies evaluating feasibility of early peritoneal catheter utilization (less than 7 days after PD catheter placement)

Study	Design	Comparison groups	Endpoints	PD catheter placement	Time to PD initiation	Outcomes
Song 2000 [21]	Prospective randomized comparative	Group 1 (n = 21): Gradual increase in exchange volume Group 2 (n = 38): Full exchange volume (2 L)	1. Catheter-related complications 2. Infectious complications 3. 1-year catheter survival 4. Duration of hospitalization	Percutaneous	<24 hours (both groups)	1. Short-term catheter complications (leak, malposition, outflow failure): No difference between two groups (p = NS) 2. Infectious complications (peritonitis, exit site/tunnel): No difference between two groups (p = NS) 3. 1-year catheter survival: Group 1, 85.7%; Group 2, 84.2% (p = NS)
Banli 2005 [22]	Prospective observational	Early initiation of PD (n = 41) No control group	Catheter-related complications (short term)	Percutaneous	6 days	Pericatheter leak (2) = 4.8% Outflow failure (2): 4.8% Peritonitis (1): 2.4%) Catheter replacement (1): 2.4%
Povlsen 2006 [23]	Retrospective with unmatched controls	Group 1: (n = 52): acute automated PD Group 2: (n = 88): planned start group	1. Technique survival (3-month) 2. Infectious complications 3. Mechanical complications	Surgical	<24 hours	1. 3-month technique survival Group 1, 86.7%; Group 2, 90% (p = NS) 2. Infectious complications: No difference between groups (p = NS) 3. Total mechanical complications: Group 1, 28.9%; Group 2, 7.7% ($p < 0.01$) 4. Catheter replacement: Group 1, 19.2%; Group 2, 3.9% ($p < 0.02$)
Yang 2010 [25]	Retrospective with unmatched controls	Group 1 (n = 226): Early start of incremental PD Group 2: (n = 84): Late-start group	Catheter-related complications within 6 months of catheter insertion	Surgical	Group 1: 2.0 ± 2.7 days Group 2: 41 ± 43 days	Complications: Group 1, 14.6%; Group 2, 13.1% (p = NS) Individual complications: Leakage: 2.2% vs. 2.4% Outflow failure: 3.1% vs. 6.0% Migration: 3.1% vs. 2.4% Exit-site infection: 1.3% vs. 0% Peritonitis: 4% vs. 2.4% Bridge hemodialysis: 31.4% vs. 57.1% ($p < 0.001$)

Abbreviations: *PD* peritoneal dialysis, *NS* nonsignificant, *n* number, *L* liter

Table 14.2 Contemporary urgent-start PD studies

Study	Design	Study groups	Main endpoints	Follow-up	PD catheter placement technique	Time to PD start	Results
Ghaffari [26] 2012	Single-center prospective observational	Group 1 (n = 18): protocol-based urgent-start PD Group 2 (n = 9): traditional PD	1. Dialysis-related outcomes 2. Infections (Peritonitis and exit-site) 3. Mechanical complications	90-days	Percutaneous	<14 days	1. Dialysis-related outcomes (Kt/V, Hgb, PTH, phos, albumin): No difference between two groups (p = NS) 2. Peritonitis: Group 1, 1:110 PMs; Group 2, 1:42 PMs Exit-site infections: Group 1, 1:55 PMs Group 2, 1:42 PMs 3. Mechanical complications: Minor leak: Group 1, 22.2%; Group 2, 11.1% Major leak: Group 1, 11.1%; Group 2, 0% Poor initial drain: Group 1, 0%; Group 2, 11.1% Primary non-function: Group 1, 11.1%; Group 2, 22.2% Hematoma: Group 1, 5.6%; Group 2, 0%
Koch [47] 2012	Single-center retrospective observational	Group 1 (n = 57): urgent-start HD Group 2: (n = 66): urgent-start PD	1. Infections 2. Mortality 3. Hospitalization	Up to 6-months (mean 4.7 months)	Laparoscopic	12 hours	1. Bacteremia (HD 21.1% vs. PD 3.0%, $P < 0.01$) 84% lower risk of bacteremia for PD group Peritonitis occurred only in 1 patient in each group 2. Mortality: No significant difference between two groups Group 1, 42.1%; Group 2, 30.3% (p = NS) 3. Hospitalizations: No difference (p = NS)
Casaretto [41] 2012	Single-center observational	Group 1 (n = 11) Urgent-start PD (no comparative or control group)	1. Technique survival 2. Mechanical complications 3. Peritonitis	90-days	Laparoscopic	<48 hours	1. 90-day technique survival 91% 2. Catheter dysfunction requiring revision in 9.1%. No leaks occurred 3. No peritonitis episodes occurred

Masseur [42] 2014	Prospective observational	Group 1 (n = 81) Urgent-start PD (no comparative or control group)	1. Technique survival 2. Hospitalization	90-days	Laparoscopic	<6 days	1. 90-day technique survival: 92.6% (75/81) 2. Hospitalizations: 25 hospitalizations. Dialysis-related hospitalization: 24% (fluid imbalance 16%; catheter malfunction 8%)
Alkatheeri [43] 2014	Single-center prospective observational	Group 1 (n = 30) Urgent-start PD (no comparative or control group)	1. Mechanical complications 2. Infections 3. Technique survival	28–1050 days (median 201 days)	Percutaneous: 20 Laparoscopic: 10	<14 days (median 6 days)	1. Mechanical complications: Minor pericatheter leak: 10% Catheter migration: 20% 2. Infections: Peritonitis:1:319 PMs; Exit-site infections:1:159 PMs 3. Technique survival: 90-day: 93.3%; Overall (end of study): 80%
Reyes-Marin [51] 2014	Open label, single-center randomized controlled trial	Group 1: (n = 80). Full-volume immediate PD Group 2: (n = 80). Delayed-PD	1. Mechanical complications 2. Infectious complications 3. Technique survival	12 months	Open surgical	Group 1: <1 day Group 2: 2–5 days (mean 79.5 hours)	1. Mechanical complications: Overall: Group 1, 12.5%; Group 2, 15% (p = NS) Leakage: Group 1, 2.5%; Group 2, 3.75% (p = NS) Migration: Group 1, 2.5%; Group 2, 5% (p = NS) Hemoperitoneum: Group 1, 1.25%; Group 2, 2.5% (p = NS) 2. Infectious complications: Peritonitis: Group 1, 1.25%; Group 2, 2.5% (p = NS) Exit-site infection: Group 1, 3.75%; Group 2, 1.25% (p = NS) 3. Technique survival: Group 1, 93.7%; Group 2, 90% (p = NS)

(continued)

Table 14.2 (continued)

Study	Design	Study groups	Main endpoints	Follow-up	PD catheter placement technique	Time to PD start	Results
Wong [45] 2016	Multicenter observational	Group 1 (n = 81). Urgent-start PD	1. Technique survival 2. PD training days 3. Mechanical complications	Median 268 days	Laparoscopic (n = 69) Percutaneous: (n = 6) Laparotomy (n = 1) Unknown (n = 5)	<14 days	1. Technique survival: 74% 2. PD training days: 9 3. Mechanical complications: Hematoma: 3% Leakage: 5% Omental wrap: 4% Poor drainage: 11% Other: 16%
Jin [48] 2016	Single-center prospective observational	Group 1 (n = 96). Urgent-start PD Group 2 (n = 82). Urgent HD	1. 30-day dialysis-related complications 2. 30-day infectious complications 3. Patient survival	3 months (actuarial survival to 1 year)	Laparotomy	<14 days	1. Overall early complication: Group 1, 5.2%; Group 2, 24.4% ($p < 0.01$) 2. Peritonitis: Group 1, 2.1%; Group 2, 0% (p = 0.548). Bacteremia: Group 1, 3.1%; Group 2, 13.4% (p = 0.003) 3. Patient survival: No difference at 3 months or 1 year
See [44] 2017	Single-center matched case-control	Group 1 (n = 26). Urgent-Start PD Group 2 (n = 76). Conventional Start PD	1. Early complications (30-day) 2. Technique survival 3. Peritonitis-free survival	2 years	Surgical	<14 days	1. Early catheter complications: Leak: Group 1, 12%; Group 2, 1% (p = 0.047) Blockage: Group 1, 4%; Group 2, 0% (p = 0.25) Migration: Group 1, 12%; Group 2, 4% (p = 0.16) Exit-site infections: Group 1, 15%; Group 2, 13% (p = 0.92) Peritonitis: Group 1, 0%; Group 2, 4% (p = 0.57) 2. Technique survival: No difference 3. Peritonitis-free survival: No difference

Abbreviations: *PD* peritoneal dialysis, *NS* nonsignificant, *Hgb* Hemoglobin, *PTH* parathyroid hormone, *phos* phosphate, *PMs* patient-months

dialysis-related outcomes, PD-related infections, and catheter-related complications. We demonstrated that dialysis-related outcomes (Kt/V urea, hemoglobin, parathyroid hormone, phosphorus, albumin) and infections (peritonitis and exit site) were no different between the urgent-start and conventional-start PD groups. We noted a higher rate of minor and major leaks in the urgent-start PD group, but these differences were not statistically studied due to the low number of events. We shared our protocols as part of a supplement to the study.

Casaretto et al. in an observational study of 11 private practice patients demonstrated that in a program with laparoscopic PDC placement with PD initiation in less than 48 hours, the 90-day technique survival was 91% (1 patient transplanted) [41]. No infectious or other complications were noted. Masseur et al. further supported these findings by demonstrating in 81 patients in a large private practice group that 90-day technique survival was 92.6% [42]. In another single-center prospective observational study, Alkatheeri demonstrated a minor pericatheter leak rate of 10%, catheter migration rate of 20%, and low peritonitis (1:319 patient months) and exit-site infection rates (1:159 patient months) [43]. Technique survival at 90 days was 93.3% and 80% at the end of the study (median follow-up 201 days).

In an Australian single-center matched case control study, urgent-start PD patients were matched 1:3 with conventional-start PD patients based on age and diabetic status [44]. The urgent-start PD group started PD on average 4 days (1–7) after PDC placement as compared to 40 days (25–70) for the conventional-start PD group. Initial fill volumes were 1.0 liter for the urgent-start PD group as compared to 2 liters for the conventional-start PD group. Leaks within 4 weeks of catheter placement were higher in the urgent-start PD group (12% versus 1%, $P = 0.047$). Catheter migration within 4 weeks of PD commencement was also higher in the urgent-start PD group (12% versus 1%, $P = 0.047$). There was no difference in catheter blockage, exit-site infections, or peritonitis episodes. While certain catheter-related complications were higher in the urgent-start PD groups, this did not seem to impact technique survival or peritonitis-free survival.

While most studies have been single-center, a small multicenter study of 81 urgent-start PD patients was completed in 22 PD centers of a large dialysis organization [45]. Twenty-one patients starting PD within 48 hours were subclassified as emergent starts, while the rest were deemed non-emergent. Comparing outcomes, 52% of the emergent group and 33% of the nonemergent group had mechanical complications. Leaks occurred in 10% of the emergent group while only in 3% of the non-emergent group. Both groups had about the same rate of drain problems (emergent, 10%; non-emergent, 12%). During the 1-year follow-up, overall technique failure was 26%, and there were no deaths.

Another larger propensity-matched study of 690 urgent-start PD patients comparing mortality, hospitalizations, and infections and comparing urgent-start PD to urgent-start HD and planned PD has been completed but not published. Data presented in abstract form demonstrated that as compared to planned PD, urgent-start PD had no significant difference in mortality (IRR 0.96; CI 0.52–1.79; $p = 0.91$) or infections (IRR 1.44; CI 0.88–2.36; $p = 0.15$) but a 45% higher rate of hospitalizations (IRR 1.45; CI 1.13–1.87; $P = 0.004$). As compared to urgent-start HD,

urgent-start PD has a 51% lower short-term mortality (IRR 0.49; 95% CI 0.29–0.84; $p = 0.009$), 39% lower rate of hospitalizations (IRR 0.61; 95% CI 0.49–0.77; $p < 0.001$), and 42% lower rate of infections (IRR 0.58; CI 0.39–0.87; $p = 0.008$) [46].

Xu et al. reviewed mechanical and abdominal wall complications associated with starting PD within 7 days of PD catheter placement in a population of 922 patients over a 10-year period with a median follow-up of 31.3 months [47]. About half the patients started PD within 1 day of catheter placement. Overall, 4.8% of patients developed abdominal wall complications at a median follow-up of 5.2 months (incidence of 1.5/100 patient years). These complications included hernias (55%), hydrothorax (25%), hydrocele (14%), subcutaneous leaks (5%), and pericatheter leak (2%). Risk factors for abdominal wall complications included male sex, history of abdominal surgeries, and lower exchange volume. No correlation was found between infusion volumes and abdominal wall complications.

A few studies have directly compared urgent-start PD with HD with a CVC. Koch et al. in a single-center observational cohort study compared morbidity and mortality in 66 unplanned PD patients with 57 unplanned HD patients with 6 months of follow-up [48]. While there was no difference in mortality (PD 30.3%; HD 42.1%, $P = 0.19$), HD patients had a significantly higher risk of bacteremia (HD 21.1%; PD 3.0%; $P < 0.01$).

The largest published experience comparing urgent-start PD and HD with a CVC is from China [49]. This retrospective study compared patient survival and dialysis-related complications in 178 patients (82 HD, 96 PD) over a 1-year period. Patients requiring emergent dialysis were excluded. PD catheters were placed via a laparotomy method by nephrologists. Intraperitoneal fill volumes ranged from 0.75 to 1.2 liters. During the first month after catheter insertion, 5.2% of PD patients and 24.4% of HD patients developed complications. The main complications in the PD group included catheter malposition (3.1%) and peritonitis (2.1%). In the HD group, there was a high incidence of catheter-related infections (11%), thrombosis (7.3%), and bleeding (3.7%). Bacteremia was significantly higher in HD patients (13.4%) as compared to PD patients (3.1%). The same research team, in a separate retrospective analysis, reviewed short-term complications specifically in 80 diabetic ESRD patients (50 PD, 30 HD) that either commenced urgent-start PD or urgent-start HD [50]. The incidence of overall complications was significantly lower in the diabetic PD population (6.0% in PD, 26.6% in HD, $P = 0.024$).

Challenges of Urgent-Start PD

Securing needed surgical resources, addressing educational deficits of PD treatment teams, and working around therapy limitations in the urgent-start period are the main challenges of urgent-start PD. While establishing a pathway to rapid PD catheter placement is a key asset, surgical support to manage PD catheter complications is just as important. Lack of timely surgical support will predispose to high early technique failure rates, which may impact both patient, staff, and physician morale.

Technique success involves having the expertise and experience to be able to manage more complicated patients. In the United States, the majority of PD clinics are small (fewer than 20 patients) and sometimes without physical space or adequate staffing to take on an influx of patients. It is preferable that when setting up urgent-start PD programs, larger clinics with a more robust and experienced staff are chosen.

The emergent need for dialysis is another issue that is difficult to address with PD. Low-volume PD provides only a small amount of urea and other small-molecule clearance, especially if done for 6–8 hours on an alternate day basis. In more emergent scenarios, HD or CRRT can be used as a bridge to urgent-start PD. While some studies have demonstrated an ability to perform "emergent-start PD," the risk of catheter-related complications including leak and migration increases, often resulting in patients requiring temporary HD with a CVC, which defeats the overall goal [23, 51]. It appears, however, that if care is taken to place a purse-string suture at the rectus muscle at the time of PD catheter placement, the increased risk of leak, even with larger exchange volumes, is mitigated [21, 52].

Conclusion

Avoiding CVCs and increasing patient choice are the core benefits of urgent-start PD. Urgent-start PD also allows patients to avoid multiple procedures since the initial dual-cuff PD catheter serves as the permanent dialysis access. This approach adds the benefit of preservation of vascular access sites, longer maintenance of residual kidney function, and all at a lower cost than urgent HD [8, 53].

While larger, higher-quality, and longer-duration studies are required, initial studies suggest that urgent-start PD is a safe and feasible choice in unplanned patients who need chronic dialysis initiation. Although rates of catheter-related complications appear to be higher in urgent-start PD than patients who start conventional PD, technique survival seems to be similar between the two groups. Additionally, urgent-start PD appears to have similar, if not better, outcomes than patients starting HD with a CVC with regard to bloodstream infections and early hospitalizations. These preliminary studies suggest once the infrastructural needs are in place, patients presenting to dialysis without a plan should have the option of being directly started onto PD through an urgent-start pathway.

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Chapter 15
Infectious Complications in Peritoneal Dialysis

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Introduction

Peritoneal dialysis (PD) patients have fewer hospitalizations due to infections when compared to hemodialysis (HD) patients. Specifically, PD patients have fewer hospitalizations due to septicemia/bacteremia, pneumonia, and cellulitis [1]. Nevertheless, peritonitis and to a lesser extent catheter exit-site infections are leading causes of PD morbidity, and peritonitis is a major cause of transfer to HD. In an analysis involving greater than 40,000 patients, infectious complications were the most frequent cause of PD patients transferring to HD [2]. Therefore, it is relevant to address the most frequent infections encountered in PD, and in this chapter, we will address exit-site infections, catheter tunnel infections, and peritonitis as well as the topic of infection prevention.

Exit-Site and Tunnel Infection

The PD catheter exit site is an important part of the PD system. The catheter exit site is the main potential entry point of bacteria from the environment into the peritoneum; therefore, it is important that the exit site is clean, dry, and well healed. A subcutaneous cuff, approximately 2–3 cm deep to the skin/exit site, is the main physical barrier to the entry of bacteria and other materials from the skin into the

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catheter tunnel. Infection at the exit site is a major risk factor for peritonitis and/or tunnel infection.

The exit site should be examined at every clinic visit, and the patient should be advised to examine the exit site daily. The presence of purulent drainage at the exit site is consistent with an exit-site infection, whereas simple erythema at the exit site may or may not indicate an exit-site infection [3, 4]. Erythema at the exit site without drainage could be a result of skin irritation (e.g., from cleansing agents), exit-site trauma, or changes seen normally after new catheter placement. Clinical judgment should be used in these cases, with attention placed on certain aspects of the exit site (Table 15.1) [5]. In the case of any exit site with exudate, a swab culture should be taken in order to guide antibiotic therapy. In the case of an erythematous exit site without exudate, empiric therapy for exit-site infection, discussed below, is likely to be helpful, whereas swab cultures are not recommended.

Initial empiric treatment of routine exit-site infections should include antibiotic therapy against *S. aureus* since this bacteria is the most commonly encountered cause of exit-site infection. Oral therapy with cephalexin should be sufficient for nonresistant streptococcal and non-MRSA (methicillin-resistant *S. aureus*) staphylococcal infections; in the case of MRSA infection, oral trimethoprim/sulfamethoxazole, clindamycin, or linezolid can be utilized, or intraperitoneal (IP) vancomycin therapy can be administered. Patients with a history of Gram-negative exit-site infection should have Gram-negative coverage added as well (*e.g.*, oral fluoroquinolone) until culture results return, after which point therapy should be tailored to culture results. Therapy should initially continue for 2 weeks for Gram-positive organisms and 3 weeks for *Pseudomonas* species. If the exit site does not appear to improve within the first week and the antibiotics given are appropriate per culture results, consideration should be given to change from oral to IP therapy for the next 1–2 weeks. Lack of response to several weeks of antibiotic therapy, especially with concurrent peritonitis, should prompt evaluation for catheter removal. Simultaneous catheter removal and replacement is a procedure wherein the infected catheter is removed and a new catheter is placed on the opposite side, in the same operation. This procedure has been shown to be effective for refractory exit-site and/or tunnel infections in PD patients and prevents the need to place a hemodialysis catheter and

Table 15.1 Evaluation of the PD catheter exit site

Inflammation
Redness of the skin
Size/diameter of inflamed area
Pain or induration
Duration of inflammation
Presence of crust at exit site or on gauze dressing
Expressible pus and/or spontaneous pus
External or internal granulation tissue prominence
Presence or absence of internal secretions
Palpation findings (tenderness, pus)

subsequent transfer to hemodialysis [6, 7]. When using this technique, patients should receive 1–2 weeks of perioperative antibiotics and should perform supine, low-volume peritoneal dialysis for the first week post-catheter placement, in order to prevent catheter leak at the new catheter site [6].

Exit-site colonization is associated with increased risk for exit-site infection; therefore, several procedures should be followed in order to reduce the risk of exit-site infection. First, practitioners should always wear a mask when examining the exit site in close proximity, in order to reduce the transfer of oropharyngeal bacteria from the examiner to the patient's exit site. Second, the exit site must be allowed to heal in a sterile environment after new catheter placement. Routine showers should be avoided until full healing of the exit site, usually 2 weeks [4]. Third, once the exit site has healed fully, routine exit-site care should involve daily cleaning as per the PD (peritoneal dialysis) clinic protocol, and the exit site should be dried fully before placing any dressing over the exit site. Lastly, it is highly recommended to apply either gentamicin or mupirocin cream to the exit site after cleaning (and drying) it thoroughly as part of a daily exit-site care regimen. Antibiotic prophylaxis at the exit site has been shown to reduce infection rates significantly [8, 9] (Table 15.2). Finally, the external portion of the catheter should be secured in order to prevent tugging of the catheter at the exit site, a risk factor for exit-site infection.

PD catheter tunnel infections typically occur in the presence of an exit-site infection and manifest as exit-site drainage with pus expressible from the tunnel as well as redness, pain, and erythema along the tunnel tract. Microbiological culture should be obtained from any expressible drainage, and empiric antibiotic therapy should commence immediately as per guidelines above for exit-site infection. Catheter tunnel infections that do not respond promptly to oral antibiotics should prompt conversion to IP antibiotic administration. Oftentimes tunnel infections will require 3–4 weeks of treatment for full resolution. As described above, refractory infections can be addressed by simultaneous catheter removal and replacement.

Occasionally the subcutaneous (superficial) catheter cuff can complicate catheter tunnel infections. Pain on palpation of the cuff, with or without erythema of the skin overlying over the cuff, is suggestive of potential cuff involvement. Recurrent exit-site or tunnel infection is another sign of possible cuff involvement. Ultrasonography can be utilized to determine if there is a peri-cuff abscess or fluid collection [10]. Unfortunately, cuff involvement in tunnel infection often leads to the need for catheter replacement if antibiotic therapy is not effective [11]. An alternative approach is surgical revision of the exit site so as to de-roof the catheter cuff and allow the exit

Table 15.2 Daily PD catheter exit-site care

Usual exit-site care (washing with antibacterial soap and water or other cleaning agents per clinic protocol)
Gentamicin cream 0.1% cream or mupirocin 2% cream
Apply to clean and *dry* exit site daily after usual exit-site care
Secure catheter externally to avoid tugging at the exit site

site to heal by secondary intention. These procedures tend to be more effective when the superficial cuff is no more than 2 cm deep to the exit site.

Peritonitis

The incidence of peritonitis has been decreasing over time in patients on chronic peritoneal dialysis, in part due to technological and procedural improvements in PD [1, 12]. Nevertheless, peritonitis remains the main infection seen in PD patients and is a major cause of PD catheter loss and transfer to HD [1, 2]. In an analysis involving >40,000 patients, infectious complications were the most frequent cause of PD patients transferring to HD [2]. Peritonitis has also been found to be the leading cause of transfer to hemodialysis in several long-term PD studies [13]. Furthermore, peritonitis can cause damage to the peritoneal membrane, sometimes irreversibly, and is a leading cause of hospitalization in PD patients [1]. In this section, we will review the causes, diagnosis, treatment, and prevention strategies for peritonitis.

Definition and Diagnosis

The basic definition of peritonitis is inflammation of the peritoneum, and infectious peritonitis can be defined as peritoneal inflammation due to any infectious organism. The International Society for Peritoneal Dialysis (ISPD) has published guidelines outlining criteria for the diagnosis of PD-related peritonitis. Specifically, peritonitis should be diagnosed when two of the following three criteria are met: (1) abdominal pain and/or cloudy effluent; (2) dialysis effluent white cell count >100/μL or >0.1 × 109/L (after a dwell time of at least 2 hours), with >50% polymorphonuclear cells; and (3) positive dialysis effluent culture [14, 15]. In the case of a positive culture without effluent leukocytosis and typical peritonitis symptoms, the effluent should be sent for repeat analysis to confirm true infection.

Peritonitis can have several clinical manifestations (Table 15.3), but in general, any patient with cloudy effluent or suspicious symptoms such as abdominal pain

Table 15.3 Clinical findings suggestive of possible peritonitis

Signs/symptoms
Fever
Abdominal pain
Nausea
Diarrhea
Cloudy effluent
Exam
Abdominal tenderness

should have their PD fluid examined for infection by sending the effluent for an immediate cell count and culture. Gram stains are helpful in that they can identify yeast early, but often gram stains have low bacterial yield in PD peritonitis. PD effluent should be sent to the laboratory promptly (within a few hours) of presentation whenever possible in order to produce the best culture results.

Proper procedures are important to establish the diagnosis and identify the organisms involved in the infection. Each PD clinic should aim for a culture-negative peritonitis rate of <20% of episodes and preferably <15% of episodes [14, 15]. Simple inoculation of blood culture bottles with PD effluent in the clinic is an acceptable and efficient routine method of obtaining cultures [16, 17]. To enhance the yield of the culture by five to ten times, the centrifugation method can be utilized; in this method, 50 mL of effluent is centrifuged at 3000 g for 15 minutes, and the sediment is resuspended in 3–5 mL of supernatant, followed by inoculation on solid culture media or standard blood culture media [18].

Peritonitis Treatment

There are a few steps to take in the early management of peritonitis aside from the selection of antibiotics. First, one must assess the need for hospitalization. Patients who appear septic or hemodynamically unstable should always be considered for possible hospitalization. Additionally, those patients who are in extreme pain and/or have mental status changes should be evaluated for the feasibility of continuation of home or self-care dialysis versus a short hospitalization stay until they are more clinically stable. Second, for patients with abdominal pain, a quick peritoneal flush (1000 mL of PD fluid inflow, immediately drained) can help clear endotoxin and inflammatory mediators and thus can reduce the symptoms of peritoneal pain. Third, IP heparin should be administered in one exchange daily until the effluent clears, in order to prevent catheter clogging. This can be done upon presentation and subsequently until the effluent is no longer cloudy. Finally, it is useful to review with the patient at the time of presentation what risk factors were present to possibly account for the peritonitis (Table 15.4).

Once the patient has been clinically evaluated, empiric antibiotics should be given as soon as possible, within 1–2 hours of presentation if possible [19]. The

Table 15.4 Possible causes of peritonitis: questions to ask the patient

Touch contamination?
Recent procedures (e.g., colonoscopy)?
Constipation?
Catheter damage?
Exit-site drainage or trauma?
Diarrhea or other GI illnesses?
Hernia?

initial empiric antibiotic regimen should include both Gram-positive and Gram-negative coverage [20, 21]. A typical initial regimen could include a first-generation cephalosporin or vancomycin, the latter reserved for those known to be or at higher risk for methicillin-resistant organisms, *plus* Gram-negative coverage with a third-generation cephalosporin, fluoroquinolone, or gentamicin. Treatment should be intraperitoneal and should continue while cultures are followed closely; antibiotics should be eventually adjusted based on culture and sensitivity results. Antibiotic treatment can be administered in an intermittent fashion (once daily, long dwell of at least 6 hours) or in a continuous fashion (antibiotics in each PD dwell). Readers can refer to published guidelines for dosing recommendations for both intermittent and continuous antibiotic regimens [20, 21]. Antibiotic dosing should take into consideration the patient's residual kidney function and size, in order to avoid inadequate antibiotic doses; when using vancomycin or gentamicin, blood levels of the drug should be monitored to ensure therapeutic dosing has been achieved (Table 15.5) [22].

Antibiotic therapy should continue for 3 weeks in the case of all infections except those with *Streptococcus* or *Staphylococcus epidermidis*, both of which can be treated for 2 weeks. *Pseudomonas* infections should be treated with two agents concurrently; acceptable agents include ceftazidime, cefepime, fluoroquinolones, and gentamicin, and treatment should always be guided by culture and sensitivity results [15]. Culture-negative peritonitis should prompt a repeat cell count and differential after 3 days of negative culture. If the cell count is consistent with a resolving infection at day 3, Gram-negative treatment can be discontinued, and treatment should continue with empiric Gram-positive treatment (vancomycin or first-generation cephalosporin) for 2 weeks [15]. One should consider tests for the isolation of rare organisms (e.g., mycobacteria, fungi) if the peritonitis does not appear to be resolving at day 3 by way of improving PD effluent cell counts.

Follow-up cell counts should be obtained in peritonitis in order to ensure adequate response to therapy. Three separate studies have shown that the follow-up cell count can help predict the outcome of peritonitis. One study involving 565 consecutive episodes in Hong Kong showed that the day 3 effluent cell count >1000 cell/mcL indicated a 64% likelihood of treatment failure. Other predictors of treatment

Table 15.5 Antibiotic doses for peritonitis: intermittent therapy

Antibiotic	Recommended intraperitoneal dosing
Cefazolin or cephalothin	15–20[a] mg/kg once daily
Vancomycin	30[a] mg/kg once, then 15 mg/kg every 3–5 days; follow serum drug levels and adjust dose to maintain therapeutic levels
Ceftazidime, cefepime (2-g load)	15–20[a] mg/kg once daily
Gentamicin, tobramycin	0.6[a] mg/kg once daily; follow serum drug levels
Ciprofloxacin	500 mg twice daily orally; for empiric usage, do not use without concurrent Gram-positive coverage

[a]Notes: (1) IP antibiotic dwell time should be a minimum of 6 hours for optimum drug absorption, (2) use the higher does for patients with significant residual kidney function [15]

failure included infection with mycobacterium, pseudomonads, and fungi [23]. Two other studies have found that the number of days with an effluent cell count greater than 100 cells/mcL is predictive of treatment failure and/or catheter loss [24, 25]. Hence, it is important to obtain follow-up cell counts several days after initiation of antibiotic therapy, even if the peritoneal effluent clears.

Refractory peritonitis is defined as failure of the effluent to clear after 5 days of culture-guided antibiotics [15]. Persistent elevated cell counts should always prompt reconsideration of the antibacterial therapy and, if elevated cell counts are prolonged beyond 5 days despite proper antibiotic therapy, should lead to consideration of catheter removal. In cases of refractory peritonitis, the patient should be transferred to hemodialysis, and antibiotic administration should continue for another 2–3 weeks. If the patient has clinical improvement (lack of peritonitis symptoms), a new catheter can be placed as early as 4 weeks after initial catheter removal.

Fungal peritonitis is uncommon but is associated with poor outcomes. It accounts for fewer than 2–5% of all peritonitis episodes but is associated with high mortality rates (5–25%), leads to catheter removal, and often leads to technique failure [26]. The first sign of possible fungal peritonitis is the presence of yeast seen on gram stain or KOH prep of the effluent. Fungal culture results can be elusive and often take days to weeks to manifest. A diagnosis of fungal peritonitis should always lead to catheter removal. In one of the largest studies of fungal peritonitis in an experienced PD center, catheter removal for fungal peritonitis was associated with a 31% mortality rate compared with a mortality rate of 91% in those patients whose catheter remained *in situ* [27]. Patients should be transferred to hemodialysis for the course of the antifungal therapy. Treatment of fungal peritonitis should include antifungal agents as dictated by culture and sensitivity reports; oftentimes an infectious disease consultation can be helpful to identify the correct antifungal therapy based on local susceptibility patterns. There are no clear guidelines regarding whether or when a patient can return to PD after fungal peritonitis; one study showed that up to one third of patients could return to PD after a median time to catheter reinsertion of 15 weeks after the initial infection, with the longest delay to catheter reinsertion being more than 6 months [28].

An association has been suggested between current or previous antibacterial use and increased risk of development of fungal peritonitis; antibacterial agents may disturb intestinal flora and lead to overgrowth of fungi, which can then cause peritonitis by migrating across the intestinal wall into the peritoneum. Several studies have shown a reduction in the fungal peritonitis rate when antifungals (oral nystatin or fluconazole) are simultaneously given with any course of antibacterial therapy, either PD-related or not [29–33]. Nystatin has the benefit of being largely non-absorbed, and therefore the risk of resistance is low. Dosing of nystatin is typically 500,000 IU four times daily during treatment with antibacterial agents and up to 4 days after the last dose of the antibacterial.

Several conditions can occur wherein peritonitis occurs after successful treatment for peritonitis. Recurrent peritonitis is defined as peritonitis within 4 weeks of antibiotic completion for a prior episode but with a different organism, whereas relapsing peritonitis is peritonitis within 4 weeks of antibiotic completion for a prior

episode with the same organism or one sterile episode [15]. Both can be treated with a full course of antibiotics as would be done for routine peritonitis. In the case of recurrent peritonitis or relapsing peritonitis (peritonitis more than 4 weeks after antibiotic completion for a prior episode with the same organism), one can consider intra-catheter thrombolytic therapy (*e.g.*, tissue plasminogen activator (tPA)), with an aim to eliminate any biofilm in the catheter that may be harboring bacteria. The rationale of using fibrinolytics in relapsing, or recurrent peritonitis, is as follows: bacterial colonization on the catheter can be sequestered by a biofilm that consists of fibrin clots or a polysaccharide matrix that protects bacteria from the antimicrobial agents, and fibrinolytic agents may allow lysis of the biofilm layer, thus allowing resolution of bacterial colonization [34, 35].

Recurrent peritonitis or relapsing peritonitis that does not resolve after two courses of antibiotics should prompt consideration of catheter removal. Simultaneous catheter removal and replacement can be considered in cases wherein the infection has been controlled (*i.e.*, the effluent cell count is less than 100 cells/μL, and culture is negative) [36]. As described above, after this procedure, patients should receive 1–2 weeks of perioperative antibiotics and should perform supine, low-volume peritoneal dialysis for the first week post-catheter placement, in order to prevent catheter leak at the new catheter site [6].

Infection Prevention

Despite the fact that infections in peritoneal dialysis have become more infrequent with time, peritonitis remains the major cause of infection in PD patients. It is useful to explore some of the most important aspects of an infection prevention schema in peritoneal dialysis (Table 15.6).

The risk for infectious complications in PD begins at the time of catheter placement. Therefore, certain procedures should be practiced during and after catheter placement in order to reduce the risk for exit-site infection and/or peritonitis after catheter placement. First, a suitable exit site should be chosen prior to catheter placement, preferably with the patient in the upright position in order to select an

Table 15.6 Key elements of peritonitis prevention

New catheter: exit site heals in a sterile environment
Complete full initial training program
Home visit
Proper exit-site care, including prophylactic topical antimicrobials at exit site
Avoidance of constipation
Retraining after peritonitis
Ongoing patient education

exit site free of belt lines and skin folds and one within the patient's clear line of sight [37, 38]. Second, the patient should be prepped with a laxative 1–2 days preoperatively. Constipation is a risk factor not only for peritonitis but also for catheter malfunction. Third, Gram-positive antibiotics should be given perioperatively; several randomized controlled trials have shown that peri-catheter placement antibiotics reduce the risk for PD infections after catheter placement [39]. Finally, the exit site should be allowed to heal in a sterile environment, as discussed above in the section regarding exit-site infections. Patients should keep the original dressing in place, barring any major bleeding or pus/exudate drainage, for at least 1–2 weeks postoperatively. It is imperative that they do not shower or wet the exit-site during this time period as well.

After catheter placement, the patient will begin PD training. It is imperative that patients receive thorough education and training in the PD technique including education on exit-site care and the possible symptoms of exit-site infection or peritonitis. They should be taught to contact the PD clinic immediately, without delay, whenever they suspect an abnormal exit site or possible peritonitis symptoms such as unexplained abdominal pain, cloudy effluent, or nausea/vomiting. Oftentimes a delay in the treatment of PD-related infections can lead to worse outcomes. Since prevalent PD patients may have not experienced any PD complications for months before an episode of peritonitis or exit-site infection, they may delay seeking medical attention for hours to days after signs and symptoms of possible infection; therefore, they too should receive routine reeducation regarding the signs and symptoms of exit site and/or peritonitis during the monthly PD clinic visit.

A home visit should be performed before or during the training period, with a goal toward helping the patient optimize the home environment to allow for PD success and reduce the risk of infection. Attention should be paid to certain aspects of the home environment such as adequate lighting in the PD "room," the presence of a clean and uncluttered work surface, an organized storage system, avoidance of pets in the PD "room" and PD storage areas, and closeable windows in the PD area, among other things [40]. It is also useful to perform a home visit whenever a patient changes residences and after an episode of peritonitis, again with the same intent to optimize the home environment for PD. At the home visit post-peritonitis, it is also useful to observe the patient perform the PD connection procedure, to ensure proper technique.

Peritonitis can be associated with certain invasive procedures, and antibiotic prophylaxis can be helpful to reduce the risk of infection in the setting of dental procedures as well as colonoscopy. One study examined 77 CAPD patients who underwent 97 colonoscopies in Hong Kong between 1994 and 2006 and found that no peritonitis occurred post-procedure in 18 patients who were given prophylactic antibiotics, whereas there was a 6.3% risk of peritonitis after colonoscopy if prophylactic antibiotics were not given [41]. Table 15.7 shows suggested prophylactic antibiotic regimens for both dental and lower GI procedures.

Table 15.7 Antibiotic prophylaxis prior to invasive procedures in peritoneal dialysis

Dental procedures:
Amoxicillin 2.0 g 2 hours before
Clindamycin 600 mg for PCN-allergic
Colonoscopy or GYN procedures:
Ampicillin + ciprofloxacin (or gentamicin) + Flagyl
Aminoglycoside overnight + oral metronidazole ± ampicillin 1 gram PO
Fluconazole added in invasive gynecological procedures
Perform procedure with dry abdomen, delay restarting PD dry for 8–12 hours after procedure

Infection Monitoring

PD infections should be monitored regularly in every PD center as part of a continuous quality improvement (CQI) program. Patterns of infection should be reviewed and root causes of infection identified in order to help reduce overall infection rates. It has been recommended that the following be monitored: the yearly incidence of peritonitis, specific organism rate, percentage of peritonitis-free patients, and organism susceptibilities. Additionally, recommendations from the ISPD suggest that the peritonitis rate should be reported as the number of episodes per patient-year, with a goal of at least less than 0.50 infections per patient-year [15]. Some centers are now reporting peritonitis rates of less than 0.20 per patient-year (personal reference). Infection monitoring has been shown to reduce peritonitis rates in several studies [42, 43].

Summary

Infectious complications specific to peritoneal dialysis include exit-site or tunnel infections and peritonitis. Certain procedures, both at the time of catheter placement and subsequently during maintenance PD therapy, can reduce the risk of PD-related infections. Empiric antibiotics should be given whenever a PD infection is clinically suspected; antibiotic selection can be tailored after microbiological data is eventually known. Infection monitoring is an important part of the CQI program for every PD program and can lead to reduced infection rates.

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Chapter 16
Noninfectious Complications of Peritoneal Dialysis

Hao Yan and Joanne M. Bargman

PD Catheter Malfunction

PD catheter malfunction is defined as outflow failure with or without inflow failure due to catheter migration or kink, mechanical obstacle in the catheter lumen or transfer set, or encapsulation around the catheter tip. Recent studies have shown a catheter malfunction rate varying from 4% to 13% with conventional or modified open surgical implantation [1–3] and better outcomes with advanced techniques [4, 5]. However, it is still a major cause of PD technique failure [6].

Catheter malfunction can be one-way or two-way obstruction. One-way obstruction refers to poor outflow, while two-way obstruction presents with both interrupted or even completely blocked inflow and outflow. Given potential intraperitoneal dead space, less drainage compared to installation volume in the first dialysate exchange after catheter insertion or long-time cessation of PD does not necessarily mean catheter malfunction, and the catheter function should be evaluated with infusion of more dialysate.

One-way obstruction is frequently caused by constipation, catheter migration, or incomplete wrap around intra-abdominal portion of the catheter. The catheter tip can migrate into upper quadrants of the abdomen or into a loculated pocket. Sometimes migration is the result of omental wrap. Stool retention in bowel and catheter migration can be detected by abdominal plain radiograph, and an experienced operator can use ultrasonography to diagnose dislocated catheter accurately

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[7]. Due to the limitation of the two-dimensional image, simultaneous abdominal anterior-posterior and lateral views or abdominal computerized tomography (CT) may be needed to provide more information about the catheter location and its relationship with nearby organs [8]. Redundant omentum is the most likely to cause encasement around the catheter, and it usually happens early after catheter insertion. Under the negative pressure of outflow, omentum is sucked into the catheter lumen via the side ports, occluding the drainage. Inflow may not be affected since the dialysate flow can flush the intraluminal tissue back though the side ports. With the advent of laparoscopy, some previously unrecognized causes have been found, including fimbriae of the fallopian tubes and proliferation of vascularized fibrous tissue from the parietal or visceral peritoneum [9, 10].

Two-way obstruction is often related to intraluminal fibrin or blood colt or catheter kink. Complete encasement by the omentum or rarely by a fibrin sheath can form a compartment around the catheter tip [11, 12]. Clot results from intra-abdominal bleeding or occasionally hematoma in the adjacent tissues or organs [13]. They often introduce resistance when irrigating the catheter using a syringe, and sometimes the obstacle is visible in the catheter lumen. Catheter kink can be identified by radiograph showing an unexpected rigid angle along the subcutaneous or intra-abdominal tubing. Extraluminal fibrin sheath usually needs to be diagnosed by laparoscope or fluoroscope.

After catheter malfunction is recognized, a scheme for diagnosis and treatment should be initiated (Fig. 16.1). Efforts to promote bowel movements can be the fundamental treatment for all types of catheter malfunction, particularly one-way obstruction. Increasing physical activity may be helpful to reposition the dislocated catheter. Though not always rewarding, vigorous irrigation to the catheter with saline (50 ml or more) using a syringe can be a choice to dislodge one-way obstruction caused by incomplete wrap; more importantly, in the case of two-way obstruction, it possibly expels the intraluminal fibrin or colt and recanalizes the catheter. If irrigation does not work, fibrinolysis therapy can be considered. Heparin (1000 U/mL), urokinase (2000 IU/mL), or tissue plasminogen activator (t-PA, 1 mg/mL) can be added in saline (usually 10 mL), and the solution is kept in the catheter lumen for 1 hour, followed by aspiration using a syringe [14, 15]. For those with abundant fibrin in the effluent, 1000 U/L heparin added in the dialysate for each exchange is recommended.

If these conservative treatments fail, fluoroscopic manipulation or surgical intervention should be considered. A stiff guide wire can be inserted into the catheter lumen under fluoroscopic guidance, and it can reposition a migrated catheter and can clear out the fibrin or clot in the lumen [16, 17]. However, this procedure is technically challenging. Also, it cannot prevent recurrent obstruction. Laparoscopy provides direct visualization of the intra-abdominal anatomy, and catheter salvage can be achieved by manipulation such as catheter reposition, intraluminal obstacle clearance, unwrapping of the omentum, and adhesion lysis (Fig. 16.2); even more, with advanced techniques including omentopexy and catheter tip fixation, it effectively prevents recurrence and allows patients to resume PD shortly after surgery [18, 19]. Other surgical techniques for catheter salvage include minilaparotomy

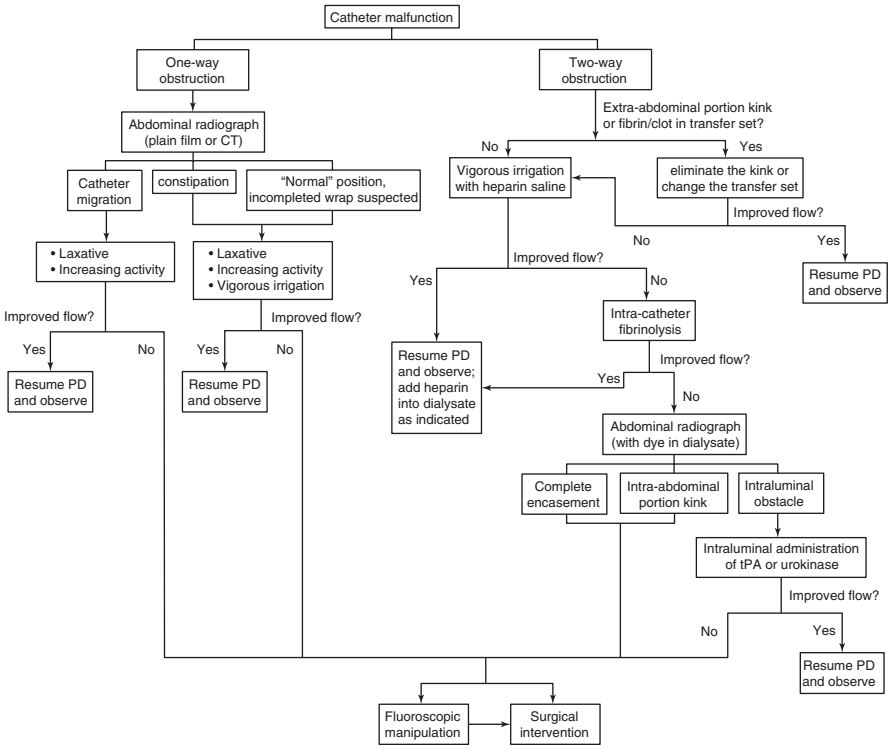

Fig. 16.1 Scheme for diagnosis and management of peritoneal dialysis catheter malfunction

[20] and utilization of special instruments [21], but the experience is limited. In extreme cases, the malfunctioning catheter has to be removed and replaced by a new one.

Inflow and Drain Pain

Some patients complain of abdominal pain during dialysate exchanges in the absence of catheter-related complications, involving either instillation or drainage. It influences the patient's quality of life and may cause cessation of PD.

Inflow pain usually occurs at the beginning of infusion and can be multifactorial. It may be due to the dialysate flow quickly striking the bladder or rectum. The infusion through a coiled catheter is relatively more diffuse and gentle, probably reducing the inflow pain relative to a straight-tip catheter. Slowing the infusion rate may attenuate this mechanical action. Otherwise, leaving a residual amount of fluid in the abdomen after drainage, called tidal PD, provides a buffer pool to relieve inflow pain. In extreme cases, this phenomenon has to be treated with fluoroscopic or

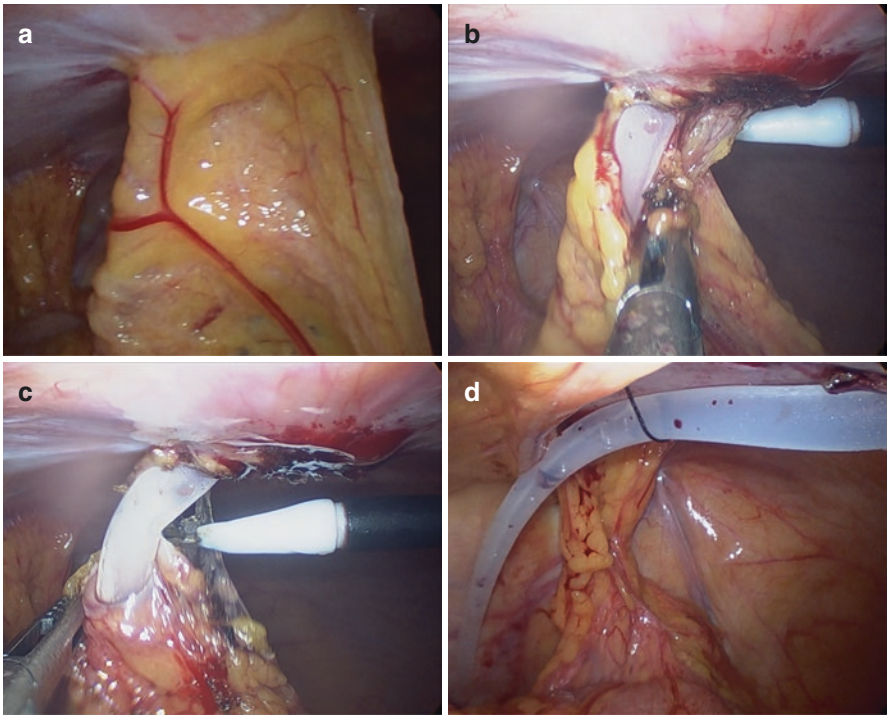

Fig. 16.2 A 46-year-old male patient with a history of appendicectomy received peritoneal dialysis catheter insertion using open surgical technique. The procedure was difficult, and intra-abdominal adhesion was speculated. However, it succeeded and the catheter flush was satisfying. Despite an abdominal plain film showing catheter tip right in the pelvic cavity on the first postoperative day, two-way obstruction was observed 1 week after insertion. Conservative treatments were not rewarding, and laparoscopic manipulation was performed 20 days after insertion. Laparoscopy showed that the intra-abdominal portion of the catheter was completely encased by omentum, and the omentum adhered to the parietal peritoneum at the site of catheter entry (Panel A). Omental adhesion was observed at the other part of peritoneal cavity as well. Adhesiolysis (Panels B and C) and catheter tip fixation (Panel D) were performed. Peritoneal dialysis treatment has been uneventful afterward

laparoscopic manipulation to adjust the position of the catheter tip, or even with catheter reinsertion. Additionally, the temperature of the dialysate should be moderate to avoid thermal or cold stimulus [22], and avoiding hypertonic dialysate has been reported to be helpful [23].

Another important cause is the acidity of conventional dialysate. The PH of conventional lactate buffered dialysate is 5.2–5.5. The acidic dialysate is gradually neutralized after approximately 1 hour of dwelling [24], and the discomfort should subside. Relatively more biocompatible PD fluids using bicarbonate or a combination of bicarbonate and lactate provide a neutral PH value of 7.0–7.4. Some studies have shown their benefit to alleviating inflow pain [25–27]. Because of the neutralization of the dialysis fluid during the dwell, acidic dialysis fluid is not a cause of outflow pain.

Some patients experience pain on drainage in the rectal or genital areas, particularly at the end of outflow. There is remarkable variation in the prevalence, ranging from 4% to 37% among different centers in a same territory as reported [28]. It is more prevalent in patients using a cycler while occasionally can be seen in CAPD patients. The hydraulic suction by a cycler exerts more aggressive mechanical stress to the sensitive parietal peritoneum or the external bowel wall compared to the siphoning on CAPD. The other cause may be that the insertion site is too low in the patient's pelvis, so that when dialysate is completely drained, the catheter tip lies against adjacent structures.

To solve the problem, firstly laxatives can be applied to the patient. Increased peristalsis and evacuated bowel may help the catheter move into a better position. If it fails, tidal PD as adopted in treating inflow pain is also applicable [29]. A tidal volume of 10–50% is practicable. Additionally, a switch to another brand of cycler or CAPD can be an option. For CAPD patients, the approach is simply terminating the drainage before the abdomen is completely emptied.

Complications Related to Increased Intra-abdominal Pressure

Intra-abdominal pressure (IAP) is the steady-state pressure within the abdominal cavity, which results from the interaction between the abdominal wall and viscera. It is normally around 0 cmH_2O and oscillates according to respiratory phase and abdominal wall resistance. Under certain conditions such as obesity, it may sustain at a level of 13–20 cmH_2O without clinical significance [30].

In the general population, IAP predominantly depends on body mass index (BMI) [31–34]. The IAP of the drained peritoneal cavity averages approximately 8 cmH_2O [32]. A 2 L intraperitoneal volume (IPV) in supine position results in various IAP values from 13.5 to 18.8 cmH_2O [32–34]. Every 500 ml increase in IPV is associated with a linear elevation of 1.1–1.3 cmH_2O in IAP [32, 35, 36]. IAP is the lowest when a patient is in a supine position. It increases 2–4 cmH2O in the standing position. The sitting position introduces another increment of 1.5–2 cmH_2O. Physical activities such as coughing and straining can lead to transient intra-abdominal hypertension as high as tenfold [37].

Elevated IAP and anatomic defects of the peritoneal cavity boundary lead to hernias, genital and abdominal wall leaks, and hydrothorax caused by pleuroperitoneal communication.

Hernias

Hernias occur in 6%–9% of PD patients according to population-based studies [38, 39] and in some single center observations more than 20% [40, 41]. Incidence varies between 0.04 and 0.08 episodes/patient-year in different cohorts [39, 42]. The mean time on PD before the development of hernia varies from months to years [43–45].

The presence of hernia poses a threat to PD technique survival [39], not only because of irreparable anatomic lesions in some cases but also rarely as a result of refractory peritonitis complicating hernia.

Demographic features such as older age and male gender are risk factors of hernia formation [38, 39]. Polycystic kidney disease (PKD) patients are prone to develop hernias [38, 39, 42], which may be the result of increased IAP and deficient connective tissue strength. The risk of herniation increases by approximately 20% for each year on PD [39, 43]. Those with smaller body habitus may be predisposed, perhaps because the dwell volumes are not adjusted proportionately to the body size [46]. Other risk factors include multiparity, previous hernia repair, history of multiple laparotomies, and midline incision for PD catheter placement [38–40, 42, 43].

Though IAP is supposed to play a role in herniation, studies have shown that IAP values are not different between PD patients with and without hernias [32–34]. Therefore, weakness or defects in the supporting structures of the abdomen are probably important in the pathogenesis of hernias.

In the early days, there was a predominance of hernia at the incision site or through the catheter placement site [43]. The abdominal incision for the implantation of the dialysis catheter is a major potential weakness, especially when it is made in the midline which is an anatomically weak area [47]. Paramedian incision through the rectus muscle is a better option to reduce the risk of perioperative leaks and hernia formation [48], and with the improved PD catheter insertion techniques, this type of hernia has become less common and accounts for about 22% of abdominal hernias [38, 39]. Instead, recent reports have shown that inguinal hernia is the most frequent type, representing 40% to 50% of all hernia events [38, 39]. Patent *processus vaginalis* is another area of potential weakness for herniation, which is more common in males than in females. Increased IAP during PD may push bowel and dialysis fluid into the *processus vaginalis*, resulting in an indirect inguinal hernia. Boys may be predisposed to this complication, and if they develop a unilateral inguinal hernia, both sides should be repaired prophylactically [49]. The other common hernias include umbilical hernia (12–31%), femoral hernia (2–4%), and transdiaphragmatic hernia (1–7%).

Asymptomatic hernias may be occult and only noticed when bowel strangulation occurs. Most hernias present as a painless lump which is more obvious in upright position or during activities that increase IAP, sometimes accompanied by dialysate leak. A rare variation of hernias is enterocele [50], which occurs when the intestine prolapses and descends into the lower pelvic cavity and pushes at the top part of the vagina to create a bulge. We observed a case of enterocele in a Chinese female PD patient with prolapse of uterus. Rarely bowel herniates through the weak parts of the diaphragm including the foramen of Bochdalek, the foramen of Morgagni, and the esophageal hiatus to cause transdiaphragmatic hernias which can present as a retrosternal air–fluid level or juxtacardiac mass [51]. Usually ultrasonic exam and computer tomography (CT) can detect hernias accurately.

The most worrisome complications are incarceration and strangulation of bowel, manifesting as a tender lump, recurrent Gram-negative peritonitis, bowel obstruction, or perforation. This can occur through almost any kind of hernia but especially

a small one [52, 53]. Umbilical hernias may have a propensity for bowel strangulation [54, 55]. It is important to search for occult hernias if a patient presents with peritonitis, especially if caused by enteric organisms.

Pre-existing hernias can be repaired simultaneously with catheter insertion [56, 57]. In order to improve the patients' quality of life and reduce the risk of PD technique failure, hernias warrant surgical repair to avoid enlargement, subsequent leak, bowel incarceration, and strangulation. Hernia repair with mesh is reported to have a lower risk of recurrence in contrast with that without mesh placement [58], and it may afford a quicker return to full-volume dialysis [59, 60]. Mesh repair can be done with open surgical technique or under laparoscopy. Preperitoneal retro-rectus mesh placement with minimal breach of the peritoneum is assumed to be better in reducing the risk of mesh infection from peritonitis, compared to intraperitoneal onlay mesh placement with exposure of the mesh to the peritoneal cavity. However, studies comparing these methods are scarce.

Usually it is not necessary to convert the patient to hemodialysis around the hernia repair [61]. Patients can carry out their normal PD regimen up to the time of surgery. They should be drained for the operation. Various postoperative PD protocols have been shown to be safe and effective. Our protocol is as follows: PD is suspended for the first 48 hours after repair and then gradually reintroduced; CAPD patients are prescribed intermittent PD (IPD) three times per week for 10 hours per day for 2 weeks, followed by five exchanges of low volume (1–1.5 L) CAPD or 2 weeks, and return to the presurgery prescription by 4 weeks; patients on continuous cycling PD (CCPD) received 1 week of IPD followed by 4 weeks of nocturnal IPD and returned to the original dose in 5 weeks [62]. In the Renji Hospital, abdominal hernia repair with mesh placement was performed in 20 Chinese CAPD patients. All the patients restarted PD using a cycler 24 hours after operation with an initial dwell volume of 1 L. The dwell volume gradually increased to 2 L during the next 3 weeks, and then the preoperative CAPD regimen was resumed. No hernia recurrence or mesh infection was observed within 1-year postoperative follow-up [63]. Apart from adjustment in PD prescription, the patients need to avoid factors inducing high IAP. Those who cannot tolerate early PD reintroduction or would be at risk of underdialysis with low-dose PD should be considered for temporary hemodialysis.

Abdominal Dialysate Leaks

Loss of peritoneal membrane integrity, such as an opening or a tear, leads to dialysate leak in PD patients. The common body structures involved in dialysate leaks include abdominal wall, external genitals, and occasionally retroperitoneum; while pleuroperitoneal communication is also a leak, it will be discussed below.

This complication can be classified as early and late leaks according to whether it occurs within 30 days after PD catheter placement. Generally, early leaks are related to catheter insertion and manifest as "visible" moisture or leakage at catheter

exit site or incision wound which can be identified as dialysate by a positive glucose dipstick. There is also collection in the catheter tunnel or subcutaneous swelling in soft tissue around the surgical area, which can be detectable by ultrasound or CT. Current guidelines of the International Society for Peritoneal Dialysis (ISPD) suggest starting PD at least 2 weeks after catheter insertion whenever possible [64], in order to ensure surgical wounds in the peritoneum and each layer of abdominal wall tissue are completely healed. We have shown in a cohort study comprising 657 patients that the incidence of leaks among patients commencing PD within and after 2 weeks of catheter insertion were nonsignificantly different (1.5% vs. 0%), suggesting expertise in catheter placement technique and proper urgent start PD protocol can lead to acceptable outcomes [3]. However, caution should be taken in patients who are malnourished, obese, or receiving long-term steroid or mTOR treatment. Stopping PD temporarily or employing PD regimens with minimal impact on IAP for 2 weeks is effective to treat early leaks, while in refractory cases catheter removal and reinsertion should be performed [65]. Apparent leaks at the exit site or through the wound increase the risk of PD-related infections [66], and prophylactic antibiotic may be necessary [67].

Late leaks are often related to a mechanical tear in the peritoneum, resulting in dialysate extravasation into the abdominal wall, external genitalia, or retroperitoneal cavity, which may be coincident with hernias. Frequently, patients complain of localized fullness, edema, and sometimes decreased ultrafiltration. On clinical examination, an asymmetric appearance of the abdomen may be observed in a standing position. 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 the catheter lying across the abdomen look deeper and more prominent than usual. There are two pathways through which leaks into external genitalia take place [68]. One is from a patent *processus vaginalis* to form a hydrocele or labia majora edema, and this pathology is more common in men than in women. 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 [69]. Secondly, dialysate can track through the soft tissue plane from the catheter insertion site, a soft-tissue defect within a hernia, or a peritoneo-fascial defect (Fig. 16.3). In these cases, genital edema can be associated with edema of the anterior abdominal wall and settle over the penis or *mons pubis*.

Retroperitoneal leaks occur rarely in PD patients and could be a quite common cause of acute ultrafiltration failure [70, 71]. It is usually characterized as a sudden decline in ultrafiltration but normal PD catheter function. The retroperitoneal space is able to accommodate a large amount of fluid, and there is no apparent localized sign on physical examination. Nephrologists often face difficulties in diagnosing this complication and need to rule out other causes of fluid overload. Concomitant hernia and pleuroperitoneal leak are not uncommon in this setting [70].

CT scan employing iodinated contrast in dialysate is helpful to diagnosing leaks [70, 72]. In order to maximize the sensitivity of the study, it is recommended to use the largest PD volume tolerable, encourage the patient to take different body

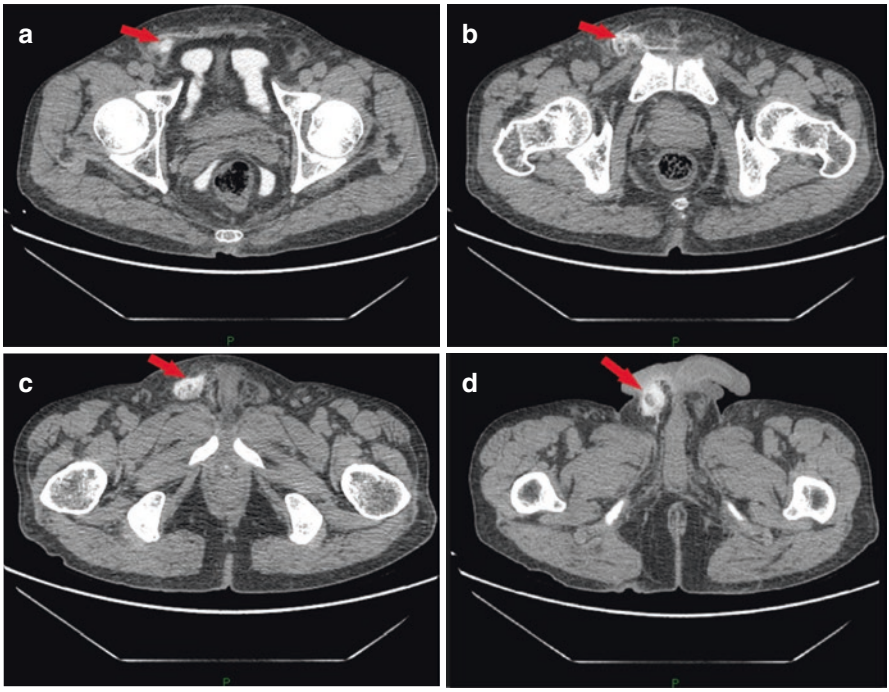

Fig. 16.3 A 60-year-old male polycystic kidney disease patient who had been on peritoneal dialysis for 17 months developed scrotum edema. Computerized tomographic scan with dye in dialysate showed a clear pathway of dialysate seepage through the abdominal wall to the right side to the scrotum. A coincident hernia was found on laparotomy and was repaired with mesh

positions, and perform plain CT scan 2–3 hours after the labelled dialysate is infilled to facilitate fluid egress from the peritoneal cavity [72]. Normally, dialysate should be confined in peritoneal cavity. When there is a retroperitoneal leakage, CT scan shows dialysate labeled by contrast breaks through peritoneal membrane and assembles in retroperitoneal space, usually asymmetrically (Fig. 16.4). This method is also effective in demonstrating other types of leaks or hernias. For instance, it can distinguish the different pathways leading to genital edema described above and guide the further intervention. Magnetic resonance imaging (MRI) also can detect retroperitoneal leak (Fig. 16.4), using the dialysate per se as the tracer, and it possibly has advantages in circumventing the risk of allergy and renal toxicity from the iodine contrast [70]. Abdominal scintigraphy with technetium-99 m is also an option to diagnose leaks and hernias [73, 74].

Leaks to abdominal wall and external genitals usually require surgical correction, especially those accompanied with hernias and those unresponsive to low IAP PD regimens or temporary PD discontinuation, and recurrence is not rare [65]. Report on surgical intervention to repair retroperitoneal leak is scarce. Usually it needs PD cessation to allow the tear on the peritoneum to heal up. Some studies

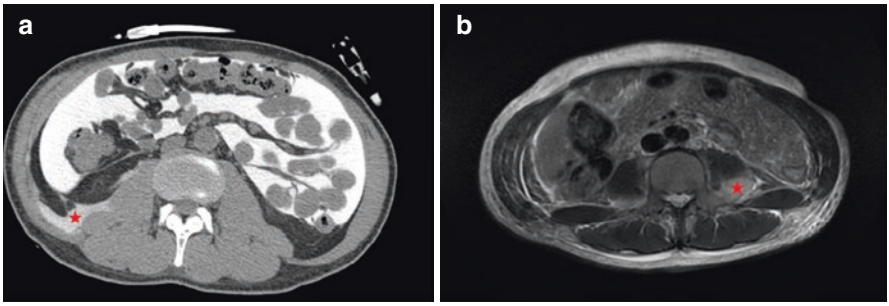

Fig. 16.4 Computerized tomography with dye in the installed dialysate (Panel A) and magnetic resonance imaging (Panel B) demonstrating retroperitoneal leaks (star) in two individual cases

show a high rate of resolution in retroperitoneal leak even without interruption to PD [70, 71]. However, according to our experience, it may be related to high risk of permanent transfer to HD.

Hydrothorax

The prevalence of pleuroperitoneal leak ranges from 0.6% to 3% [75–77]. It may be more prevalent in female PD patients [78]. As observed in the Renji Hospital, it happened in 0.9% of 1708 PD patients over 29 years, among which two-thirds happened in women. This complication has been suggested to be more prevalent in those with PKD, as is the case with hernias and genital edema [79]. It predominantly occurs on the right side [75], probably because of the presence of the heart and pericardium which prevents fluid flux across the left hemidiaphragm. Occasionally hydrothorax can be seen on the left side or bilaterally. Rarely isolated pericardial effusion can be the only manifestation of pleuroperitoneal leak [80].

Possible mechanisms for hydrothorax in PD patients include congenital and acquired diaphragmatic defects, pleuroperitoneal pressure gradient, and lymph drainage disorders. When there is a defect on the diaphragm, the boundary between the peritoneal cavity and the pleural cavity, pressure gradient between increased IAP and physiological negative pressure in the pleural space drives dialysate into the pleural cavity. Some pleuroperitoneal communication arises from congenital histological changes in diaphragm, including lack or absence of common tissue, tendons, and skeletal muscle tissues which is displaced by disordered fibrous connective tissue [81]. In this context, hydrothorax usually happens very quickly after PD initiation. However, it also occurs in patients on long-term PD, suggesting an acquired manner exists. Presumably, those patients have attenuated tissue separating pleural from peritoneal space, and it may take repeated exposure to raised IAP 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 [82]. The communication between the cavities may be a one-way flow, possibly attributing to the pressure gradient, a valve-like defect, and tamponade action of the subphrenic hepatic capsule. Another mechanism is postulated to be disordered lymph drainage, particularly in the right hemidiaphragm where the lymphatic system is most abundant.

The severity of symptoms depends on the amount of pleural effusion. A considerable proportion of PD patients may remain asymptomatic [75], and hydrothorax may be detected incidentally on routine chest radiographs. When there is massive hydrothorax, the patient complains of dyspnea, usually complicated by reduced ultrafiltration. Sometimes the symptoms are akin to congestive heart failure, but cannot be relieved by using hypertonic dialysate. Instead, it may aggravate since more ultrafiltration leads to even higher IAP that triggers further flux of dialysate into the pleural space. Physical examination is consistent with pleural effusion.

Hydrothorax is easily detectable by ultrasonic study, chest radiography with a posterior-to-anterior view, or plain CT scan; however, these imaging studies cannot differentiate the origin of the pleural effusion. Thoracentesis can attenuate respiratory embarrassment and perform a diagnostic role. Hydrothorax consequent to pleuroperitoneal leak should be a transudate with a high glucose concentration. A glucose concentration gradient between the pleural effusion and a simultaneous blood sample greater than 3 mmol/L suggests a high probability of PD-related hydrothorax [83]. However, if the fluid has remained in the pleural cavity for a long time without new dialysate installation, there can be significant glucose absorption into the circulation, making the result of pleural fluid glucose measurement equivocal. Similarly, the use of a glucose-free dialysate such as icodextrin can result in lack of a glucose gradient in the pleural fluid. Methylene blue can be instilled in the peritoneal cavity as a tracer, and blue staining of the pleural fluid provides evidence of an origin in the peritoneal cavity. However, it may cause chemical peritonitis, and the blue staining may be too faint to be recognized. Contrast CT peritoneography [84, 85] and peritoneal scintigraphy [86] in the similar way as previously discussed can identify pleuroperitoneal communication, providing greater sensitivity.

Thoracentesis, and sometimes a concomitant pleural drain, is necessary when there are acute or persistent symptoms of dyspnea. Discontinuing PD usually leads to resolution of pleural effusion [75], while refractory hydrothorax suggests there may be a mono-directional communication. Generally, interruption to PD is needed in majority of the cases. However, there have been reports about successful management by using a cycler and PD prescription of frequent exchanges with small dialysate volume [87]. Theoretically, resealing of the transdiaphragmatic communication is possible in those as a result of peritonitis, in which the integrity of cell layers overlying a diaphragmatic defect is transiently lost. A systemic review showed that spontaneous healing of the diaphragmatic defect can be achieved in 53% of the cases [88], but according to our experience, it only accounts for less than 10%.

Intrathoracic administration of various agents has been used to induce pleurodesis, including oxytetracycline, talc, and autologous blood [75, 88–90]. Some of the procedures are painful and are associated with an increased risk of infection [91].

More importantly, experience with these methods is limited. Operative repair under thoracotomy or visual-assisted thoracoscopy (VATS) is a more definitive treatment for pleuroperitoneal leak. A communication between peritoneal and pleural space may be visualized. To increase the detection rate, 2–3 L of dialysate can be infused into the peritoneal cavity, and the diaphragm is inspected from the pleural side for seepage through holes or blisters. Suture with or without reinforcement with Teflon felt patches, mesh repair, or pleurodesis can be applied to the defects, providing successful continuation of PD [92].

Abnormal PD Effluent Appearance

Normally, PD effluent is transparent and colorless or pale yellow. A change in the appearance of used dialysate usually indicates some physiological or pathological conditions. The most frequent abnormal appearance is turbidity, which is often associated with peritonitis, but also can be noticed in the presence of fibrin, neoplastic cells, and inflammatory reactions to medications and even dialysate itself [93, 94]. The other relatively common abnormalities include hemoperitoneum and chyloperitoneum.

Hemoperitoneum

Bloody effluent, namely, hemoperitoneum, indicates the presence of blood in dialysate drainage. As little as 2 mL of blood can render 1 L of dialysate noticeably blood-tinged. Hemoperitoneum has a wide differential diagnosis, as shown in Table 16.1.

A number of gynecological issues are related to hemoperitoneum, among which menstruation may be the leading cause, accounting for more than one-third of the benign episodes [95]. One mechanism is that the shed uterine tissue and blood flow into the peritoneal cavity through the fallopian tubes and the other may be peritoneal endometriosis shedding simultaneously with the intrauterine endometrium during menstruation. The peritoneal bleeding may start a few days prior to the appearance of blood per vagina, coincident with the timing of menstrual pain [96]. Women of childbearing age may also experience hemoperitoneum simultaneous with ovulation at mid-cycle [95, 97]. In this instance, bleeding is probably from the ovary with the rupture and release of the ovum. Hemoperitoneum associated with menstruation or ovulation is recognized by their occurrence in non-menopausal women and the periodicity. Women of reproductive age should be reassured. However, potential risks of exacerbation of anemia and peritonitis is noteworthy. Furthermore, a ruptured ovarian cyst and rarely pathological pregnancy have been reported to be sources of hemoperitoneum [98–102].

Table 16.1 Causes of hemoperitoneum

Gynecological
Menstruation
Ovulation
Ruptured ovarian cyst
Endometriosis
Pathological pregnancy including raptured ectopic pregnancy
Neoplastic
Renal cell carcinoma
Colon adenocarcinoma
Hepatoma
Hepatic metastases
Polycystic diseases
Polycystic kidney disease
Polycystic liver disease
Gastrointestinal
Catheter-induced splenic injury
Spontaneous splenic rupture in chronic myelogenous leukemia
Colonic perforation in dialysis amyloid
Spontaneous rupture of splenic infarct
Acute cholecystitis
Post-colonoscopy
Intraperitoneal connective tissue pouch
Pancreatitis
Gastric pseudoaneurysm
Hematological
Idiopathic thrombocytopenic purpura
Anticoagulation therapy
Diseases of the peritoneal membrane
Sclerosing peritonitis
Peritoneal calcification
Radiation-induced peritoneal fibrosis
Miscellaneous
Leakage from intraperitoneal or extraperitoneal hematoma
Post-pericardiocentesis
Angiomyolipoma of kidney
IgA nephritis
Mixed connective tissue disease
Extracorporeal lithotripsy
Spontaneous rupture of umbilical vein
Abdominal aortic aneurysm

Causes other than gynecological physiology and pathology should be carefully investigated to rule out acute or malignant etiologies, especially those associated with rapid changes in serum hemoglobin level, localized abdominal symptoms and signs, or changes in the patient's overall condition. Recurrent hemoperitoneum may

be a harbinger of disease of the peritoneal membrane itself such as the inflammatory phase of encapsulating peritoneal sclerosis.

Hemoperitoneum increases the risk of intraperitoneal blood coagulating and catheter obstruction. Therefore, use of intraperitoneal heparin (500–1000 U/L) until effluent recovers the normal appearance has been recommended. Intraperitoneal heparin is not absorbed, so it does not worsen the bleeding or lead to systemic anticoagulation. If intraperitoneal bleeding is caused by minor injury involving only small blood vessels, the use of rapid exchanges with dialysate at room temperature can be helpful to speed resolution. It is postulated that the relatively cool dialysate induces peritoneal vasoconstriction which leads to hemostasis.

Chyloperitoneum

A milky-white appearance of dialysate effluent is a unique character of chyloperitoneum. When there is interruption of the lymphatic drainage from the gut to the main lymphatic trunks, chylomicrons rich in triglycerides flux into the peritoneal cavity. The cloudy fluid may wax and wane, depending on what kind of fatty acids the patient is ingesting. It usually occurs after a meal rich in long-chain fatty acids and clears some time afterwards.

The diagnosis is suggested by the typical appearance of the dialysate, and peritonitis needs to be excluded. Lipoprotein electrophoresis shows lipid staining at the origin, a characteristic of chylomicrons. When the dialysate is separated into layers upon standing, the supernatant stains positively for fat with Sudan Black and dissolves with ether. The triglyceride concentration in the effluent is above 110 mg/dL, which is higher than that of plasma.

The diagnosis warrants further investigation into the causes. However, the etiology of chyloperitoneum is obscure (Table 16.2). The most common cause is neoplasm, particularly lymphoma.

The management of chyloperitoneum is based on treating its underlying cause. Temporary cessation of PD could accelerate the healing of chylous leak. A diet of medium-chain instead of long-chain fatty acids may be helpful until its resolution, and parenteral nutrition can be an alternative. Octreotide has been reported to resolve chyloperitoneum in a PD patient. It blocks somatostatin receptors in the intestine and decreases intestinal fat absorption, intestinal blood flow, and lymph secretion [103].

Other Abnormal PD Effluent Appearance

Rifampicin can stain the effluent orange. Fluorescein used in eye angiography for diabetic retinopathy screening may lead to a yellow fluorescent color in the effluent bag. When there is a leak from the biliary system, effluent presents a yellow-green color. Cola-like dialysate may indicate the existence of methemalbumin or metmyoglobin. In hemorrhagic pancreatitis, heme is released from red blood cells as a result

Table 16.2 Causes of chyloperitoneum

Obstruction by cell proliferation
Lymphoma
Lymph node extension of a cancer of an abdominal or pelvic organ
Lymphangioleiomyomatosis
Obstruction by infections
Mycobacteria-related infections
Lymphatic filariasis
Trauma
Blunt or penetrating abdominal trauma
Abdominal surgery (including dialysis catheter insertion)
Thoracic surgery (thoracic duct trauma)
Excessive lymph production or less venous drainage
Congestive heart failure
Constrictive pericarditis
Superior vena cava syndrome
Cirrhosis
Medications
Manidipine, benidipine, nisoldipine, nifedipine, lercanidipine
Diltiazem
Aliskiren
Miscellaneous
Pancreatitis
Lupus disease with mesenteric involvement
Nephrotic syndrome
Sarcoidosis
Retroperitoneal fibrosis
Whipple's disease
Children: Congenital anomalies of the lymphatic system Obstructive intestinal lesions Lymphangioma Battered child syndrome

of hemolysis, and then it combines with albumin to form methemalbumin [104]. If a PD patient experiences severe rhabdomyolysis, there can be myoglobin and red blood cells in effluent, which lead to the production of metmyoglobin [105].

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is a rare but devastating complication among patients undergoing long-term PD. It is characterized by greatly thickened peritoneal membrane and dense layers of fibro-connective tissue that encapsulate the intestinal loops, leading to recurrent bowel obstruction and malnutrition.

The prevalence varies between 0.4% and 3.7%, and among patients on PD for more than 5 years, it could be as high as 18.4%; the incidence ranges from 1.4 to 13.6 episodes/1000 patient-years [106]. The appreciable variation may be a result of different diagnostic criteria, clinician's expertise, and practice patterns among PD programs. A considerable proportion of cases happens after PD cessation. Long PD duration is a universally accepted determinant for occurrence of EPS. Other risk factors such as higher dialysate glucose exposure, frequent and severe peritonitis, history of abdominal surgery, use of β-blocker, UF failure, higher peritoneal permeability, and kidney transplantation have been reported by several studies; however, due to lack of consistency or significant interactions with long PD vintage, they are not reliable indicators.

EPS is associated with high mortality. Once again, longer time on PD is a risk factor of death among EPS patients [107]. Fortunately, with early diagnosis and developing management, it seems that the outcomes have improved [108], and the survival rate of post-transplantation EPS patients may be superior to that of those developing EPS during PD or after PD technique failure [109].

The diagnosis of EPS is established when both functional and structural features present. EPS can progress slowly and asymptomatically for a long period. At the early stage, there is an inflammatory state manifesting with fever, fatigue, anorexia, weight loss, bloody dialysate or ascites, anemia, hypoalbuminemia, and elevated C-reactive protein. Later, it progresses to the encapsulating stage in which the capsule starts to form but has not progressed enough to impair intestinal peristalsis; thus, bowel obstruction is still absent. However, the symptoms of intestinal obstruction appear with the aggravating capsulation process over time, including abdominal pain, nausea, vomiting, constipation, and abdominal mass, which define the ileus stage. The intermittent ileus can be relieved by conservative treatment, but the intervals between recurrence episodes shorten with time, and it ultimately develops to complete bowel obstruction.

Structural changes can be detected by different imaging studies [110]. The most commonly used method is abdominal CT scan, and it shows great discriminant value and reproducibility [111, 112]. The most prevalent findings related to EPS are peritoneal calcification, peritoneal thickening, bowel wall thickening, bowel tethering, loculation, and bowel dilatation (Fig. 16.5). However, these findings, especially thickening of the bowel wall, also can be seen in patients on long-term PD, and only a combination with the clinical feature of ileus is diagnostic. Furthermore, CT is not indicated as a screening tool for EPS, since it may occur within a year or less after a normal CT scan [113]. On laparotomy, the encapsulating phase is characterized by a cocoon like encapsulation of opaque tissue enclosing some or all of the small intestine [114]. The pathologic changes of EPS are not discriminative from those found in long-term PD patients, so biopsy is not diagnostic [115].

Generally PD should be discontinued after a diagnosis of EPS is made. However, it is unclear whether the cessation of PD can prevent EPS progression, especially given that there could be retention of intra-abdominal inflammatory factors after PD catheter removal. Several reports advocate the use of peritoneal lavage using dialysate after switch of dialysis modality to hemodialysis to treat EPS [116, 117].

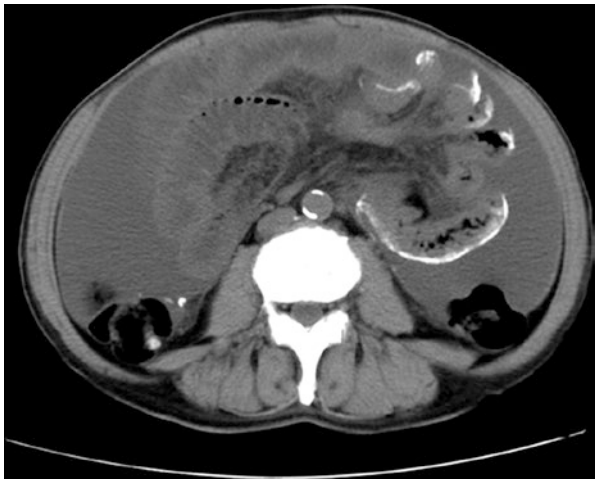

Fig. 16.5 A 64-year-old male patient who had been on peritoneal dialysis (PD) for 13 years was diagnosed with encapsulating peritoneal sclerosis when he was still on PD. Computerized tomographic scan showed peritoneal calcification, peritoneal thickening, bowel dilatation, bowel tethering, and bowel wall thickening

Nutritional support is a crucial conservative treatment, and it is usually delivered by parenteral nutrition therapy. EPS of early stage can be ameliorated by this method [118]. Several medications have been used to treat EPS, including corticosteroids, tamoxifen, and immunosuppression, and the result remains controversial [119, 120]. Perhaps these drug therapies may only exert beneficial effects in the early stage when the inflammation is active. Surgical intervention is more definitive for those who have already developed into the ileus stage. The procedure may consist of peritonectomy, enterolysis, and partial enterectomy [121, 122]. Bowel perforation and refractory postoperative infections are the main complication of the surgery. However, a dedicated surgical team can be associated with better results [108, 121, 123].

There is no evidence supporting pre-emptive switching of long-term PD patients to HD, but at a certain time point, usually 5 years after PD commencement, the patients should be notified about the risk of this complication even after discontinuation of PD, though the majority will not develop EPS. Several strategies has been speculated to be beneficial to prevent EPS, including minimizing dialysate glucose exposure, use of neutral PH solutions with low GDPs [124], prevention of peritonitis, and peritoneal lavage after PD cessation [125], but further study is needed to validate these approaches.

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Chapter 17
ESKD Complications: CKD-MBD

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In healthy individuals, normal serum concentrations of calcium and phosphorus are maintained through the interaction of three hormones: parathyroid hormone (PTH), calcitriol (1,25-dihydroxyvitamin D), which is the active metabolite of vitamin D, and fibroblast growth factor 23 (FGF-23). Circulating or soluble klotho also plays a role in mineral homeostasis. These hormones act on four primary target organs: the bone, kidney, intestine, and parathyroid glands. The kidneys play a critical role in the regulation of normal serum calcium and phosphorus concentrations and of the three hormones. Derangements in mineral homeostasis are common and develop early in patients with chronic kidney disease (CKD). By the time patients reach end-stage kidney disease (ESKD), these abnormalities are universally observed. As CKD progresses, the body attempts to maintain normal serum concentrations of calcium and phosphorus by altering the production of calcitriol, PTH, FGF-23, and klotho. Eventually these compensatory responses become unable to maintain normal mineral homeostasis, resulting in (1) altered serum concentrations of calcium, phosphorus, PTH, calcitriol, FGF-23, and klotho, (2) disturbances in bone remodeling and mineralization (often referred to as "renal osteodystrophy") and/or impaired linear growth in children, and (3) extraskeletal calcification in soft tissues and arteries. In 2006, the term chronic kidney disease–mineral and bone disorder (CKD-MBD) was developed to describe this triad of abnormalities in biochemical measures, skeletal abnormalities, and extraskeletal calcification [1]. The abnormalities that constitute CKD-MBD are interrelated in both the pathophysiology of the disease and the response to treatment. All the components of CKD-MBD are associated with increased risk of fractures, cardiovascular disease, and mortality in

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patients with ESKD. To further understand the complex integration of these abnormalities in CKD-MBD, each component will be independently discussed.

Biomarkers: Calcium, Phosphate, and 1,25-Dihydroxyvitamin D

Calcium and phosphate homeostasis in advanced chronic kidney disease (CKD) is complex, and dysregulation of calcium is directly related to the dysregulation of serum phosphate and 1,25-dihydroxyvitamin D which develops early as kidney disease progresses.

Patients with advanced kidney disease often develop hypocalcemia. The development of this electrolyte disorder is multifactorial and related to decreased kidney production of 1,25-dihydroxyvitamin D and elevated serum phosphate [2, 3]. As kidney disease progresses, there is a loss of renal mass, which ultimately results in decreased proximal tubular 25-hydroxyvitamin D_3 1-α-hydroxylase (CYP27B1) activity and correlatively a decrease in production of 1,25-dihydroxyvitamin D from 25-hydroxycholecalciferol. This, in turn, affects gastrointestinal absorption of calcium, which contributes significantly to the development of hypocalcemia. 1,25-Hydroxyvitamin D production is further suppressed by elevated FGF-23 concentrations found in advanced kidney disease. Serum elevation of phosphate due to decreased renal excretion in the setting of reduced kidney function also lowers available ionized calcium by binding it in the vascular space or precipitating deposition of calcium–phosphate in extraskeletal tissues. Maintenance of appropriate physiologic concentrations of serum calcium despite these described pathways of dysregulation and regulation of serum concentration of phosphate and 1,25-dihydroxyvitamin D is further influenced by circulating hormones which comprise the PTH–vitamin D–FGF-23 axis [4].

Biomarkers: Parathyroid Hormone

PTH is secreted by chief cells in the parathyroid gland and works in the regulation of serum calcium and phosphate concentrations. PTH affects change on serum calcium and phosphate concentrations by targeting receptors located on the bones and kidneys in an effort to maintain homeostasis. PTH stimulates bone remodeling through the stimulation of osteoblasts and indirect stimulation of osteoclasts. As PTH concentrations increase, the net effect is to increase bone resorption resulting in calcium and phosphate release from bone and increased serum calcium and phosphate concentrations. PTH also acts upon the kidney to reduce urine calcium excretion, reduce urinary phosphate reabsorption (increasing phosphate excretion), and increase renal production of 1,25-dihydroxyvitamin D.

The serum PTH concentration is influenced by many factors that exert positive or negative feedback mechanisms on PTH secretion. Phosphate exerts a positive effect on PTH through stabilization of PTH mRNA and thereby increases secretion when hyperphosphatemia occurs [5]. The parathyroid gland senses changes in serum ionized calcium concentrations via parathyroid calcium sensing receptors (CaSR), which mediates a negative feedback inhibition on the secretion of PTH when ionized calcium levels are high [6]. 1,25-Dihydroxyvitamin D is also known to exert negative feedback inhibition on PTH secretion [7] through binding of the parathyroid vitamin D receptor (VDR) and direct suppression of the PTH gene transcription [8]. Fibroblast growth factor-23 (FGF-23) also acts to inhibit PTH secretion through downregulation of PTH gene expression, decreased PTH secretion, and decreased PTH cell proliferation through the parathyroid klotho–FGF receptor [9, 10].

Biomarkers: FGF-23 and Klotho

FGF-23 is a hormone produced by osteoblasts and osteocytes that works in the regulation of serum calcium, phosphate, 1,25-dihydroxyvitamin D, and PTH. α-klotho acts as a co-receptor for FGF-23, and FGF-23 mitigates its effects on serum calcium, phosphate, and 1,25-dihydroxyvitamin D through binding with its klotho–FGFR1 receptor complex which is found in kidney and parathyroid gland tissue. One of the key regulators for bone secretion of FGF-23 is phosphate. Hyperphosphatemia has been shown in human phosphate loading studies to increase FGF-23 concentrations [11, 12], and FGF-23, in turn, reduces phosphate reabsorption by the kidney through downregulation of Na-Pi 2a cotransporters in the proximal tubules and increases urine phosphate excretion [13].

Serum FGF-23 decreases PTH secretion as discussed above; elevated PTH, however, has been shown to increase FGF-23 concentration in the blood [14, 15]. This interaction between PTH and FGF-23 completes a bone parathyroid hormonal axis [14]. FGF-23 is also a component in another hormonal axis. Elevated serum concentrations of PTH increase renal production of 1,25-dihydroxyvitamin D, and as discussed above, 1,25-dihydroxyvitamin D has negative feedback inhibition on PTH production. Elevated concentrations of serum 1,25-dihydroxyvitamin D have been found in human studies to increase FGF-23 concentrations in the blood [16, 17]. FGF-23 then acts upon the kidney through its klotho–FGFR1 receptor complex and suppresses 25-hydroxyvitamin D_3 1-α-hydroxylase (CYP27B1) activity while stimulating 24-hydroxylase (CYP24A1) causing both reduced production and inactivation of 1,25-dihydroxyvitamin D [13, 18]. It is this loop of positive and negative feedback that comprises the PTH–vitamin D–FGF-23 axis [4].

Klotho proteins produced by the kidney can be found as membrane-anchored (that act as co-receptors for FGF-23) or soluble proteins. Freely circulating, soluble klotho has also been shown to effect changes in serum calcium homeostasis. This soluble klotho increases calcium reabsorption in distal convoluted tubules and

connecting tubules through enzymatically cleaving the extracellular domain of TRPV5 calcium channels located there, which keeps the TRPV5 calcium channels in the cell membranes [19, 20]. Calcium then moves through these channels down electrochemical gradients and enters the cells. Serum elevations in 1,25-dihydroxyvitamin D also upregulate klotho expression [21] which then works in concert with FGF-23 to suppress 1,25-dihydroxyvitamin D as noted above.

Secondary and Tertiary Hyperparathyroidism

One of the most widely recognized complications of advanced CKD and ESKD is hyperparathyroidism. This occurs in the setting of increased secretion of PTH by the parathyroid gland, which could be related to a primary disorder in the parathyroid gland (primary hyperparathyroidism, which will not be discussed here), increased secretion of PTH due to an appropriate stimulus (secondary hyperparathyroidism), or inadequately regulated secretion of PTH (tertiary hyperparathyroidism).

By definition, secondary hyperparathyroidism (SHPT) is characterized by increased levels of PTH secretion required for the maintenance of normal serum calcium levels in the setting of kidney impairment. This elevation of PTH simulation is multifactorial caused by hypocalcemia, decreased 1,25-dihydroxyvitamin D, and hyperphosphatemia, all of which occur as advanced kidney disease develops. Hyperphosphatemia in advanced kidney disease is a common problem, especially in patients undergoing dialysis. Epidemiologic studies have shown peritoneal dialysis (PD) patients have lower average serum phosphate concentrations compared to hemodialysis (HD) patients [22, 23]; however, a subsequent study found that PD patients are exposed to higher time averaged phosphate concentrations compared to HD patients [24]. The development of the underlying hypocalcemia is multifactorial related to elevated serum phosphate, decreased renal production of 1,25-dihydroxyvitamin D, and increased FGF 23 production [2, 3]. In the setting of prolonged sustained increased secretion of PTH to maintain calcium homeostasis, parathyroid hyperplasia develops. With the development of parathyroid gland hyperplasia, nodules develop within the gland which have decreased expression of both the VDR and CaSR, thus rendering the tissue less responsive to the circulating concentrations of ionized calcium and 1,25-dihydroxyvitamin D and potentiates risk for progression to tertiary hyperparathyroidism [9, 25].

In addition, although FGF-23 is known to act upon the parathyroid gland to decrease PTH secretion, in advanced CKD and parathyroid gland hyperplasia, there is decreased cellular membrane expression of the klotho–FGFR1 [26]. It is presumed that this mechanism of downregulation of klotho–FGFR1 results in failed inhibition of PTH secretion despite high circulating levels of FGF-23 found in advanced CKD [2, 27]. Animal model studies have shown that FGF-23 can act independently on the parathyroid gland to suppress PTH secretion via a klotho-independent, calcineurin-mediated FGF-23 signaling pathway, but this does not appear to be a dominant pathway for PTH regulation [28].

Sequelae of SHPT include renal osteodystrophy, increased fracture risk, vascular calcifications, and cardiovascular disease; thus, treatment of this disease is important in managing morbidity and mortality in CKD patients. Treatment of SHPT consists of management of calcium, phosphate, and 1,25-dihydroxyvitamin D dysregulation. Control of hyperphosphatemia through dietary control and oral phosphate binders are common first-line treatments. Increased elimination of phosphate through dialysis is another cornerstone in treatment of hyperphosphatemia in ESKD patients. Though phosphate is a small anion with a molecular weight of 96 Daltons (Da) and should fall within the water-soluble, low-molecular-weight category of uremic toxins, it has characteristics which cause it to have significantly different clearances in HD and PD patients than other small molecular uremic toxins. Phosphate exhibits hydrophilic characteristics, and it is encased by an aqueous cover which increases its effective molecular weight. It is mainly distributed in the intracellular space and has a slow intra-/extracellular solute transfer rate. Additionally, a proportion of serum phosphate is bound to serum calcium, sodium, or magnesium in the form of salts. These factors all contribute to characteristics that lead to a significantly slower diffusion time compared to its proportionally sized counterpart, urea (60 Da), and in dialysis causes it to act similarly to a middle molecule [29, 30].

Elimination of phosphate through dialysis varies between patients and dialysis modalities. Phosphate clearance through HD can be increased by increasing the frequency of HD sessions while decreasing the length (short daily sessions), increasing the length of sessions on three times a week conventional HD regimens, or changing to nocturnal HD sessions with variable frequency. Clearance through PD is complex, and patients have variable clearance that is driven by individual patients' trans-membranous peritoneal transport characteristics and the characteristics inherent to phosphate. Studies have found that clearance of phosphate in patients on PD is independently associated with dwell time and not significantly influenced by dwell volume, ultra-filtrate volume, or number of exchanges and that phosphate clearance is significantly greater in continuous ambulatory PD compared to automated PD especially in slower peritoneal transporters [24, 31, 32]. Since the removal of phosphate in PD is dependent on dwell time, having dialysis fluid dwell for the full 24 hours will optimize this removal. Often when patients begin PD, they have sufficient residual renal clearance of phosphate that serum levels can be controlled with night cycler dialysis and a dry day. However, if phosphate intake is high, or residual renal clearance of phosphate declines over time, adding a day dwell will contribute significantly to improving removal of this anion.

Further medical management of SHPT includes interventions such as calcitriol and other synthetic vitamin D receptor activators (VDRA) which have been shown to reduce PTH levels through binding of the VDR and inhibiting PTH gene transcription [8, 33]. However, they increase the risk of hypercalcemia and hyperphosphatemia. Prolonged, chronic increased secretion of PTH can lead to parathyroid gland hyperplasia, and ultimately, hypercalcemia can develop. This severe form of SHPT is generally seen in patients with long-term advanced CKD and patients on dialysis. Calcimimetics, such as cinacalcet and etecalcitide, allosterically bind to

CaSR and increase their sensitivity to serum calcium concentrations. These calcimimetics have been found to effectively lower PTH and FGF23 concentrations while not increasing serum calcium concentrations [34–37]. Although etecalcitide must be administered intravenously and thus cannot conveniently be used in PD patients, cinacalcet has been found to be equally effective in both PD and HD patients. Inappropriately elevated PTH can be related to other underlying comorbidities including vitamin D deficiency. It is important that this be evaluated and addressed as repletion of vitamin D stores can aid in reduction of PTH without further treatment needs [27, 38].

Alternately, tertiary hyperparathyroidism (THPT) is characterized by inappropriately increased levels of PTH despite hypercalcemia which is related to autonomic function of multiple hypertrophied parathyroid glands refractory to medical management. Most often THPT is seen in patients on dialysis or after kidney transplantation. As noted above, severe SHPT can also present with hypercalcemia but can be controlled with medications. Gland hyperplasia can be categorized into two distinct forms, diffuse hyperplasia and nodular hyperplastic glands, which are related to monoclonal chief cell growth. As previously mentioned, CaSR and VDR are both downregulated in hyperplastic parathyroid glands, which likely contributes to resistance to calcitriol and calcium [39–41].

Like SHPT patients, patients with THPT are at increased risk for renal osteodystrophy, fractures, vascular calcification, and cardiovascular disease. These patients may also present clinically with symptoms associated with hypercalcemia including pruritus, mental status changes, muscle weakness, or worsening kidney allograft function. Treatment for THPT is centered on surgical management with subtotal or total parathyroidectomy. Studies evaluating the recurrence of hyperparathyroidism after subtotal vs total parathyroidectomy with and without autotransplantation found no difference in recurrence rate; however, total parathyroidectomy without autotransplantation was associated with increased risk of hypocalcemia [42]. Recent studies have suggested that ultrasound-guided ablation therapy may be useful [43]; unfortunately, there presently are no comparative or long-term studies to assess the usefulness of this approach.

Renal Osteodystrophy

Bone remodeling is a dynamic process occurring constantly in all individuals as osteoblasts and osteoclasts form and resorb bone in a balanced and regulated manner. Renal osteodystrophy describes a multifactorial disorder of bone remodeling and morphology, and it is present in patients with all stages of CKD. Key factors that contribute to the development of ROD is dysregulation in serum calcium and phosphate concentration leading to systemic alterations in the hormones that help regulate these electrolytes.

An important factor in the pathophysiology of ROD is 1,25-dihydroxyvitamin D deficiency which leads to reduced intestinal absorption of calcium and propagates

increased PTH secretion seen in secondary hyperparathyroidism. This underlying pathophysiology of advanced CKD and hyperphosphatemia also driving increased PTH secretion have been found to cause a high turnover bone disease known as osteitis fibrosa which is classically seen in ROD [44]. Osteitis fibrosa is characterized by increased bone remodeling with increased activity of both osteoclasts and osteoblasts. There is increased bone resorption and increased bone formation; however, this new bone matrix is osteoid (unmineralized) and nonlamellar (not parallel) bone and found predominately in the cortical osteons of long bone [45]. Histological examination of osteitis fibrosa reveals net bone resorption with marrow and peritrabecular fibrosis in addition to increased cortical porosity which may contribute to osteopenia and increased risk for fractures [44–46]. Mixed uremic osteodystrophy is another high-turnover bone disease and differs from osteitis fibrosa in that there is an underlying defect in mineralization [1, 47].

Low-turnover bone disease is another form of ROD and is also referred to as adynamic bone disease. This form of ROD occurs when ESKD patients are overtreated with calcium and/or VDRAs, thereby suppressing the level of PTH secretion needed for normal rates of bone turnover. In adynamic bone disease, there is decreased bone formation and, secondarily, decreased mineralization, which may also be associated with hypercalcemia. PD is considered a risk factor for adynamic bone due to prolonged exposure to high calcium concentrations found in the dialysate [48, 49], and multiple studies have found low-turnover bone disease to be the most prevalent form of ROD in PD patients [50, 51].

Osteomalacia is another form of low-turnover ROD but is associated predominately with aluminum toxicity when aluminum was previously used more in the treatment of ESKD patients. Aluminum toxicity causes increased bone matrix synthesis by existing osteoblasts but defective mineralization resulting in unmineralized osteoid and inhibiting osteoblast differentiation [45]. Another cause of osteomalacia is severe vitamin D deficiency which can be related to primary deficiency (related to malnutrition/malabsorption), kidney disease, or medications (like antiepileptic drugs). Patients with osteomalacia have elevated serum bone alkaline phosphatase early in the pathophysiologic process but if left untreated will escalate to vague muscular symptoms and later bony pain, proximal muscle weakness, and abnormal gait [52]. Therefore, it is important that the underlying etiology of osteomalacia be identified and addressed as ongoing severe vitamin D deficiency can also worsen secondary hyperparathyroidism and its associated sequelae. Both high- and low-turnover bone disease result in reduced healthy bone formation and, as a result, do not allow the bone to work as it normally would to buffer the excess calcium and phosphate in the serum, resulting in hypercalcemia and hyperphosphatemia potentially accelerating the development of extraskeletal calcifications [45, 53, 54].

Bone biopsy is the gold standard for diagnosis of ROD (although infrequently performed), and treatment for ROD is centered on maintaining normal serum calcium and phosphate concentrations through use of phosphate binders and VDRAs. Calcium concentration in PD dialysate should be tailored to individual patient's needs, but it is generally recommended to use calcium concentrations 2.5–3.0 mEq/L due to this increased risk for hypercalcemia [49, 55]. Use of

aluminum-based phosphate binders has significantly decreased and is limited to short courses of therapy, generally less than 1–2 months, to reduce incidence of aluminum toxicity. The goal of treatment is targeted toward controlling secondary hyperparathyroidism, reducing PTH secretion, and maintaining normal serum calcium concentrations [45, 56]. The Kidney Disease: Improving Global Outcomes (KDIGO) does not recommend routine use of calcitriol or other VDRAs prior to the use of calcimimetics, due to increased risk of hypercalcemia, but rather the use of VDRAs and/or calcimimetic therapy should be reserved for treatment in progressive secondary hyperparathyroidism with consideration of the underlying serum calcium and phosphate consentrations [56].

Osteopenia/Osteoporosis

Osteoporosis is characterized by low bone mass and increased bone fragility. Skeletal derangements associated with CKD-MBD place patients with CKD at a higher risk for fragility fractures than the general population, and several studies have found that ESKD patients have a fourfold higher risk for hip fracture than non-dialysis patients [57–59]. Additionally, hip fractures in advanced CKD and ESKD patients were found to be associated with higher morbidity and mortality than compared to the general population [59, 60].

The pathophysiology of osteopenia and osteoporosis in CKD patients is multifactorial, and complicated by traditional risk factors such as age, gender, and weight and underlying renal osteodystrophy. The 2017 KDIGO recommends screening patients with dual energy X-ray absorptiometry to assess fracture risk in patients with CKD-MBD and/or risk factors for osteoporosis [56]. Multiple longitudinal studies have validated the use of the World Health Organization T score for fracture risk classification and diagnosis of osteopenia and osteoporosis in advanced CKD patients [61–63]. Though bone biopsy is considered the gold standard for diagnosis of ROD, bone biopsies are no longer suggested prior to the initiation of therapy for osteoporosis understanding that this diagnostic tool is not widely available or easily attainable and therapy should not be withheld in patients at high risk for fracture [56]. Alternatively, treatment decisions can be guided through the use of biomarkers such as serum PTH and bone-specific alkaline phosphatase which can be used for the evaluation of bone turnover [64].

As with ROD, the first-line treatment for osteoporosis in CKD patient is management of CKD-MBD with phosphate binders and VDRAs. Traditional treatments of osteoporosis used in the general population such as calcium supplementation may not be feasible in the CKD population, given risks for hypercalcemia in severe SHPT or adynamic bone disease, but other lifestyle interventions such as smoking cessation, weight bearing exercise, fall prevention, and improved nutrition are encouraged. Pharmacologic interventions specific to osteoporosis include osteoanabolic agents and antiresorptive agents.

Osteoanabolic agents are forms of recombinant PTH or PTH-related peptide. High-turnover bone disease related to hyperparathyroidism should not be treated with osteoanabolic agents, but low-turnover bone disease in CKD patient are a target demographic for this medication. Teriparatide, an osteoanabolic agent, has been studied in multiple CKD patient populations and found to be both safe with variable efficacy in increasing bone mineral density [65–67]. Antiresorptive agents inhibit osteoclast-mediated bone resorption and should not be used in patients with adynamic or low-turnover bone disease. Bisphosphonates, an antiresorptive agent, is normally cleared by the kidney and therefore previously avoided in patients with CKD due to concerns about accumulation in the skeleton and oversuppression of bone turnover. However, recent studies have shown that bisphosphonates can be used in CKD patients of various stages safely, but none of these studies included patients with advanced stage 4 disease or on dialysis [68–70]. Another antiresorptive agent, denosumab, has also been shown to be safe to use and effective in patients with advanced CKD and ESKD [71–73], but romosozumab, a newly released anabolic agent, has not been studied in patients with CKD [74].

Extraskeletal Calcifications

Extraskeletal calcifications in CKD predominately manifests in the form of vascular calcifications of the arteries or arterialized veins. Calcium phosphate in the form of hydroxyapatite is deposited either in the intimal or medial layer of vessels which causes distinct subtypes of vascular calcification.

Intimal calcification occurs in classic atherosclerotic plaques and is associated with inflammation and lipid deposition. Vascular calcification seen in advanced kidney disease usually occurs as arterial medial calcifications (AMC). The hydroxyapatite crystal deposition occurs in the tunica media along the elastic laminae and typically is not associated with inflammation [53, 75]. AMC is associated with significantly increased vessel stiffness and reduced compliance [76] which in turn is associated with hypertension, left ventricular hypertrophy, and heart failure.

It is no longer presumed that the underlying etiology of vascular calcification is due to passive deposition attributable solely to elevated calcium phosphate product seen in advanced CKD, but rather it is due to complex, multifactorial processes. Studies evaluating the effects on hyperphosphatemia on vascular smooth muscle cells (VSMC) have found that elevated serum phosphate concentrations causes loss of smooth muscle lineage markers SMα-actin and SM22α and increased expression of osteoblastic differentiation markers Runx2, Osf2/Cbfa1, osteopontin, osteocalcin, and alkaline phosphatase [77–80]. These changes in cell signaling markers results in phenotypic change of VSMC to osteochondrogenic-like cells that contain matrix vesicles and are capable of laying down mineralization-matrix of bone collagen and noncollagenous proteins [81]. These phosphate- and calcium-enriched matrix vesicles are released into the extracellular space and act as a nidus for

calcium phosphate nucleation and mineralization. Similar to this, apoptotic bodies from dying VSMC released during apoptosis also act as a nidus for mineralization [54, 82].

Beyond hyperphosphatemia, other studies evaluating uremic serum effect on VSMC have also noted increased upregulation in osteoblastic differentiation markers including Runx2, Cbfa1, and alkaline phosphatase which implicates the uremic milieu found in advance CKD patients contributes independently to the calcification of vasculature [83, 84]. Increased synthesis of alkaline phosphatase also plays a significant role in vascular mineralization as alkaline phosphatase is a pro-calcification enzyme and disrupts anti-calcification mechanisms in the vessel wall. Key calcification inhibiting proteins produced by smooth muscle cells include pyrophosphate and osteopontin which are inactivated by alkaline phosphatase [85] in addition to downregulation of other calcification inhibitors like fetuin-A and klotho [53]. One study has suggested that the accelerated vascular calcification noted in ESKD is a direct result of dialysis treatment itself causing VSMC apoptosis and thereby reduction of VSCM-derived calcification inhibitors [86].

A study examining adipocytes (which share a common origin with osteocytes in mesenchymal stem cells) found that in the presence of hyperphosphatemia, there is increased expression of Runx2, a key transcription factor associated with osteoblast differentiation, which can induce fully differentiated mature adipocytes to become osteoblast-like cells with subsequent mineralization [87]. Furthermore, other studies have suggested that adipocytes may contribute to VSMC proliferation and calcification through unidirectional paracrine stimulation via secretion of proteins such as leptin and VEGF-A [87–89].

Treatment to reduce vascular calcifications is focused on the reduction of serum phosphate as discussed above, but no studies have shown that targeting any level of phosphate concentration improves vascular calcifications. The use of non-calcium-based phosphate binders has been shown to reduce vascular calcifications to a greater degree than calcium-based binders [53]. Additionally, animal studies have shown that sevelamer and lanthanum binders have prevented vascular calcifications in uremic murine models [90, 91]. Calcimimetics can also be used to inhibit the development of vascular calcifications and have been shown to reduce aortic calcification scores in HD patients [92, 93].

Patients undergoing long-term (>10 years) PD may also develop a unique but rare form of calcification not found in HD patients, peritoneal calcifications. Histologically, a significant proportion of long-term PD patients may have microscopic peritoneal calcifications which can be found along peritoneal facing surfaces, and in one study these microscopic peritoneal calcifications were associated with highly sclerosed tissues and extracellular precipitation adhesive protein osteopontin [94]. Large peritoneal calcifications in PD patients, which are detectable through imaging studies such as computed topography scans, have been associated with complex, dialysis-related peritonitis and multiple abdominal surgeries [95]. Peritoneal calcifications related to PD are considered benign and have not been found to be associated with aortic calcifications or serum concentrations of calcium, phosphate, or PTH [96].

Cardiovascular Disease

A serious comorbidity in patients with ESKD is cardiovascular disease (CVD) and is the leading cause of death within this patient population [97]. According to the US Renal Data System (USRDS) Annual Data Report, CVD accounted for 48% of all ESKD patients' deaths, and a study, using data from the USRDS evaluating ESKD patients from 2003–2013, found that when compared to general population, HD patients have a higher CVD mortality risk compared to PD patients (HR 13.64 compared to 7.86, respectively) [98]. Comorbidities that occur in ESKD patients include sudden cardiac death, coronary artery disease, congestive heart failure, acute myocardial infarction, valvular heart disease, peripheral arterial disease, atrial fibrillation, ventricular arrhythmias, venous thromboembolism, pulmonary embolism, cerebrovascular accident, transient ischemic attack, and pulmonary hypertension (HTN) [97, 99]. There have been multiple studies examining coronary artery disease in HD patients compared to PD patients, and none have found that HD patients have significantly more coronary artery disease compared to PD patients [100–102]. The pathophysiology related to the elevated incidence and prevalence of CVD in the ESKD population compared to the general population is very complex and multifactorial.

Patients with advanced CKD often have many medical comorbidities which contribute to the cause and progression of underlying kidney disease including diabetes mellitus (DM) and HTN. Additionally, CKD patient have disease-related risk factors that include CKD-MBD, anemia, chronic inflammation, and malnutrition, and the increased risk for CVD seen within this population could be ascribed solely to their prevalent medical comorbidities. However, large meta-analyses have found that CKD and albuminuria are risk factors for CVD independent of DM and HTN and that patients who have CKD and albuminuria without DM or HTN had similar cardiovascular mortality risk as CKD patients with albuminuria and DM or HTN [103, 104].

The elevation of several hormones in advanced CKD, such as PTH and FGF-23, occur as a means to maintain homeostasis in calcium and phosphate serum concentrations; but these elevated hormones also function as uremic toxins affecting many organs in the body including the heart. Serum PTH concentrations increase as CKD advances in response to low serum calcium and 1,25-dihydroxyvitamin D concentrations as described above. Animal studies have found that elevated PTH concentrations can activate cardiac fibroblasts leading to inter-myocardiocyte fibrosis and collagen deposition [105] and increased rate heart rate and earlier cellular death of cardiac cells [106]. FGF-23 serum concentrations also increase in advanced kidney disease due to elevated serum phosphate and PTH concentrations, and one study examining the difference in serum FGF-23 concentrations in HD and PD patients has found that HD patients have significantly higher serum FGF-23 levels compared to PD patients independent of serum PTH, phosphate, and calcium levels [107]. Studies have found that FGF-23 acts upon the heart through a klotho-independent receptor, FGFR4, and is associated with cardiomyocyte hypertrophy and left ventricular

hypertrophy [108]. FGF-23 has also been shown to promote diastolic dysfunction, congestive heart failure, and arrhythmias [109, 110]. Even though PD patients have lower FGF-23 levels, no studies have demonstrated a difference in CVD.

Increased vascular calcification, as discussed above, is a major risk factor for development and propagation of CVD in CKD patient population. Vascular calcification can result in increased pulse pressure and pulse wave velocity which then contributes to reduction in diastolic coronary perfusion and left ventricular hypertrophy [111]. Advanced CKD patients also have a high incidence of valvular calcification which contribute significantly to morbidity and mortality in this patient population [112].

Other disease-specific risk factors also play a significant role in advanced CKD patients' development and progression of CVD. Volume status in these patients is difficult to measure and control, especially in ESKD patients on dialysis. Acidosis has been found to negatively impact not only bone and mineral metabolism but also increase vascular stiffness and vascular calcifications in dialysis patients [113].

It is widely accepted that statin therapy reduces cardiovascular mortality in the general population. A meta-analysis of 80 randomized controlled trials including 51,099 patients found that use of statins reduced all-cause mortality and incidence of cardiovascular events in CKD patients not on dialysis; however, statins did not reduce all-cause or cardiovascular mortality in patients on dialysis [114]. In addition, this study also did not find a reduction in cardiovascular events despite noted decrease in serum cholesterol levels of patient who were on dialysis.

Calcific Uremic Arteriolopathy

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a manifestation of extraskeletal calcification which almost exclusively occurs in patients with advanced CKD and predominantly in patients on dialysis. It is a rare complication in ESKD patients affecting 1–5% of patients on dialysis [115, 116] and is associated with a 60–80% mortality rate [116]. Although there have been a small number of studies by one research group that have suggested that PD is a risk factor for the development of CUA [117, 118], there have been no other studies that substantiate these findings, and studies on the incidence of CUA in the PD population are very limited.

Lesions in CUA are characteristically associated with superficial necrosis related to tissue ischemia (commonly with an associated black eschar), subcutaneous fat necrosis, and poor wound healing [116]. Clinically, patients present with livedo reticularis and tender, indurated subcutaneous plaques occurring mainly on the breast, abdomen, and lower extremities [119]. Histopathologic examination of CUA lesions characteristically reveals medial calcification of subcutaneous arterioles, venules, and capillaries, endovascular fibrosis, and intravascular thrombi, although the presence of endovascular fibrosis and intravascular thrombi is variable [119, 120]. The exact mechanism in the pathogenesis of CUA remains unclear. CKD

patients on HD have increased intravascular calcifications which affects many organ systems causing various other comorbidities, but only a very small number develop this rare complication.

Classically, a high calcium phosphate product has been associated with increased risk for the development of CUA [115, 121], and other risk factors such as obesity, diabetes mellitus, hyperparathyroidism, and warfarin use have also been recognized. PTH specifically appears to have a significant role in the pathogenesis of CUA. Case reports have shown that CUA can occur in patients with primary hyperparathyroidism [122] and after kidney transplantation in patients with tertiary hyperparathyroidism [123]. These case studies would suggest that PTH plays an independent role in the pathogenesis of CUA and lesion development is not strictly associated with the uremia found in dialysis-dependent patients.

Animal studies have shown that warfarin may cause calcifications in rat arteries [124]. Warfarin, a vitamin K antagonist, inhibits a specific vitamin K-dependent matrix G1s protein (MGP) which is a key calcification inhibitor [125, 126]. Additionally, CKD patients who have significant nutritional deficits may also be affected by low availability of Vitamin K and have insufficient levels to act as a cofactor for the phosphorylation and gamma carboxylation of MGP. Nutritional supplementation of vitamin K was shown to restore carboxylated MGP levels in animal studies [126].

Patients on dialysis with CUA have a 1-year survival rate of 29% and 2-year survival rate of 14.5% [127]. Wound care in patients with CUA lesions is vital considering that the leading cause of mortality in these patients is infection and sepsis. Wound debridement, either through chemical or surgical means, should be handled on a case-by-case basis due to ischemia, poor wound healing, and high risk for infection. Hyperbaric oxygen therapy is an adjunctive therapy that can be considered to aid in wound healing. A small case series showed that 58% of patients who received treatment with hyperbaric oxygen had improved wound scores and 11 out of 34 patients in that cohort had complete wound healing [128]. Additional adjunctive therapies include bisphosphonates to mitigate bone loss and reduce serum calcium concentrations in the setting of elevated PTH and Vitamin K supplementation as previously discussed above [127, 129].

The primary modality for treatment of CUA is use of sodium thiosulfate which is typically given intravenously with dialysis three times weekly during the last 30 minutes of HD. As discussed above, data on the incidence of CUA in PD patients and treatment with sodium thiosulfate is limited. There are strategic complications in arranging the administration of sodium thiosulfate to PD patients as intravenous administration requires patients to come to the PD dialysis unit to receive the medication whereas HD patients are able to receive dosing with normal scheduled treatments. Typically, sodium thiosulfate is administered during HD not only due to access availability but also to blunt the effects of metabolic acidosis which potentially could occur with treatment. There are a small number of studies in which PD patients have received thrice weekly intravenous sodium thiosulfate with minimal side effects and no significant development of acidosis [130, 131]. Sodium thiosulfate can also be administered intra-peritoneally three times weekly [132] or orally at

variable dosing; however, bioavailability of oral sodium thiosulfate has been found to be very low and may not result in therapeutic benefit [133]. Intralesional injections of sodium thiosulfate have also been shown to be helpful [134]. The mechanism by which sodium thiosulfate works to improve CUA lesions is not clearly understood. Previously thought to improve CUA lesions through calcium chelating properties or lowering ionized Ca concentrations through acidification of the blood [135], other studies have suggested that sodium thiosulfate reduces oxidative stress and promotes vasodilation [136] and that sodium thiosulfate has vascular calcification-inhibiting properties [93, 137]. Although some clinicians may choose to convert PD patients to HD in the setting of CUA, there have been no studies performed evaluating whether this results in improved morbidity or mortality.

Reducing underlying mineral derangements is also a key target for treatment of CUA. The use of non-calcium phosphate binders and intensifying dialysis either in frequency or length of treatment time to lower the calcium–phosphate product are strategies that can be applied in this patient population. Patients who were previously on warfarin for anticoagulation should be changed to alternate medications. Traditionally, heparin injections are used in this patient population, but non-vitamin K antagonist oral anticoagulants like apixaban have also been safely used in HD patients with atrial fibrillation and deep vein thrombosis [138].

Summary

CKD-MBD is an important comorbidity of advanced CKD and ESKD which contributes significantly to the mortality within this patient population. Maintaining physiologic homeostasis of serum calcium, phosphate, and 1,25-dihydroxyvitamin D is the cornerstone of ongoing care in these patients to prevent the development and progression of parathyroid, cardiovascular, and bony disease and the sequelae of extraskeletal calcification. Through the use of close laboratory monitoring, dietary modification, and medications, this balance can be maintained and reduce the effects of CKD-MBD on patients with advanced kidney disease.

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Chapter 18
Anemia Management in Peritoneal Dialysis

Ramy Hanna and Anjay Rastogi

Introduction

In the United States, 37 million people have chronic kidney disease (CKD) [1], and the current prevalence of end-stage kidney disease (ESKD) is also approaching nearly 750,000 patients [2]. Only 7–10% of patients with ESKD are being started on PD, for an estimated prevalence of 50–75,000 patients [1].

Correction of anemia in the setting of CKD and ESKD is an important management goal [3]. The development of anemia exacerbates risks of coronary artery disease (CAD) so prevalent in these populations [4, 5]. Further, fatigue and lower health-related quality of life (HRQoL) scores are strongly correlated with anemia in CKD/ESKD patients [6].

It is becoming clear that after the implementation of the US Kidney Health Initiative (US-KHI), PD will become an increasingly favored modality for cost and convenience [7]. There is increasing evidence of favorable outcomes with regard to preservation of residual kidney function (RKF) [8].

The "at-home" care model of patients with PD will require special attention to anemia of ESKD/CKD management. Iron management and erythropoiesis-stimulating agents (ESAs) require more planning when the patient is primarily undergoing therapy at home rather than receiving injectables and infusions of medications on hemodialysis [9]. The new hypoxia-inducible factor-prolyl

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hydroxyl inhibitor (HIF-PHI) drugs present great opportunities for a new class of agents that are oral and maybe optimally suited for the peritoneal dialysis population [10]. The challenges of caring for an ever-expanding group of dialysis patients at home will require new strategies and innovative approaches to deliver quality care remotely.

Pathophysiology of Anemia in End-Stage Kidney Disease

Anemia in end-stage kidney disease is a consequence of reduced erythropoietin production resulting in impaired red blood cell generation [11]. There is also development of iron deficiency, a part of which is ostensibly related to blood loss on dialysis membranes/machines (in hemodialysis). This is not routinely experienced in patients undergoing peritoneal dialysis [12]. Figure 18.1 explains the pathophysiology of anemia in CKD and ESKD, with attention to different factors between HD and PD.

The main source of biological erythropoietin production is the pericytes of the kidney tubules. With CKD/ESKD, these pericytes are either lost with the shrinking kidney mass or differentiate to myofibroblasts [13]. This results in ever-shrinking amounts of biologically- derived erythropoietin [13]. This is the primary mechanism of decreased bone marrow production of erythroblasts and development to

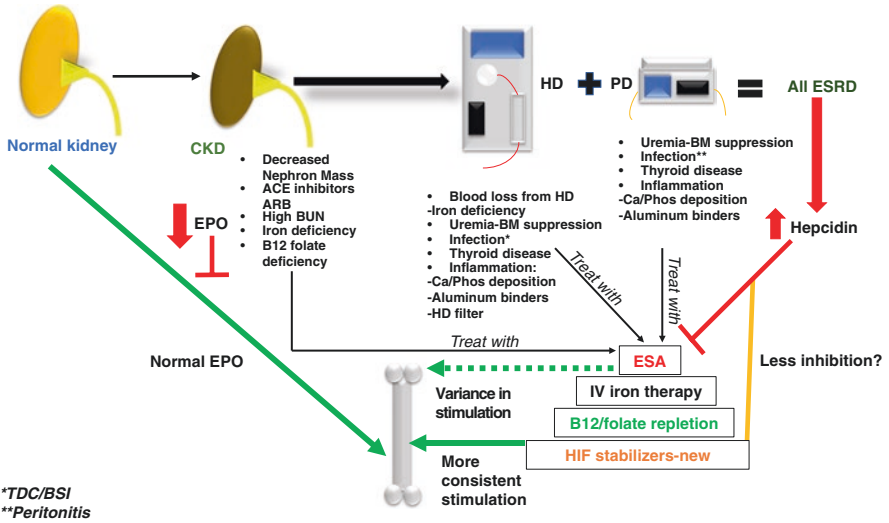

Fig. 18.1 Factors contributing to anemia in CKD and ESKD. ACE angiotensin converting enzyme, ARB angiotensin receptor blockers, B12 cyanocobalamin, BM bone marrow, BUN blood urea nitrogen, Ca calcium, CKD chronic kidney disease, EPO erythropoietin, ESKD end-stage kidney disease, HD hemodialysis, HIF hypoxia-inducible factor, Phos phosphorus, TDC tunneled dialysis catheters

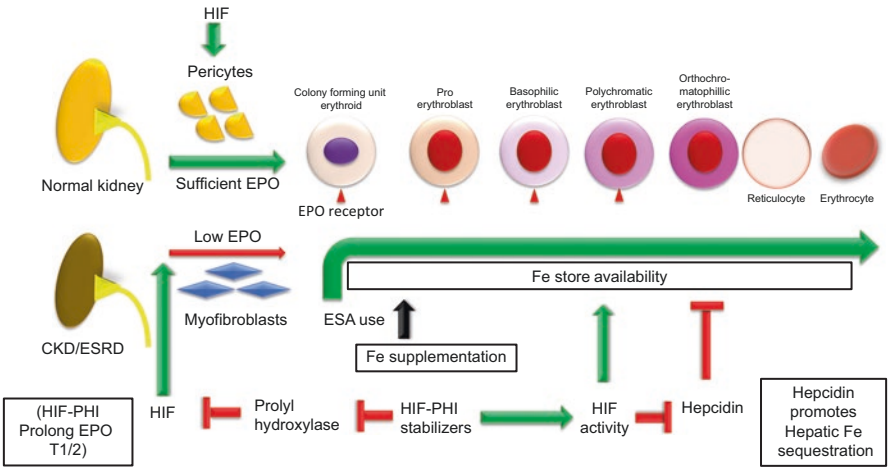

Fig. 18.2 Erythrogenesis in normal kidney and in CKD/ESKD. EPO erythropoietin, ESAs erythropoiesis-stimulating agents, Fe iron, HIF-PHI hypoxia-inducible factor-prolyl hydroxylase inhibitor, $T_{1/2}$ half-life

reticulocytes and, later, erythrocytes. Calcium/phosphorous deposition, vitamin b12 (cyanocobalamin)/folate deficiency, iron deficiency, aluminum-based binders, a rise in urea and ultimately uremia, and dialysis filter and procedurally related inflammation are additional hypothesized causes of anemia in CKD and ESKD [3].

The inflammation seen in CKD and ESKD is the subject of a new area of research within anemia in CKD, and that is the reduced utilization of iron stores due to hepcidin dysregulation [14]. Hepcidin is hypothesized to be related to increased secretion from activated macrophages, due to inflammation and vascular injury related to calcium deposition and dialyzer membrane-related inflammation [15]. There are also concerns of iron overload and cardiovascular risk related to high levels of hepcidin [15]. Hepcidin levels can also directly exert effects on patient outcomes and costs by inducing ESA resistance [10, 15]. Figure 18.2 displays the usual physiology of erythrocytosis, pathophysiology in CKD/ESKD patients, and pharmacology of common treatment options.

Rationale for Anemia Treatment

CKD and ESKD both lead to increased cardiovascular strain due to volume overload. This is especially pronounced in ESKD in HD and PD patients where volume overload results in left ventricular hypertrophy (LVH) [16]. Thus, anemia in the setting of LVH and ESKD results in increased risks of ischemia due to inability to supply myocardial oxygen demand (MVO2). Patients with CKD- and ESKD-related anemia have higher progression of coronary artery disease (CAD), congestive

heart failure (CHF), and even atherosclerotic vascular disease (ASVD) [17–21]. The current treatment goal is a hemoglobin target of 10–11.5 g/L (but less than 12 g/L). The risk of treating to higher hemoglobin was noted in multiple studies that demonstrated a higher risk of stroke, myocardial infarction, and venous thromboembolism [22]. Though higher hemoglobin reduced subjective feelings of fatigue in HD and PD patients, these benefits are not substantial enough to justify the overall systemic risks [23].

Anemia in ESKD was treated with blood transfusion and intravenous (IV) iron prior to the advent of ESAs [24]. The original ESA indication given by the US FDA was for the reduction in need of blood transfusions. This was extremely helpful in the CKD and ESKD population, resulting in less risk of blood-borne illnesses and less risk of foreign antigen sensitization, which may limit options for transplantation. The mechanism of ESA agents is simply the direct stimulation of erythrocyte precursors (erythroblasts) to divide and develop into reticulocytes and mature red blood cells. This requires free iron stores without which bone marrow progenitor development will not be possible [25, 26]. Risks of iron supplementation include oxidative damage in CKD, and in ESKD an increased risk of infection has been seen in some studies [27, 28], but not others such as the PIVOTAL trial and the dedicated follow-up infection sub-study [29, 30]. Table 18.1 discusses cardiovascular

Table 18.1 Oral and parenteral iron formulations for use in peritoneal dialysis

Agent	Route	Usual dose	Usual schedule	Side effects
Iron sulfate	Oral	325 mg	TID	Constipation, poor bioavailability, and absorption
Iron gluconate	Oral	240–320 mg	TID to QID	Poor bioavailability and absorption
High-molecular-weight iron dextran	Intravenous	100 mg injection	2–3 times a week for limited duration	Anaphylaxis, infection risk, renal oxidative stress risk in CKD
Low-molecular-weight iron dextran	Intravenous	100 mg injection	2–3 times a week for limited duration	Anaphylaxis, infection risk, renal oxidative stress risk in CKD
Iron sucrose	Intravenous	100 mg injection	2–3 times a week for limited duration	Anaphylaxis, infection risk, renal oxidative stress risk in CKD
Ferric gluconate	Intravenous	125 mg injection	2–3 times a week for limited duration	Benzyl alcohol reactions
Ferumoxytol	Intravenous	510 mg injection	Followed by 1 repeat dose 3 days to 8 days after initial dosing	Will cause enhancement on MRI scanning up to 3 months after

CKD chronic kidney disease, *Mg* milligram, *MRI* magnetic resonance imaging, *QID* four times a day, *TID* three times a day

risks in CKD and ESKD patients, and Fig. 18.2 shows the effect of physiology of ESAs in promoting erythropoiesis.

Role of Iron in Anemia Therapy and Evidence for Use

Given the activation of hepcidin discussed above, iron deficiency and relative iron deficiency are common comorbid issues in ESKD patients, including those on PD [26]. The supplementation of iron then becomes a central focus in the management of anemia [25]. In patients receiving ESAs, the demand for iron is also higher, resulting in a need for more iron supplementation to ensure ESA effectiveness [31].

Oral iron, while easy to use, is poorly absorbed and has been proven to be less effective than IV iron. This holds true for peritoneal dialysis patients specifically as well [28]. Iron sulfate, in particular, can aggravate constipation, though iron gluconate is associated with a lower incidence of constipation [32]. IV iron is better tolerated and allows more efficient use of ESAs [31]. The PIVOTAL trial also has allowed insight into a proactive versus reactive IV iron strategy [30]. It has been found that a proactive IV iron loading strategy is associated with lower cardiovascular event rate and a lower rate of ESA utilization in HD [30]. Though these findings are likely generalizable, a specific trial in PD patients with IV iron has not yet been done [30].

Avoidance of blood transfusions can thus be maximized with proper IV iron use in HD and PD patients [25, 30, 31]. It is important to monitor ferritin and iron saturation parameters to avoid hepatic iron overload [28]. In CKD patients, there are some concerns about oxidative stress with IV iron use, but these concerns are greatly lessened in ESKD patients [27, 28]. Infectious complications of IV iron use, however, are possible. In general, IV iron is to be avoided in active infections but should be used to avoid risks of blood-borne pathogen exposure (with transfusion) [27, 28]. Maintenance iron strategy seems to be associated with less infection risk than bolus iron infusions [27, 28]. Immune sensitization [33], transfusion reactions, and general strain on healthcare resources are also undesirable side effects of blood transfusion that can be avoided with optimal iron use and ESA administration [22]. The available oral and intravenous iron formulations are compared and contrasted in Table 18.1, along with dosing recommendations for those agents.

Erythropoiesis-Stimulating Agents and Evidence for Use

Erythropoiesis-stimulating agents are recombinant erythropoietin products that have been artificially produced [34–36]. There are compounds similar to biological erythropoietin alpha and others that have been altered to change their half-life (darbepoetin) [37]. These have been in clinical use since the 1980s–1990s and were a major development in CKD and ESKD care [38].

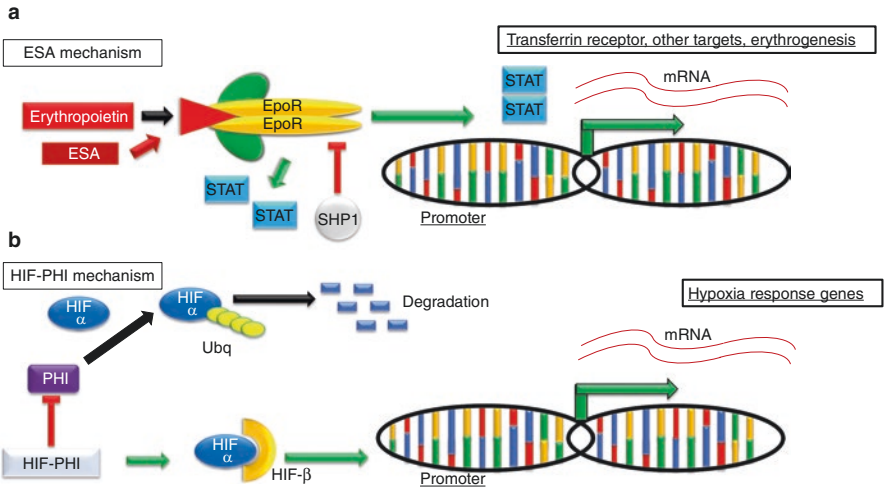

Fig. 18.3 Molecular biology of ESA and HIF stabilizing agents. (**a**) ESA mechanism. (**b**) HIF-PHI Mechanism. EpoR erythropoietin receptor, ESA erythropoiesis-stimulating agent, mRNA messenger RNA, HIF-α hypoxia-inducible factor alpha, HIF-β hypoxia-inducible factor beta, PHI prolyl hydroxylase inhibitor, SHPI-1 SH2-domain containing protein; STAT signal transduction and transcription protein, Ubq ubiquinone. Note ubiquinone-tagged proteins are marked for proteasome degradation

Newer developments include a depot form that limits hemoglobin variability (methoxy polyethylene glycol-epoetin beta) [9, 39]. These agents all function in a similar fashion once they reach cell signaling machinery, namely, the stimulation of the erythropoietin receptor and the transmission of that signal via phosphorylation to signal transducer and activator of transcription (STAT) protein [40]. The translocation of STAT protein from the cytoplasm to the nucleus results in promotor binding of genes encoding the transferrin receptor and other proteins that stimulate erythropoiesis. See Fig. 18.3 for schematic of ESA mechanism of action [40].

The primary FDA indication given to all ESAs is to prevent the need for blood transfusion in end-stage kidney disease, and they are often used in the setting of CKD as well [41]. The use of these agents is associated with a U-shaped safety curve, with underuse being associated with anemia and poor cardiovascular outcomes [5, 19]. Overuse, however, similarly results in higher risks of cardiovascular, cerebrovascular, and thromboembolic events [22]. The correction of anemia to the standard 10–11.5 g/L is associated with improved health-related quality of life (HRQoL) questionnaire rating, less fatigue, and improved cardiovascular morbidity and mortality rates [38]. The dangers of elevated hemoglobin far outweigh any benefits of correcting hemoglobin to normal levels [38]. Limiting factors due to cost, injectable route, and risk of antibodies forming to drug have also driven a search to use the lowest effective dose of drug to achieve desired effect [42]. While correcting to a target of 11–12 g/L is cost-effective, beyond these targets, there are both cost and risk barriers that present an unfavorable risk/benefit ratio [42].

Table 18.2 Doses of erythropoietin analogues used in end-stage kidney disease

Agent	Route	Usual dose	Usual schedule	Side effects
Erythropoietin-alpha	IV SQ	300 units/Kg 2000 units–20,000 units	TI week ($T_{1/2}$ = 4–13 hours)	High hemoglobin >12 g/L associated with adverse CV and cerebrovascular events Worsening of existing malignancy
Darbepoetin- alpha	IV SQ	0.45 mcg/Kg 25 mcg to 500 mcg doses	Every 4 weeks ($T_{1/2}$ = 24–144 hours)	High hemoglobin >12 g/L associated with adverse CV and cerebrovascular events Worsening of existing malignancy
Methoxy polyethylene glycol-epoetin beta	IV SQ	0.6 mcg/kg 60–360 mcg doses	60–180 mcg every 2 weeks 120–360 mcg every 4 weeks $T_{1/2}$ 119–124 hours (HD lower $T_{1/2}$, PD higher $T_{1/2}$)	High hemoglobin >12 g/L associated with adverse CV and cerebrovascular events Worsening of existing malignancy
Erythropoietin beta not approved by US FDA (in use in EU)				
Erythropoietin delta not approved by US FDA (in use in EU)				
Erythropoietin omega not approved by US FDA (in use in EU)				

CV cardiovascular, *FDA* US Food and Drug administration, *EU* European Union, *G* gram, *HD* hemodialysis, *V* intravenous, *Kg* kilogram, *L* liter, *mcg* micrograms, *PD* peritoneal dialysis, *SQ* subcutaneous, $T_{1/2}$ half-life, *TI week* three times a week

These drugs can be injected intravenously, and this is often done during HD; in CKD and PD patients, the subcutaneous route is preferred [43]. Please see Table 18.2 for available ESAs with data on $T_{1/2}$, cost, routes of injection, and structural particulars. Dosing recommendations are also included for short- and long-acting ESAs in Table 18.2. Intraperitoneal delivery of ESAs has been successfully administered in a dry abdomen with greatly enhanced bioavailability as reported in Bargman et al. [44].

Hypoxia-Inducible Factor Stabilizers and Evidence for Use

Hypoxia-inducible factor (HIF) is normally produced in response to low oxygen conditions, and this induces erythropoietin production in addition to several other hypoxia response genes [10]. HIF is then degraded by prolyl hydroxylase which marks HIF for ubiquitin tagging and eventual degradation by the proteasome. The mechanism of HIF stabilizer-PHI is the prevention of hydroxylation of HIF by prolyl hydroxylase, the interruption of ubiquitin tagging, and the provision of a steadier signaling promoting erythropoietin transcription and translation [45–48]. See Fig. 18.3 for the mechanism of action of this novel class of anti-anemia agent [49].

The first agent approved by the US FDA of the HIF-PHI class was roxadustat, and it was also novel in that it is an oral agent [50]. The trials marking its approval were placebo controlled, and they showed efficacy [51]. An unexpected benefit was a visible reduction in hepcidin levels [52] and suggests that HIF-PHI agents may make iron more available for use in erythropoiesis [52]. Head-to-head studies against other ESAs demonstrated superiority or noninferiority as well [53].

Currently a large variety of HIF-PHI agents are undergoing FDA phase 2 clinical trial testing. The new agents in development include daprodustat [54], vadadustat [55], molidustat, enarodustat, and desidustat [56–60]. Some agents have shown greater than desired/goal increases in serum hemoglobin. The biological erythropoietin level needed to achieve these increases, however, is lower than the usually prescribed doses of other directly acting ESAs [49].

Further, the oral administration of these agents solves many issues with drug storage, availability, administration logistics, and cost concerns. The availability of an oral agent makes this class of agents very appealing for the PD population [49]. Given the concern noted earlier about erythropoietin and poor outcomes with normalized hemoglobin, the use of these agents should be closely monitored to ensure that hemoglobin levels stay in the 10–11.5 g/L range [38]. It is not known if the same deleterious effects of higher hemoglobin will be noted with HIF-PHI agents as with other ESA compounds. It is prudent though to follow the same precautions at this point, with the available evidence [38].

Difference Between Anemia Therapy in Peritoneal and Hemodialysis Patients

There are various subtle differences between the HD and PD populations summarized here. The pathophysiology of anemia in ESKD is similar among CKD, HD, and PD populations [12]. HD populations, though, have a lower threshold for injectable therapies given availability of nursing care three times a week, access to the blood stream, and intensive in-center monitoring [12]. This logistical setup does not translate to superior outcomes and comes at a great cost, however [12]. The acute and chronic risks of blood loss in HD circuits, infection risk in patients undergoing HD with tunneled dialysis catheters (TDC), and inflammation risk due to the HD circuit are factors aggravating anemia of ESKD in this population with no correlate in the PD population [61].

The PD population, however, has several challenges. There are fewer opportunities for nursing care; the use of longer-acting injectables capable of being injected subcutaneously is thus more optimal for PD [12]. Long-acting ESA analogues of erythropoietin alpha and longer-acting erythropoietin beta agents all are dosed subcutaneously in the PD population. As mentioned, the promise of oral HIF-PHI

agents with their oral administration is optimal in the PD population. In addition to the ease of administration, the new generation of HIF-PHI's effect on hepcidin may reduce need for iron loading and increase iron availability [12]. This is helpful, since PD patients are not often available for intravenous iron therapy, and this approach may improve the efficacy of the usually poorly bioavailable oral iron therapy [12]. Another important approach is the potential use of intraperitoneal ESA, which, if done correctly via a dry abdomen, results in greatly improved pharmacokinetics and bioavailability [44].

The Need for Further Workup

While it is very likely that anemia in the setting of CKD/ESKD (including HD and PD) is likely due to erythropoietin deficiency and/or resistance related to hepcidin or other factors, some red flags should spur investigation [62]. It has been noted recently that there is a significant number of patients with CKD and ESKD who have macrocytic anemia and vitamin B12 (cyanocobalamin) deficiency in CKD and ESKD populations [63]. It is important to note, though, that high B12 levels are deleterious and should be avoided based on recent studies [64].

A strongly microcytic anemia with findings, signs, and symptoms suggestive of gastrointestinal bleeding should spur a gastroenterological evaluation and upper and lower tract endoscopy to locate any occult bleeding or malignancy. (Remember that PD patients need antibiotic prophylaxis before endoscopy and should undergo these procedures with an "empty" peritoneal cavity.) This is especially important in patients on ESAs, who may have a risk factor as ESAs can promote tumor angiogenesis [62].

In cancer patients, while ESAs can be used, their management must be in the hands of an oncological physician who knows how they may affect the treatment and prognosis of an underlying malignancy [65]. Ideally oncology and nephrological consultants would co-manage such patients in close collaboration so as to ensure both nephrological and oncologic guidelines are met [62].

The use of ESAs may not stop the need for blood transfusions due to development of ESA resistance, neutralizing antibodies, and hepcidin hindering iron availability. Packed red cell transfusions may still be needed to keep hemoglobin >7 or >8 in patients with cardiac risk factors [62]. If blood transfusions do not improve with ESA, a thorough malignancy and even a hemolytic anemia workup should be undertaken [65]. In some cases, bone marrow biopsy may reveal a plasma cell dyscrasia, myelodysplastic syndrome, or underlying malignancy. Rarely thrombotic microangiopathy or paroxysmal nocturnal hemoglobinuria may be uncovered, as both these diseases may have been occult causes of ESKD in anemic patients [66].

Table 18.3 When to pursue more workup in anemia of CKD/ESKD patients

High MCV >100 (B12 deficiency, liver disease)
Low MCV <80 (iron deficiency)
Hemolysis (high LDH, schistocytes)
Unexplained thrombotic events in context of anemia
Evidence of bleeding (including irregular/abnormal menses)
Evidence of malignancy
High-dose ESA or other therapy without effect
Change in pattern of response to ESA despite iron loading
No response to ESAs and IV iron
Hemoglobinuria
Hematochezia or melena/red blood per rectum
Pregnancy
Hypothyroidism
Hyperthyroidism
Suspicion of anti-erythropoietin antibodies

ESA erythropoiesis-stimulating hormone, *IV* intravenous, *LDH* lactate dehydrogenase, *MCV* mean corpuscular volume

Table 18.3 lists alarm signs that suggest the need for further consultation and workup in PD/ESKD patients with anemia.

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Chapter 19
Peritoneal Dialysis in Diabetic Patients

Cheuk-Chun Szeto

Introduction

Diabetes mellitus and chronic kidney disease (CKD) are both common, serious, and costly medical problems. In 2017, there were 476 and 697 million diabetic and CKD patients, respectively, around the world [1]. CKD causes over 1.2 million deaths globally every year, of which over one-third have diabetic kidney disease [2]. In many parts of the world, 50% of end-stage kidney disease (ESKD) patients newly put on dialysis nowadays have diabetic nephropathy as the underlying renal diagnosis [3]. The presence of diabetes is also consistently associated with a markedly elevated risk of cardiovascular disease and death in dialysis patients.

Peritoneal dialysis (PD) is a life-saving treatment of ESKD, and, being a home-based and inexpensive modality of dialysis, the utilization of PD has been increasing in many parts of the world [4, 5]. However, diabetic patients have specific problems after receiving PD, and there are areas that clinicians must be cautious while treating diabetes in PD patients.

PD for Diabetic Patients

Choice of PD as the Dialysis Modality

The choice of dialysis modality for diabetic patients involves multiple considerations and may not be purely medical or scientific. Hemodialysis is feasible in many

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patients but would be a concern when there is underlying cardiovascular disease or hemodynamic instability, which are both common in diabetic patients. Furthermore, it is often technically difficult to establish a permanent vascular access, and diabetic patients are at high risk of developing catheter-related blood stream infection [6]. Many diabetic patients are elderly, have limited mobility, and may have logistic difficulty to come to the hemodialysis center thrice weekly.

In contrast, there are a number of advantages to use PD as the modality of treatment for diabetic patients with ESKD. Being a home-based therapy, frequent travel to the dialysis center and restriction of daily activity are avoided. As a continuous therapy, hemodynamic and biochemical stability are maintained. Although peritonitis is always a concern, the risk is probably balanced by that of catheter-related blood stream infection as in the case of hemodialysis. However, glucose absorption from PD solution may pose problems to diabetic and metabolic control, and protein loss to PD effluent may aggravate malnutrition and sarcopenia.

Metabolic Consequence of PD

With conventional glucose-based PD solutions, 50–80% of the instilled glucose is absorbed. The carbohydrate load to the patient depends on the glucose concentration of the PD solution, frequency of dialysis exchange, and the peritoneal transport characteristics. On average, around 50–150 g/day of glucose is absorbed, which is equivalent to 200–600 kcal/day and could contribute to 10–30% of the daily caloric requirement of a diabetic patient.

Glucose absorption leads to a number of metabolic consequences [7]. Appetite is suppressed, but the effect is usually counterbalanced by the improvement of uremia. Weight gain is common after the initiation of PD. Glucose intolerance, insulin resistance, and the development of an atherogenic lipid profile are often observed. In an observational study, Kim et al. [8] noted that the median weight gain after 1 year of PD was 2.3 kg. The magnitude of weight gain was more severe in diabetic patients and was related to systemic inflammation and rapid decline in residual kidney function [8]. In another study of 444 new PD patients, Choy et al. [9] reported a mean weight gain of 1.34 kg after 1 year of PD. Nearly 25% patients had weight gain over 3 kg, which was more common in diabetic patients [9]. However, the magnitude of weight gain during the first year of PD was not associated with adverse clinical outcome [9].

With the high prevalence of obesity and substantial weight gain after PD, a large proportion of diabetic PD patients develop overt metabolic syndrome. A study of 329 prevalent PD patients showed that over 95% diabetic PD patients (and 62% of nondiabetic ones) fulfilled the diagnostic criteria of metabolic syndrome [10]. However, the overall survival, cardiovascular survival, and technique survival did not differ between patients with and without metabolic syndrome, irrespective to the diabetic status [10].

With the continuous glucose exposure, nondiabetic patients may develop hyperglycemia after the initiation of PD therapy. In an observational study of 252 nondiabetic patients newly started on PD, fasting plasma glucose levels were greater than 200 mg/dL in 21 patients (8.3%), and fasting plasma glucose was 126–200 mg/dL in 48 patients (19.0%) [11]. Seven patients required insulin therapy, and three required low-dose sulfonylurea therapy [11]. In this study, obesity was not a risk factor of hyperglycemia after PD, but even mild hyperglycemia was associated with worse survival rate [11]. The result indicates that fasting plasma glucose should be monitored in nondiabetic patients after initiation of PD.

Glucose-Sparing Strategies

In view of the adverse metabolic consequences, it is logical to minimize glucose exposure in diabetic PD patients. Possible strategies of glucose sparing are summarized in Table 19.1. To start with, the need of hypertonic PD cycles should be reduced by dietary salt and water restriction. Diuretics, especially loop diuretics, should be used liberally. Residual kidney function should be preserved by avoiding nephrotoxic agents (e.g., nonsteroidal anti-inflammatory agents and aminoglycosides). Previous randomized controlled trials suggest that angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are effective in preserving residual kidney function [12].

On the other hand, ultrafiltration from PD could be optimized without excessive exposure to hypertonic glucose-based solution by appropriate design of the PD regimen and use of glucose-free solutions. Utilization of glucose-polymer (i.e., icodextrin) solution notably improves glycemic control and leads to favorable metabolic profiles in diabetic patients [13, 14]. Johnson et al. [15] showed that HbA1c decreased from 8.9 to 7.9 in diabetic patients treated with icodextrin solution. Amino acid-based PD solution is also often used to reduce the insulin requirement of diabetic PD patients, although it was originally developed for its nutritional benefit. A small study showed that replacement of glucose with amino acid-based

Table 19.1 Strategies of reducing glucose exposure for diabetic PD patients

(A) Non-dialysis[a]
Dietary salt and water restriction
Liberal use of diuretics
Preservation of residual kidney function
(B) Dialysis
Icodextrin PD solution
Combination regimen of glucose polymer and amino acid-based solutions

[a]The aim is to reduce the use of hypertonic PD cycles

solution had beneficial effects on glucose and lipid metabolism [16]. Combination regimens that use both icodextrin and amino acid-based solutions on the diabetic control of PD patients have further been tested in a randomized control trial [17]. In this study, 251 diabetic PD patients were randomized to a low-glucose combination regimen or a conventional glucose-based one [17]. After 6 months, the mean glycated hemoglobin, serum fructosamine level, and lipid profiles improved in the combination group but remained unchanged in the control group [17–19]. However, there was a trend of more serious adverse events, including those related to extracellular fluid volume expansion, in the combination group [17]. Taken together, available studies strongly support that glucose sparing solutions substantially improves the glycemic control and leads to a favorable metabolic profile in diabetic PD patients. Other studies also show possible beneficial effects on peritoneal function [14]. However, the long-term benefit on cardiovascular event or patient survival has not been demonstrated.

Management of Diabetic PD Patients

Specific Problems

A number of specific problems are noteworthy in diabetic patients undergoing dialysis, and some of which are specific for PD. First, it is actually difficult to define diabetes in PD patients because there is no true fasting state unless PD is withheld overnight before the fasting blood test. Oral glucose tolerance test may not be reliable in advanced kidney failure because glucose level elevation is prolonged as a result of uremia-related insulin resistance. Insulin requirement is unpredictable. Insulin resistance is well recognized, while insulin sensitivity also occurs because of reduced insulin catabolism and renal gluconeogenesis. The metabolism and excretion of many oral hypoglycemic agents are reduced. In spite of the glucose load from PD solution, there is usually little mental symptom from gross hyperglycemia because there is no polyuria or osmotic diuresis. As a result, insulin but not much intravenous fluid is needed for the treatment of ketoacidosis or hyperosmolar state in PD patients. Advanced kidney failure leads to increased level of carbamylated hemoglobin, which cannot be distinguished with HbA1c by exchange chromatography and may affect the result of glycemic monitoring. In contrast, affinity chromatography, colorimetric, or ELISA methods of HbA1c measurement are not affected. It is also commonly believed that the risk of hyperkalemia is increased in diabetic patients undergoing dialysis because of the lack of insulin secretion, concomitant aldosterone deficiency, and transcellular fluid shift and electrolyte drift secondary to hyperglycemia. However, hypokalemia seems a more common clinical problem in diabetic PD patients [20].

Treatment of Diabetes

Insulin Therapy in PD

Insulin is the treatment of choice for diabetic patients with advanced CKD. Diabetic patients often have reduced insulin requirements when they develop advanced CKD. Since PD solution contains glucose, the insulin requirement of these patients would theoretically increase after commenced on PD. However, in an observational study of 60 diabetic patients newly started on PD, the average increment in dosage was only 0.10 ± 0.22 unit/kg/day [21]. The increase in insulin dosage correlates with the number of hypertonic PD cycle required per day, with each extra 2.5% dextrose 2L exchange results in an average of 7.5 unit/day increase in insulin requirement [21]. In other words, diabetic patients usually have little increase in insulin requirement after initiation of PD unless they require hypertonic PD cycles. In another study, plasma C-peptide concentration and duration of diabetes, reflecting a decrease in beta-cell reserve, were the main determinants of insulin requirement after PD, while dialysis adequacy had no effect on the insulin requirement [22].

In addition to the standard subcutaneous injection, intraperitoneal (IP) insulin has been advocated for diabetic PD patients. Use of IP insulin injection has the advantages of a continuous therapy, elimination of subcutaneous injection, and a physiological route of absorption via the portal circulation. However, the regimen is often complicated, and the risk of peritonitis is always a concern. This approach is not commonly used nowadays.

Oral Hypoglycemic Agents

Although insulin is often the preferred agent for treating diabetic patients undergoing dialysis, a non-negligible proportion of patients have mild hyperglycemia and could be well controlled by oral hypoglycemic agents. Metformin, the first-line oral hypoglycemic agent for the general population, is contraindicated in advanced kidney failure [22]. The metabolism and excretion of many other oral hypoglycemic agents are also reduced in kidney failure, and dosage adjustment is often necessary. For sulfonylureas, glyburide or glibenclamide should be avoided, while glipizide or gliclazide may be used at a low dose [22]. Most of the dipeptidyl peptidase 4 (DPP-4) inhibitors (i.e., gliptins) could be used with dosage reduction, except that linagliptin does not require dosage adjustment [22]. For glitinides, repaglinide could be used without dose reduction, while nateglinide should be avoided because of the accumulation of active metabolites [22]. Thiazolidinediones could also be used at the usual dose, although the risk of fluid retention and heart failure should be considered [23]. Incretin mimetics (e.g., exenatide) and α-glucosidase inhibitors should be avoided [22].

Target of Glycemic Control

There are few published data dedicated on the relation between diabetic control and clinical outcome in PD patients. Although there is no evidence that a tight diabetic control preserves residual kidney function in PD patients, diabetic control would still be important for the prevention of other microvascular and macrovascular complications. The role of tight diabetic control, however, is controversial. In the UKPDS study, 3867 new patients with type 2 diabetes were randomized to tight or conventional diabetic control (HbA1c 7% versus 7.9%) and then followed for up to 15 years [24]. Intensive blood glucose control by either sulfonylureas or insulin substantially decreases the risk of microvascular (mostly retinopathy) but not macrovascular complications (myocardial infarction or stroke) [24]. In the ADVANCE study, 11,140 patients with type 2 diabetes were randomly assigned to either standard or intensive glucose control (HbA1c 7.3% versus 6.5%) and then followed for 5 years [25]. In this study, intensive glucose control yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events but primarily as a consequence of a 21% relative reduction in nephropathy [25]. The consideration is, however, different in high risk (e.g., dialysis) patients, who have a different risk-to-benefit ratio. In the ACCORD study, 10,251 high-risk patients were randomized to receive intensive therapy (target HbA1c below 6.0%) or standard therapy (target HbA1c 7.0–7.9%) [26]. In this study, intensive glycemic control increases the mortality and did not significantly reduce major cardiovascular events as compared with standard therapy, but hypoglycemia and weight gain were more common in intensive group [26]. Similarly, in the Veterans Affairs diabetes trial, intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications [27]. Taken together, it would be reasonable to liberalize HbA1c target in PD patients in order to reduce the risk of hypoglycemia.

Hypoglycemia

Diabetic patients with kidney disease has an increased risk of hypoglycemia. The high risk of severe hypoglycemia reflects altered insulin and drug pharmacology, including metabolite accumulation, inadequate gluconeogenesis, and flattening of the relationship between mean glucose control and HbA1c [28]. The combination of hypoglycemia and kidney failure is associated with a high mortality in type 2 diabetic patients [29, 30].

Glycemic Monitoring

The method of monitoring diabetic control should be considered. Traditionally, HbA1c – the glycated hemoglobin level – is used, but the level is often falsely low in patients with CKD because of the reduced red cell life span and low-grade

hemolysis. On the other hand, HbA1c may also be falsely high in patients with advanced CKD because of severe acidosis or carbamylation of hemoglobin. In a cross-sectional study of 258 diabetic dialysis patients, Peacock et al. [31] showed that HbA1c was 1% lower for the same degree of mean serum glucose level as compared to diabetic patients without nephropathy. For that reason, capillary blood glucose monitoring assumes particular importance for assessment of glycemic control in dialysis patients. Although the traditional approach is to check capillary blood glucose at fasting, pre-meal and bedtime, postprandial blood glucose testing may be helpful in patients with gastroparesis. For patients receiving icodextrin solution, specific attention should be paid on factitious hyperglycemia due to the interference with glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) assay for blood glucose measurement in several brands of glucometer, while GDH nicotinamide adenine dinucleotide (GDH-NAD) assay used by some other brands is not affected.

Treatment of Other Cardiovascular Risk Factors

Blood Pressure

Control of blood pressure is one of the key factors in reducing cardiovascular morbidity and mortality in diabetes [32]. Both the KDOQI [33] and KDIGO [34] recommend a low blood pressure target for patients with diabetes and (pre-dialysis) CKD, although the evidence is weak. The recent SPRINT trial supports a systolic blood pressure target of 120 mmHg (versus 140 mmHg) for high-risk patients [35], but the result of this trial may not be applicable to patients with diabetes or advanced kidney failure [36]. Taken together, a blood pressure target of 130/80 is reasonable and evidence-based, but implementation of this blood pressure target also requires assessing patient preferences, concurrent medical conditions, and careful monitoring for adverse effects of therapy [36].

In pre-dialysis diabetic patients, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is the preferred antihypertensive agent because these drugs show cardiovascular and renal protection beyond blood pressure control as compared to other drug classes. Preservation of residual kidney function remains a relevant concern in dialysis patients, and ACE inhibitor or ARB should still be the preferred choice of antihypertensive agents in view of their cardiovascular benefits and the effect of preserving residual kidney function [12, 37]. For optimal blood pressure control, the KDIGO guideline also recommends a sodium intake below 90 mmol per day (i.e., 5 g of sodium chloride) [34]. Sodium restriction may also enhance the antihypertensive effect of ACE inhibitor or ARB. However, two studies reported that a very low 24-h urinary sodium excretion (a surrogate marker of dietary sodium intake) was paradoxically associated with increased all-cause and cardiovascular mortality in diabetic patients [38, 39].

Volume Control

Diabetic PD patients have a high prevalence of volume overload, which is a strong predictor of patient survival and cardiovascular event [40]. Despite substantial fluid accumulation, many patients remain asymptomatic. In an observational study of 212 diabetic patients without clinical edema, the average volume of overhydration, as determined by bioimpedance spectroscopy, was 5L [40]. Vigorous volume control also facilitates the achievement of blood pressure target. However, there is limited evidence that vigorous fluid control reduces cardiovascular mortality or heart failure in diabetic PD patients.

Lipid

Dyslipidemia is common in diabetic PD patients [41], but there is little evidence that treatment of hyperlipidemia reduces the rate of cardiovascular event or mortality. In both German Diabetes and Dialysis Study [42] and the AURORA Study [43], statins did not significantly reduce the rate of cardiovascular events in diabetic and nondiabetic patients receiving hemodialysis. In the SHARP study, which recruited 6382 pre-dialysis and 3056 dialysis patients (2540 hemodialysis and 496 PD), lipid lowering with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events in pre-dialysis CKD with not chronic dialysis patients [44]. The latest Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group recommends that lipid-lowering therapy should not be initiated in dialysis patients, but statins could be continued for patients who are already taking this drug at time of dialysis initiation [45].

Antiplatelet and Antithrombotic Therapy

The use of antiplatelet and antithrombotic agents for the prevention of cardiovascular disease in diabetic patients with advanced kidney disease has not been robustly studied [28]. It has been questioned whether the balance of benefit and harm of antiplatelet therapy is the same in diabetic patients with kidney disease [46]. Given the high rates of thrombotic and embolic events in advanced kidney failure and the potential harms associated with antiplatelet or antithrombotic agents, the use of these therapies and novel oral anticoagulants requires further evidence and should be individualized [28].

Treatment of Other CKD Complications

Anemia

Anemia is a common complication in CKD, and it tends to occur earlier in patients with diabetic nephropathy than nondiabetic individuals with a comparable kidney function [47]. The cause of excessive anemia in patients with diabetic nephropathy

is multifactorial [48]. Diabetes is associated with an inappropriately low erythropoietin response for the degree of anemia, probably due to abnormal glycosylation of the cytokine; a better diabetic control is associated with a higher erythropoietin level [49]. Chronic hyperglycemia can lead to hypoxia in the renal interstitium, which results in impaired production of erythropoietin by the peritubular fibroblasts [48].

Anemia in diabetic nephropathy is an independent contributor to the pathogenesis and progression of other diabetes-related complications, notably left ventricular hypertrophy. In diabetic patients, correction of anemia improves quality of life and may delay the progression of diabetic complications [48]. Clinicians should follow the current KDIGO recommendations on the treatment of anemia in diabetic PD patients [50].

Mineral Bone Disease

There are subtle but important differences in the spectrum of mineral bone disease between diabetic and nondiabetic CKD [51]. In the former, adynamic bone disease often predominates over hyperparathyroidism, and vitamin D deficiency is common. Uremia impairs the production of cholecalciferol from 7-dehydrocholesterol by ultraviolet-B light radiation [52]. Reduced formation of 1,25-dihydroxycholecalciferol is due to profound tubulointerstitial injury and early loss of 1α-hydroxylase activity [52]. Hyperglycemia also downregulates vitamin D receptor in various tissues, contributing to the functional vitamin D deficiency [52].

Some other bone problems may also be specific for diabetic patients [51]. For example, poorly controlled diabetes is associated with hypercalciuria, which predisposes to bone loss. Patients with advanced diabetes have an increased risk of fall and fracture because of poor vision and peripheral neuropathy. Although not commonly used nowadays, thiazolidinedione has been reported to be associated with accelerated loss of bone mineral density.

Conclusion

In summary, the management of diabetic PD patient requires attention to multiple aspects. For diabetic patients newly put on PD, weight gain and its consequential metabolic changes are a concern. Worsening of diabetic control is not common unless the patient needs hypertonic PD cycles. Glucose-free PD regimens may further facilitate diabetic control. For the management of diabetes in PD patients, the targets of glucose and blood pressure control need to be individualized with careful balance of the risk and benefit. ACE inhibitor and ARB should be continued as much as possible. Statin may also be continued if it has been started before dialysis. Anemia is particularly common and severe in diabetic PD patients and deserves specific attention. Since adynamic bone disease is common, parathyroid hormone should not be excessively suppressed.

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Chapter 20
Peritoneal Dialysis in Special Situations

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Introduction

Peritoneal dialysis (PD) is used widely and successfully in treatment of end-stage kidney disease (ESKD) patients. The continuous nature of the therapy and its home-based, self-care character make it advantageous for certain subgroups of patients. This chapter focuses on the use of PD in subgroups of ESKD patients who require special considerations.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) ranks as the most common hereditary kidney disease and the fourth leading cause of ESKD in the United States, with a prevalence rate of 4.7% [1]. Globally, polycystic kidney disease affects 4–6 million people and accounts for ESKD prevalence of up to 10% in certain countries. ADPKD patients present mainly with renal cysts, enlarged kidneys and intra-abdominal complications including cyst rupture, cyst infection, liver cysts, diverticulitis, and abdominal wall hernias. In the process of cyst growth,

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approximately 45% of patients progress to ESKD by the age of 60 and up to 75% by the age of 70 [2].

Previously, the presence of ADPKD was considered, by some, as a relative contraindication to peritoneal dialysis (PD) as a kidney replacement modality. The basis of this thinking was that the enlarged kidneys, which would, for various reasons, impair the patient's ability to tolerate the intraperitoneal volume of PD fluids and associated complications.

In recent years, several studies have analyzed clinical outcomes, patient and technique survival, and other complications regarding ADPKD undergoing PD, with different results.

One of the earliest studies of ADPKD patients undergoing PD, which was a small retrospective trial, paired 26 ADPKD patients with 26 non-ADPKD contemporary controls, in which no significant difference was found in patient or technique survival between the two groups. The transfer reasons from PD to hemodialysis (HD) were not different between ADPKD patients and controls [3].

Several subsequent studies [4–8] regarding PD technique survival have demonstrated similar findings. A retrospective study with longer follow-up involving 56 ADPKD cases compared with 56 age- and sex-matched nondiabetic patients on PD revealed no significant difference in mortality, PD technique survival, or the number of patients switching to HD [8].

In a multicenter historical prospective matched-cohort, involving 106 ADPKD and 212 non-ADPKD patients, all ADPKD patients initiated PD during the study window, simultaneously 2 consecutive non-ADPKD paired on PD (1:2 enrollment ratio). Peritoneal dialysis in ADPKD patients was associated with lower mortality rate and similar overall rate of technique failure, compared with non-ADPKD patients. Despite this, most technique failures were directly related to ADPKD itself (such as nephrectomy and leakage) [6].

A larger study from the French PD registry analyzing 4162 incident ESKD (nondiabetic) and 344 ADPKD cases between 2002 and 2008 demonstrated baseline lower comorbidity scores and younger age in the ADPKD group. Significantly, similar patient and technique survival in both groups were shown [7, 9].

A meta-analysis in 2018 featured a combination of 12 cohorts, including 14,673 patients on PD (931 ADPKD and 13,742 non-ADPKD). In this study, ADPKD, as the cause of ESKD, found to have a lower mortality risk, when compared with other etiologies. The risk of technique failure and peritonitis were not significantly different between the two groups, but abdominal hernia risk was significantly higher, and dialysate leakage also occurred in the ADPKD group compared with the non-ADPKD group.

The finding of lower mortality in ADPKD patients on PD was unexpected and challenged the traditional view that PD should be avoided. The underlying explanation for this is not known for certain, but a few points should be noted. First, it should be pointed out that a few studies [4, 10, 11] have also shown survival benefits in ADPKD patients on HD compared with those with other causes of ESKD, especially if diabetes is excluded [11] because it has been viewed as a poor prognostic factor in PD patients [12, 13]. Second, ADPKD progresses to ESKD at a younger

age and with fewer comorbidities and a better functional status than those with other etiologies of ESKD, which are good prognostic factors [14, 15].

In the meta-analysis, the higher risk of abdominal hernia and dialysate leak, both resulting from increased abdominal pressure, presumably due to enlarged polycystic kidneys within the abdominal cavity, was significantly demonstrated. Notably, this did not translate to higher technique failure, suggesting that abdominal hernia and dialysate leak are readily treatable without the need of transferring to HD.

The ADPKD patients should be considered at increased risk for abdominal hernia and leak. The prescription should be geared to limiting the intraperitoneal volume and thus the intraperitoneal pressure. Consideration should be given to night cycler PD wherein the patient dialyzes in the supine position, with lower consequent intraperitoneal pressure. If there is sufficient residual kidney function, the patient could be empty of dialysis fluid during the day. If the patient needs a long day dwell for sufficient solute removal, consideration should be given to using a lower fill volume for the day dwell than that used for the overnight exchanges.

Peritonitis risk also did not differ between the ADPKD and non-ADPKD group despite a higher risk of diverticulitis [16] and cyst infection [17, 32] in ADPKD group, both of which are usually caused by enteric Gram-negative bacteria.

It is possible that the microbiological profile of ADPKD-related peritonitis may be distinct from peritonitis in non-ADPKD, so the overall peritonitis rate did not differ in the two groups. However, a study regarding long term outcome of ADPKD patient on PD [8] reported the microbiological culture results did not show significant differences in the incidence of Gram-negative infection in ADPKD compared with controls.

In closing, the preponderance of data supports that ADPKD patients can safely perform PD with equivalent outcomes to other patients on PD and also compared with patients on HD. Personalization of PD prescriptions may allow effective methods to reduce complications and to expand the use of PD in ADPKD patients.

Chronic Heart Failure

Managing severe heart failure (HF) in patients refractory to diuretic therapy is a major challenge. While HD is conventionally reserved for patients with ESKD, PD has long been proposed for management of congestive HF [18]. PD offers potential advantages over extracorporeal therapy (EC), including less neurohumoral activation, better preservation of residual kidney function, the possibility of daily therapy in a home setting, and tighter control of sodium balance [19–21].

In chronic dialysis patients, PD was associated with better preservation of residual kidney function, which was considered a factor contributing to longer survival [22, 23]. A prior systematic review evaluating the before and after effects of PD in patients with HF found that hospitalization days declined significantly, with a lower class by the New York Heart Association (NYHA) criteria and better left ventricular ejection fraction (LVEF) [24].

A meta-analysis evaluated the clinical outcomes of PD compared to EC therapy in HF. Through a comprehensive search strategy, data was retrieved from 31 studies, including the largest study presently [25].

All the four observational, non-randomized studies [25–29] compared PD against EC therapy (HD or UF), and there was no significant difference in the mortality rates with either modality. Interestingly, application of PD in HF showed effective symptom relief. Almost all studies reported an improvement in the symptom score, when measured by the NYHA grade, and positive effects on LVEF with most studies reporting an increase in EF, typically ranging between 2% and 31%.

Moreover, the benefit of PD was a significant reduction in hospitalization rate and length of stay [30, 31].

The technique of PD in HF was variable. It appears that the most common technique employed was intermittent PD with manual exchanges using dextrose-based solutions. PD prescription in this highly variable cohort with different cardiac and renal status was largely focused on achieving adequate UF for the individual patients.

Peritonitis was reported as the commonest complication with the rate ranging from 0.02 to 0.46 episodes per patient-year. This rate is similar to other ESKD patients on PD, which, according to the ISPD guidelines, should be no more than 0.5 episodes per year at risk [32].

The option of a home-based therapy with family/community support may be an attractive option to patients especially if it results in lower hospitalization rates and duration of hospitalization. For the purpose of HF, PD can be performed intermittently based on weight gain or symptoms, empowering the patient to provide self-care and improve his/her quality of life.

However, the level of evidence is still weak as only observational data are available. There is inadequate evidence comparing PD to EC therapy, but limited data suggest similar mortality rates for either form of therapy.

Liver Cirrhosis

The exact prevalence of combined ESKD and cirrhosis is unknown, but few studies have shown 4–6% ESKD patients have the comorbidity of cirrhosis [33, 34]. The combination of ESKD and cirrhosis represents difficult management scenarios due to unstable hemodynamics and fluid balance compounded by coagulopathy, malnutrition, and encephalopathy.

PD can be considered as an alternative therapy in cirrhotic patients undergoing HD [35, 36].

In general, hemodialysis is the most prevalent RRT modality in cirrhosis with ESKD. The potential problems with HD in cirrhotic patients have been well described as hemodynamic instability, coagulopathy, and meeting dialysis adequacy goals. Intradialytic hypotension occurs frequently in cirrhotic patients undergoing HD.

Several observational studies supported PD as a substitute for RRT in those with complications associated with HD [37–39].

Three out of five patients transferred to PD due to hemodynamic instability during HD treatments. All patients were reported to have good hemodynamic tolerance, and similar to the prior study, mortality was not related to PD, but driven by cirrhosis complications [36].

A retrospective study compared 21 cirrhotic PD and 41 control PD to analyze survival outcomes of PD patients with liver cirrhosis. The survival of 5 years and hospitalization rates were similar in cirrhotic PD and non-cirrhotic PD patients.

More recently, several studies analyzed survival outcomes from cirrhotic patients undergoing PD and HD. Two different data sets from different centers, with 340 HD patients and 85 PD and 1116 HD patients and 279 PD, respectively, were studied retrospectively. Statistical data from both these cohorts demonstrated lower all-cause mortality in cirrhotic patients undergoing PD compared with HD.

Patients with cirrhosis are at increased risk of infections for several reasons, including reduction in leukocyte phagocytosis and recruitment, altered complement activity, and abnormal function of the reticuloendothelial system [23]. These abnormalities contributing to the development of spontaneous bacterial peritonitis (SBP) is suspected to be secondary to the hematogenous spread of enteric organisms to the peritoneum or transmural migration crossing the bowel mucosa. So, concern may arise that cirrhotic patients on PD are at increased risk of peritonitis, due to the inherent risk of SBP, and catheter- and technique-related peritonitis. Additionally, another risk factor for infections is thought to be the lactate-buffered PD solutions [40].

A retrospective review of 21 cirrhotic and 41 controls on PD showed a trend to a lower rate (statistically not significant) of peritonitis in the cirrhotic group. Interestingly, this study showed Gram-positive bacteria as the most common causative agent while excluding SBP as an inciting event. Additionally, while SBP is a strong risk factor for the development of hepatic encephalopathy, none of the patients in this cohort developed that complication following peritonitis episodes [37].

With the concerns of peritonitis, a retrospective analysis compared peritonitis rates between cirrhotic ($n = 25$) and non-cirrhotic ($n = 36$) PD patients with hepatitis B virus infection. There was no difference in the peritonitis rates or peritonitis-free survival in the two groups [38]. Time to first peritonitis was also similar in the groups, as were the rates of Gram-positive and Gram-negative infections. Treatment response rate and outcomes did not differ either [38]. Oral antibiotic prophylaxis has been recommended in cirrhotic patients with ascites, to prevent development of spontaneous bacterial peritonitis [41].

Common complications with PD are secondary to poor tunnel maturation (early) and increased intra-abdominal pressure (late) and include internal and external leaks, umbilical and inguinal hernias, and catheter malposition. Thirty-three cirrhotic on PD were compared with 33 controls on PD. Not only was there no difference in the early technical complications amid the two groups, but overall complications and surgical interventions were also similar [15, 21].

Abdominal Surgeries and Abdominal Complications

Patients with abdominal surgeries or other abdominal complications are not considered good candidates for PD and that prevalent PD patients needing abdominal surgery are commonly switched to hemodialysis. However, some data show that, when appropriately planned, PD can still be an acceptable option for ESKD with certain abdominal complications, undergoing abdominal surgery, or in pregnancy, etc [42].

Diverticular Disease of the Colon

Clinicians might be reluctant to offer PD to patients with colonic diverticulosis, because of the theoretical increase in the risk of peritonitis [43, 44].

In 1990, Tranæus et al. [45] used barium enema to assess 129 patients at start of PD and suggested that the risk factors significant for the development of peritonitis included more than 10 diverticula; diverticula size exceeding 10 mm; and diverticula found in the ascending, transverse, or descending colon (but not in the sigmoid colon).

Yip et al. [46] evaluated 604 PD patients for diverticulosis by colonoscopy or barium enema. Of those patients, 24% were found to have diverticulosis, with the most common site being the ascending colon and the organism most frequently associated with peritonitis being *Escherichia coli*. The investigators concluded that the presence of diverticulosis was an independent risk factor for the development of enteric peritonitis.

In general, PD is safe for patients who have diverticulosis. Episodes of diverticulitis that cause inflammation of the bowel wall theoretically lead to higher risk of translocation of organisms across the bowel wall into the peritoneal cavity. It is unclear whether holding PD during an attack of diverticulitis lessens the risk of bacterial translocation, but holding PD could be considered in patients who have sufficient residual kidney function. A history of recurrent diverticulitis is a concern when considering PD as a possible kidney replacement therapy.

Abdominal Hernia

Abdominal hernia affects 12–37% of PD patients [47, 48].

In 2003, Balda et al. [49] assessed the effect of hernias in patients on PD and demonstrated that hernia recurrence rates were low without negatively affecting PD technique survival.

In 2011, Wakasugi et al. [50] retrospectively analyzed nine patients on continuous ambulatory peritoneal dialysis (CAPD) with abdominal hernias. All these

patients undergoing hernia repair did not switch to HD, which suggested the possibility that perioperative HD can be skipped.

Moreover, from the 6-year experience of Sodo et al. with repair of abdominal hernias and simultaneous placement of a PD catheter, hernia recurrence and peritonitis were not reported during a mean follow-up of 551 days with continued PD [51].

Thereafter, based on the clinical experience and literature reviews, Khoury et al. [52] recommended the following:

- Careful initial examination before placement of the PD catheter to rule out any type of hernia
- Periodic abdominal examination after insertion of the PD catheter
- Elective hernia repair before initiation of PD
- Bilateral hernia repair for any young male patient with an inguinal hernia on one side

Abdominal Surgery in PD

Hsu et al. [53] described five patients undergoing radical nephrectomy by the retroperitoneal approach, preserving the peritoneal membrane, which helped in the immediate initiation of PD after the surgery. The authors preferred the retroperitoneal approach to the transperitoneal approach to preserve the peritoneal membrane due to no significant complications during the wound healing or peritoneal leakage over the postoperative period.

Malavade and Bargman's study [54] showed wound dehiscence or other surgical complication didn't present on the patients with nephrectomy and later started dialysis within 1 year. But, the risk for incisional hernia and retroperitoneal PD fluid leak were high, postoperatively.

Other surgeries, such as bariatric surgery in the form of sleeve gastrectomy, were also described in a PD patient by Imam et al. [55], which showed the patient did very well both in surgery and PD treatment.

Plus, laparoscopic cholecystectomy in 11 PD patients with the same procedure in 33 patients not on PD demonstrated none of PD-encountered peritonitis, leaks, or hernias, as Ekici et al. [56] reported.

Favorable outcomes in PD patients with stomas were described by Korzets et al. [57] in 1992. And in 1998, Twardowski et al. [58] demonstrated with 6-year data that PD can still be applied in PD patients with abdominal complications just using pre-sternal PD catheters, which was also successfully used in children by Chadha et al. [59].

As suggested by the reports described above, PD can be performed safely in such scenarios. An assessment of abdominal surgeries, and the possible complications, including abdominal surgeries, in this patient population, with appropriate tailoring of the PD prescription, can allow these patients to remain on PD without compromising their quality of life or increasing their healthcare expense.

Pregnancy

Although those receiving peritoneal dialysis are at a high risk of encountering maternal and fetal complications, the occurrence of successful pregnancies in women with end-stage kidney disease undergoing PD is becoming more common. With developed dialysis technology, women in this population should be monitored by a dedicated team of renal physicians and an obstetric team to ensure the best maternal and fetal outcomes.

The first successful full-term pregnancy in an ESKD patient on HD was first reported in 1971 by Confortini et al. [60]. Subsequently, in 1983, the first sustained pregnancy on PD was reported in a patient who had been receiving the treatment for 2.5 years. Despite the many challenges faced by pregnant ESKD women, the rate of successful pregnancy and live birth has increased to approximately 30% from the 1990s [61, 62]. From the 54 reported cases of pregnant women receiving PD available in the literature since 1983, 47 cases (87%) have resulted in a successful pregnancy, but only 6 cases were full-term deliveries [63, 64].

Preliminary data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) showed that the live birth rate of HD patients on conception was approximately twice as likely as on PD patients [65].

In another large survey of pregnancy and ESKD from the United States, 1.1% of reproductive-aged women receiving PD conceived versus 2.4% on hemodialysis [66].

This lower conception rate in PD women has been postulated to be related to the presence of fluid in the abdominal cavity or inadequate dialysis intensity [65].

Interestingly, once conception was successful, infant survival was not significantly different between the hemodialysis and PD patients. It is also suggested that the outcome of pregnancy was better in women who conceived before starting dialysis than in women who conceived after starting dialysis [66].

The improved pregnancy outcomes are presumably related to amount of residual urine, conception during peri-initiation of the PD period, medication adjustment, tailoring PD prescription, blood pressure control, and correction of metabolic and nutrition profiles.

The goal of 2.2–2.6 for Kt/V in pregnant women on dialysis was suggested [66, 67]. But in the practical sense, most nephrologists would rather treat the patients clinically by monitoring blood parameters and adjusting the PD prescription as needed than following the Kt/V indicators. In the guideline published in 2015 [68], the authors do not recommend using Kt/V and/or peritoneal creatinine clearance as a measurement of dose of dialysis in pregnancy due to the lack of studies considering these markers in correlation to pregnancy outcomes.

Anemia should be managed with erythropoiesis-stimulating agents (ESAs) and vitamins [68]. The usual dose of ESA (Epogen) for a patient on PD is 50 U/kg twice weekly and should be frequently adjusted upward by 50–100% due to increasing body weight. Iron supplementation at a dose of 1–15 mg/day and folic acid 1 mg/day enhance the efficacy of ESA, and iron stores should be assessed before ESA is initiated. It is advisable that the hemoglobin levels be maintained at 10–11 g/dL, hematocrit at 30–35%, and serum ferritin of 200–300 μg/mL [68].

The patient's fluid status should be reviewed by the nephrologist and obstetrician closely. Ideally, a weekly or fortnightly ultrasound of the uterus should be carried out from the second trimester onward to assess the growth and weight of the fetus. Dry weight must be reviewed continuously because weight gain is expected to reach between 0.3 kg and 0.5 kg of weight per week during the second and third trimesters.

Blood pressure should be controlled with pregnancy-safe medications, such as long-acting nifedipine, labetalol, or methyldopa [69]. Management of hypertension in pregnancy to a tighter target is not associated with adverse neonatal effects or pregnancy outcomes, as the data from the Control of Hypertension in Pregnancy Study (CHIPS) has shown, which randomized women with diastolic blood pressure of 85 or 100 mmHg [70].

It should be pointed out that malnutrition is often caused by the lack of appetite experienced by pregnant women on PD due to the sugar load in dialysate and the delayed gastric emptying effect of dialysate inside the peritoneal cavity. It can also be caused by the hypercatabolic effect of pregnancy in ESKD and the decreased appetite induced by acidosis and urea levels. The recommendation for those PD patients who are at risk of protein depletion is 1.4–2.1 g per kg body weight/day of protein. In early pregnancy, water-soluble vitamins and minerals are essential, including folic acid. Other vitamins that should be supplemented are vitamin C, thiamine, riboflavin, niacin, and vitamin B6. And also the positive calcium balance should be retained with sufficient supplementation of calcium and vitamin D3 (Ref).

Several theoretical advantages are offered by PD to the pregnant patients: the continuous therapy avoids the fluid shifts and blood pressure variations, frequently seen in HD, and no heparin is required, which is thought to reduce bleeding complications. However, some complications specifically to PD have been reported in pregnancy including peritonitis and exit site infection. And also the complications, such as hemoperitoneum [71, 72], catheter malposition [73], catheter-related pain [74], and PD catheter-related uterine trauma, remain as concerns or challenges of PD therapy [72].

Conclusion

Peritoneal dialysis is a very effective, relatively inexpensive, and safe form of kidney replacement therapy. It is important to keep an open mind about the different subgroups of ESKD patients who can benefit from the therapy.

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Chapter 21
Survival Outcomes with Peritoneal Dialysis

Martin J. Schreiber Jr

Overview

Maybe Charles Darwin was correct when he suggested the following: *It is not the strongest of the species that survive, nor the most intelligent, but the ones most responsive to change*. Survival is the act of living through something life-threatening or adjusting to an unanticipated change in life. End-stage kidney disease (ESKD) is definitely a life-threatening change, yet the survival outcome any specific individual patient experiences can be quite variable, signifying the complexity of what determines "survival."

The survival outcomes statistics for patients with ESKD typically do not account for variations by country, study analytical design, provider and patient characteristics, and care delivery model. The issue of which dialysis modality leads to better survival is a complex one and likely depends on a myriad of patient-specific factors and practice patterns not fully captured in published reports of modality comparisons on "survival."

This chapter reviews the modality comparisons and the impact of study design on patient survival results, survival differences in specific subpopulations, multiple predictors of survival, infrastructure/processes, and approaches to discussing survival with ESKD patients.

Survival Outcomes in ESKD Versus the General Population

According to the US Renal Data System (USRDS) 2018 report [1], at every age, patients with ESKD on dialysis have significantly increased mortality when

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compared with nondialysis patients and individuals without kidney disease. At age 60 years, a healthy person can expect to live for more than 20 years, whereas the life expectancy of a patient aged 60 years who is starting hemodialysis (HD) is closer to 4 years. Among patients aged 65 years or older who have ESKD, mortality rates are six times higher than in the general population [2]. The 5-year survival rate for a patient undergoing long-term dialysis in the United States is approximately 35% and approximately 25% in patients with diabetes.

For ESKD patients, the highest mortality rate occurs within the first 6 months of initiating dialysis. Mortality then tends to improve over the next 6 months, before increasing gradually over the next 4 years [1]. It is interesting to note that the vulnerability of dialysis patients is still increasing due to the growing number of diabetics, elderly, and patients with a history of cardiovascular disease (CVD), and yet overall mortality rates continue to improve.

The crude mortality rate among all ESKD patients (dialysis and transplant) declined from 185.6 per 1000/year in 1996 to 137.2 per 1000/year in 2017, an absolute decrease of 48.4 per 1000/year [3]. In 2017, the dialysis modality mortality rates were 167 for HD patients and 156 for peritoneal dialysis (PD) patients per 1000 patient-years; by comparison, the mortality rates were 172 for HD patients and 152 for PD patients, per 1000 patient-years in 2013 [4]. The USRDS data demonstrates that the net reduction in adjusted mortality from 2001 to 2017 was 27% for HD patients and 42% for PD patients. Overall, mortality rates among ESKD (dialysis and transplant) patients have consistently declined over the last 16 years, with rates leveling during recent years.

In 2012, Nordio et al. [5] reviewed survival comparisons in patients treated by long-term dialysis in the Italian Dialysis and Transplantation Registry versus the general population in order to determine the prognosis of dialysis patients. The study used the relative survival method to estimate the decrease in survival directly due to dialysis therapy in 27,642 patients; 22,756 (82.3%) patients were treated with HD only and 3265 (11.8%) with PD only. Five-year observed and expected survivals were 47.4% and 85.0%, respectively, yielding a relative survival estimate of 55.6% versus the general population. In other words, survival was 44.4% less than expected for the general population. Older age, systemic diseases, and diabetes showed the strongest association with excess mortality. PD was associated with a lower relative excess risk in only the first year of treatment.

Analyses of differences in outcomes over time and across geographic regions are powerful tools we can apply to gain an understanding of the impact of changes or variations in practices on survival. They should provide a framework for future studies that are needed to examine which changes in practice patterns and clinical care may contribute to changes in mortality rates in patients with ESKD [6].

Decreases in excess mortality over time have been observed for patients of all ages, both during treatment with dialysis and during time with a functioning kidney transplant. In general, absolute decreases in excess ESKD-related mortality were greatest for the oldest patients. All age groups have demonstrated significant improvements in mortality risk over the past 22 years [7]. Understanding the role

that the dialysis modality plays in overall patient survival is key to designing those practice changes and care improvements necessary to advancing survival in our dialysis patients.

Survival Outcomes Between Dialysis Modalities

As illustrated in Table 21.1, a number of studies have been published over the past 30 years that examined patient survival comparing in-center hemodialysis (ICHD) versus PD. Data on important factors known to be associated with survival in patients undergoing maintenance dialysis (MD), such as race, residual kidney function (RKF), serum albumin, body mass index (BMI), and pre-dialysis nephrology care, are not always available or included for risk adjustment in many of these studies. Also, there are likely country-level differences in practices, physician views of modality comparisons, patient candidacy for both therapies, and fundamental differences in the patient selection processes between therapies that could potentially account for some of the variability in reported outcomes.

Statistical Study Design

Both observational studies and randomized controlled trials (RCTs) fulfill a complementary and valuable role in nephrology, although the RCT is seen as a gold standard. As such, the ideal tool for dialysis modality comparisons would be RCT design, yet prior attempts at RCTs have been complicated by lack of statistical power and inadequate recruitment [8, 9]. Thus, retrospective observational trials have been utilized to examine mortality risks associated with dialysis modalities [10, 11]. However, observational studies possess residual confounding that arises from imbalances between compared treatment approaches. For example, by censoring at 90 days, the USRDS includes only patients that survive 90 days on a modality; this discounts the importance of early deaths on treatment. In addition, comorbidity reporting on the Center for Medicare and Medicaid Services (CMS) Medical Evidence Form (2728 Form) fails to capture pertinent clinical information.

Some reports have grouped patients by age, presence or absence of diabetes, comorbidity index, vintage on dialysis, and other factors to decrease selection bias on modality comparison of outcomes and thus decrease biased conclusions.

Addressing these analytical design concerns has fostered an increase in propensity-matched studies. Propensity score matching (PSM) confers additional advantages over alternative designs by reducing selection bias between therapies. The propensity score allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the characteristics of a RCT [12].

Table 21.1 Characteristics of modality comparison (peritoneal dialysis and hemodialysis) in select studies, 1995–2020

Year of publication	Author	Data source	Years of study	Statistical methods	Number of patients studied	Survival comments
1995	Bloembergen [13]	US Renal Data System (USRDS)	1987–1989	Poisson regression; 3 national cohorts of prevalent patients on CAPD	170,700 patient-years at risk	19% higher mortality PD vs HD (relative risk [RR] = 1.19). Risk was found to be insignificant ($P > 0.05$) < 55 years old; significantly higher >55 years and > in diabetics. RR of PD/HD < 1 year 1.1 vs > 1 year 1.21
1999	Collins [105]	USRDS	1994–1996	As-treated Cox regression	HD: 99,048 PD: 18,110	PD equal or lower risk of death vs HD except for diabetics older than 55 years
2002	Keshaviah [106]	HD: Regional Kidney Disease Program (RKDP) PD: CANUSA	HD: 1987–1995 PD: 1990–1993	Match dose comparison, Cox proportional hazards model	HD:968 PD:680	Kt/V less effect on patients <45 years than >45 years (especially diabetes, CAD); 2-year outcomes similar HD: PD if Kt/V controlled. A 1-unit increase in Kt/V associated with 8% lower risk of death while on CAPD. Controlling for dialysis dose PD = HD independent of age, diabetes, history of CVD
2003	Ganesh [45]	USRDS and CMS Medical Evidence Form	1995–1997	Non-proportional Cox regression model, intent-to-treat (ITT), as-treated	HD: 93,900 PD: 14,022	In both diabetic and nondiabetic patients with CAD, those treated with PD had significantly poorer survival compared with HD (ITT RR: 1.20, 1.23). Among diabetics, patients with CAD treated with PD had a 23% higher RR of death

2004	Vonesh [107]	USRDS	1994–1996	Proportional and non-proportional hazards regression	HD: 35,906 PD: 46,234	HD was associated with an increased risk of death in 30% of the ESRD population comprised of nondiabetic and younger diabetic patients with no reported baseline comorbidities. PD was associated with an increased risk of death in 40% of the population comprised of diabetic patients aged ≥45 years; 3 key factors that influence the RR of death between HD and PD identified: cause of ESRD (diabetes vs. nondiabetic), age (18–44, 45–64, ≥65 years), and baseline level of comorbidity (none vs. ≥ 1 comorbidity)
2005	Jaar [108]	81 dialysis clinics associated with Dialysis Clinic, Inc., Nashville, TN (923 pts), and New Haven CAPD (86 pts) or St. Raphael's Hospital, New Haven, CT	1995–1998	Analysis of variance for continuous variables; Pearson chi-square test for categorical variables	HD: 767 PD: 274	Risk for death PD = HD during the first year (relative hazard, 1.39 [95% confidence interval or CI, 0.64–3.06]); risk became significantly higher among those undergoing PD in the second year (relative hazard, 2.34 [CI, 1.19–4.59])
2009	McDonald [109]	Australia and New Zealand Dialysis and Transplant Registry	1991–2005	Univariate analysis, multivariate. Co-variables: logistic regression models used covariates	HD: 14,753 PD: 10,554	Treatment with PD may be advantageous initially; associated with higher mortality after 12 months. The effect of dialysis modality on survival for an individual depends on time, age, and presence of comorbidities

(continued)

Table 21.1 (continued)

Year of publication	Author	Data source	Years of study	Statistical methods	Number of patients studied	Survival comments
2011	Mehrotra [110]	USRDS	1996–1998, 1999–2002, 2002–2004	Non-proportional hazards models using a piecewise exponential survival model; marginal structural model with inverse probability of treatment and censoring weighting (IPTCW)	HD: 620,020 PD: 64,406	No significant difference in the risk for death between those treated with HD or PD through 5 years in 2002–2004; diabetic patients who started dialysis between 1996 and 2001 and were treated with PD had a significantly higher risk for death irrespective of age or additional comorbidity. In the cohort from 2002–2004 diabetic patients >65 years old continued to have a greater risk for death
2012	Yeates [111]	Canadian Organ Replacement Register (COOR)	1991–2007	Cox proportional hazards (PH) model; intent-to-treat; PH and non-PH models	HD: 32,521 PD: 14,308	Cohort of 2001–2004, patients receiving PD were associated with significantly better survival during the first 2 years of dialysis; long-term survival (3–5 years) was similar for PD and HD patients
2013	Lukowsky [112]	USRDS and DaVita Inc. (LDO)	2001–2004	Inverse probability of treatment-weighted marginal structural model (MSM)	HD: 22,360 PD: 1358	Comparing two modalities over the first 2 years of dialysis treatment, PD patients had a persistently 48% lower death risk after adjustment for known confounders, including dialysis modality switch or transplant censorship vs. HD
2014	Heaf [113]	Danish Nephrology Registry (DNR)	1990–2010	Cox proportional hazards; variance estimations	HD: 8273 PD: 3822	Overall adjusted prognosis improved by 34% (HD 30%, PD 42%) during time period of study (16% > survival in PD vs HD); PD prognosis improved consistently from 1990–1999 to 2000–2010 in all subgroups (0.95 to 0.80); PD prognosis was better than HD for the first 4 years, after which it was insignificantly worse

2014	Kumar [16]	Kaiser Permanente Southern California (KPSC) ESKD registry; integrated healthcare organization	2001–2013	Stratified Cox proportional hazards model: propensity matched (as-treated, ITT); cumulative hazard ratio (CHR)	HD: 1003 PD: 1003 (matched pairs)	Cumulative risk of death favored PD vs HD (CHR: 1.39) for up to 3 years (as-treated), 2 years (inten-to-treat) (CHR 1.26); increase death risk for HD not attributed to CVC or lack of pre-dialysis care. The 3–9-year survival was not significantly different
2015	Han [32]	Korean Health Insurance dataset	2005–2010	Multivariate Cox model stratified by confounding factors; Korean dataset and systematic meta-analysis of 15 studies for comparison	HD: 10,675 PD: 2390 (age ≥ 65 years; mean, 72.2 years)	In the first year, the survival rate in the PD group appeared to be commensurate with that in the HD group; after 1 year, however, the survival rate in the PD group seemed to be lower than that in the HD group; differences more prominent: diabetes mellitus or longer dialysis duration
2015	Waldum-Grevbo [114]	Norwegian Renal Registry	2005–2012	Cox proportional hazards model (propensity-matched analysis)	HD: 209 PD: 200	Initial dialysis modality did not impact 2-year (PD vs. HD: HR = 0.87; 95% CI, 0.67–1.12) or 5-year all-cause mortality (HR = 0.95; 95% CI, 0.77–1.17): patients <65 years, PD was superior compared to HD with regard to both 2-year (HR = 0.39; 95% CI, 0.19–0.81) and 5-year all-cause mortality (HR = 0.49; 95% CI, 0.27–0.89)

(continued)

Table 21.1 (continued)

Year of publication	Author	Data source	Years of study	Statistical methods	Number of patients studied	Survival comments
2016	Wang [115]	National Health Insurance (NHI) claims	1997–2001 2002–2006 2007–2011	One-way analysis of variance (ANOVA); cox proportional hazards regression	PD: 6904 (3 time frames)	Comparable survival PD vs. HD; 5 year survival rates from 1997–2011: 77.99% to 78.89%; PD with higher comorbidities and older. Diabetes with higher risk. Using icodextrin and APD associated with lower mortality (45% and 19%) in diabetics
2016	van de Luijtgaarden [116]	European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry	20-year study period (1993–2012, 1993–1997, 1998–2002, 2003–2007, 2008–2012)	Cumulative Incidence Competing Risks method ; Multivariable Cox regression models; propensity score matching (PSM)	HD: 158,010 PD: 38,060	Improved survival outcomes on PD compared with HD in recent years (2006 vs. 2009); propensity-matched cohort demonstrated survival advantage for PD pts. vs pts. who started treatment with HD (HR:0.80); elderly patients and diabetes mellitus as cause of ESKD: no differences in survival. Five-year survival PD vs HD, advancing 3 time-based cohorts; covariate adjustment, HR 1.2 to HR 0.91 (all patients); PSM, HR 1.02 to 0.88
2018	Wang [25]	Taiwan National Health Insurance Program database	2005–2010	Chi-square and Mann-Whitney U tests; propensity score (PS) data adjustment	HD: 46,268 PD: 6835	Overall mortality rates were lower in PD patients with or without icodextrin treatment than in HD patients (82.4 and 79.1 vs. 132.2 per 1000 person-years; among elderly PD patients, the mortality risk was lower in icodextrin users than non-users with an adjusted subhazard ratio (SHR) of 0.74 (95% CI, 0.64–0.85). Among diabetic PD patients, icodextrin users had a lower mortality rate than non-users (adjusted SHR = 0.83, 95% CI, 0.72–0.97)

2018	Wong [15]	Dialysis Measurement Analysis and Reporting (DMAR)	2004–2013	Cox regression adjusted for covariates	HD: 465 PD: 409 (eligible outpatient cohort)	Morality incidence from 31.37% to 50.02% with advancing time frames. HD and PD associated with similar survival in incident dialysis patients regardless of age. The impact of modality on survival did not vary over time
2018	Thiery [117]	Renal Epidemiology and Information Network (REIN)	2006–2008	Proportional hazards model; propensity scoring combined selection methods, marginal structures model (MSM)	HD: 12,019 PD: 1748	Planned HD vs PD: survival-favored HD. Follow-up at 5 years; median survival HD, 4.45 years; PD, 3.21 years. Patient enrollment excluded emergency/ urgent start patients (1/3 of registry pts)
2020	Elsayed [17]	11 studies: North America, Asia, Europe	2010–2018	Systemic review (PRISMA); random effects meta-analysis; propensity-based scoring strategy	114,608 PD/HD pts.: matched propensity scores	PD and HD carry equivalent survival differences unrelated to clinical efficiency; differences in survival due to combination of factors including clinical practices and evolving clinical trends

Dialysis Modality Comparisons

Over time, and after innumerable published reports on dialysis modality survival, the overall survival of incident patients treated with either PD or HD is equivocal with reported differences in survival primarily reflecting differences in clinical practices within health systems and evolving clinical trends.

However, several studies deserve further review from a historical perspective. Concerns over the outcomes of patients receiving PD were raised in an influential study by Bloembergen et al. [13] who examined the USRDS database published in 1995. The authors noted a 19% overall higher mortality for patients with ESKD treated with PD compared with HD, and for years thereafter, the debate raged positioning the impact of one modality against the other on patient survival. Vonesh et al. [14] in 2006 noted that overall patient survival was similar for PD and HD but that important differences do exist within select subgroups of patients, particularly those subgroups defined by age and the presence or absence of diabetes. Also, Wong et al. [15] demonstrated that HD and PD are associated with similar mortality among incident dialysis patients who are eligible for both modalities.

The study by Kumar et al. [16] merits special mention, because she used a propensity-matched design to monitor a defined cohort of 1003 matched pairs of patients receiving either incident HD or PD in a certain US geographic area (Southern California). The authors observed the cumulative risk of death was more than twofold higher over the course of the first year on dialysis among matched incident HD patients compared with incident PD patients in both the adjusted time-dependent, as-treated, and intent-to-treat analyses. Specifically, PD was associated with a survival advantage for up to 3 years in the as-treated analysis with no significant difference in adjusted survival thereafter and for up to 2 years in the intent-to-treat analysis with no difference in adjusted survival thereafter. Seemingly, consistent practice approaches to ESKD care, in an integrated care model, leveraging best demonstrated practice approaches could have impacted outcome results.

More recently, Elsayed et al. [17] conducted a systematic review of meta-analysis studies used to exam mortality differences between ICHD and PD. Published reports meeting the review criteria from 1993 to 2014 were evaluated. There were 214 citations with 17 cohort studies and 113,578 PSM incident dialysis patients. Based on results of the review, the authors concluded that PD and ICHD carry equivalent survival benefits, and the reported differences in survival between treatments largely reflect a combination of factors that are unrelated to clinical efficacy. This analysis uncovered significant mortality differences between HD and PD that varied by region, over time, and according to the study design. Taken together, these new findings would suggest that while the overall survival of incident patients treated with either PD or HD is similar, reported differences in survival primarily reflect differences in clinical practices within health systems and evolving clinical trends.

As we look back over the numerous papers that have compared the survival of patients on ICHD or PD coupled with the lack of a RCT and the varied study designs on validity of study conclusions, the focus should be shifting to a new approach in

dialysis assignment. Assessing the most appropriate therapy for specific subpopulations and understanding those determinants that guide therapy selection and impact patient outcome (including quality of life) should now guide the treatment decisions of incident patients and assist in identifying the transition point for modality transfer as needed for prevalent patients.

PD Survival Outcomes in Special Populations

Diabetes

Diabetic patients on dialysis have a 1.3-fold higher mortality rate relative to other primary kidney diseases; specifically examining life expectancy for patients on PD, the 5-year adjusted survival rate was only 38%, according to the USRDS report [18]. A Taiwanese cohort study [19] of 51,000 incident dialysis patients demonstrated that pre-existing diabetes was associated with an 80% increased risk of all-cause mortality (hazard ratio [HR] = 1.81).

Lee et al. [20] analyzed outcomes data from a nationwide prospective cohort in Korea of 902 patients with diabetes who started dialysis between August 2008 and December 2013; during a median follow-up period of 28 months, the relative risk of death was lower in PD compared to HD in the whole cohort. While there was no difference in survival rates in the cohort of poor glycemic control (hemoglobin A1c [HbA1c] $\geq$ 8.0%), there was a significant survival advantage of PD.

Several years later, Abe et al. [21] analyzed data from 8954 prevalent PD patients for 2 years, 2014–2015. A Cox proportional hazards regression analysis was used to determine factors that were independently associated with patient survival. After multivariate adjustment, older age, longer duration of dialysis, presence of diabetes, cardiovascular (CV) comorbidity, use of 2.5% glucose dialysate, higher C-reactive protein and phosphate levels, and a lower serum albumin level were independently associated with increased HRs for all-cause mortality. The CV event rate was significantly higher in the diabetes group than in the nondiabetes group (15.9% vs 8.7%; $P < 0.0001$). Diabetes, older age, longer duration of dialysis, CV comorbidity, and inflammation were predictors of mortality in patients on PD.

Couchoud et al. [22] conducted a systematic review of 25 observational studies, and based on the available information, there was no evidence in favor of one dialysis modality over another. However, the authors did note that differences between studies could be explained by selection bias and country-and center-specific differences in PD and HD practices.

In several additional studies, examining patient survival rates, both good glycemic control [23, 24] and the use of icodextrin dialysate solution, improved patient survival [25]. Poor glycemic control is a consistent predictor of subsequent risk of catheter tunnel and exit-site infection, but not of peritoneal infection, among diabetic patients starting PD therapy [26]. In addition, the presence of baseline diabetic

complications and a high comorbidity burden at the start of dialysis contribute to individual patient outcomes.

Previous studies [27] focused on long-term PD survival, up to 10 years, have reported that the most important characteristics of patients surviving on long-term PD were patients' age, pre-dialysis comorbidity, prolonged RKF, maintenance of adequate nutrition, low solute transport rates, and low rates of peritonitis. While diabetes is an important contributing comorbidity, a number of other factors warrant attention to optimize long-term patient survival.

Considering results from a number of studies and the working groups of the International Society for Peritoneal Dialysis (ISPD) [28], the suggested diabetic recommendations indicate that a glycosylated hemoglobin be measured at least once every 3 months in diabetic PD patients to assess glycemic control. The glycosylated hemoglobin should be targeted around 7% (53 mmol/L) in PD patients with diabetes and may be up to 8.5% (69 mmol/L) in older diabetic PD patients. A once-daily icodextrin exchange should be considered as the long-dwell dialysis solution in diabetic PD patients for better glycemic control.

Elderly Patients

There is currently no general consensus as to the best dialysis modality for the elderly patient with ESKD. As noted by Brown et al. [29] as a population, older dialysis patients may present later for dialysis, have a greater number of comorbid conditions, are at greater risk of cognitive dysfunction, and have increased levels of frailty and potential sensory impairment. Clinically, frailty presents as a composite of poor physical function, exhaustion, low physical activity, and weight loss and is associated with an increased risk of falls.

Bieber and Mehrotra [30] in a review of a large number of observational studies comparing the risk of death for older adults on PD or HD reported the results were variable with a number of characteristics believed to account for the differences. However, in the absence of existing diabetes, there did not appear to be a difference in death in older patients treated with PD or HD.

Comparison of outcomes in the elderly ESKD population, for the most part, relies on observational studies; however, most suggest that survival rates are similar, except for either elderly patients [31] with diabetes or long duration of time on dialysis (longer than 1–3 years), wherein HD appears superior [32]. And yet from a quality-of-life perspective, there appeared no significant difference between HD and PD. In essence, the dialysis modality selection in the elderly should be guided by the patient preference, unbiased information, and shared decision-making with the primary nephrologist considering the patient's therapeutic goals [33].

Staff-assisted PD may play a role in the elderly patient faced with ESKD management decisions. Smyth et al. [34] analyzed data on 148 patients with a mean age of 63 years and with 22 patients on staff-assisted PD. There was no difference in

patient survival (mean, 29.8 months) by age group or whether they were on independent PD vs staff-assisted PD.

Obesity

The association between obesity and mortality in the PD population was evaluated in the Netherlands Cooperative Study on the Adequacy of Dialysis 2 (NECOSAD) cohort [35]; study findings noted that PD patients who are obese at the start of dialysis do not have a worse survival compared with PD patients with a normal BMI. Conversely, PD patients with a low BMI during dialysis have a twofold increased mortality risk. An additional study also noted that lower BMI, lower muscle mass, weight loss, and serum creatinine decline were associated with higher death rates [36].

In 2004, Stack et al. [37] showed a heightened risk of death among PD patients with BMI $\geq$ 23.5 kg/m^2 (versus HD patients in the same BMI categories), while comparable survival was observed among those with lower BMI.

Obi et al. [38] noted that obese patients started with higher levels of RRF but had faster declines in RRF and consistently achieved lower *total* dialysis small solute clearance (Kt/V) (renal Kt/V plus dialysis Kt/V) over time despite greater increases in dialysis Kt/V. Compared with matched HD patients, PD patients had lower mortality in the BMI categories of <25 kg/m^2 and 25 to <35 kg/m^2 and had equivalent survival in the BMI category $\geq$35 kg/m^2 (P for interaction = 0.001 [vs < 25 kg/m^2]).

Failed Kidney Transplant

There is limited information about the outcomes of patients commencing PD after failed kidney transplantation. In a retrospective study [39], 328 patients registered in the French Language Peritoneal Dialysis Registry (RDPLF) who started PD after kidney transplant failure (treatment group) between January 2002 and December 2012 were compared with 656 matched never-transplanted patients having started PD during the same period (control group). Patient and PD technique survival and peritonitis episodes were analyzed. Over the observation period, patients' survival was similar between the two groups (treatment, 17 months; control, 21 months; $P = 0.34$).

Badve et al. [40] analyzed data on all patients from the ANZDATA Registry, who started PD between April 1, 1991, and March 31, 2004, and entered PD due to a failed kidney transplant (FTx) vs non-failed transplant patient source (NFTx) (13,638 NFTx vs 309 FTx). On multivariate analysis, PD patients with FTx had comparable patient mortality (weighted HR, 1.09), death-censored technique failure (adjusted HR, 0.91), and peritonitis-free survival (adjusted HR, 0.92) with those

PD patients who had failed native kidneys; the patients in the FTx group had mortality comparable with those in the NFTx group (weighted HR, 1.09).

Organ-/Disease-Specific Predictive Factors

Cardiovascular Disease

The most common cause of death in the overall dialysis population, whether PD or HD, is CVD; CV mortality is 10–20 times higher in dialysis patients than in the general population. New patients at ESKD onset have a disproportionate burden of coronary disease (CAD) [41]. Young adults (ages 22–29 years) have risks for ESKD-associated CVD that may vary from other ages [42]. Assessing the coronary structural and functional status at the start of dialysis is in many cases incomplete whether at the point of initiating dialysis or after dialysis initiation. The ISPD enacted a global work group to evaluate and provide recommendations to improve CV outcomes for PD patients in published reports, Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients Part I and Part II: Management of Various Cardiovascular Complications [28, 43]. Understanding the impact of CAD vs non-CAD, congestive heart failure (CHF), hypertension, and overhydration on the dialysis modality survival outcomes over time are critically important.

Coronary Artery Disease

The incidence, severity, and mortality of CAD is higher in dialysis patients than in the general population. The current practice approach to dialysis and CAD is informed by observational data with a significant potential for bias [44]. In 2003, Ganesh et al. [45] conducted a historical prospective cohort study of 11,000 incident ESKD patients with and without CAD from 1995–1997; the data utilized for this analysis came from the CMS 2728 Form. Both diabetic patients and nondiabetic patients with CAD experienced higher mortality on PD compared with HD (36.1% vs 33.7%). In contrast, nondiabetic patients without CAD had similar survival on PD or HD.

As summarized in the USRDS 2018 report [1], ESKD patients have lower survival when CVD conditions are present; PD patients had a lower burden of CAD, heart failure, and peripheral arterial disease, as compared with their HD counterparts (57.7% vs 70.6%). However, a higher percentage of PD patients had revascularization procedures vs ICHD patients overall. In a nationwide, Taiwanese population-based cohort study [46], with a long follow-up period of 13 years, HD patients (n = 1404) had a higher independently associated, de novo CAD risk in comparison with the PD patients (n = 220) regardless of their gender, age, and diabetes status. Targeting modifiable CVD risk factors (traditional and kidney disease related) should be employed to improve CVD outcomes in PD patients [47].

Arrhythmias

Clinically significant arrhythmias are common in HD patients to a greater degree than in those on PD. Bradycardia and asystole rather than ventricular tachycardia may be key causes of sudden death in HD patients. Associations with the temporal pattern of dialysis suggest that modification of current dialysis practices could reduce the incidence of sudden death [48]. For patients on PD, the risk factors for the occurrence of ventricular arrhythmias (VAs) in continuous ambulatory peritoneal dialysis (CAPD) were examined in 47 patients by echocardiography, dipyridamole-thallium tests, and biochemical profile; the group with VA had a greater cardiac mass index dependent only on an increased left ventricular internal diameter [49].

For comparison with the non-uremic population with end-stage heart failure due to dilated cardiomyopathy, independent predictors of prognosis include intravenous inotropic requirement ($P < 0.001$), maximal, tolerated captopril dose ($P = 0.013$), and systolic blood pressure ($p = 0.003$) [50]. In ambulatory patients with stable NYHA class III heart failure, the severity of VAs using the Lown classification, exercise tolerance, and left ventricular ejection fraction are important determinants of survival [51].

Congestive Heart Failure

Heart failure is associated with significant increases in morbidity and mortality in dialysis patients; approximately 15%–28% of patients being dialyzed have been diagnosed with CHF [52]. Ejection fraction can be normal in ESKD until late in the disease course [53]. A differential injury compromising ventricular function through cardiac ischemic stunning can occur on HD without evidence on PD [54]. Dialysis type has been reported to preserve longitudinal and radial left ventricular mechanics; left ventricular systolic function has been reported to deteriorate earlier in HD patients when compared with PD [55], as monitored by the use of speckled tracking [56]. Both low systolic blood pressure (BP) and alterations in pulse pressure (PP) have been described as risk factors for mortality in patients with CHF on dialysis [57]. Lertdumrongluk et al. [58] observed a U-shaped association between change in pulse pressure during HD and all-cause mortality with large declines or rises in pulse pressure associated with higher mortality. In a study of 306 patients on PD [57], elevated pulse pressure was associated with an increased risk of all-cause and cardiovascular death; the study demonstrated that for each increment of 1 mmHg in pulse pressure, there was a 2.7% increased hazard of all-cause death [95% confidence interval (CI) 1.001–1.054, $P = 0.039$] and a 4.1% increase in risk for cardiovascular mortality (HR, 1.041). Additionally, in PD patients with CHF, low BP has been associated with significantly greater mortality risk (HR, 3.13) for systolic BP $\leq$ 100 mmHg vs patients with systolic BP 111–120 mmHg [59].

A study by Sens et al. [60] from the French Renal Epidemiology and Information Network (REIN) Registry found that the risk of mortality was elevated in patients

with ESKD and CHF who received PD compared with those who received HD. Median survival time was 20.4 months in patients receiving PD versus 36.7 months in the HD group. Patients in the PD treatment group were older and had higher rates of New York Heart Association (NYHA) stage III–IV classification than in the HD group. In assessing prior reports, selection bias and unmeasured confounding bias may distort the true mortality risk associated with PD and HD.

Blood Pressure Abnormalities and Variability

Abnormalities in BP levels (low systolic BP [<100 mmHg], pulse BP) are associated with all-cause and CV mortality and duration of hospitalization, especially in patients with a history of CHF and diabetes and those treated with antihypertensive medications on PD. Uncontrolled BP is correlated with an increase in left ventricular hypertrophy (LVH), left ventricular mass index [61], and cardiothoracic ratio (CTR).

Jang et al. [62] noted that PD is no better than HD with regard to overall BP control; the same is true for frequency of BP fluctuations over time [63]. Additionally, a narrow PP below 40 mmHg was associated with increased mortality when compared to PP > 60 mmHg. As demonstrated by a Turkish study [64], remote monitoring of automated PD patients may provide better control of peripheral BP and decrease of central hemodynamic parameters via controlling excess body water.

Hydration Levels: Over- or Underhydration

Volume control is a modifiable risk factor. Both volume and sodium overload, often aggravated by loss of RKF and ultrafiltration failure (UF), are the predominant mechanisms underpinning hypertension in PD patients [47]. Overhydration contributes to this risk of death as it is associated with hypertension, increased left ventricular mass, and reduced arterial dispensability. And yet, overly aggressive treatment of blood pressure (<110 mmHg systolic BP) and volume status in PD patients should be cautioned against due to the potential negative impact of low blood pressure on hastening the decline and loss of residual kidney function [65].

Bioimpedance analysis (BIA) [66, 67] has been utilized in many PD programs to evaluate volume and nutrition status, and the results have been shown to predict survival. More recently, a portable whole body bioimpedance spectroscopy device (or body composition monitor [BCM]) has been employed to measure volume status in PD patients [68]. The BCM measures the impedance spectroscopy at 50 different frequencies between 5 kHz and 1 MHz.

Peritonitis

Peritonitis and the frequency of peritonitis has been independently associated with higher risk of all-cause, CV, and infection-related mortality in PD patients, and its impact on mortality is more significant in patients with longer PD duration. The

impact of peritonitis on late CV mortality of PD patients suggests a link between acute inflammation and CV outcomes.

Ye et al. [69] studied 1321 patients. After adjusting for confounders, peritonitis was independently associated with 95% increased risk of all-cause mortality (HR, 1.95), increased risk of CV mortality (HR, 1.90), and near fourfold increased risk of infection-related mortality (HR, 4.94). Further analyses showed that peritonitis strongly influenced mortality in patients who dialyzed longer than 2 years.

An analysis of 2405 episodes of peritonitis in 5707 patients (48% males, 44% diabetes, 73% hypertensive) from the Brazilian PD (BRAZPD) II cohort study noted that patients with one episode of peritonitis presented a 22% increase in the HR of late CV mortality compared to those who never experienced peritonitis (HR, 1.22) [70]. Adjusted hazard for CV mortality showed a stepwise negative effect on survival for each additional peritonitis episode of infection: two episodes (HR, 1.78), three episodes (HR, 2.81), and four episodes (HR, 3.84).

Residual Kidney Function (RKF)

The contribution of RKF cannot be overstated as an independent predictor of survival in patients on dialysis [71]; each glomerular filtration rate increase of 5 L/week/1.73 m^2 resulted in a 12% mortality reduction independent of dialysis clearance in a previous cohort study [72]. Preservation of RKF is associated with improved survival in both HD and PD [73, 74]. Several studies [75, 76] have demonstrated that there is a differential advantage for RKF preservation for patients on PD when compared to HD-treated patients. In a study of 1032 PD patients compared to 811 HD patients from the Dialysis Morbidity and Mortality Study (DMMS), PD had a 65% lower risk of RKF loss than those treated with HD, and patients on HD were three times more likely to have lost RKF as PD patients. Marants et al. [77] uncovered the pathophysiologic mechanism for RKF loss, by directly measuring intradialytic renal perfusion, and confirmed that the decrease in renal perfusion represents the first key step toward characterizing RKF loss in patients on HD due to "kidney stunning." Preserving RKF is vital, and loss in RKF contributes to inflammation, anemia, malnutrition, LVH, volume overload, hypertension, and CVD and interacts with these factors to increase morbidity and mortality.

Htay et al. [78] reported on a secondary analysis of data from the *bal*ANZ trial, performed in 15 centers in Australia, New Zealand, and Singapore, to identify independent predictors of RKF and urine volume (UV) in 161 incident PD patients observed for 19.5 ± 6.6 months. RKF declined from 7.5 ± 2.9 mL/min/1.73 m^2 at baseline to 3.3 ± 2.8 mL/min/1.73 m^2 at 24 months. Common modifiable risk factors consistently associated with preserved RKF and residual UV were use of biocompatible PD solutions (which themselves are associated with diminished ultrafiltration) and achievement of higher systolic BP, lower peritoneal UF, and lower dialysate glucose exposure over time. Several reports have also highlighted the relation between RKF and left ventricular structure [79] and different functional performance [80].

A retrospective cohort study [81] evaluated whether the RKF decline over time, in addition to baseline RKF, increased risk of mortality and anuria in 581 PD patients. Rapid RKF decline (≥ 0.09 decline) over a 12-month period was associated with a 2.6-fold increase in the risk of death (HR, 2.60) and a twofold increase in anuria (HR, 2.06). Each quartile of increasing severity of RKF decline over a 12-month period increased risk incrementally for death. The impact on mortality and RKF preservation was particularly severe for those with diabetes mellitus.

Highlighting the potential for considering PD as a "preservation technique," He et al. [82] noted that initiating PD was associated with a slower rate of RKF decline compared to the rate in the pre-dialysis period as reported by individual glomerular filtration rates (GFR) for approximately 12 months before and after PD in 77 new Chinese PD patients.

Hypokalemia

An increased incidence of hypokalemia can contribute to overall cardiac risk for death in PD patients. The incidence of hypokalemia was analyzed by Torlen et al. [83] in 10,468 PD patients and 111,651 HD patients treated by a large dialysis organization. PD patients have a greater likelihood of developing hypokalemia (serum potassium <4 mmol/L). There was a U-shaped relationship between time-averaged serum potassium and all-cause and CV mortality of PD patients, with adjusted HRs of 1.51 for all-cause mortality for potassium <3.5 mEq/L and 1.52 for potassium ≥5.5 mEq/L.

Frailty

Frailty is a multidimensional characterization of an individual, previously consisting of three or more of the following criteria: unintentional weight loss; exhaustion; slow gait speed; muscle weakness; and low levels of physical activity [84]. Frailty has been associated with an increased risk of adverse health outcomes and mortality [85]. Brar et al. [86] conducted a prospective cohort study of 109 home dialysis patients (76 on PD, 33 on HD) assessed by four frailty assessment tools: Fried frailty criteria, short physical performance battery, physician impression, and nurse impression for a median follow-up period of 3.3 years; frailty, as defined by subjective or objective criteria, was associated with a more than twofold risk of death or technique failure. These findings were independent of age, sex, albumin, hemoglobin, and comorbidity, suggesting that the operational definitions of frailty capture nontraditional risk factors for adverse outcomes in this population.

Peritoneal Membrane Transport Type

Peritoneal transport has an impact on clinical outcomes, but it is not constant in PD patients. A 10-year study of 470 PD patients from Hong Kong [87] examined the changing trend of peritoneal transport and its impact on patient outcomes. Mean

dialysate-to-plasma creatinine ratio (D/P Cr) dropped significantly in the first year and remained constant thereafter. A slow, increasing trend was observed after year 5. There was no significant difference in patient survival rates based on baseline transport group; D/P Cr only became a significant risk factor for mortality by year 3 and onward.

Icodextrin may provide advantages over standard glucose dialysate in responding to transport changes over time on PD. In a study from Korea, Han et al. [88] analyzed data on 2163 incident PD patients (641 icodextrin and 1522 non-icodextrin) over 23.7 months to investigate whether icodextrin provides patient survival advantages versus standard glucose dialysate. The results demonstrated that death occurred in 92 (14.4%) patients in the icodextrin group compared with 128 (20.0%) in the non-icodextrin group, suggesting that icodextrin may play a role in optimizing patient survival; the authors did not detail the peritoneal equilibration test results but did note that 63.7% of patients had diabetes. A Chinese study [89] involving 217 incident PD patients noted that icodextrin use was associated with a significantly lower risk of death (adjusted HR = 0.33).

Process/Infrastructure Factors

Unplanned Starts and PD Patient Survival Outcomes

Seemingly, patient survival is largely determined by the CV health status at initiation of dialysis, and even the best dialysis modality will not reverse the CV damage that has accumulated in the pre-dialysis stage [90]. Whether ESKD patients are presenting for PD or HD, pre-dialysis care impacts outcome after initiating treatment. As such, the lack of sufficient pre-dialysis care and pre-dialysis education should lead to classifying patients as "increasing risk"; pre-dialysis care matters [91].

As detailed in the 2019 USRDS Report, analyzing data through 2017, 33.4% of incident ESKD patients had received little or no pre-ESKD nephrology care, 19.2% of patients starting ESKD therapy were reported on the CMS 2728 Form as not having received nephrology care before ESKD onset. An additional 14.1% had an unknown duration of pre-ESKD nephrology care. Because treatment characteristics, such as erythropoiesis-stimulating agent use and dietary care, for the unknown group were similar to those with no pre-ESKD nephrology care, one may assume that up to 33.3% of new ESKD cases received little or no pre-ESKD nephrology care.

Modality Transitions and PD Patient Survival Outcomes

Mortality risk after transfer from PD to HD may be influenced by the cause of PD technique failure, the clinical status of the patient, and the intensity of management during the transition. Reported results on survival post transfer from PD to HD lack

effective patient comparisons, incorporate varied study designs, and are few in number [92]. In an ANZDATA study, patients transferred to conventional hemodialysis (CHD) due to inadequate dialysis or mechanical complications had lower mortality risk after transition to CHD than those with infectious causes of PD technique failure. In contrast, transfer to CHD due to social reasons was associated with an increased mortality risk once transferred. Globally, mortality after transition to CHD can be as high as 25% if the transition is unplanned. Most patients who switch from PD to CHD do so permanently, as 24% of patients returned to PD after 30 days on CHD, while only 3% did so after 180 days on CHD [93].

Significantly greater mortality risks are evident for both diabetic and nondiabetic patients who switch therapies during follow-up irrespective of their original modality assignment [45]. Accordingly, increased vigilance should be given to diabetic patients transitioned to alternate modalities.

Dialysis modality switch was associated with increased mortality risk, but switch from PD to HD within 6 years did not show significant hazard of mortality in a data analysis from the Korean Society of Nephrology on 21,840 incident dialysis patients [94]. In the future, the findings from the INTErnational Group Research Assessing Transition Effects in Dialysis (INTEGRATED) initiative [95] will potentially assist with learnings helpful in managing modality transitions.

Discussing PD Survival Outcomes with ESKD Patients

Dialysis-dependent ESKD is a serious illness with high disease burden, morbidity, and mortality. Survival rates are determined from a broad array of different patients with varied disease burden, which can impact individual patient outcomes. Discussing these issues with patients can be difficult and most nephrologists differ in their approach to survival discussions compared with oncologists discussing cancer treatments and outcomes [96, 97].

It is important for patients to understand that survival rates do not necessarily predict how an individual with specific characteristics will do on dialysis. In many cases, statistics may be dated and do not account for variations in individual characteristics as outlined in this chapter; an individual's prognosis may be different based on the individual variables of the patient.

Fewer than 10% of patients on dialysis report having had a conversation about goals, values, and preferences with their nephrologist, although nearly 90% report wanting this conversation. In multiple studies, timely discussions about serious illness care goals, however, have been associated with enhanced goal-consistent care, improved quality of life, and positive family outcomes without an increase in patient distress or anxiety [98]. Discussions regarding survival are especially important in the population older than 70 years. Mortality in the first year on dialysis for

individuals over age 75 years old approaches 40%, and even those with better prognoses face multiple hospitalizations and declining functional status [99].

Patients on PD and their caregivers were purposively sampled from nine dialysis units across Australia, the United States, and Hong Kong to identify and rank outcomes and discussed the reasons for their choices [100]. The ten highest ranked outcomes were PD infection, mortality, fatigue, flexibility with time, BP, PD failure, ability to travel, sleep, ability to work, and effect on family. Mortality was ranked first in Australia, second in Hong Kong, and 15th in the United States; factors that affect a patient's functional status (e.g., pain, mobility, flexibility of time, ability to work) were more important to US patients than mortality.

Cancer is generally associated with multiple symptoms, diminished functional status, and adverse changes in a patient's health-related quality of life (HRQOL) [101, 102]. Also, the quality of survival (QoS) tool is a patient-centric concept used in cancer discussions that helps decision-making and patient communication. Both the HRQOL tool and the QoS map exercise could provide a framework to assess patient status and monitor ESKD patients and thus would be helpful in modality discussions with patients by nephrologists [103].

What matters most to patients with ESKD has been explored by St Clair Russell and Boulware [104]; they described the different approaches to options education and a concept of "don't tell but ask," with the purpose of helping families connect the dots through engaging both the patient and family in options education. This framework for survival discussions is critically important to achieving holistic patient care decisions for the ESKD patient.

Conclusion

Understanding the complexity of "survival" matters and is at the core of devising strategies to extend it. Recognizing what we have learned about determinants of PD survival outcomes and what matters most in designing care models should guide modality selection. Nephrologists should focus on risk factor prevention and control when making treatment decisions, emphasizing the concept of "the right therapy for the right patient at the right time". Above all, placing the patient at the center of care is critically important for making treatment decisions that extend "quality survival" on PD.

In addition, timely organ/disease assessment and designing action steps that neutralize or prevent complications are critical for extending PD survival. Survival discussions with ESKD patients and care partners may be difficult but can be invaluable for charting the best course of treatment for the individual patient based on what we know regarding the link between dialysis modality and survival for that individual patient.

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Chapter 22
Quality of Life in Peritoneal Dialysis

Jack Beadle and Edwina A. Brown

Introduction

The World Health Organization (WHO) defines health as 'a state of complete physical, mental and social well-being not merely the absence of disease'. The treatment of disease can also be associated with significant social, psychological and physical burdens, so it follows that measures of health don't focus merely on the absence of disease but on the well-being of the patient and on treatment satisfaction.

The concept of QOL is subjective and is multidimensional, reflecting an *individual* patient's perception of their position in life, in the context of their values and culture, which is affected by their expectations, concerns and their support networks [1]. This is a broad definition, but the impact of disease and treatment on a patient's physical, social and psychological well-being has come to be defined as health-related quality of life (HRQOL) [2].

End-stage kidney disease (ESKD) is a major cause of morbidity and mortality worldwide and is associated with a significant symptom burden for patients [3]. Despite the resources devoted to treatment of kidney disease, improvements in dialysis and management of comorbidities, patients continue to experience significant morbidity and a reduced quality of life (QOL) [4]. Treatment with kidney replacement therapy (KRT) in the form of peritoneal dialysis (PD), haemodialysis (HD) or transplantation allows patients to survive the lethal complications of kidney disease but is associated with major impairment of health-related quality of life (HRQOL) for all modalities [5]. As survival rates for patients with ESKD have improved, and patients have prolonged time on treatment, focus has shifted to HRQOL as an important outcome measure for patients on dialysis.

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There is evidence that a lower QOL in patients with ESKD is associated with increased risk of death and hospitalisation and correlates better with these outcomes than surrogate markers such as serum albumin level [6]. Peritoneal dialysis patients with low HRQOL scores have increased mortality, even correcting for comorbidity, PD modality, demographic variables and laboratory variables [7].

Improvements to a patient's QOL, through the provision of high-quality PD and patient care, have the potential to improve patient outcomes. A focus on measures of HRQOL is increasingly recognised as an important outcome metric for the success of peritoneal dialysis [8].

Measurement of Quality of Life

End-stage kidney disease is associated with a considerable burden of physical symptoms and the psychological, social and treatment-related aspects of KRT. Methods to quantify HRQOL in long-term conditions attempt to score the impacts of treatment and disease across aspects of physical, social and psychological domains. In the USA, there is a requirement that dialysis facilities ask patients to complete assessments of HRQOL annually and be assessed for depression and for pain once a year [9]. Nevertheless, the best methods for assessing HRQOL in PD patients and the frequency with which this should be done remain unclear.

There are a variety of assessment tools available for measuring HRQOL, but there is no 'gold standard' for use in a PD population. Objective measures, such as the Short Form 36 (SF-36), have been validated in chronic disease and allow comparison across a range of chronic health conditions. Other scoring systems, such as the KDQOL-36, have additional scales related to specific aspects of kidney disease and dialysis.

Common Assessment Tools

Short From 36 (SF36): A generic measure of HRQOL for use in the general population.

- It is not kidney disease, or treatment, specific but allows comparison with a range of chronic health conditions.
- It measures eight health domains including physical (physical activity; role limitations due to physical health; pain and general perception of health) and mental (levels of energy and fatigue; limitations on social activity; role limitations due to emotional problems and general mental health) domains, with higher scores associated with better health.
- The physical and mental domains are summarised in physical (PCS) and mental component summaries (MCS).
- Variants of this form exist, such as the SF12.

KDQOL-36: Based on the SF12 with additional scales focusing on outcomes related to kidney disease

- These include items such as the burden of kidney disease, work status, sexual function and sleep.
- In the observational Dialysis Outcomes and Practice Patterns Study (DOPPS) of over 7000 HD patients, lower KDQOL-36 scores were associated with a higher risk of death and hospitalisation [10].

Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS)

- Determine the presence of symptoms of depression. They are not used for the diagnosis of depression.

For HRQOL assessment scores to be relevant to an individual patient, there needs to be a recognition that an individual's priorities and perceptions change over time [11, 12], through different stages of kidney disease and across different modalities of kidney replacement therapy [13].

Subjective measures of HRQOL – patient-reported outcome measures (PROMs) – are likely to be better at reflecting the patient experience but can be difficult to compare between studies and may be difficult to interpret. Initiatives attempting to standardise the reporting of relevant patient reported outcomes in peritoneal dialysis patients, such as SONG-PD [8], aim to establish core outcomes to be reported in trials in PD to enable comparison between interventions.

Quality of Life in Kidney Replacement Therapy

End-stage kidney disease is associated with a significant impairment in HRQOL compared to the general population [13], which persists across all forms of kidney replacement therapy [14]. Treatment for kidney disease aims to improve survival and maintain a patient's QOL, but there is evidence that HRQOL continues to deteriorate despite patients on HD or PD having lower SF36 scores than a pre-dialysis population [13].

Kidney transplantation is associated with a better QOL than HD or PD [15, 16] but is not a feasible treatment for everyone.

PD and HD as dialysis modalities have their own individual advantages and disadvantages. PD has the advantage of being a home-based therapy that allows for increased patient independence and freedom – to travel or to work – but is associated with a lower technique survival over time. HD has the advantages of being suitable for patients unable to perform their own dialysis, and of long-term technique survival, however, it is associated with haemodynamic instability and worse cognitive decline in older patients [17].

Studies comparing HRQOL between HD and PD have not consistently found a significant advantage of one of the other, perhaps reflecting the fact the different

modalities have different advantages in different 'domains' of HRQOL. One study of 232 community-based HD and 201 PD patients in Singapore, for example, showed significant physical and emotional impairment of QOL in both patient groups compared to a healthy population but noted advantages of PD in patient autonomy and patient flexibility and advantages to HD in the domains of physical and emotional function [18]. On the other hand, a Saudi study showed advantages to PD across all domains except physical function [19].

Despite this, meta-analyses of studies have failed to show a significant advantage of one modality over another. An Iranian meta-analysis of 2212 dialysis patients showed no significant difference between QOL scores in HD or PD patients [20], whilst another meta-analysis showed the only statistically significant difference between the modalities was an advantage of PD in the burden of kidney disease [21].

The most complete recent meta-analysis comparing QOL outcomes between HD and PD looked at 4318 patients across 15 studies [22]. This analysis showed advantages to PD across three HRQOL domains, though this was not statistically significant. There was, however, a significant variation based on the date of publication and study location, with newer studies favouring peritoneal dialysis and older studies, the majority of which were conducted in the USA, favouring haemodialysis.

Patient Priorities for Outcomes in PD

As a home-based treatment for ESKD, PD has a number of significant benefits in terms of flexibility, the ability to work, the ability to travel, and the ability to have needle-free treatment. Nevertheless, it is challenging – requiring dialysis to be scheduled into patients' lives several days each week, demanding fastidious attention to hygiene and technique and necessitating a degree of patient or caregiver responsibility and training.

Many of the factors affecting a PD patient's QOL reflect aspects of health specific to peritoneal dialysis – such as the need to be vigilant for peritonitis, to manage bowel habits to facilitate effective dialysis and deal with catheter-related complications. Whilst the aims of PD as a treatment modality are to prevent death from uraemia and help manage fluid and electrolytes, treatment-related outcomes which are important to patients and to caregivers can vary, and there is an increasing understanding of the mismatch between the priorities of patients and physicians when it comes to determining what high-quality dialysis means.

One study, reporting the priorities described by groups of PD patients in three countries (Hong Kong, Australia and the USA), reported a mix of clinical (death, infection, blood pressure control and dialysis failure) and nonclinical outcomes (including fatigue, flexibility with time, sleep, work and impact on family and friends) [12]. Rather than mortality, the most important outcomes for many patients and carers reflected anxieties about preventing infection – peritonitis, line and tunnel infections. This was partly because infections were associated with pain, hospitalisation and a potential failure of dialysis. The top 10 outcomes identified by PD patients as important is listed below (Table 22.1.)

Table 22.1 Patient-reported outcomes in peritoneal dialysis [12]

Peritoneal dialysis infection
Death
Fatigue
Flexibility with time
Blood pressure
Failure of peritoneal dialysis
Ability to travel
Quality of sleep
Ability to work
Effect of treatment on family and friends

https://cjasn.asnjournals.org/content/14/1/74
Clinical outcomes (infection, death, failure of dialysis) and patient reported outcomes were the highest priorities for PD patients
Focus groups in three countries (Australia, Hong Kong and the USA) asked what were the most important outcomes for them

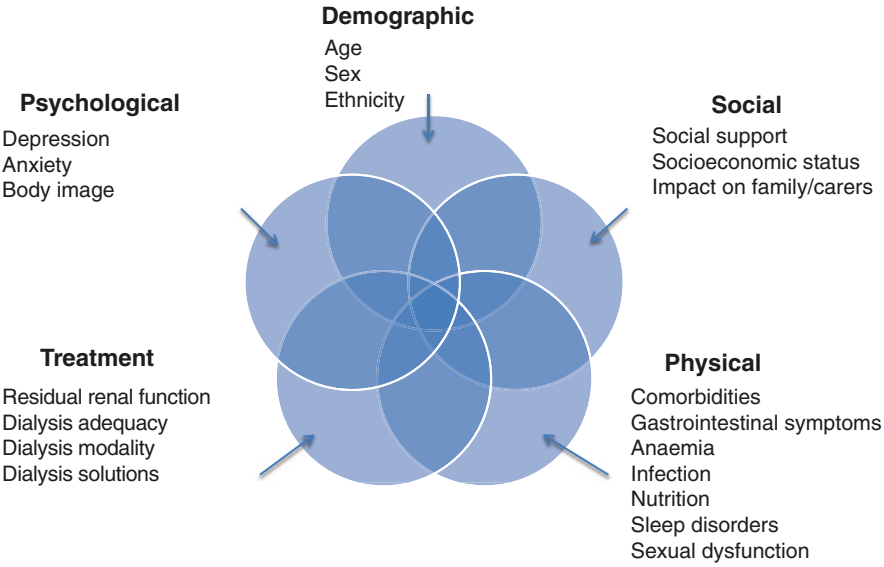

Fig. 22.1 Factors associated with HRQOL in PD

Factors Associated with Quality of Life in PD

HRQOL encompasses multiple domains of health including physical, psychological, social and treatment-related spheres (Fig. 22.1). Some of these factors and their effects on HRQOL in PD patients are outlined below.

Demographic Factors

Perceptions of QOL are individual and are affected by a range of cultural and demographic variables.

Sex

Female sex has been associated with lower HRQOL scores in CKD populations in the USA [23] and in ESD populations in Europe [24], although these did not specify the specific domains across which scores were reduced. Female sex was found to be the strongest predictor of the burden of kidney disease domain in haemodialysis patients in one study [25]. Despite sex differences in the rate of progression of kidney disease [26] and sex-related differences in access to healthcare around the world [27], there are very few studies directly assessing the effects of sex on HRQOL in PD patients.

One study of PD patients in the UK noted an association of male sex with lower HRQOL scores, across a number of domains; this was postulated to be related to difficulties adapting to chronic illness and changes to a role as 'head of the household' [28]. Another study in the USA showed a reduction in satisfaction with care scores in black men on PD, compared to black women and white PD patients [29]. There is evidence that gender makes a difference in symptoms of sexual dysfunction in PD [30], with women on PD experiencing significantly lower sexual function scores than healthy peri- or postmenopausal controls.

Ethnicity

Minimisation of differences in the standards of healthcare received by patients of different ethnic or socio-economic groups is central to the high quality of care in dialysis patients. Biochemical measures of dialysis adequacy, such as calcium phosphate product and haemoglobin targets, have been shown to vary in different ethnic groups independently of socio-economic status [31], as has patient survival [32], but the relationships between ethnicity and other dialysis-related outcomes, such as HRQOL, have been less widely reported.

In the USA, there is evidence that black patients on dialysis report better overall health and fewer negative effects of kidney disease than white patients [33] and with higher satisfaction with care on PD [29]. A UK study comparing HRQOL between patients of white and Indo-Asian backgrounds showed a significant reduction in perceived QOL in Asian patients across the domains of physical health, mental health and kidney disease [34]. Physical health and kidney disease scores were associated with more social deprivation in the Asian group. Asian patients were more likely to be living in houses with extended families, and it was argued that home-based treatment modalities, such as PD, might have an impact on the social

perception of their illness. There were no differences in HRQOL scores between HD and PD patients, however, when adjusted for ethnicity.

In contrast, a Dutch study showed significant differences in social characteristics, such as marriage, and perceptions of health between Caucasian, black and Asian dialysis patients, but no differences in the physical or mental component summaries of HRQOL [32].

One potential concern when assessing HRQOL scores across different ethnic groups is whether scoring systems such as KDQOL or SF36 are of comparable validity between ethnic groups or if enough consideration is given to language barriers in patients and caregivers.

The relative significance attached to a variety of patient-reported outcomes in PD patients has been shown to vary from country to country, with more weighting attached to QOL-reported outcomes in some countries compared to others – reflecting differences in culture or healthcare provisions [35] and perhaps implying that the domains assessed in HRQOL scores are not equally applicable to all groups.

Age

The proportion of older patients on dialysis is increasing. Older patients tend to have more comorbidities, frailty and cognitive and sensory impairments than younger patients and have a shorter life expectancy, with a limited long-term survival on dialysis.

Frailty is associated with worse QOL scores for older patients on dialysis, regardless of their modality, and is related to an increased risk of cognitive impairment, falls hospitalisation and death [36]. Older and younger patients have different health expectations, and older patients prioritise outcomes associated with quality, rather than longevity of life [12]. Home-based treatment, such as PD, would appear to offer significant advantages in older population for whom the principal determinants of HRQOL are greater independence and control [37]. Concerns about length of time on PD are less of an issue for older patients, with the risk of encapsulating peritoneal sclerosis only 5% even after 5 years, suggesting that lifestyle and quality of life may be more important considerations [36]. Nevertheless, the majority of older patients are started on HD. The North Thames Dialysis Study showed no difference in 12-month mortality between HD and PD patients aged over 70 [38], whilst the BOLDE study showed that in closely matched groups of older dialysis patients, PD patients suffered less illness intrusion than those on HD [39].

Frailty alone should not be a barrier to home-based therapy in patients for whom in-hospital HD would be a significant burden. Availability of assistance by family members or paid carers enables frail older patients to have peritoneal dialysis at home. Assisted PD is associated with increased treatment satisfaction for older patients, compared to HD [40], and is not associated with a significant worsening of caregiver QOL, compared to self-care CAPD or APD [41].

Social Factors

Socio-Economic Status

As predictors of HRQOL on PD, family income and levels of education were not associated with impaired QOL in an evaluation of 1674 PD patients in Brazil [42].

Social Support Networks

Social networks are important determinants of HRQOL for patients with chronic health conditions. One study comparing social support networks and their impact on HRQOL scores in dialysis patients found that PD patients had larger social networks than HD patients, particularly family networks, and received more social support [43]. Larger social networks are associated with higher participation and lower anxiety, and closer interpersonal relationships were associated with increased psychological well-being. The size of social networks for both PD and HD patients declines over time, but the identification of a supportive network may have a positive effect on continuing engagement with therapy and QOL .

Burden on Caregivers

Many of the physical and psychosocial burdens of ESKD are shared by patient's caregivers and are associated with significant lifestyle changes. Older, frailer and more comorbid patients on PD may become increasingly dependent on support from carers or family in performing exchanges and connecting and disconnecting from dialysis or in their activities of daily living. The effects of dialysis modality on the QOL and burdens of caregivers are incompletely understood. One study suggested that PD is associated with reduced caregiver burden and lower levels of depression than HD; however, patients with more than two comorbidities were excluded from this study, so it is unclear whether these results can be extrapolated to a frailer, more comorbid population [44]. A systematic review of 5367 caregivers showed impaired HRQOL scores in carers compared to the general population, but no significant difference between different dialysis modalities [45].

Psychological Factors

Depression

Depression is associated with increased mortality [46], lower HRQOL [47] and poorer treatment compliance [48] in dialysis patients and anaemia, nutritional status and lower residual kidney function in PD [49]. In PD patients, depression is

associated more strongly with QOL measures than biochemical parameters of dialysis adequacy, such as KT/Vurea [47], and depression has been found to correlate with rates of peritonitis [50]. Whilst the prevalence of depression based on clinical interviews of dialysis patients is around 23%, self-reported symptoms of depression occur in 39% [51]. Symptoms of depression appear to be particularly concerning for carers and families of PD patients, as it is felt that this is out of their control [12]. Studies have shown that improvement of depressive symptoms is associated with improved treatment satisfaction in APD and CAPD patients [52]. Depression can be difficult to treat in patients on dialysis; most of the studies have been done in HD. One small study has shown that drug therapy may be efficacious [53], but this needs to be repeated in larger numbers.

Anxiety

Symptoms of anxiety have also been shown to correlate more strongly with QOL than measures of PD dialysis adequacy [47] and are common in incident PD patients [54]. High levels of anxiety are a predictor of technique survival and mortality in PD [55], suggesting that treatment of anxiety might be an effective means of improving outcomes in PD.

Body Image

Body image disturbance is common in dialysis patients and is associated with anxiety and depression [56]. Increasing levels of depression and anxiety in PD patients are associated with worsening body image and sexual satisfaction; however, body image perception is better in PD patients than HD patients [57].

Physical Factors

Sexual Dysfunction

Sexual dysfunction is common in patients on PD [58] and is a significant contributor to HRQOL, although the importance given to it appears to vary with patient's age [12] . One study of sexual dysfunction in PD patients in Taipei [30] showed the prevalence of erectile dysfunction in men was 51.9% and was associated with older age and higher fasting glucose levels. In women, lower sexual function was associated with higher levels of depression, older age and treatment with APD. APD is associated with night-time restrictions, but there was no association with sexual dysfunction in men, and the much larger Dutch NECOSAD cohort [59] found that patients on APD scored higher on levels of sexual function than patients on CAPD.

Nutrition

Nutrition plays a significant role in the physical and mental well-being of PD patients, with evidence that markers of nutrition and inflammation, such as serum albumin, decline over time on PD [28]. Malnutrition in dialysis patients is important, but is not always visually apparent, and may be exacerbated by the gastrointestinal effects of PD, with symptoms of pain, bloating and constipation and laxative use and dietary restrictions imposed to manage electrolyte levels. Nutrition is particularly important in older dialysis patients where lower energy intake is associated with a smaller social support network and lower PCS of HRQOL scores [60]. In addition, lower protein intake is associated with socio-economic deprivation, depression and reduced PCS HRQOL scores.

Management of fluid status, gastrointestinal symptoms and diet have been identified as important outcomes to patients [12], and accurate nutritional assessment and support may be an important adjunct to managing volume overload, hypertension and physical and mental well-being [61].

Gastrointestinal (GI) Symptoms

Gastrointestinal symptoms such as nausea, bloating, vomiting and abdominal pain are extremely common in PD patients, which may be a reflection of the use of the peritoneal space for dialysis [62]. An increased burden of GI symptoms is associated with impaired psychological well-being and with deficiencies in nutritional status.

Sleep Disorders

Sleep disorders are common in patients with ESKD and are associated with increased mortality and reductions in QOL [63]. Poor sleep is associated with reduced physical activity, due to daytime dysfunction due to sleepiness, and anxiety and depression. Sleep apnoea events were reduced in patients switching from CAPD to nocturnal PD and correlated with improvements in overnight KT/V and CrCl [64]; however, there are few studies examining the effect of treating sleep disturbance on HRQOL in PD patients.

Disease-Related Factors

Anaemia

Anaemia is commonly encountered in patients with CKD and is associated with both increased mortality [65] and a reduced HRQOL, particularly in physical domains such as vitality and physical performance [66]. Treatment of anaemia is

associated with benefits to HRQOL in PD, with significant improvements to emotional well-being in patients treated with erythropoiesis-stimulating agents (ESA) and improvements in patient's emotional roles associated with increasing haemoglobin and ferritin concentrations [67].

Infection

Infection is a major cause of anxiety and concern in PD patients as it is associated with physical pain, risk of hospitalisation, mortality and potential end of PD treatment [68]. Reducing the risk of peritonitis and catheter-associated infection places a heavy burden on patients and carers to pay rigorous attention to aseptic technique, hand hygiene, personal hygiene and an ability to recognise problems and deal with these. Depression in PD patients is associated with increased rates of peritonitis and elevated inflammatory markers [50], as are factors such as dependent personalities, educational attainment and literacy levels [69]. Infection and inflammation are correlated with lower levels of haemoglobin, elevated inflammatory markers and poorer nutrition, which are themselves associated with impairment in HRQOL scores. Episodes of peritonitis, but not exit-site infections, are independently associated with a decline in HRQOL over time, particularly in the domains of treatment satisfaction [28]. Many risk factors for peritonitis are potentially modifiable, and reducing rates of infection is likely to have a significant impact on hospitalisation and HRQOL.

Treatment-Related Factors

Residual Kidney Function

In the pre-dialysis period, a declining glomerular filtration rate (GFR) is associated with a deterioration in QOL measures, throughout the stages of CKD [13]. Preservation of residual kidney function is an important concept in PD, but there are few studies investigating its effect on HRQOL. A lower weekly renal KT/V, as a marker of residual kidney function (RKF), has been associated with depression and reduction in HRQOL across all domains [70], suggesting that maintaining residual kidney function might be an attractive way of preserving HRQOL in PD patients. Whilst comparison of groups of PD patients with and without residual kidney function has shown no difference QOL scores [71], preservation of RKF can lower the dialysis burden by reducing daily exchanges and/or days on dialysis.

Small Solute Removal

The PD prescription is often increased to achieve 'target' levels of small solute removal as measured by Kt/Vurea or creatinine clearance without good evidence that this affects mortality or morbidity. Insufficient solute removal, however, is

associated with an increased symptom burden, as demonstrated in one study where incident CAPD patients in Hong Kong were randomised to three separate KT/V targets [72]. Patients with a total KT/V < 1.7 had significantly more clinical symptoms and more severe anaemia; however, there was no difference in survival or hospitalisation and no benefits observed in increasing dialysis prescription to achieve KT/V > 2.

Moreover, in the ADEMEX trial, whilst HRQOL was strongly predictive of patient survival and hospitalisation, there was no evidence that increasing creatinine clearance targets had any effect on long-term HRQOL [73].

Whilst increasing dialysis prescription may have an effect on symptom burden, this may be offset by other factors affecting HRQOL, such as the number of exchanges patients are performing, which may affect their perception of the burden of treatment.

PD Modality (APD, CAPD)

A prospective study randomising patients to CAPD or APD showed that the nocturnal dialysis occurring with APD meant that patients had significantly more time for work, family and social engagements; however, sleep disturbance was found to be more common in the APD group [74]. Despite this, there was no difference in HRQOL scores between the modalities. Whilst there may be advantages in choosing one PD modality over another for individual patients, studies have not demonstrated a consistent difference in HRQOL between patients undergoing APD or CAPD.

PD Solutions

Compared to conventional glucose-based PD solutions, newer PD solutions, with lower concentrations of glucose and glucose degradation products, are designed to improve the health and viability of the peritoneal membrane. Biocompatible PD solutions are associated with preservation of RKF and native urine output, although the relationship between the two is confounded by reduced ultrafiltration and possible volume overload [75]. High peritoneal glucose loads are associated with symptoms of depression and sexual dysfunction in male PD patients [76]. Comparisons between icodextrin and high concentration glucose-containing solutions have shown reduction is symptoms such as dizziness, abdominal cramps and lack of appetite, translating into increased KDQOL scores in the domains of health perception, physical functioning and role in patients switched from glucose-containing PD solutions to icodextrin in one trial [77]. Nevertheless, it is unclear if newer solutions are associated with consistent benefits to HRQOL in larger studies.

How Can We Optimise QOL in PD?

There are a wide variety of factors that can affect an individual's HRQOL, and whilst not all of these are modifiable, recognition of domains of difficulty for patients, or focusing on patient-centred outcomes, could provide possible strategies for improving the HRQOL of individual dialysis patients.

Tailoring a PD prescription around an individual person's requirements, such having a day, or weekend, off of PD, allows patients and caregivers to manage their own time flexibly and personalise their regimen around home, work and social commitments. In addition to the factors outlined above, offering patients choice can result in increased treatment satisfaction and identifying priorities or concerns important to individual patients.

The importance of an integrated multidisciplinary team for PD patients cannot be understated. The role of nurse-led management is important, in educating patients and families in the pre-dialysis stage, identifying potential areas in need of support and providing a contact point for patients. Comprehensive pre-dialysis education and follow-up has been associated with improved sleep, social function and emotional well-being in HRQOL scores [78].

Conclusions

Improvement of a patient's quality of life should be a priority of good PD care. In our responsibility to ensure best quality care, we must recognise the importance of patient priorities, psychological well-being and treatment satisfaction alongside other outcome measures such as hospitalisation, infection and adequacy.

HRQOL correlates strongly with patient outcomes and is often more important to patients than survival, particularly in chronic illnesses. An individual approach, focusing on symptom management, social support, psychological well-being, choice and independence, should be considered in optimising treatment choices for each patient.

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Chapter 23
Incremental Peritoneal Dialysis

Mihran Naljayan

Introduction

Home dialysis continues to have an increasing rate of utilization in the United States in incident dialysis patients based on USRDS data available from 2016 [1]. There were 124,675 incident ESKD patients in the United States. Of these patients, 87.3% were initiated on hemodialysis and 9.7% on PD, and 2.8% received a preemptive kidney transplant. Despite the high numbers of incident patients beginning on hemodialysis (HD), there has been a significant increase in the number of incident ESKD patients beginning on a home kidney replacement modality. Specifically, there was an 85.6% increased use of home dialysis since 2016 when compared to 2007. PD continues to be more utilized than home HD, although there was a 108.1% increase in home HD in 2016 when compared to 2007. Despite that large increase, home HD use remains only 3.1% in the incident ESKD patients. Overall, there has been an increase in the number of incident PD patients by 60.2% since 2000.

Interestingly, the estimated glomerular filtration rate (eGFR) for incident ESKD patients at the initiation of dialysis has increased in 2016 when compared to 1996 with 38.6% of patients having an eGFR ≥10 mL/min in 2016 as compared to 12.9% [1]. This increase is despite the IDEAL study that demonstrated starting dialysis at a higher eGFR has no significant survival advantage when compared to starting dialysis with a lower eGFR [2]. In this study, patients were initiated on PD or HD based on provider and patient choice, and a subset of the patients were initiated on incremental PD or incremental HD. Incremental PD is defined as a PD prescription that is less than full dose. It can be defined in different ways including continuous

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cyclic peritoneal dialysis (CCPD) overnight with dry days, CCPD fewer than 7 days a week, or continuous ambulatory peritoneal dialysis (CAPD) with fewer than four exchanges in a day possibly including a dry period as well [3]. Incremental HD is defined as fewer than three sessions a week. This study was not designed to compare the effects of incremental versus standard dose of dialysis, but other studies that will be reviewed in this chapter evaluate outcomes of these patients. As more patients are initiated on PD than in prior years, and more patients are initiated at an eGFR >10 mL/min, incremental initiation of kidney replacement therapy seems to be a viable option for these patients. This chapter will review the benefits and risks of using incremental PD for the ESKD patient.

Adequacy and Residual Kidney Function

In PD, one metric of adequacy is a measure of small solute clearance, with a target weekly Kt/V_{urea} of 1.7–2.0. This is a combination of both peritoneal and residual kidney Kt/V_{urea}. In patients with significant residual kidney function (RKF), a lower dose of dialysis may be used to achieve the same adequacy targets. Clearance may be defined in multiple ways, but most commonly small solute clearance is measured with Kt/V_{urea} for both HD and PD. Other solutes such as protein and hydrophobic toxins have different transport characteristics than urea, and these are not measured when calculating clearance using Kt/V_{urea} [4]. Other factors not taken into consideration are salt and volume removal. These clearance measurements do not account for factors such as nutrition and quality of life. Lastly, increasing small solute clearance in PD has not shown improvement in outcomes, but higher RKF has been shown to improve outcomes [5]. Beta(2)-microglobulin clearance is a measure of middle molecular clearance. Studies have evaluated the differences between beta(2)-microglobulin clearance between patients on HD and PD, but Yamamoto et al. studied the difference between serum levels in those patients with higher RKF on PD versus those with less RKF. They found that patients with higher RKF had lower serum beta(2)-microglobulin levels [6]. This suggests differences in solute clearance between the kidney and the peritoneal membrane. Although clearance between some small solutes may be similar, other substances are not cleared at the same rate or efficiency between these two filtration systems. We measure clearance in terms of Kt/V_{urea} for both renal and peritoneal clearance, but these two, the kidneys and the peritoneal membrane, are not equivalent when considering clearance of other solutes. Maximal utilization of renal clearance would therefore increase clearance of other solutes that are not adequately removed by the peritoneal membrane. Clearance can be viewed as a total target that is achieved. Initially when starting dialysis, less peritoneal dialysis clearance is necessary to achieve the total clearance required since there is a more significant contribution of renal clearance, but as the RKF declines, more peritoneal contribution will be needed in order to achieve the required total clearance (see Fig. 23.1).

The decline of RKF is an important factor in survival. Data from the CANUSA study shows that RKF has an impact on survival whereas peritoneal clearance does

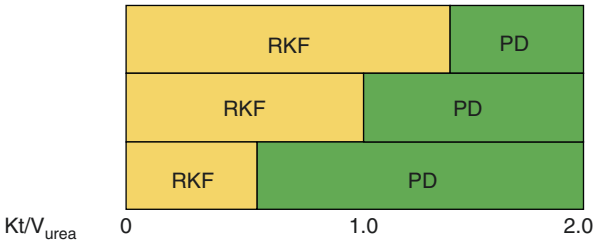

Fig. 23.1 Total Kt/V_{urea} showing various degrees of PD and RKF as the components. (Image adapted from Bargman et al. [4])

not [7]. This suggests that maintenance of RKF is vital to improve outcomes in ESKD patients. Patients on PD have less of a decline of the RKF than patients on HD [8]. If a patient is maintained on PD longer, then it is possible that they will retain their RKF for a longer period of time. Utilization of incremental PD may also decrease this loss of RKF. In one study comparing prescriptions utilizing icodextrin with dextrose versus dextrose solutions alone, patients with dextrose solutions alone had more of a decline in their residual urine output [9]. There may be hastening of RKF loss with additional dextrose utilization. Golper et al. reviewed the concept of the "intact nephron in reverse" hypothesis wherein the incremental initiation of dialysis may suppress factors that promote the decline of kidney function [10]. For example, Davenport A. discussed the concept of RKF loss in patients on routine thrice-weekly hemodialysis and stated that hypovolemia with repeated episodes of intradialytic hypotension likely plays a large role in the loss of RKF [11]. However, in PD, patients are maintained in a slightly more hypervolemic state, and therefore incremental initiation of PD may preserve RKF. Therefore, with incremental PD, less dextrose exposure and inhibiting the promotors of renal decline initially may help to maintain RKF longer while the patient remains on PD.

Technique Survival in PD

Ultrafiltration (UF) failure is one of the main reasons for dropout from PD. Volume overload is due to a combination of peritoneal fibrosis and loss of RKF. Peritoneal fibrosis is attributed to two different processes: peritoneal fibrosis and peritoneal inflammation [12]. The mesothelial cell changes of the peritoneal membrane are felt to be driven primarily by glucose and glucose degradation products contained in the peritoneal dialysis solutions [13–15]. Over time, as patients are exposed to these solutions, fibrosis of the peritoneum develops. This fibrosis leads to a decrease in the ability of water to transport across the peritoneal membrane. The dextrose exposure also leads to neovascularization which alters membrane transport characteristics leading to a high transport status of the membrane. Both of these changes together lead to diminished peritoneal UF over time. With the decline in RKF over time, in combination with these fibrotic changes, patients are unable to achieve the daily UF volumes needed to stay on PD. This ultimately leads to transfer from PD

to HD (another solution to the diminished ultrafiltration is bimodal therapy with PD and HD – see Chap. 30).

Incremental PD inherently decreases the dextrose exposure to the peritoneal membrane [16]. As patients are started on incremental PD, the cumulative exposure in those first few months to years is significantly less than those patients who start full-dose PD. Over time, as patients transition to full dose PD, their cumulative dextrose exposure also remains less and therefore may lengthen the time it takes for significant fibrosis and neovascularization of the peritoneal membrane to occur. This may delay the likelihood of ultrafiltration failure as noted previously. Further studies are needed to see if this is indeed the case.

Incremental PD may provide a small amount of clearance that relieves uremic symptoms. As patients progress to end-stage kidney disease, symptoms of uremia progressively worsen. With the addition of a small amount of PD as patients develop these symptoms, the added clearance of these solutes may resolve these symptoms. This can improve the patient's quality of life and allow them to get back to feeling more "normal."

Quality of Life

Quality of life is another important feature of PD. The psychosocial "burnout" of PD is another one of the top reasons for dropout from PD [17]. Performing four manual exchanges daily with CAPD or 8–10 hours of cycler therapy every night can be burdensome for the patient, especially since there are no "days off" from the therapy. Incremental PD offers the opportunity to decrease the number of exchanges and have less time on the cycler or less frequent days of therapy, which may lead to a decrease in "burnout." In a patient who is new to dialysis, incremental PD may offer a stepwise initiation to therapy. It is imperative that a patient understand that over time, as the RKF declines, more PD will be needed to achieve adequacy and maintain volume status. A recent study showed that even missing one HD treatment a month increases a patient's risk for mortality and hospitalization, and patients in some countries are more likely to miss than in other countries which suggests some cultural differences [18]. There have been no studies that show that missing one PD treatment a month increases the risk for mortality or hospitalization likely due to the fact that PD is typically performed 7 days a week. This daily therapy is what leads patients to develop burnout; therefore, incremental PD allows patients to have some flexibility in their treatments. Further studies are needed to evaluate the improvement in quality of life in patients on incremental PD when compared to those on conventional PD or conventional HD.

Physicians and sometimes patients and their caregivers want to know what maximizes their chances of survival on a specific type of therapy in addition to improving their quality of life. With a lower dose of dialysis prescribed, outcomes data for both technique survival and patient mortality is needed. As noted previously, adequacy using Kt/V_{urea} is not a predictor of survival in PD. Various groups have evaluated

both technique and mortality outcomes in patients on incremental PD. A Canadian cohort found no significant difference in mortality between patients on incremental PD versus those on conventional PD [3]. An Italian study found that more patients are being placed on incremental PD, particularly with CAPD, and that larger clinics tend to use incremental PD more in their patients [19]. Another study showed that using three versus four daily exchanges in CAPD had no significant difference on RKF or urine volume [16]. As more nephrologists become comfortable with manipulating dialysis prescriptions based on RKF, more patients will likely be transitioned to incremental PD who have adequate RKF.

Prescription Design

The challenging part of developing such a modified prescription is knowing how much dialysis is necessary to deliver an adequate dose of dialysis while maintaining patients in a euvolemic state. Guest et al. developed a computer-generated model using urea kinetics to determine what volume of dialysate would be needed to achieve a weekly Kt/V_{urea} of 1.7 in patients with various degrees of RKF using CAPD [20]. As would be expected, as the RKF declines, significantly more volume or higher dextrose-containing solutions are needed to achieve the target Kt/V_{urea} and maintain adequate UF. Another study was also performed using kinetic modeling to determine what volume of dialysate would be needed to perform thrice-weekly PD to achieve the target Kt/V_{urea} [21]. These types of studies are great to explain the theory of why a decreased total volume of dialysate can still achieve target adequacy and UF goals, and the clinical studies outlined previously validate the outcomes of these prescriptions. However, further studies and tools are needed to be developed for physicians to easily calculate necessary volumes of dialysis based on RKF so that prescriptions can be designed when a patient initially starts dialysis. As stated above, the peritoneal membrane and the nephron have different effects on solute clearance, so simply adding the Kt/V_{urea} from both is a gross oversimplification of clearance.

After initiation, adequacy should be measured to ensure appropriate adequacy is achieved. It is equally important to measure a 24-hour urine monthly to assess RKF so that if there is a precipitous drop in RKF for any reason, an appropriate increase in the dialysis prescription can be made. This can ensure patient safety when performing incremental PD (Fig. 23.2).

Incremental PD and Incremental HD

Incremental PD cannot be discussed without also reviewing the concept of incremental HD. As noted previously, incremental HD is defined as HD fewer than three times a week. Recommended dose of dialysis as measured by adequacy for various

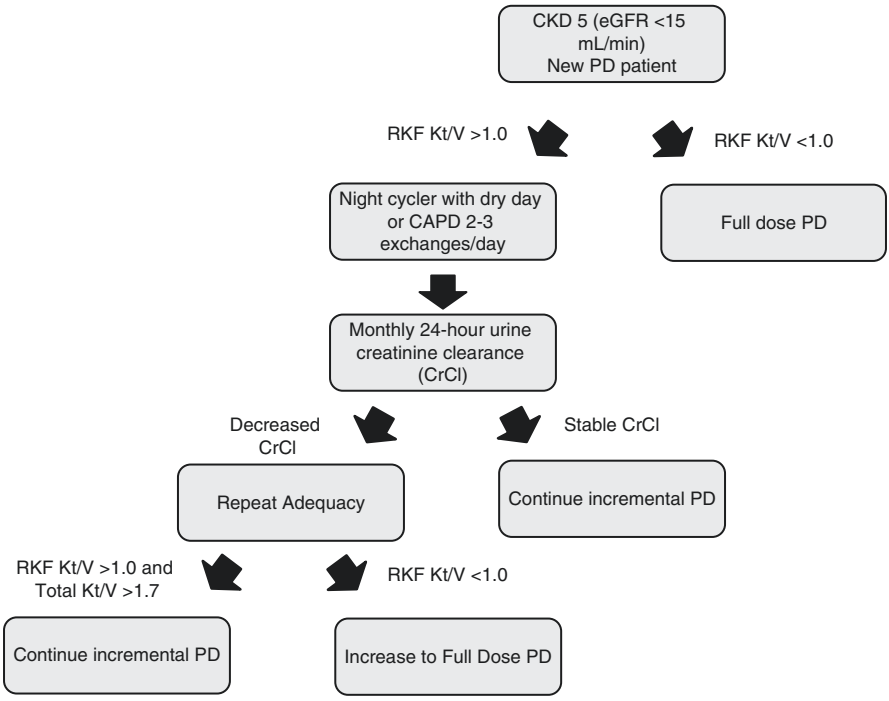

Fig. 23.2 Designing a peritoneal dialysis prescription for an incident ESKD patient starting PD

governing bodies based on recommended guidelines [22] has been established through hemodialysis and peritoneal dialysis trials evaluating clearance and mortality [7, 23, 24]. For PD, as noted previously, a weekly Kt/V_{urea} should be ≥1.7, and for HD, the weekly Kt/V_{urea} should be ≥3.6 with a minimum single pool Kt/V_{urea} of ≥1.2. However, currently, particularly in the United States, RKF is not considered when calculating Kt/V_{urea} for HD patients, and the current recommendation of the minimum single pool $Kt/V_{urea} \geq 1.2$ is solely based on the contribution of the hemodialysis treatment. Furthermore, with the current in-center HD model of thrice-weekly HD in the United States, incremental HD is difficult to perform from a regulatory and staffing standpoint, particularly in dialysis clinics within the large dialysis organizations that build their models for staffing and utilization of HD chairs on a thrice-weekly model. It is also difficult to obtain appropriate adequacy targets in incremental HD for the in-center patient if the RKF component is not measured. The National Kidney Foundation guidelines from 2015 suggest a target standardized Kt/V of 2.3 per week, but the calculation also includes the RKF component [22].

The average thrice-weekly HD patient spends between 3 and 4 hours at each HD treatment. This is a cumulative time on therapy of 9–12 hours a week, which does not include transportation time to and from the facility, wait time before the chair is available and the machine is prepared, cannulation of the access, removal of the needles and achieving hemostasis, and any pre- and post-assessments by facility nursing staff. When also considering these factors, patient may spend up to 20 or

more hours a week away from home and "getting dialyzed." As discussed previously, data has shown that HD decreases RKF faster than PD [8]. However, a recent meta-analysis by Garofalo et al. showed that both incremental PD and incremental HD had less loss of RKF in the first year when compared to full-dose dialysis [25], though better prospective trials are needed to distinguish further the benefit between these approaches.

Performing less frequent HD not only may preserve RKF but also decreases the amount of time a patient is spending during their week "getting dialyzed." This may contribute to a better quality of life as well. Further studies are needed to evaluate this concept. There are many studies published evaluating various benefits of an approach of incremental HD including maintenance of RKF, cost, and quality of life [26–29].

Ultimately, the key to any incremental dialysis approach is ensuring the patient is receiving the optimal type of dialysis to achieve clearance of uremic toxins, maintain appropriate volume status, and improve their quality of life. This may be achieved by the incremental kidney replacement therapies when a patient has a higher eGFR, but clinicians need to be mindful of RKF decline and appropriately adjust dialysis prescription to maintain these clinical outcomes (Table 23.1).

In summary, patients can do well with incremental PD prescriptions. These prescriptions decrease the amount of dextrose exposure to the peritoneal membrane while maintaining RKF and helping patients with burnout due to the burden of therapy (Table 23.2). This can all be done while maintaining adequate dialysis,

Table 23.1 Key features between incremental HD, incremental PD, conventional CAPD, CCPD, and HD

	Incremental CAPD	Conventional CAPD	Incremental CCPD	Conventional CCPD	Incremental HD	Conventional HD
Time on therapy	<24 hours (1–3 exchanges)	24 hours (4–5 exchanges)	<8 hours (overnight cycler, dry day or less than 7 days a week)	24 hours (overnight CCPD with day dwell)	2–4 hours per treatment, 1–2 times a week	3–4 hours per treatment, 3 times per week
Kt/V_{urea}	RKF ≥ 1.0 Total ≥ 1.7	RKF <1.0 Total ≥ 1.7	RKF ≥ 1.0 Total ≥ 1.7	RKF < 1.0 Total ≥ 1.7	Total weekly ≥2.1	Per treatment ≥1.2
RKF contribution	Necessary	N/A	Necessary	N/A	Necessary	N/A

Table 23.2 Advantages and disadvantages to incremental PD

Advantages	Disadvantages
Utilization of RKF for maximal solute clearance	Monthly 24-hour urine collections
Maintenance of RKF	Patient refusal to increase prescription as RKF decreases
Decreased number of exchanges	Electrolyte disturbances
Decreased waste with less utilization of dialysate	Uremia
Decreased risk for peritonitis with fewer exchanges in CAPD	Hypervolemia
Improved quality of life	
Decreased dextrose exposure to peritoneum	

obtaining euvolemia, and decreasing costs and waste by using less supplies when unnecessary.

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Chapter 24
Pediatric Peritoneal Dialysis

Raj Munshi and Bradley A. Warady

Introduction and Epidemiology

The prevalence of end-stage kidney disease (ESKD) in children (<21 years of age) is 20-fold less than that in adults [1–3], with an incidence that varies from 4 to 14 per million age-related population (pmarp) globally, with the highest incidence rates in developed countries [4]. In 2016, kidney replacement therapy was provided to children in 84 countries [4]. The incidence rate of ESKD in those younger than 20 years of age among European countries was reported to be 8.3 pmarp, with a prevalence of 58 pmarp from 2009 to 2011. In the United States, the point prevalence of children aged 0–21 years with ESKD was 99.1 per million population (pmp) in 2016 [1]. The prevalence in the United States has remained stable, but the incidence rate has decreased by 21.1% from 17.5 pmp in 2004 to 13.8 pmp in 2016 [1].

The primary causes for ESKD in children are congenital anomalies of the kidney and urinary tract (CAKUT) and primary glomerular disease, with CAKUT being the most common cause in Europe and Australia/New Zealand and primary glomerular disease slightly more prevalent in the United States [1–3].

In Australia and New Zealand, 70% of prevalent pediatric ESKD patients treated with dialysis have been reported to receive peritoneal dialysis (PD). Among all countries, children less than 10 years are more likely to be on peritoneal dialysis than hemodialysis (HD) [1–3]. Peritoneal dialysis is often the preferred modality in children as it allows vascular access to be avoided, which can be particularly difficult to maintain free of complications in a young child. Peritoneal dialysis is also

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Table 24.1 Absolute and relative contraindications for peritoneal dialysis

Absolute contraindication	Relative contraindication
Abdominal wall defects (i.e., omphalocele or gastroschisis)	Presence of ileostomy and colostomies
Bladder exstrophy	Infants with significant organomegaly
Diaphragmatic hernia	Inadequate living situation for home dialysis
Obliterated peritoneal cavity	Lack of appropriate caregiver support
Peritoneal membrane failure	Impending/recent major abdominal surgery
	Imminent transplantation

associated with more regular school attendance, better hemodynamic and metabolic control with less stringent dietary restrictions, and better preservation of residual kidney function than HD [5, 6]. Finally, few absolute and relative contraindications exist for the performance of PD in children (Table 24.1). In this chapter, we will discuss peritoneal dialysis therapy for infants and children with ESKD.

Access

Catheter Characteristics

A well-functioning access is mandatory for the successful performance of PD. The Tenckhoff catheter remains the most common catheter used for chronic PD in children [7]. The catheter is composed of siliconized rubber, with an intraperitoneal segment which can be straight or curled, and one or two Dacron cuffs. The subcutaneous tunnel configuration of the catheter can be either straight or with a preformed curve to the catheter described as the swan neck configuration [7, 8]. The three possible orientations of the catheter exit site are upward, lateral, or downward. Current data (2007–2015) from the International Pediatric Peritoneal Dialysis Network (IPPN) Registry derived from more than 2000 patients from 105 pediatric nephrology centers in 38 countries and recent data (2011–2014) from 734 children cared for in 29 participating sites of the Standardizing Care to Improve Outcomes in Pediatric ESRD (SCOPE) Collaborative have demonstrated that the majority of catheters used in children were Tenckhoff catheters with a curled intraperitoneal segment, with two cuffs, a swan neck tunnel configuration, and either a lateral or downward exit site orientation (Table 24.2) [9, 10]. In most (64.3%) cases described in SCOPE, the catheter was accompanied by a titanium adapter. Pediatric curled catheter size varies from 42 cm to 62.5 cm from cuff to tip. For infants, 23-cm catheters from cuff to tip are available.

There is no clear advantage between the single- and double-cuff catheters when the single cuff is placed in the rectus sheath as compared to a subcutaneous

Table 24.2 Catheter characteristics [9, 10]

	IPPN (n = 2453)	SCOPE (n = 734)
Catheter (%)		
Tenckhoff	95.9	96.8
Intraperitoneal configuration (%)		
Curled	68.5	94.1
Straight	27.4	5.9
Cuffs (%)		
Two	86.3	73.3
One	13.7	26.8
Subcutaneous tunnel (%)		
Swan neck	62.9	68.6
Straight	37.1	28.1
Exit site (%)		
Up	14.1	3.9
Down	53	51.5
Lateral	32.9	44.6

placement [11]. Whereas data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) initially suggested that double-cuff catheters were associated with reduced episodes of peritonitis and exit site infections [12], this experience was not replicated in recent studies from SCOPE and the IPPN [9]. The IPPN data also did not reveal the number of cuffs to be a risk factor for catheter revision [10].

The theoretical benefit for the swan neck configuration is that it allows the catheter to exit the skin in a downward orientation while allowing the distal end of the catheter to enter the peritoneal cavity in an unstressed condition, thus reducing the risk for migration out of the pelvis. The SCOPE collaborative did not find a difference in peritonitis rates when comparing catheters with swan neck and straight tunnels [9]. The SCOPE collaborative, though, did find that upward orientation of the exit site and a plastic adapter as compared to titanium were associated with an increased risk of infection [9].

The presumed advantages of the curled intraperitoneal catheter segment include an increased number of side holes for the exchange of fluid; better separation between the bowel and abdominal wall, thus protecting the holes from obstruction from bowel or omentum; less pain from inflow due to dispersion of the fluid; and potentially less trauma to the bowel [8]. A Cochrane meta-analysis of 13 randomized controlled trials in 2013 demonstrated no difference in the incidence of exit site or tunnel infections, peritonitis, or catheter malfunction due to migration or leakage when comparing coiled and straight catheters among adult patients [13]. Surprisingly, recent data from the IPPN demonstrated that the curled catheter with a swan neck tunnel was associated with a significantly higher risk for access revision (OR, 1.3; 1.04–1.63) [10].

Surgical Considerations

Preoperative considerations include ensuring that any constipation is treated, as constipation is associated with post-placement catheter migration and peritonitis [14]. The child should be examined to determine the best placement for the catheter exit site. In children who are in diapers, the exit site should be above the diaper area to reduce the risk for contamination. Many young children with CAKUT also have stomas (e.g., vesicostomy, ureterostomy, and colostomy), which will also influence where the exit site is placed. To help meet nutritional demands, children often require a gastrostomy tube/button that should ideally be contralateral to the location of the exit site. Treatment guidelines also suggest that gastrostomy creation should be performed either prior to or concurrently with PD catheter placement to reduce the risk of peritonitis [15–17]. As in adults, the belt line should also be avoided when selecting the exit site location, and the exit site should be lateral or downward facing and on the opposite side of any stoma; consideration for a chest location of the exit site may be necessary on occasion [18].

The preoperative exam should also include an inspection for hernias, as the frequency of hernias in PD patients is reported to be between 11.8% and 53%, with a higher risk in the youngest patients [19–21]. Inguinal hernias usually occur in the first year of life; they are often bilateral and most require surgical correction. Umbilical hernias can also worsen as a result of the increased intraperitoneal pressure that occurs during PD. Due to the high prevalence of hernias, peritoneography or laparoscopic inspection is performed at the time of catheter placement, and if detected, surgical correction of the hernia is performed at that time.

Preoperative antibiotic administration within 60 minutes prior to skin incision has been shown to reduce the risk of early peritonitis after placement of the PD catheter [18]. A first-generation cephalosporin is recommended, but the antimicrobial choice should be tailored based on local susceptibilities and public health considerations. Vancomycin is recommended if a patient is colonized with methicillin-resistant *Staphylococcus aureus*. In children with lower gastrointestinal stoma, a single dose of an aminoglycoside is also recommended [18].

The laparoscopic approach to catheter placement in children is preferred over the open surgical technique [22–24]. The laparoscopic approach allows for smaller peritoneal incisions, thus reducing the risk of dialysate leakage. It also allows for inspection of the abdomen for hernias. Compared to the open surgical placement in an adult study, the laparoscopic approach is associated with a lower rate of catheter flow dysfunction (6–6.9% vs. 10.4–17.1%) [22]. During placement of the catheter, an omentectomy/omentopexy is also performed at some centers. Performance of an omentectomy has reduced the rate of catheter occlusion among children from 10–22.7% when it is not performed to 5% [25, 26]. If not performed with the initial catheter placement, a subsequent omentectomy can be performed if there is omental wrapping of the catheter resulting in obstruction.

The goals of early exit site care post-catheter placement are to prevent bacterial colonization during the healing phase and to prevent local trauma by minimizing

mobilization of the catheter until the exit site is healed [27, 28]. The dialysis catheter should be secured via an adhesive tape to prevent torqueing, but sutures at the exit site are to be avoided as the sutures themselves may act as a reservoir for bacteria. The dressing should have multiple layers of gauze to wick away any discharge during early healing, and dressing changes should be limited to once weekly by a professional trained in sterile technique until the site is healed, unless the dressing is soiled or wet. An occlusive dressing should not be used as it may trap the fluid at the exit site and create an environment for bacterial growth. Submersion of the catheter or exit site in water via bathing, showering, or swimming should be avoided during healing.

General recommendations are to delay the use of the catheter for regular dialysis when possible, for at least 10–14 days [18, 29]. This is due to the concern for leakage of dialysis fluid to increase the risk of infection [30, 31]. The risk of leakage with early use (<7 days) was not seen in the Italian peritoneal dialysis registry or in the recent IPPN registry [10, 32]. However, data from the SCOPE collaborative demonstrated that early catheter use (<14 days after insertion) was associated with an increased risk of peritonitis (OR. 1.9; 1.2–3.1, $p < 0.001$) within 60 days of insertion [33].

The IPPN registry recently published its experience with PD catheter revisions from 2007 to 2015. Overall, the revision rate was 1 per 83.2 patient-months. Risk factors included younger age, diagnosis of CAKUT, use of a swan neck tunnel with a curled intraperitoneal portion, and presence of an ostomy. Indications for access revision were mechanical dysfunction (60%), dialysate leakage (6%), peritonitis (16%), and exit site/tunnel infection (12%). In 6%, the reason was not reported [10].

Chronic Catheter Care

The goal of chronic exit site care is to prevent the development of exit site and tunnel infections. Both early and chronic exit site cares mandate cleansing of the exit site with a nonirritating, nontoxic cleansing agent. Numerous cleansing agents are available such as povidone-iodine, chlorhexidine, Amuchina solution/hypochlorite solution, hydrogen peroxide, sodium hypochlorite, octenidine, etc., with none proving superiority [18, 34]. In the SCOPE collaborative, the most common cleansing agent used is sodium hypochlorite, but many centers do not use any cleansing solution after the PD catheter tract has healed. The optimal frequency of dressing changes and exit site cleansing is unclear, but current recommendations from the adult ISPD guidelines are to perform catheter exit site care at least twice weekly and every time after a shower [34]. Regular application of a topical antibiotic at the exit site is also recommended by the ISPD guidelines because of adult data which clearly shows that application of an antimicrobial cream or ointment at the exit site is associated with a decreased frequency of catheter-related infections [18, 29]. Mupirocin is effective against gram-positive skin flora, but its use has been associated with an increased incidence of gram-negative infections, specifically *Pseudomonas*

aeruginosa [35, 36]. A subsequent systematic review determined that gentamicin was associated with fewer exit site infections caused by gram-negative organisms and had comparable efficacy to mupirocin against gram-positive organisms [37]. The use of alternating mupirocin and gentamicin or polysporin triple compound ointment has been associated with an increased risk of fungal peritonitis and is therefore not generally recommended [38, 39]. Medicinal honey has demonstrated antimicrobial action against a broad spectrum of bacteria and fungi, including methicillin-resistant *Staphylococcus aureus* and multidrug-resistant gram-negative organisms. However, a randomized trial in adult peritoneal dialysis patients demonstrated that medicinal honey resulted in an increased risk of exit site infection and peritonitis in those with diabetes, and therefore its regular use could not be recommended [40]. Whereas these data do not extrapolate to the pediatric PD patient for whom diabetes is a rare complication, the successful use of medicinal honey has only been seen in a small series of eight children who demonstrated a reduction in infection and improvement in the appearance of the exit site [41].

Technology

Automated Cycler

Most pediatric PD patients receive some form of automated peritoneal dialysis (APD), although continuous ambulatory peritoneal dialysis (CAPD) is conducted in some regions where limited financial resources restrict the use of APD. A significant benefit of APD in children, in addition to precluding the need for PD procedures during the day in most cases, is the presence of volumetric controls at lower volumes. As described below, the ideal PD fill volume for children <2 years of age is 600–800 ml/m^2 body surface area (BSA) and in older children 1100–1400 ml/m^2, with the daytime fill generally half of the nighttime volume. Since the BSA of children younger than 2 is typically 0.2–0.5 m^2, full fill volumes for these children can range from 120 ml to 400 ml, volumes that are easily delivered by a cycler. In the United States, two companies, Fresenius and Baxter, provide peritoneal dialysis machines. The minimum fill volume for the Fresenius Liberty models is 500 ml, whereas the Baxter HomeChoice cycler allows fill volumes as low as 60–100 ml. Characteristics of a new cycler from Baxter, Amia, include a higher minimum fill volume of 300 ml, but it also permits remote monitoring of the home dialysis procedure by the dialysis center, an important development in PD technology that ideally will result in improved patient care and outcomes for children and adults.

Peritoneal Dialysis Solutions

Peritoneal dialysis solutions in children are the same as those used by adults. Available dialysis solutions are differentiated by its buffer (lactate vs. bicarbonate), osmotically or oncotically active agents (glucose or icodextrin and amino acids),

single-chamber vs. multi-chamber solution bags, and final pH of the solution (5.5–6.5 vs. 7.0–7.4). These solutions are also differentiated as biocompatible vs. incompatible. Conventional peritoneal dialysis fluids are single-bag solutions characterized by a high glucose concentration (>10–50X normal serum concentration), giving it high osmolality, high lactate concentration (>35X normal serum levels), and acidic final solution (5.5–6.5). Given the single-chamber design, lactate is chosen as the buffer to prevent precipitation of calcium and bicarbonate. Animal data has demonstrated lactate-associated toxicity such as altered cytokine release, reduction of antioxidants, and induction of neoangiogenesis [42–44].

Heat is used during the sterilization process of peritoneal dialysis solutions which, along with the prolonged storage of solutions, results in the generation of glucose degradation products that are associated with toxicity to the peritoneum. The glucose degradation products have been linked experimentally to peritoneal membrane thickening, pathologic changes to the peritoneal vasculature, and damage to the mesothelial cell lining the peritoneum [45, 46]. Glucose degradation products are precursors for advanced glycation end-product (AGE) formation that further accelerates the process of vascular and tissue aging throughout the body [47]. Data on the benefits of more biocompatible solutions, which are not available in the United States, have been mixed. An animal model demonstrated that exposure to more glucose degradation products resulted in more albuminuria, higher glomerulosclerosis index score, and tubulointerstitial damage, suggesting a role in the deterioration of residual kidney function [48]. In a prospective multicenter trial among 21 children who were randomized to either a single-chamber bag with a high generation of glucose degradation products (GDP) or a double-chamber bag with a lower concentration of GDPs, the patients dialyzed with the dual-chamber solution had a significantly reduced plasma concentration of AGEs [49]. A prospective randomized crossover trial in 28 children over 28 weeks comparing a lactate-based buffer vs. a purely bicarbonate-based buffer with a physiologic final pH demonstrated improved correction of metabolic acidosis and increased mesothelial cell mass associated with the use of the bicarbonate-based solution [50]. However, another study comparing the same lactate-based vs. pure bicarbonate-based solution in 37 children over 1 year did not demonstrate an advantage of either solution in achieving or maintaining metabolic acid/base balance. It did demonstrate improved preservation of ultrafiltration with the use of the purely bicarbonate-based solution [50]. To date, the most robust study to assess the histopathologic effect of neutral pH, biocompatible PD solutions in children performed histomorphometry and molecular analysis on 256 peritoneal and 172 omental specimens from 56 children with normal kidney function, 90 children with end-stage kidney disease at the time of catheter insertion, and 82 children undergoing PD with biocompatible solutions. There were no children undergoing PD with conventional solutions [51]. The study demonstrated early peritoneal angiogenesis (within 6 months) with a twofold increase of blood microvessel density, increased endothelial surface area, and submesothelial thickness and inflammation. As peritoneal dialysis vintage increased, so did submesothelial inflammation and epithelial to mesenchymal transition leading to submesothelial thickening that was most pronounced after 4 years of PD [51]. Based on these findings, the belief that biocompatible solutions marked by neutral pH, low-glucose degradation products, and reduced lactate better preserve the

peritoneal membrane, prevent ultrafiltration failure, and reduce peritonitis episodes due to better host defenses remains unfounded [52].

Icodextrin-based solutions, which use icodextrin instead of glucose as the osmotic agent, are characterized as being more biocompatible due to the lower concentration of glucose degradation products, no direct glucose exposure to the peritoneum, and its iso-osmolar property. Icodextrin is a large glucose polymer derived from corn starch and, due to its large size (1.7–45 KD), is not avidly transported across the peritoneum resulting in a higher reflection coefficient and improvement in solute and water removal. Icodextrin drives ultrafiltration via the generation of colloidal osmotic forces similar to albumin. As compared to glucose-containing solutions, ultrafiltration increases over time associated with the use of icodextrin and is sustained for over 12 hours; in turn, it is recommended that icodextrin be utilized once a day during the longest dwell in patients with suboptimal ultrafiltration capacity. In young infants, the efficacy of icodextrin can be limited, whereas its efficacy in older children may be dependent on the long dwell exchange volume, with a minimum fill volume of 550 ml/m^2 being associated with improved icodextrin-related ultrafiltration [53, 54].

Amino acid (1.1%)-based peritoneal dialysis solutions are potentially more biocompatible due to a lack of glucose or glucose degradation product exposure of the peritoneum. Nutritionally, they offer a source of calories other than glucose. The biocompatibility of amino acid solutions has, however, been questioned after experimental studies have demonstrated increased inflammatory markers such as IL-6 [55], suppressed leukocyte recruitment [56], and increased neoangiogenesis associated with their use [57]. Alternatively, long-term exposure in rats demonstrated preserved ultrafiltration capacity similar to what occurs with dual-chambered solutions [58]. At present, there is very limited use of these solutions in pediatrics as alternative means to address nutritional needs, such as supplemental tube feedings, are successful.

A recent Cochrane systematic review comparing biocompatible peritoneal dialysis solutions (with the absence of amino acid solutions) to conventional solutions demonstrated that low GDP, neutral pH solutions improved residual kidney function and urine volume preservation, although this finding was seriously confounded by reduced ultrafiltration with these solutions. The study was inconclusive in terms of the impact on differences in peritonitis rates and other adverse events such as hospitalizations. Icodextrin was associated with reduced volume excess status without compromising residual kidney function. The IPPN registry also found that biocompatible solutions were associated with improved linear growth among children who initiated dialysis at age younger than 2 years. Interestingly, the IPPN found that the use of amino acid solutions was not associated with better linear growth [59].

Prescribing Peritoneal Dialysis to Children

The goals of PD in children, as in all forms of kidney replacement therapy, are to achieve and maintain euvolemia and normotension; optimize nutritional status, growth, and development; and limit medications. Small solute clearance has also

been a recommended outcome metric, and the 2006 KDOQI guidelines recommend a weekly total (dialysis plus residual kidney function) Kt/V_{urea} of ≥1.8. More recently, however, a decreased emphasis on Kt/V is being recommended because of a lack of evidence supporting a correlation between Kt/V and outcome in PD patients [60]. At the same time, patient- and caregiver-reported outcomes are being recognized as important contributors to the prescription process and shared decision-making for chronic PD and will be incorporated into the soon-to-be published recommendation from the International Society for Peritoneal Dialysis (ISPD) for high-quality care in both children and adult PD patients [61, 62].

An emphasis on phosphorus management because of the morbidity and mortality associated with cardiovascular disease in the PD population will also be highlighted in the pediatric recommendations. As stated above, the goal fill volume in children age >2 years is 1100–1400 ml/m^2 at night while supine and 600–800 ml/m^2 for children <2 years. Calculating fill volume based on weight (30–50 ml/kg) risks underfilling the peritoneum resulting in suboptimal dialysis. In contrast, because there is a direct relationship between the peritoneal surface area and BSA in infants and young children, scaling the fill volume by BSA optimizes recruitment of the peritoneum for dialysis [63]. The smaller fill volume in children <2 years is based on the tolerability of the fill volume for infants. Increasing fill volumes above 1400 ml/m^2 for older children and adolescents risks increasing the intraperitoneal pressure too high and increasing morbidity from pain, dyspnea, hydrothorax, hernia formation, gastroesophageal reflux, and loss of ultrafiltration due to increased lymphatic absorption [64]. The relationship between hydrostatic intraperitoneal pressure and increasing intraperitoneal fill volumes in children has been well studied by Fischbach (Table 24.3) [65].

The peritoneal equilibration test (PET) continues to be the most frequently used clinical tool to assess the peritoneal membrane transport capacity and assist the PD prescription process. Modification of the PET in children from the procedure conducted in adults consists of using a standardized fill volume to 1100 ml/m^2 in children >2 years and the prescribed fill volume (usually 600–800 ml/m^2) in children <2 years. A 2.5% dextrose solution is utilized for the PET, unless the evaluation is being performed to evaluate ultrafiltration failure and function of aquaporin channels in which case a 4.25% dextrose solution is utilized [66]. Both the traditional 4-hour and the modified short (2-hour) PET have been validated in children [67, 68].

In general, most children on automated peritoneal dialysis (APD) are prescribed dwell times of around 1 hour and receive nightly therapy for 8–12 hours. In some cases, characterization of the membrane transport capacity with the PET may

Table 24.3 Intraperitoneal pressure as related to intraperitoneal volume [63]

	Intraperitoneal pressure (cmH_20)	Intraperitoneal volume (ml/m^2 BSA)
Adults	13.4 ± 3.1	1585 ± 235
Children > 2 years	5.2 ± 2.6	600 ± 50
	8.2 ± 3.8	990 ± 160
	14.1 ± 3.6	1400 ± 50

permit fewer exchanges with no less efficacy. Nightly APD allows for optimizing the fill volume with the lowest increase in intraperitoneal pressure while patients are supine and allows children to be free to attend a full day of school during the day without having to conduct dialysis. Adjustment of the dwell time should be made based on clinical and laboratory parameters such as growth, residual kidney function, peritoneal membrane function, phosphate clearance, and ultrafiltration [64]. In all cases, the use of dialysis solution with the lowest dextrose concentration should be prescribed because of the potential membrane injury that can occur with hypertonic solutions and limit the use of PD for children who require a lifetime of kidney replacement therapy [69].

Infectious Complications

Exit site infections and peritonitis continue to be a major source of morbidity and mortality in children who receive chronic PD. A recent study from the SCOPE collaborative demonstrated an exit site infection rate of 0.25 episodes per dialysis year among 857 catheters between 2001 and 2014. Age less than 2 years was protective, while children 6–12 years of age had the highest risk for exit site infection. Having a stoma was not associated with an increased risk for development of an exit site infection. Finally, 6% of patients with an exit site infection developed peritonitis [70].

The diagnosis of peritonitis is considered when the effluent is cloudy and the patient has abdominal pain with or without a fever. An empiric diagnosis of peritonitis is made if the effluent white blood cell count is greater than 100/mm^3 and at least 50% of the WBCs are polymorphonuclear leukocytes [18]. Blood culture bottles are recommended to be the preferred technique for bacterial culture of the PD effluent in the adult peritonitis guidelines, whereas centrifugation of 50 ml of PD effluent at 3000 g for 15 minutes, followed by resuspension of pellet in 5–10 ml that is directly inoculated on solid culture media, is recommended in the pediatric guidelines. Both guidelines accept both approaches as suitable techniques to culture the PD effluent, with a goal of reducing the frequency of culture-negative peritonitis and isolating causative organisms to facilitate appropriate antibiotic therapy.

Peritonitis episodes are costly to the medical system as hospitalization for peritonitis is associated with a median cost of $13,665 (7871–$28,434), which does not include the cost to the family from missed work, missed school, finding care for siblings, etc. [71]. Recent data from SCOPE has demonstrated a peritonitis rate of 0.46 infections per patient year [9]. The organism distribution was gram-positive (38%), culture-negative (25%), gram-negative (19%), polymicrobial (10%), and fungal (8%). *Staphylococcus epidermidis* was the most common gram-positive organism, and *pseudomonas* was the most common gram-negative organism identified in the SCOPE. Risk factors for infections included age ≤2 years, upward

directed catheter exit site, and touch contamination [9]. Of the peritonitis episodes, 77% resolved with treatment, 6% required temporary removal of the catheter, and 12% resulted in a change in dialysis modality [9]. Fungal peritonitis was associated with an increased rate of hospitalization, catheter removal, and technique failure as compared to bacterial and culture-negative peritonitis [72]. Interestingly, in nearly 50% of patients who experienced fungal peritonitis, this infection was their first peritonitis episode, and only 17% of patients had a history of peritonitis within 30 days of the fungal peritonitis episode [72]. The only independent risk factor for fungal peritonitis was age less than 2 years at the time of catheter insertion.

International data from the IPPN from 2001 to 2004 revealed a peritonitis rate of 1.4 infections per patient year [73]. The study demonstrated geographic variability in organism type (Fig. 24.1) and outcomes. Overall technique failure requiring change in dialysis modality was 8%, and 89% of episodes were successfully treated with intraperitoneal antibiotics [73]. More recent data from IPPN demonstrates a rate of 0.44 infections per patient year among 3162 patients from 43 countries [74].

Infants appear to be the most vulnerable population for infection, as has been demonstrated by the NAPRTCS for decades. The SCOPE collaborative recently investigated the epidemiology and risk factors for peritonitis in children <1 year of age, from the time their PD catheter was placed, even prior to being discharged home for outpatient dialysis. Over an observational period of 1 year following PD catheter placement, this cohort demonstrated an overall annualized peritonitis rate of 0.76 infections per patient year, with an exceptionally high rate of 1.73 infections per patient year during the initial hospitalization prior to hospital discharge [75]. Risk factors for infection included age <30 days at the time of catheter placement,

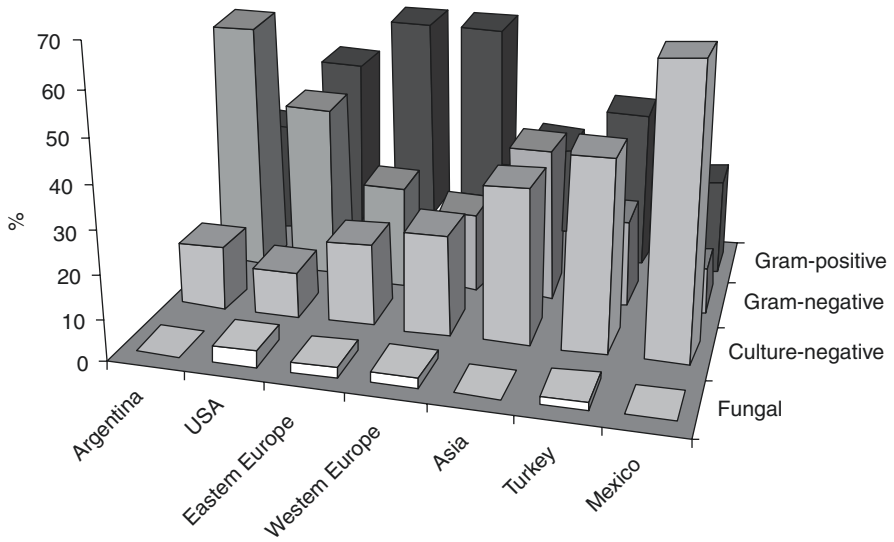

Fig. 24.1 Distribution of culture results according to regions [71]

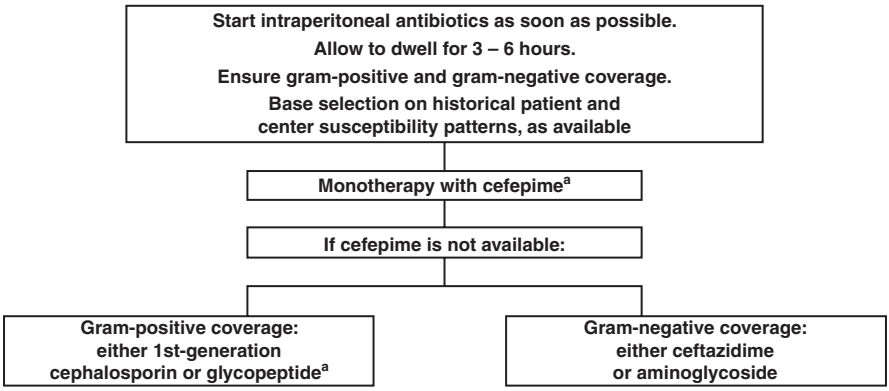

Fig. 24.2 Empiric therapy [18]. [a]If the center's rate of methicillin-resistant *Staphylococcus aureus* (MRSA) exceeds 10%, or if the patient has history of MRSA infection or colonization, glycopeptide (vancomycin or teicoplanin) should be added to cefepime or should replace the first-generation cephalosporin for gram-positive coverage. Glycopeptide use can also be considered if the patient has a history of severe allergy to penicillins and cephalosporins

polycystic kidney disease as primary kidney disorder, history of nephrectomy prior to or concurrent with the PD catheter placement, and insertion of a gastrostomy tube after placement of a PD catheter [75]. Infants who experienced peritonitis had reduced survival (86.3 vs. 95.6%) and a longer initial hospitalization (82 vs. 60 days) as compared to those infants who were infection-free [75].

The International Society for Peritoneal Dialysis (ISPD) has provided guidelines for the prevention and treatment of exit site infections and peritonitis in children [18, 34]. Recommendations for the empiric treatment (Fig. 24.2) of peritonitis highlight the need for antibiotic therapy that addresses gram-positive and gram-negative infections, with consideration of fungal prophylaxis with antibiotic exposure. Also emphasized is the fact that intraperitoneal antibiotic therapy is preferred for patients suspected to have peritonitis, unless bacteremia is suspected in which case intravenous antibiotic therapy is required. Recommendations for modification of the antibiotic therapy once the organism has been isolated and for the duration of therapy are also included in the guidelines. As noted above from SCOPE and as demonstrated by the IPPN, in most cases, attention to these recommendations will result in resolution of the infection. However, at least temporary catheter removal is often necessary in the setting of refractory peritonitis to preserve membrane function. Table 24.4 describes recommendations/catheter care bundles for preventing peritoneal dialysis catheter-related infections from the SCOPE collaborative which are based on the 2012 pediatric ISPD guidelines and which have been associated with a substantial decrease in the peritonitis rate within SCOPE participating sites [18, 76, 77]. The recommendations are categorized into three broad categories: peritoneal dialysis catheter insertion bundle, patient and caregiver training bundle, and follow-up care bundle.

Table 24.4 Standardizing Care to Improve Outcomes in Pediatric ESRD (SCOPE) collaborative practice bundles to prevent peritoneal dialysis catheter-related infections [74]

Peritoneal dialysis (PD) catheter insertion bundle	Patient and caregiver training bundle	Follow-up care bundle
Exit site (ES) orientation should be downward or lateral position	Training should be performed by a trained pediatric PD nurse	Perform objective score of exit site per ISPD guidelines [18]
Single-dose of first-generation cephalosporin (vancomycin if MRSA) is administered within 60 minutes prior to incision	Training should cover all aspects of the ISPD guidelines [18] and include specific procedures for hand hygiene per WHO guidelines, ES care, aseptic connection technique	Review key aspects of hand hygiene per WHO guidelines, ES care, and aseptic technique
No sutures at the exit site	Trainer to trainee (or family) ratio should be 1:1	Repeat concept and demonstration test every 6 months
ES dressing should not be changed for 7 days postoperative unless soiled, loose, or damp	Appropriate teaching aides and attention to adult learning techniques should be utilized	Query for touch contaminations or other breaks in aseptic technique and whether they were treated per ISPD guidelines
ES dressing should be changed by a health professional if changed within 7 days postoperative	Post-training concept and demonstration test should be administered	Patient/caregiver to receive training after a peritonitis episode
Sterile procedure should be utilized for dressing changes until ES is healed	Home visit performed	
PD catheter is immobilized until ES is healed		
PD catheter is not used for PD for at least 14 postoperative days		

Noninfectious Complications

Mechanical complications were the most common cause of catheter revisions in the first year post-PD catheter insertion among participants from the IPPN registry [10]. Impairment of flow of the peritoneal fluid, either into the peritoneal cavity or during drainage, can occur due to luminal obstruction with fibrin or blood, catheter malposition, constipation, extraluminal catheter occlusion by omentum or adhesions, or secondary to kinking of the catheter. Leakage of the peritoneal fluid from the catheter exit site is a risk early post-catheter placement, usually in the first month post-insertion [10]. Increased intraperitoneal pressure, a weak abdominal wall, and the location of PD catheter placement can also increase the risk for leakage. Intraperitoneal pressure will be increased with large fill volumes, as well as with patient activities such as exercise or aggressive coughing. Very young children or

children with a history of numerous abdominal surgeries may have a weak abdominal wall. Children with Eagle-Barrett syndrome (EBS) which consists of a triad of abdominal muscle deficiency giving them the characteristic prune belly appearance, urinary tract abnormalities, and cryptorchidism also require special consideration. Their abdominal wall defect often raises concern regarding a possible increased risk of dialysate leakage, outflow failure, and infection. A single-center retrospective study in six EBS patients with nine non-EBS peritoneal dialysis patient controls did not, however, demonstrate an increased risk for infectious and noninfectious complications [78]. An earlier retrospective study among six patients with EBS without controls demonstrated better outcomes among patients with a laparoscopic approach to catheter placement [79]. Implantation of the catheter in the midline of the rectus as compared to a paramedian approach in all children has also been associated with an increased risk for leakage [80]. The placement of fibrin glue at the time of PD catheter placement has decreased the frequency of dialysate leakage associated with the early use of the catheter on occasion [81].

Pain or discomfort during filling can occur due to the sensation created from the jet of the infusing fluid, the acidity of the fluid, or cooler temperature of the fluid leading to discomfort. Adding base to the solution or using solutions with physiologic pH will often reduce discomfort during inflow. Warming the fluid and reducing the flow of the fill will also alleviate some discomfort. Pain during draining is also a not infrequent finding among patients on PD. Tidal PD, which is characterized by the maintenance of a prescribed residual peritoneal fluid volume in-between exchanges, has proven to alleviate “drain pain” in many patients [82].

Development of a hydrothorax, where there is a pleuroperitoneal connection, is the result of leakage of peritoneal fluid into the pleural space. This usually occurs in the right chest, and risk factors include an abnormal lymphatic system, increased intraperitoneal pressure, and congenital diaphragmatic defects [83]. Therapy typically consists of temporary cessation of PD. In those patients for whom such an approach is not possible, frequent small volume exchanges can be trialed. Thoracocentesis is required if the patient has shortness of breath. If conservative management of temporary cessation of peritoneal dialysis is not successful, pleurodesis or surgical repair of the diaphragmatic hernia may be required [84].

Encapsulating peritoneal sclerosis (EPS) is a serious complication of long-term chronic peritoneal dialysis that results from extensive sclerotic thickening of the peritoneum that leads to encasement of bowel loops and a markedly increased risk for morbidity and mortality. Clinically, patients can present with significant abdominal pain, abdominal mass, weight loss, emesis, fever, constipation, ultrafiltration failure, and/or hemoperitoneum. The process is usually slow and unlike an acute abdomen [85]. This diagnosis should be considered in patients on long-term PD who experience a progressive decrease of their ultrafiltration capacity. In regions such as Japan where many patients receive dialysis for years, the permitted duration of PD is limited as a strategy to decrease the development of EPS [85].

Anterior ischemic optic neuropathy is an acute ischemic disorder of the optic nerve head that results in sudden blindness in about 1% of children on chronic PD [86]. The greatest risk for this complication appears to be the development of

hyponatremic hypovolemic hypotension during infancy. Infants are particularly prone to hyponatremia due to their more efficient clearance of sodium as compared to older children and adults [87]. Convective clearance of sodium in infants is also higher as they require a relatively larger ultrafiltration volume per unit BSA due to their solely liquid diet. Sources of nutrition for infants (breast milk and formula) are also low in sodium. In those infants who are polyuric, the urine is yet another source of sodium loss. Thus, infants on chronic PD typically require sodium supplementation to keep up with losses, prevent hyponatremic hypovolemia, and optimize growth [86].

Outcome: Morbidity and Mortality

Growth limitation is a major morbidity seen among children on peritoneal dialysis, with the highest risk of short stature among children who start dialysis at a younger age [1, 2, 88]. Correction of acidosis, control of osteodystrophy, provision of adequate nutrition, and use of recombinant growth hormone therapy are important interventions designed to optimize growth [17]. School absenteeism is also high among children with ESKD, but in Australia/New Zealand, more children on peritoneal dialysis or with functioning transplant were able to attend unmodified school as compared to those treated with hemodialysis [3]. Anemia is also common in children on PD, with hemoglobin values >11 g/dL associated with improved survival [89]. Mortality is much higher in children with ESKD as compared to their age-matched healthy population [1–3]. Mortality is lowest among transplant patients, with all-cause mortality rates among hemodialysis and peritoneal dialysis patients in the United States being 5.4 and 2.2 times higher than in transplanted patients, respectively [1]. The primary causes of mortality in children on dialysis are cardiovascular disease and infection.

Unique Population: Infants

Infants with ESKD, defined as patients <1 year of age, are a population that push the technological and ethical limitations in medicine. Technical challenges include the patient's small size; their thin subcutaneous tissue layer for tracking and securing the PD catheter; their nutritional, developmental, and infection-related challenges; and the comorbidities (e.g., cardiovascular, neurologic, pulmonary) that often exist and that increase the complexity and burden of care for parents and healthcare providers. Ethical challenges arise as decisions are being made for the patient who is not able to advocate for themselves, and decisions made by the family and providers have lifelong implications.

Infants with ESKD are at higher risk for morbidity and mortality compared to older children. At the turn of this century, only 50% of pediatric nephrologists

offered dialysis to infants, likely the result of their poor survival rate and their frequent associated comorbidities [87]. NAPRTCS data for patients initiating dialysis as infants from 1992 to 1999 revealed 73% survival at 3 years. Thankfully, in the past two decades, there have been substantial improvements in survival [90]. Data from NAPTRCS have demonstrated the overall survival of infants initiating dialysis between 2000 and 2012 to be 85%, and neonates (<30 days of age at initiation) experienced a 3-year survival of 78.6% [91]. Survival among 264 infants from 32 countries from Europe, Australia, New Zealand, and Japan who initiated chronic dialysis as neonates was 81.2% at 2 years and 76.4% at 5 years. The main causes of death in this cohort of patients were infection (35.6%) and cardiac disease (8.9%). Growth retardation was seen in 63% of patients [92]. Very recent data derived from the United States Renal Data System (USRDS) from 2000 to 2014 showed patient survival of children starting dialysis as neonates (<1 month of age) at 1 and 5 years of 86.6% and 74.6%, respectively. These results are substantially improved compared to neonates who initiated dialysis from 1990 to 1999 for whom the 1- and 5-year survival rates were 76.9% and 63.8%, respectively. This trend was also seen among infants who initiated dialysis between the ages of 1 and 12 months of life in the USRDS database where 1- and 5- year survival from 2000 to 2014 was 89.6% and 79.3% as compared to 80.8% and 61.6% from 1990 to 1999 (Fig. 24.3) [93].

Infants who survive the early period of dialysis most often receive a kidney transplant at 2–3 years of age. Most important is the fact that their success post-transplant

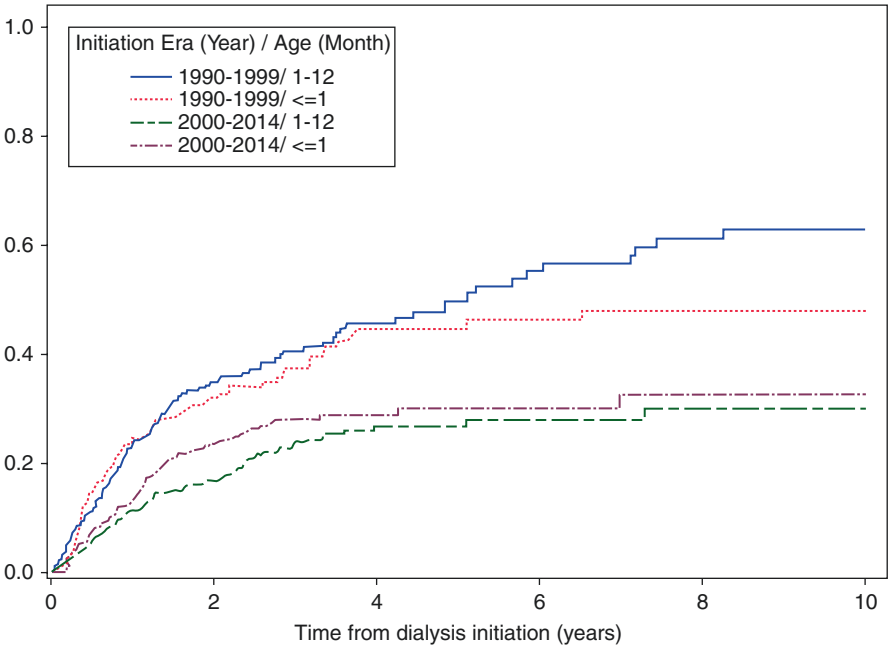

Fig. 24.3 Mortality among children initiating dialysis as neonates and infants in the USRDS database [89]

is better than all other pediatric age groups post-transplant [90, 94]. Despite these improved outcomes, additional data pertaining to short- and long-term quality of life, growth, and development are needed to better inform parents and caregivers when confronted with decisions regarding the advisability of initiating long-term dialysis therapy in this unique and often complex group of patients [95, 96].

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Chapter 25
The Principles of Drug Dosing in Peritoneal Dialysis

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Introduction

The prevalence of chronic kidney disease (CKD) is significantly increasing, impacting approximately 23 million Americans. Greater than 660,000 have end-stage kidney disease (ESKD) requiring dialysis [1]. It is estimated that in the United States, only approximately 10% of patients with ESKD receive peritoneal dialysis as kidney replacement therapy. In comparison, the utilization of PD is much higher in other countries. The latest estimate indicates that over 270,000 patients are receiving peritoneal dialysis worldwide accounting for 11% of all the kidney replacement modalities [2]. Peritoneal dialysis patients are at increased risk for infections, cardiovascular complications, anemia, and adverse drug reactions, all of which contribute to the greater morbidity and mortality compared to both the general population and CKD I–III patients [3–9]. Polypharmacy is a common problem in patients with end-stage kidney disease; work from a cross-sectional study in the province of Ontario, Canada, has established that end-stage kidney patients take, on average, 12 ± 5 distinct medications per day (about 19 pills daily), with 70% reported potentially inappropriate [10, 11].

The goal of treatment and drug dosing is to achieve therapeutic plasma concentration while reducing toxicity and avoiding major drug interactions. Studies documenting the impact that dosing and medication errors have on the morbidity and

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mortality of patients with renal insufficiency emphasize the need for careful prescribing and close monitoring of renal and extra-renal functions [12, 13]. In recent papers, even medications with wide therapeutic windows have been shown to increase morbidity, fall rates, and hospitalization rate when not adjusted appropriately based on kidney function [14, 15].

For most drugs, efficacy and safety are reported in the general population, and many studies exclude patients with advanced kidney disease, in particular peritoneal dialysis patients. Furthermore, even post hoc analyses often fail to include patients on dialysis. Any recommendations about drug dosing in peritoneal dialysis patients should be used with caution. Unfortunately, most drug dosing guidelines have been published with recommendations that are supported with limited clinical evidence or, at best, from poor-quality data and study design in HD patients [16]. Therefore, these factors complicate the picture for making drug dosing recommendations in peritoneal dialysis patients. Here, we will try, based on accurate and limited evidence-based medicine, to discuss the pharmacokinetics and dosing of common medications prescribed to patients with ESKD on peritoneal dialysis [17].

Pharmacokinetic Alterations in Chronic Kidney Disease

Broadly, pharmacokinetics defines a drug's behavior and characteristics over time in the body before reaching its therapeutic site of action and includes the study of drug absorption, distribution, metabolism, and elimination. Thorough understanding of each property and the modifiable variables, predicted plasma concentrations, drug activity, and toxicity can be estimated. The kidney is largely responsible for drug elimination but also, directly and indirectly, influences drug absorption, distribution, and metabolism [17–20]. Discerning these physiologic changes is essential, especially among healthcare providers prescribing medications in peritoneal dialysis patients [21].

Absorption

Absorption and bioavailability are dependent on the route of exposure and drug characteristics. Although intravenous administration bypasses many absorptive barriers, most medications in the outpatient are taken orally. In peritoneal dialysis patients, the absorption is hindered for many reasons. Drug interactions may occur with commonly co-prescribed medications such as phosphate binders or calcium supplements. These agents are known to chelate medications such as quinolone antibiotics, thus decreasing their absorption and therapeutic efficacy [16]. Oral absorption is limited by high molecular weight (>500 Da) and low gastrointestinal permeability. Mucosal edema might reduce epithelial permeability and thereby

affect drug absorption. This edema may enhance the absorption of hydrophobic agents while decreasing the absorption of hydrophilic agents. In states of uremia from ESKD, slowed peristalsis or uremia-induced vomiting will further hinder or delay the absorption of many oral agents [22]. Intraperitoneal (IP) drug administration can be an effective method of drug delivery in PD patients. Although many drugs can and have been administered via IP administration for many years, no standardized treatment protocol has been developed in terms of schedule, dwell time, type of drug, or carrier solution. Today, IP drug administration is limited to antibiotics and heparin. Other drugs such as insulin have been used, but most studies indicate an unpredictable bioavailability when given intraperitoneally. In addition, many drugs are not compatible with peritoneal dialysis solutions [23, 24].

Volume of Distribution

The volume of distribution (Vd) is the theoretical volume describing a drug's concentration in the blood or plasma. A small Vd is typically found among hydrophilic drugs. Although Vd is relatively constant for a given drug, factors such as obesity, thyroid function, total body protein, age, sex, kidney function, and volume status can all influence this parameter. Volume status is important, especially in patients with more advanced kidney disease such as peritoneal dialysis patients given the predisposition to become volume overloaded. Compartmental fluid shifts between the intracellular and extracellular space may alter Vd, resulting in drug levels falling outside their therapeutic window. Aminoglycosides are one class of medication that has both a narrow therapeutic window and a small Vd; this contributes to the difficulty in achieving therapeutic levels while trying to avoid toxicity [25]. Additionally, protein binding and total body protein influence drug distribution as only unbound active drugs/metabolites are able to interact with their cellular target and exert their pharmacologic effect. Disease states that alter total body protein levels, such as glomerular disease, predispose patients to altered free drug concentrations. Further, compounding protein binding is accumulation of uremic toxins in the peritoneal dialysis population. This altered drug affinity for albumin inadvertently increases the risk of adverse events [26]. This is well-documented with phenytoin as uremia decreases the percentage of protein binding in the plasma, leading to an increase in free drug concentration and hence predisposing the patient to toxicity [27]. When given intraperitoneally, most lipophilic drugs are absorbed primarily through the portal circulation and are subject to significant first-pass metabolism through the hepatobiliary system before reaching systemic circulation and target organs. One major therapeutic implication of this extensive first-pass metabolism is that there is a greater risk of treatment failure and insufficient plasma concentrations of many drugs. For hydrophilic agents with Vd less than 1 L/kg such as most antibiotics, drugs can be given intraperitoneally with expected achieved plasma concentration similar to intravenous drug administration. In summary, IP drug administration should be limited to drugs with proven efficacy and safety through this route [28, 29].

Metabolism

Current guidelines for drug dosing in peritoneal dialysis are primarily based on factors affecting the renal clearance of the drug. There is limited data about the effects of kidney impairment on drug metabolism in peritoneal dialysis patients. It has been proposed that the increased cytokines, PTH, and uremic toxins may downregulate cytochrome activity in the liver and gastrointestinal tract, contributing to altered drug metabolism [30]. Additionally, kidney impairment may decrease drug transport capacity, further decreasing metabolism; however, in patients on dialysis, drug metabolism has been noted to improve for unclear reasons [31]. While dosage adjustment primarily pertains to renally cleared medications, it should be noted that dialysis also predisposes patients to accumulation of metabolites and byproducts of primarily hepatically metabolized medications, thus posing a risk of drug accumulation and adverse drug reactions [32]. Meperidine, a narcotic agent, undergoes biotransformation to normeperidine, which is renally eliminated, and in dialysis patients can accumulate and lower the seizure threshold, most notably in those with uremia [33]. Finally, administration of insulin through peritoneal dialysis has been associated with subcapsular hepatic steatosis. Hepatic dysfunction may alter cytochrome enzymatic system expression and drug metabolism activities [34, 35].

Elimination

The kidney is a vital organ for drug elimination, primarily occurring through glomerular filtration and tubular secretion. Drug dosage adjustment for reduced kidney function should be considered in PD patients. However, the challenge is how to accurately dose patients to avoid toxicity while ensuring therapeutic benefits. Estimating kidney function in patients with residual kidney function and drug elimination through dialysis determines the influence of peritoneal dialysis on drug disposition. In patients with peritoneal dialysis, the access to the peritoneal cavity provides an opportunity to deliver and remove medication effectively. The effective peritoneal dialysis prescriptions provide a urea clearance of about 10 ml/min. Since most drugs are larger than urea, drug removal is approximately 5–7.5 ml/min. In general, removal of drugs on PD has not been well-studied and is based on theoretical considerations of molecular size and chemical makeup of the drug.

In a healthy kidney, proteins are too large to be excreted, but in peritoneal dialysis patients with glomerular disease, proteinuria exists and enhances elimination of protein-bound drugs. In peritoneal dialysis, the peritoneum is used to remove excess fluid, correct electrolyte problems, and remove drugs and toxins. This allows only drugs of certain sizes to move from an area of greater concentration to lower concentration. Many peritoneal dialysis patients continue to have some residual kidney function and eliminate between 10% and 30% of the fraction of plasma concentration. Intraluminal albumin binds to loop diuretics, such as furosemide inhibiting its

action on the loop of Henle, effectively, creating a state of diuretic resistance in some patients [22]. Increasing dosage and frequency of diuretic administration could overcome this problem. Tubular secretion is also affected and increases the accumulation of organic acids which compete for elimination with drugs such as methotrexate, cephalosporin, and sulfa compounds, ultimately increasing the risk of drug toxicity [22, 36, 37].

Drug Adjustments in Patients on Peritoneal Dialysis

Drug dosing adjustments in CKD are individually based, and the extent of pharmacokinetic changes varies with different drugs. Depending on the medication and its indication, loading doses can be beneficial in achieving a therapeutic steady state early in most patients, especially in medications with a longer half-life, such as digoxin, and antimicrobial agents. In patients on peritoneal dialysis, the same loading dose is given, as this accelerates time to reach a therapeutic plasma concentration. The maintenance dosing ensures therapeutic steady state and is adjusted by manipulating either the frequency or dosage, the latter being more common [21]. Impaired kidney function can necessitate drug level monitoring to ensure therapeutic levels and is commonly assessed by checking a peak level which occurs 60–120 minutes after oral intake, or 30 minutes after IV administration. Another option includes checking a trough, which occurs just before the next scheduled dose and is commonly seen with vancomycin, even among patients with normal kidney function. In general, patients with peritoneal dialysis require smaller doses compared to the general population and hemodialysis patients. Careful consideration of medication adjustments should be made for all patients.

Our recommendation is to develop a systematic approach to drug dosing in peritoneal dialysis patients. This will help to limit medication errors and improve therapeutic benefits while minimizing serious toxicities.

- Step 1: Identify patients with risk factors for adverse reactions.
- Step 2: Identify the drug's pharmacokinetic behavior.
- Step 3: Adjust dose according to kidney residual function, risk of toxicity, and potential risk of drug failure.
- Step 4: Identify potential drug interactions that impact plasma concentrations.
- Step 5: Establish a monitoring plan.

The first step involves identifying patients at risk for drug adverse reactions with chronic kidney disease. For example, metformin is a very effective agent for the management of adult Type-2 diabetic patients with normal kidney function, but the use of metformin should be avoided in PD patients due to risk of lactic acidosis [38]. The next step is to identify and understand the pharmacokinetic behaviors of each individual agent or active moiety. Then, one must discern the percentage of the drug or active metabolite eliminated unchanged through the kidney and how this will be influenced by peritoneal dialysis. In general, drugs that are fully metabolized or lack

active metabolites do not require dosage adjustment; however, medications eliminated unchanged through kidney or active metabolites eliminated through the kidney often require adjustment. Finally, the dosage should be adjusted according to consideration of residual kidney function, drug toxicity, and potential risk of treatment failure. Healthcare providers also should assess drug-drug interactions that might influence plasma concentrations. Even with appropriate dosing schedules, toxicity and adverse events can occur, so balancing efficacy and risks of toxicities while also monitoring toxicity is important.

Peritoneal Dialysis and Clearance

Dialysis is the treatment of choice for ESKD when there is no option for kidney transplantation, but many modalities exist, including continuous, intermittent, extended duration, peritoneal, and hemofiltration, all of which differ in surface area, flow rates, membrane charge, and pore size contributing to unique dialyzability of medications [39]. Each modality requires unique medication adjustments, emphasizing the healthcare providers' role in individualizing therapy. For example, peritoneal dialysis can be administered continuously vs intermittently, and while peritoneal dialysis is generally not as effective as HD in a given session for drug removal, the continuous nature may enhance and allow for increased drug removal [21]. Most guidelines and recommendations for drug dosing do not consider the duration of dialysis or type of dialysis. Healthcare providers should utilize their clinical and scientific knowledge of clinical pharmacokinetic and estimate the drug removal for each individual patient. Drug characteristics also contribute to their dialyzability, including lipophilicity, ionic status, protein binding, and molecular weight, the latter being most significant, with medications larger than 1000 Daltons being poorly dialyzed [40]. Protein-bound medications are not freely available to be dialyzed. In general, medications that are >70% protein-bound are not dialyzable. Table 25.1 shows drug factors influencing intraperitoneal drug therapy.

Conversely, for drugs not eliminated through dialysis, drug accumulation might occur resulting in supratherapeutic levels and potential toxicities [17, 21]. These variations in drug elimination experienced among dialysis patients complicate achieving and maintaining therapeutic drug levels. Furthermore, most dialysis drug dosing guidelines do not account for duration and type of dialysis in regard to

Table 25.1 Drug factors influencing intraperitoneal drug therapy [41]

Drug characteristic	Favorable to dialysis	Unfavorable to dialysis
Molecular weight	<500 Da	>1000 Da
Water solubility	Water-soluble	Not water-soluble
Volume of distribution	Vd <1 L/kg	Vd >2 kg/L
Protein binding	Low, <90%	High, >90%
Renal clearance	High, >50%	Low, <50%

dosage adjustments. Healthcare providers should use their clinical judgment according to dose-limiting toxicity and pharmacokinetic properties of each drug to make a decision about appropriate drug adjustment.

Commonly Prescribed Medications

Drug administration in peritoneal dialysis is similar to non-dialysis patients, but intraperitoneal (IP) administration also exists. Although for many years IP administration of the drugs has been reported and conducted, no standard treatment in terms of dose, duration, schedule, indwelling time, or solution has been established. In most cases, healthcare providers must ensure that the pharmacotherapeutic agents can penetrate the peritoneal surface and reach the site of action in order to exert the pharmacodynamic effect. For example, under circumstances where vascular access is limited, antimicrobial agents such as vancomycin may be administered IP, allowing for easy access leading to therapeutic blood levels and effective infection eradication [42]. However, most drugs are not well-studied to establish AUC and/or cavity-to-plasma ratio; thus, FDA approval for IP administration is limited, requiring healthcare providers to rely on drug characteristics and pharmacokinetic properties in order to optimize the care of the patients while minimizing adverse drug reactions. Herein we discuss the classes of commonly prescribed medications. Table 25.2 highlights the effect peritoneal dialysis has on commonly prescribed medications [43].

Antimicrobial Agents

Infection is a leading cause of morbidity and mortality in CKD patients on dialysis. Most antibiotics require maintenance dosing adjustment as they are either partially or completely excreted renally. In critically septic patients, hemodynamic changes can result in reduced organ perfusion and, if prolonged, cause organ dysfunction. This is associated with alterations in clearance and volume of distribution, both of which significantly contribute to the pharmacokinetics of antimicrobials, ultimately making drug dosing a challenging issue for healthcare providers [44, 45]. Without dosage adjustments, renal insufficiency predisposes to renal and extra-renal toxicity. Peritoneal dialysis differs from HD for antibiotic dosing in that peritoneal dialysis does not remove drug as efficiently; thus, smaller doses are required. Furthermore, in HD, many drugs require dosing to occur after dialysis, whereas this is not the case for peritoneal dialysis. Daptomycin is an example where decreased dosing is required. If not adjusted, daptomycin exhibits extra-renal toxicity, specifically predisposing to rhabdomyolysis if not adjusted. Daptomycin is highly protein-bound and cannot be given intraperitoneally. Conversely, β-lactams have large therapeutic windows allowing for more aggressive dosing schedules in the setting of peritoneal

Table 25.2 Effect of peritoneal dialysis on commonly prescribed medications [43]

Drug name	Peritoneal dialysis [No]	Drug name	Peritoneal dialysis [Yes]	Drug name	Peritoneal dialysis [Unlikely]	Drug name	Peritoneal dialysis [No data]
Amiodarone	No	Aminocaproic acid	Yes	Amoxapine	U	Amiloride	ND
Amitriptyline	No	Aspirin	Yes	Anistreplase	U	Aminoglutethimide	ND
Amlodipine	No	Carisoprodol	Yes	Antithymocyte globulin ATG	U	Aminosalicylic acid	ND
Amoxicillin	No	Cefaclor	Yes	Aprotinin	U	Amprenavir	ND
Amphotericin B	No	Cefepime	Yes	Asparaginase	U	Anagrelide	ND
Ampicillin	No	Cefotetan	Yes	Atorvastatin	U	Anastrozole	ND
Amrinone	No	Cefsulodin	Yes	Atovaquone	U	Arbutamine	ND
Atenolol	No	Ceftazidime	Yes	Atracurium	U	Ardeparin	ND
Azlocillin	No	Cephradine	Yes	Basiliximab	U	Atropine	ND
Aztreonam	No	Clavulanic acid	Yes	Bepridil	U	Auranofin	ND
Betaxolol	No	Diazoxide	Yes	Bicalutamide	U	Azathioprine	ND
Bezafibrate	No	Edetate calcium (EDTA)	Yes	Bromfenac	U	Azithromycin	ND
Bleomycin	No	Enalapril (enalaprilat)	Yes	Bromocriptine	U	Baclofen	ND
Bupropion	No	Esmolol (ASL-8123)	Yes	Buflomedil	U	Benazepril (benazeprilat)	ND
Captopril	No	Fluconazole	Yes	Bumetanide	U	Benzquinamide	ND
Carbamazepine	No	Flucytosine	Yes	Butorphanol	U	Betamethasone	ND
Carbenicillin	No	Gentamicin	Yes	Calcitriol	U	Bethanechol	ND
Cefadroxil	No	Imipenem	Yes	Carprofen	U	Biapenem	ND
Cefamandole	No	Kanamycin	Yes	Celecoxib	U	Bisoprolol	ND
Cefazolin	No	Lithium	Yes	Cerivastatin	U	Bretylium	ND

Cefixime	No	Mannitol	Yes	Cetirizine	U	Buspirone	ND
Cefmetazole	No	Meprobamate	Yes	Chlordiazepoxide	U	Busulfan	ND
Cefodizime	No	Methyldopa	Yes	Chlorprothixene	U	Butalbital	ND
Cefonicid	No	Minoxidil	Yes	Chlorthalidone	U	Caffeine	ND
Cefoperazone	No	Netilmicin	Yes	Cilostazol	U	Candesartan	ND
Ceforanide	No	Nitroprusside	Yes	Cinoxacin	U	Capecitabine	ND
Cefotaxime	No	Phenobarbital	Yes	Cisapride	U	Capreomycin	ND
Cefoxitin	No	Ritodrine	Yes	Cisatracurium	U	Carbidopa/levodopa	ND
Cefpirome	No	Spectinomycin	Yes	Citalopram	U	Carboplatin	ND
Cefpodoxime	No	Streptomycin	Yes	Clomipramine	U	Carboprost	ND
Ceftizoxime	No	Sulfisoxazole	Yes	Clonazepam	U	Carmustine	ND
Ceftriaxone	No	Tobramycin	Yes	Clopidogrel	U	Carnitine	ND
Cefuroxime	No			Clorazepate	U	Carteolol	ND
Cephalexin	No			Clozapine	U	Carumonam	ND
Cephalothin	No			Codeine	U	Carvedilol	ND
Cephapirin	No			Daclizumab	U	Cefdinir	ND
Chlorambucil	No			Dalteparin	U	Cefmenoxime	ND
Chloramphenicol	No			Deflazacort	U	Cefprozil	ND
Chloroquine	No			Delavirdine	U	Cefroxadine	ND
Chlorpheniramine	No			Diazepam	U	Ceftibuten	ND
Chlorpromazine	No			Diclofenac	U	Chloral hydrate	ND
Chlorpropamide	No			Diflunisal	U	Cilastatin	ND
Cidofovir	No			Diphenhydramine	U	Cilazapril	ND
Cimetidine	No			Docetaxel	U	Cisplatin	ND
Ciprofloxacin	No			Donepezil	U	Cladribine	ND
Clindamycin	No			Dopamine	U	Clarithromycin	ND

(continued)

Table 25.2 (continued)

Drug name	Peritoneal dialysis [No]	Drug name	Peritoneal dialysis [Yes]	Drug name	Peritoneal dialysis [Unlikely]	Drug name	Peritoneal dialysis [No data]
Clodronate	No			Doxacurium	U	Clemastine	ND
Clofazimine	No			Doxercalciferol	U	Cyclophosphamide	ND
Clofibrate	No			Dronabinol	U	Cycloserine	ND
Clonidine	No			Droperidol	U	Dacarbazine	ND
Cloxacillin	No			Efavirenz	U	Dactinomycin	ND
Colchicine	No			Enoxaparin	U	Danaparoid	ND
Cortisone	No			Eprosartan	U	Dapsone	ND
Cyclacillin	No			Estazolam	U	Daunorubicin	ND
Cyclosporine	No			Ethacrynic acid	U	Deferoxamine	ND
Cysteamine	No			Ethambutol	U	Desmopressin	ND
Cytarabine	No			Etodolac	U	Dexfenfluramine	ND
Desipramine	No			Felodipine	U	Dexrazoxane	ND
Dexamethasone	No			Fenofibrate	U	Dezocine	ND
Dicloxacillin	No			Fenoprofen	U	Dibekacin	ND
Didanosine	No			Ferric gluconate	U	Diethylpropion	ND
Digitoxin	No			Ferrous (iron) salts	U	Dihydroergotamine	ND
Digoxin	No			Fexofenadine	U	Diphenoxylate/atropine	ND
Diltiazem	No			Filgrastim	U	Dipyridamole	ND
Dirithromycin	No			Finasteride	U	Disopyramide	ND
Dobutamine	No			Flecainide	U	Dolasetron	ND
Doxazosin	No			Fluphenazine	U	Doxorubicin	ND
Doxepin	No			Flurazepam	U	Encainide	ND
Doxycycline	No			Flutamide	U	Ephedrine	ND
Enoxacin	No			Fluvastatin	U	Epinephrine	ND
Epoetin alfa	No			Fluvoxamine	U	Epoprostenol	ND
Erythromycin	No			Fosphenytoin	U	Eptifibatide	ND

Ethchlorvynol	No			Furosemide	U	Ergocalciferol	ND
Ethinyl estradiol	No			Gallopamil	U	Ethosuximide	ND
Etoposide	No			Glimepiride	U	Famciclovir (penciclovir)	ND
Famotidine	No			Glipizide	U	Felbamate	ND
Fenoldopam	No			Glucagon	U	Fenfluramine	ND
Fleroxacin	No			Glyburide	U	Fentanyl	ND
Fluoxetine	No			Gold sodium thiomalate	U	Floxuridine	ND
Flurbiprofen	No			Hexobarbital	U	Fludarabine	ND
Fosinopril (fosinoprilat)	No			Hydrochlorothiazide	U	Flumazenil	ND
Fusidic acid	No			Hydrocortisone	U	Fluorouracil	ND
Gadodiamide	No			Hydroxyurea	U	Fomepizole	ND
Gemfibrozil	No			Ibuprofen	U	Foscarnet	ND
Glutethimide	No			Idarubicin	U	Fosfomycin	ND
Guanfacine	No			Immune globulin (human)	U	Gabapentin	ND
Haloperidol	No			Indapamide	U	Gadoversetamide	ND
Heparin	No			Indomethacin	U	Gallium	ND
Hydralazine	No			Irinotecan (SN-38 metabolite)	U	Ganciclovir	ND
Hydroxyzine	No			Iron dextran	U	Ganirelix	ND
Imipramine	No			Isoniazid	U	Gemcitabine	ND
Insulin	No			Itraconazole	U	Glatiramer	ND
Interferons	No			Ketoprofen	U	Granisetron	ND
Isosorbide dinitrate	No			Ketorolac	U	Grepafloxacin	ND
Isosorbide mononitrate	No			Lamivudine	U	Guanabenz	ND

(continued)

Table 25.2 (continued)

Drug name	Peritoneal dialysis [No]	Drug name	Peritoneal dialysis [Yes]	Drug name	Peritoneal dialysis [Unlikely]	Drug name	Peritoneal dialysis [No data]
Isradipine	No			Lamotrigine	U	Guanadrel	ND
Ketoconazole	No			Lansoprazole	U	Guanethidine	ND
Labetalol	No			Levobupivacaine	U	Halofantrine	ND
Leflunomide	No			Levofloxacin	U	Hirudin	ND
Lincomycin	No			Levonorgestrel	U	Hydrocodone	ND
Lomefloxacin	No			Levothyroxine	U	Hydromorphone	ND
Loratadine	No			Lidocaine	U	Hydroxychloroquine	ND
Losartan	No			Lomustine	U	Ibutilide	ND
Mechlorethamine	No			Lorazepam	U	Ifosfamide	ND
Methadone	No			Lovastatin	U	Indinavir	ND
Methaqualone	No			Maprotiline	U	Iodixanol	ND
Methicillin	No			Meclofenamate	U	Iopromide	ND
Methimazole	No			Mefenamic acid	U	Irbesartan	ND
Methotrexate	No			Mefloquine	U	Isocarboxazid	ND
Metoclopramide	No			Meperidine	U	Isoproterenol	ND
Metronidazole	No			Mesalamine (5-ASA)	U	Letrozole	ND
Mexiletine	No			Mesoridazine	U	Leuprolide	ND
Mezlocillin	No			Methylphenidate	U	Levamisole	ND
Miconazole	No			Metolazone	U	Levorphanol	ND
Minocycline	No			Midazolam	U	Lisinopril	ND
Mitoxantrone	No			Mirtazapine	U	Loperamide	ND
Morphine	No			Misoprostol	U	Loracarbef	ND
Mycophenolate (mycophenolic acid)	No			Molindone	U	Loxapine	ND
Nafcillin	No			Montelukast	U	Mangafodipir	ND

Nifedipine	No			Moricizine	U	Melphalan	ND
Nimodipine	No			Muromonab-CD3	U	Mercaptopurine	ND
Nisoldipine	No			Nalmefene	U	Meropenem	ND
Nitroglycerin	No			Naproxen	U	Mesna	ND
Nizatidine	No			Nefazodone	U	Metaproterenol	ND
Norethindrone	No			Nelfinavir	U	Metformin	ND
Nortriptyline	No			Nicardipine	U	Methenamine	ND
Ofloxacin	No			Nitrendipine	U	Methylprednisolone	ND
Olanzapine	No			Norfloxacin	U	Metoprolol	ND
Ornidazole	No			Olsalazine	U	Miacalcin	ND
Oxacillin	No			Omeprazole	U	Midodrine (de-glymidodrine)	ND
Pefloxacin	No			Ondansetron	U	Miglitol	ND
Pemoline	No			Orlistat	U	Milrinone	ND
Penbutolol	No			Oxaprozin	U	Mitomycin	ND
Penicillin G	No			Oxazepam	U	Mivacurium	ND
Pentamidine	No			Paclitaxel	U	Modafinil	ND
Phenytoin	No			Paroxetine	U	Moexipril	ND
Piperacillin	No			Pegaspargase	U	Nabumetone	ND
Polythiazide	No			Pentobarbital	U	Nadolol	ND
Prazosin	No			Pergolide	U	Naloxone	ND
Prednisone	No			Perphenazine	U	Naltrexone	ND
Probucol	No			Phenylbutazone	U	Naratriptan	ND
Procainamide	No			Pioglitazone	U	Nevirapine	ND
Propafenone	No			Piroxicam	U	Nicotine	ND
Propoxyphene	No			Pramipexole	U	Nicotinic acid	ND

(continued)

Table 25.2 (continued)

Drug name	Peritoneal dialysis [No]	Drug name	Peritoneal dialysis [Yes]	Drug name	Peritoneal dialysis [Unlikely]	Drug name	Peritoneal dialysis [No data]
Propranolol	No			Prazepam	U	Nilutamide	ND
Protriptyline	No			Prochlorperazine	U	Nitrofurantoin	ND
Pyrazinamide	No			Promazine	U	Nomifensine	ND
Quinapril (quinaprilat)	No			Propofol	U	Octreotide	ND
Quinidine	No			Pseudoephedrine	U	Omapatrilat	ND
Quinine	No			Quazepam	U	Orbofiban	ND
Quinupristin/ dalfopristin	No			Rabeprazole	U	Orphenadrine	ND
Ranitidine	No			Raloxifene	U	Oxybutynin	ND
Reserpine	No			Recainam	U	Oxycodone	ND
Rifampin	No			Repaglinide	U	Oxymorphone	ND
Roxithromycin	No			Reviparin	U	Pamidronate	ND
Salsalate	No			Rifabutin	U	Pancuronium	ND
Secobarbital	No			Rifapentine	U	Pantoprazole	ND
Sucralfate	No			Rilmenidine	U	Paricalcitol	ND
Sulbactam	No			Rimantadine	U	Penicillamine	ND
Sulfamethoxazole	No			Ritonavir	U	Pentazocine	ND
Tazobactam	No			Rofecoxib	U	Pentosan polysulfate	ND
Teicoplanin	No			Ropinirole	U	Pentostatin	ND
Temocillin	No			Rosiglitazone	U	Pentoxifylline	ND
Terazosin	No			Saquinavir	U	Perindopril (perindoprilat)	ND
Tetracycline	No			Sertraline	U	Phenelzine	ND
Theophylline	No			Sevelamer	U	Phentermine	ND
Ticarcillin	No			Sibutramine	U	Phentolamine	ND

Timolol	No			Sildenafil	U	Phenylpropanolamine	ND
Trifluoperazine	No			Silver	U	Pimagedine (aminoguanidine)	ND
Trimethoprim	No			Simvastatin	U	Pimozide	ND
Valproic acid	No			Somatropin	U	Pindolol	ND
Vancomycin	No			Spirapril (spiraprilat)	U	Plicamycin	ND
Verapamil	No			Spironolactone	U	Pralidoxime	ND
Warfarin	No			Sufentanil	U	Pravastatin	ND
				Sulindac	U	Primidone	ND
				Tacrolimus	U	Procarbazine	ND
				Tamsulosin	U	Promethazine	ND
				Telmisartan	U	Pyrimethamine	ND
				Temazepam	U	Quetiapine	ND
				Teniposide	U	Ramipril (ramiprilat)	ND
				Terbinafine	U	Reteplase	ND
				Testosterone	U	Risperidone	ND
				Thioridazine	U	Rizatriptan	ND
				Thiothixene	U	Rocuronium	ND
				Ticlopidine	U	Rufloxacin	ND
				Tiludronate	U	Sargramostim	ND
				Tolazamide	U	Selegiline	ND
				Tolbutamide	U	Sermorelin	ND
				Tolmetin	U	Sertindole	ND
				Tolterodine	U	Sirolimus	ND
				Torsemide	U	Sisomicin	ND
				Tramadol	U	Sotalol	ND

(continued)

Table 25.2 (continued)

Drug name	Peritoneal dialysis [No]	Drug name	Peritoneal dialysis [Yes]	Drug name	Peritoneal dialysis [Unlikely]	Drug name	Peritoneal dialysis [No data]
				Trazodone	U	Sparfloxacin	ND
				Triazolam	U	Stavudine	ND
				Trifluprom azine	U	Streptozocin	ND
				Trimetrexate	U	Sumatriptan	ND
				Trimipramine	U	Tacrine	ND
				Troglitazone	U	Tamoxifen	ND
				Tropisetron	U	Terbutaline	ND
				Ursodiol	U	Thalidomide	ND
				Valsartan	U	Thiethylperazine	ND
				Vecuronium	U	Thioguanine	ND
				Venlafaxine	U	Thiotepa	ND
				Zafirlukast	U	Tiagabine	ND
				Zileuton	U	Tinidazole	ND
				Zolpidem	U	Tirofiban	ND
						Tizanidine	ND
						Tocainide	ND
						Tolcapone	ND
						Topiramate	ND
						Topotecan	ND
						Trandolapril (trandolaprilat)	ND
						Tranexamic acid	ND
						Tranylcypromine	ND
						Trapidil	ND
						Tretinoin	ND

							Triamterene	ND
							Trihexyphenidyl	ND
							Trovafloxacin	ND
							Valacyclovir	ND
							Vigabatrin	ND
							Vinblastine	ND
							Vincristine	ND
							Zalcitabine	ND
							Zidovudine/GZDV	No/Yes
							Zolmitriptan	ND

dialysis. For some antimicrobial agents, an unadjusted loading dose is recommended in order to achieve therapeutic levels more rapidly. In peritoneal dialysis patients, in general practice, when drug is given intraperitoneally, it is best to administer drugs with the longest indwelling time possible, allowing for prolonged exposure to therapeutic levels [46]. In patients who can tolerate oral medications, oral route should be employed; however, it should be noted that iron, calcium, and phosphate binders are frequently co-prescribed among peritoneal dialysis patients. These can interact and bind oral antimicrobial agents such as fluoroquinolones, resulting in decreased absorption. In these circumstances, it is recommended that antimicrobial dosing occur 2–4 hours after supplement and phosphate binders to allow maximal antibiotic absorption [47].

Peritonitis is one of the major complications associated with peritoneal dialysis. Most commonly caused by gram-positive bacteria (coagulase-negative *Staphylococcus* spp., *Streptococcus* spp., *S. aureus*, *Enterococcus* spp., *Corynebacterium* spp.) followed by gram-negative (*Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*), failure to obtain positive cultures is not uncommon [48]. This occurs most often because many patients are started on empiric antibiotics prior to obtaining cultures on peritoneal dialysate. In the setting of presumed peritoneal dialysis infection, empiric IP antibiotics should include both cefazolin or vancomycin for gram-positive cultures and cefepime, ceftazidime, or aminoglycosides for gram-negative cultures until the culture and sensitivity reports are available (Table 25.3). Treatment duration is typically 2–3 weeks depending on severity (see Chap. 15). Clinical improvement should be seen in 48–72 hours, and the catheter should be removed if cloudy effluent persists greater than 5 days.

A retrospective analysis of a large University Health Network Home Peritoneal Dialysis database offered important insights into the treatment of peritonitis in adult patients with residual kidney function who received antimicrobial agents. Objectively, treatment failure was found to occur in 28 of 80 patients [32%] with residual kidney function. In contrast, treatment failure was reported only in 16% of anuric patients. In addition, a significantly higher rate of recurrence was reported [21% vs 10%] in patients with residual kidney function. This study highlights the importance of residual kidney function and drug elimination. Patients with residual kidney function eliminate medications more rapidly, which could lead to pharmacotherapeutic failure [49].

Analgesics

In concordance with the general population, pain prevalence has been reported at 40–60% of patients receiving dialysis [50]. Although a majority of analgesics are metabolized by the liver, thus requiring minimal adjustment, peritoneal dialysis patients often have increased sensitivity to analgesic agents [32]. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are often considered first-line pharmacologic agents for mild pain, but given the sodium retention, hypertension,

Table 25.3 Intraperitoneal dosing in peritonitis [5, 42]

Antimicrobial	Intermittent IP (in one exchange per day)	Continuous IP	
		Initial loading dose (per liter of dialysate)	Maintenance dose (per liter of dialysate)
Aminoglycosides			
Amikacin	2 mg/kg	Continuous IP administration not recommended	
Gentamicin	0.6 mg/kg		
Tobramycin	0.6 mg/kg		
Cephalosporins			
Cefazolin	15 mg/kg	500 mg	125 mg
Cefepime	1 gram	500 mg	125 mg
Ceftazidime	1–1.5 grams	500 mg	125 mg
Penicillins			
Amoxicillin	Intermittent IP administration not recommended	250–500 mg	50 mg
Ampicillin		None	125 mg
Oxacillin		None	125 mg
Nafcillin		None	125 mg
Penicillin G		50,000 units	25,000 units
Other			
Vancomycin	15–30 mg/kg every 5 days, or every 2 days for patients with RRF* and based on serum drug levels	1 gram	25 mg (adjust based on serum drug levels)
Aztreonam	–	1 gram	250 mg
Ciprofloxacin	–	50 mg	25 mg
Daptomycin	–	100 mg	20 mg
Linezolid	Oral: 600 mg bid	None	Oral: 200–300 mg daily
Ampicillin-sulbactam	2 grams every 12 hours	1 gram	100 mg
Imipenem-cilastatin	500 mg every 12 hours	250 mg	50 mg
Trimethoprim-sulfamethoxazole	Oral: one DS daily	None	Oral: one DS tablet twice daily
Antifungal			
Fluconazole	200 mg every 24–48 hours	–	–

and renal and gastrointestinal toxicity, NSAIDs should be used with caution in this population unless lacking effective alternatives. If used, non-selective COX inhibitors with a short half-life such as ibuprofen or salsalate are preferred as they exhibit less extra-renal effects but still have the same potential for nephrotoxicity and compromise of residual kidney function. In general, COX2 inhibitors are avoided because of the increased cardiovascular risk, which is already at high risk in peritoneal dialysis patients [51, 52]. In pain non-responsive to acetaminophen, alternative options include low-dose opiates such as hydrocodone, oxycodone, and hydromorphone with a goal to slowly up-titrate to avoid toxicity. Morphine and meperidine

should be avoided in peritoneal dialysis patients due to active metabolites increasing toxicity (Table 25.3) [53]. Other alternatives to oral agents include topical NSAID analgesics such as diclofenac, providing local relief and conferring reduced systemic concentrations and side effects such as gastrointestinal and cardiovascular, but large trials assessing for non-renal toxicity are lacking in peritoneal dialysis patients [54, 55].

Neuropathic pain is also common among patients on peritoneal dialysis. Tricyclic antidepressant amitriptyline is metabolized hepatically and does not accumulate; however, these pharmacologic agents have significant anticholinergic side effects which may limit their use. Gabapentin and pregabalin are extensively renally cleared, so dose reduction is necessary but can be used to effectively treat both neuropathic pain and pruritus associated with uremia [56] (Table 25.2). Overall, there have been limited studies assessing the proper dosing of analgesics in peritoneal dialysis, but the general rule of starting low and titrating up is recommended to avoid adverse reactions [57].

Anticoagulation Agents

Patients on dialysis may have increased risk of bleeding due to platelet dysfunction but occasionally have indications for anticoagulation such as atrial fibrillation and venous thromboembolism. Although warfarin remains the anticoagulant of choice given its hepatic metabolism, there is a significant risk of bleeding, vascular calcification [58, 59], and calciphylaxis [60, 61] with the use of warfarin. Dose adjustment remains the same to achieve a goal INR of 2–3 for most indications [62]. In acute settings requiring anticoagulation, unfractionated heparin is still preferred as low molecular weight heparins are renally excreted and should be avoided, but if unable, adjustment based on kidney function with weekly factor Xa level monitoring is recommended. Other agents including factor Xa inhibitor rivaroxaban and direct thrombin inhibitor dabigatran are contraindicated in patients on peritoneal dialysis due to renal clearance making effects difficult to predict [63]. Among the newer agents, apixaban has the most favorable pharmacologic profile, allowing for use in peritoneal dialysis setting following dosage adjustment [64, 65]. However, the treatment with apixaban or newer agents has not yet been associated with a lower incidence of new stroke, transient ischemic attack, or systemic thromboembolism in dialysis patients [66].

Diuretics and Antihypertensive Agents

Hypertension is very common among peritoneal dialysis patients and plays a dual role in declining residual kidney function as well as the progression of cardiovascular disease. Cardiovascular disease is the number one cause of death in peritoneal

dialysis patients, emphasizing the need for aggressive risk factor modification. Most antihypertensive agents including beta-blockers, calcium channel blockers, nitrates, and other centrally acting drugs need minimal adjustment. It is important for the PD patient with residual kidney function to stay euvolemic. Euvolemia has been associated with prolonged survival. Unfortunately, loop, thiazide, and potassium-sparing diuretics are often discontinued in patients with chronic kidney disease patients upon initiating peritoneal dialysis [67]. PD patients are at greater risk of fluid accumulation and peripheral edema due to sodium retention. In the CANUSA study, the relative risk of death increased with increased age, diabetes, previous history of cardiovascular disease, decreased serum albumin, and decreased urine volume. Urine outputs of 250 ml/day were associated with a 36% mortality rate reduction [68, 69]. Sodium and water retention increases blood pressure which increases mortality and cardiovascular morbidity. A recent nationwide prospective cohort study of 692 PD patients demonstrated that urine volume of 100 ml/day is independently associated with a lower risk of mortality. Interestingly in this study, only residual kidney function, not e-GFR, was significantly associated with survival benefit after adjustment for potential confounders. It has been also shown that diuretics in PD patient may protect residual kidney volume and provide better control of blood pressure, hyperkalemia, and significant proteinuria [70]. Lv et al. compared the use of furosemide 120 mg daily vs placebo in a pilot study of 26 PD patients. After 6 months, the diuretic group had less problems with edema, overall weight gain, and adequate blood pressure control compared to the placebo arm ($P < 0.05$) [71]. In general, the use of diuretics could increase both fluid and sodium removal which proved to improve mortality and morbidity related to edema and was also found to be helpful for hypertension and cardiovascular complication of dialysis. Besides the use of loop diuretics, Witoon et al. have reported that the combination of furosemide, hydrochlorothiazide, and spironolactone results in higher urine output and better volume control compared to furosemide alone [72]. The primary concern with loop diuretics is development of ototoxicity. However, the data is limited and is only a concern when given intravenously with aminoglycosides infused at a rapid rate. Maximal recommended oral doses of loop diuretics found to be effective are furosemide 320–400 mg, torsemide 50–100 mg, and bumetanide 8–10 mg. Furosemide is the most commonly used loop diuretic but with variable absorption between 10% and 60% compared to the 80–100% with torsemide and bumetanide [69]. It is important to mention that diuretics have no effects on the cardiovascular endpoint or surrogate marker in anuric dialysis patients. ACE inhibitors are common first-line antihypertensive agents due to cardioprotective characteristics and more effective than other antihypertensive drugs in reducing proteinuria and in slowing the rate progression of residual kidney decline over time in PD patients [73].

Both ARB and ACE-I should be considered in PD patients with hypertension or cardiovascular complications. Compared to other drugs, both agents can preserve small but significant residual kidney function. Both hyperkalemia and hypokalemia are very frequent in patients on PD and should be closely monitored [73]; however, the use of these agents necessitates caution in patients with inadequate dialysis and dietary noncompliant patients as well [74]. Otherwise, most other antihypertensive

medications are well-tolerated and require mild- to moderate-dose adjustments. Beta-blockers are an excellent class of drug to use in peritoneal dialysis patients because of their ability to reduce sympathetic activities and cardiovascular consequences in addition to their anti-dysrhythmic properties [75]. However, recent studies have suggested that sudden death in dialysis patients may be the result of bradyarrhythmias, in which case the use of beta-blockers will have to be reconsidered.

Hypoglycemia Agents

Diabetes is the most common cause of CKD worldwide, with 40% of DM patients having advanced CKD [76, 77]. The management of blood glucose in peritoneal dialysis patients is complex and challenging. This population is at increased risk of both hypoglycemia and hyperglycemia because insulin clearance decreases, while glucose is used in dialysate solutions. Insulin therapy is the foundation of management of diabetes in peritoneal dialysis patients since most oral diabetes drugs are contraindicated or not recommended in this population. Insulin doses should be adjusted according to fasting blood glucose and A1c [glycosylated hemoglobin] levels. However, in diabetic patients with ESKD, elevated blood urea nitrogen may falsely cause the formation of carbamylated hemoglobin, which is indistinguishable from A1c. In peritoneal dialysis patients, the dialysate solution has significant amounts of glucose which may increase insulin requirements. Most commonly, oral anti-hyperglycemic agents are discontinued at the initiation of dialysis to avoid complications. Sodium-glucose cotransporter inhibitors require glomerular filtration of glucose to mediate their pharmacodynamic effects and are not effective, and their use is contraindicated in patients on peritoneal dialysis [78, 79]. Thiazolidinediones are associated with fluid retention and thus should be also avoided in peritoneal dialysis patients [55, 57]. Metformin is excreted completely unchanged in the urine and is, therefore, contraindicated in the peritoneal dialysis patients due to the risk of lactic acidosis [38]. Sulfonylureas or insulin secretagogues pose a risk in peritoneal dialysis patients because of active metabolites, but if the oral hypoglycemic agent is used, glipizide, sitagliptin, and saxagliptin are preferred, given their shorter half-life and lack of active metabolites. Despite their lack of active metabolites, all agents should be started at low doses and slowly uptitrated, watching for signs of hypoglycemia [80].

Conclusion

Drug dosing in patients on peritoneal dialysis can be challenging as there are multiple patient and therapeutic factors contributing to dosing adjustment and recommendations. The prevalence of CKD is rising rapidly which inevitably increases

dialysis used for management in ESKD. Many patients require dosing adjustment to ensure and maintain optimal therapeutic effect while reducing the risk of toxicities. Despite the plethora of publications and resources guiding clinician dosing, slight variations exist, emphasizing the need for strong clinical judgment and application in the correct clinical context. In general, recommendation for drug dosing in peritoneal dialysis patients is to initiate at a low dose, monitoring for adverse drug reaction and toxicity with slow up-titration. Given that HD is more commonly studied, a general rule to remember is that because peritoneal dialysis is not as effective at drug removal, lower doses are required, and post-dialysis dosing is not usually required. While this burden often falls on the primary care nephrologists, clinical pharmacy is frequently available for guidance and best consulted should questions or concerns arise.

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Chapter 26
Commonly Asked Questions About Peritoneal Dialysis

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Should Every Patient at the Start of Peritoneal Dialysis Have a Preemptive "Backup" Arteriovenous Access?

The transition from peritoneal dialysis (PD) to hemodialysis (HD) is a critical and high-risk period for PD patients. One hypothesis is that the transition to HD almost inevitably means using a tunneled catheter and may contribute to increased mortality [1]. More optimal transition might include starting with an AV access, which rarely occurs [2]. It is very hard to know who is going to fail PD because many technique failure causes are unpredictable [1]. In a retrospective cohort study between 2004 and 2011, Patrick G. Lan Dial (2015) and his group analyzed 4781 incident PD patients, of whom 1699 transferred to hemodialysis [1]. They evaluated the predictors of transfer from PD to HD at 6–12 months after starting PD, and they found multiple predictable and unpredictable factors including PD-related peritonitis, which was the most common cause of the transition, PD-catheter related problems, inadequate dialysis, patient preference, and inability to manage self-care [1]. However, they failed to identify any clinically significant factor that can be used to predict the transition [1]. Also, they observed that patients who started on HD with

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a central venous catheter (CVC) at the time of modality change had higher mortality (hazard ratio 1.37, 95% confidence interval (CI) 1.11–1.68, $p = 0.003$) and a borderline significant reduction in the incidence of transplantation (subhazard ratio 0.76, 95% CI 0.58–1.00, $p = 0.05$) [1]. The increase in mortality and reduction in the incidence of transplantation attributed to an increase in the incidence of the infection related to the CVC and hospitalization [1]. Given these results, we would think about preparing patients with preemptive AV access at the time of PD start, but we must take into account the potential rate of AV failure. In most recent years, the frequency of primary AV fistula failure has increased significantly, and the interventions needed for the secondary failure increased as well [3]. Also, we should be mindful of the adverse cardiac effects of the unused AV fistula, and its enduring cosmetic impact after kidney transplantation. Based on the available data, it is uncertain that there is any benefit of having preemptive AV access for every patient at the time of PD start. We need to improve the clinical care pathway to identify the patients at risk of switching from PD to HD and plan their transition by preemptively creating AV access only in that at-risk cohort. It is more important to predict which patient is going to fail PD than to put AV access preemptively in every patient.

Do I Have to Switch a Peritoneal Dialysis Patient to Hemodialysis After Hernia Repair?

Switching a peritoneal dialysis patient undergoing elective hernia repair to interim hemodialysis is not necessary most of the time [4]; Shah et al. PDI 2006 reviewed the feasibility of undergoing hernia repair in PD patients without switching them temporarily to HD [4]. This was a single-center retrospective study which included 50 PD patients, 42 of them on continuous ambulatory peritoneal dialysis (CAPD) and the rest on continuous cycling peritoneal dialysis (CCPD). Moreover, 25 patients had umbilical hernia, 18 patients inguinal hernia, 5 patients incisional hernia, and 2 patients epigastric hernia without the need for interim hemodialysis [4]. They were on their regular PD prescription until the morning of the hernia repair, drained their effluent before surgery, then remained off dialysis for 48 hours postoperatively, and were closely monitored clinically and with blood work [4]. The PD was gradually restarted with a low fill volume 1–1.5 liters and upgraded the amount slowly as needed up till 4 weeks postoperatively, where they resumed their original prescription [4]. The average total follow-up was 33 months, and no hyperkalemia or PD-leakage and no early hernia recurrence were noted [4]. However, 13 patients had a recurrence of the same hernia after 19 months; 4 patients had hernias at different sites after an average of 55 months [4]. This rate of recurrence may seem high, but this was before mesh was used as a standard for hernia repair to limit the hernia recurrence [5, 6]. Several factors are important in deciding which PD patient will need HD bridging after the hernia repair, such as the location of the mesh, whether

it is intraperitoneal or totally extraperitoneal, and the presence of residual kidney function. If the location of the mesh is intraperitoneal, it is better to avoid using the PD for several weeks to allow the healing and mesothelial covering of the mesh to prevent the risk of leak and peritonitis infecting the mesh. Also, holding PD without the need to bridge with HD can be achieved easily if the patient has adequate residual kidney function (perhaps 5 ml/min or more).

Is Peritoneal Dialysis Possible in Patients with Liver Disease and Ascites?

Peritoneal dialysis (PD) is an attractive option in patients with chronic liver disease complicated by ascites accompanied by chronic kidney failure. PD has several advantages in this patient population compared to in-center hemodialysis, including reduced cost; better quality of life; less need for regular ascites drainage by paracentesis; a more hemodynamically tolerable modality of dialysis; no need for anticoagulation, as these patients are already at high risk of bleeding; and PD keeping hepatitis B and hepatitis C patients out of the hemodialysis unit. Many cirrhotic patients who suffer from malnutrition will benefit from the caloric load absorbed from the PD. However, there are concerns raised regarding the use of PD in these patients. One concern is PD catheter healing in the setting of the tense ascites. Other issues include the volume of PD fluid and its contribution to increasing the intra-abdominal pressure and, consequently, the possibility of hernia or leak of dialysate. Moreover, the risk of PD-related peritonitis and worsening of malnutrition with protein loss during PD are concerning.

Given these concerns, few small single-center studies evaluated the outcomes of PD in cirrhotic patients with chronic kidney failure. De Vecchi et al. AJKD 2002, a single-center retrospective study, has assessed the outcomes of 21 cirrhotic patients treated with PD in comparison to 41 PD patients in the control arm [7]. Both groups were similar at the start of PD, and the survival rate was not different between cirrhotic and control groups [7]. Seven cirrhotic patients died an average of 10 ± 7 months after the beginning of PD [7]. Causes of death were terminal liver failure (n = 5), hepatocellular carcinoma (n = 1), and peritonitis (n = 1) [7]. Ten control patients died an average of 44 ± 21 months—causes of death were mainly cardiovascular complications (n = 6) [7]. Also, both peritonitis rate and technique survival were similar in both groups [7]. Gram-positive organisms caused the majority of peritonitis in cirrhotic patients in contrast to the expected organisms in spontaneous bacterial peritonitis, which might be explained by the regular washout of the abdominal cavity with PD flush [7]. Moreover, the PD-related complications were similar in both groups, except more hypotension was noted in cirrhotic patients in comparison to the control group, which can be explained by the vasodilatation seen in advanced liver disease [7]. A more recent retrospective study of patients at a single center in Korea included 33 patients who initiated PD with liver disease

between 2007 and 2014 and matched 33 individuals as control [8]. Both groups were similar in the rate of early technical complications, peritonitis rates, and there was no difference in break-in time; 61% started PD within 48 hours of PD catheter insertion [8]. Also, most cirrhotic patients have worsened malnutrition due to the significant daily loss of protein especially at the beginning of PD, which decreases with time, as shown previously in other studies [7, 9]. Based on the current data, PD is possible in cirrhotic liver patients. With taking specific measures like an early referral to a nephrologist, consideration of advanced laparoscopic paramedian PD catheter insertion with a purse-string suture at the deep cuff, and continuous drainage of ascites post implantation to avoid buildup and leak, and, finally, consider continuous ambulatory peritoneal dialysis (CAPD) over automated peritoneal dialysis (APD) to have control over the drained volume to obviate full-volume drains if it isn't well-tolerated.

Can We Continue Peritoneal Dialysis After Cardiac Surgery?

Cardiovascular diseases are a common cause of death in patients with end-stage kidney disease (ESKD) [10, 11]. It includes coronary artery disease, valvular heart disease, and arrhythmias. For these reasons, patients with ESKD may require cardiac surgeries such as coronary artery bypass grafting (CABG) and cardiac valve replacement surgeries. There is a misperception, especially among intensivists, that PD is not sufficient in post-cardiac surgery patients on mechanical ventilation and might worsen their respiratory status. Management of PD patients post-cardiac surgery remains a source of conflict among the nephrologists, intensivists, and cardiac surgeons. We, as nephrologists, have been pressured from the intensivists and cardiac surgeons to switch these patients to hemodialysis unnecessarily postoperatively. Continuing PD post-cardiac surgery has several advantages: it is widely available, has fewer resources needed, and minimizes the risk of vascular access-related bacteremia, which is essential, especially in patients with recent valve replacement. The ultrafiltration achieved by using high-concentration PD solution of 4.25% is the same as that produced by 24 hours of continuous kidney replacement therapy (CKRT). Kumar et al. studied the outcomes of PD versus HD after cardiac surgery [12]. They looked at the 30 days of operative mortality as the primary outcome of the study, which was the same in HD and PD patients at 11% and 10%, respectively—no difference in the 2-year survival between the two groups [12]. The approximate length of stay in the cardiac surgical unit was significantly shorter in PD patients (2 days vs. 4 days, $p = 0.05$), although the total length of the hospital stay did not differ [12]. PD is associated with shorter intubation time ($p = 0.06$) and less postoperative infections ($p = 0.08$) [12]. Two PD patients required a temporary conversion to hemodialysis, one of whom had a dialysis leak [12], but the site of the leakage and whether it was related to the surgical procedure were not mentioned. We can conclude that PD is effective as HD after cardiac surgery and hemodynamically tolerable in patients who are hemodynamically unstable in the

intensive care unit (ICU). We can do continuous cycling PD (CCPD) for 24 hours in the ICU if necessary.

Can Peritoneal Dialysis Patients Swim?

Swimming with a PD catheter is thought to increase the risk of infections [13]. The evidence to confirm or reject that is insufficient. There is one survey study conducted across 39 Australian PD units [13]. Almost all PD units reported that patients on PD do swim despite only 77% of PD units advocating swimming [13]. Swimming in seawater (85%) or in a private swimming pool (90%) were recommended [13]. There were seven reported exit site infections and two episodes of peritonitis associated with swimming with a PD catheter [13]. Based on the available data, we can conclude that, overall, PD patients are not recommended to swim in public pools as the contaminated water may lead to exit site infection. But swimming in clean ocean water or a clean chlorinated private swimming pool has been recommended. The PD catheter and exit site should be covered with either a waterproof dressing or a colostomy bag before swimming. As soon as the patient finishes swimming, they should take the bandage off, clean the exit site with soap and water, dry it thoroughly, apply antibiotics to the exit site, and cover with fresh gauze.

Can We Do Peritoneal Dialysis in Patients with a G-Tube?

Enteral feeding is recommended for patients who cannot maintain adequate oral nutrition [14]. Gastrostomy feeding is the preferred method of enteral nutrition. A gastrostomy tube has different ways to be inserted: percutaneously, surgically, or radiologically as indicated in each patient [15]. Percutaneous endoscopic gastrostomy (PEG) is a procedure of choice in patients who need long-term tube feeding [16]. PEG tube insertion in PD patients has some challenges, but it is not necessarily contraindicated. Problems relate to the poor healing of the PEG tube site, leak of gastric contents in the peritoneum, and the risk of enteric organisms or fungal peritonitis after PEG tube insertion. The evidence of PEG tube insertion in PD patients is based on case series, and most of the data are limited to pediatric studies. Fein et al.'s single-center retrospective study assessed the outcomes of PEG feeding in ESKD on PD. Of the ten PD patients, nine failed to eat because of neurological causes—two patients had functioning PEG tubes before starting PD and had no consequences [17]. Only two of eight patients already on PD continued with their regular PD prescription without any interruption at the time of PEG placement; both patients immediately developed peritonitis [17]. Of the six patients who were switched and maintained on HD, two developed peritonitis within 1 week of starting PEG feeding [17]. The other four had no consequences from PEG feeding while being kept on HD, but one developed peritonitis when PD resumed. Of the five

patients who developed peritonitis, three had fungal peritonitis [17]. In another case report by Dahlan et al., a 79-year-old female on PD who underwent PEG tube insertion and switched to interim HD developed a leak around the PEG tube site 1 week later, and enteric and fungal peritonitis complicated by shock and died subsequently on the tenth day post-PEG insertion [18]. Based on the current studies, we can conclude that if the patients already have a well-healed PEG, then they can be considered for PD. There is measurable, but acceptable, risk for complications. However, in patients who are already on PD, there is very high risk of complications, and we don't recommend it. To decrease the risk of complications, we recommend surgical insertion of PEG tube over percutaneous insertion if no contraindications, prophylactic antibiotic and antifungal at the time of PEG tube insertion, delay the use of the PEG tube until healing is achieved, approximately 6–8 weeks. Using prophylactic antimicrobials before PEG tube insertion and extending the duration of interim HD do not eliminate the risk of peritonitis but might reduce the risk [17]. Also, another consideration is the type of tube feeding. Avoiding placement of the feeding tube into the abdominal cavity might overcome the risk of complications. There is one case report in Japan about using percutaneous transesophageal gastro-tubing (PTEG) for feeding in PD patients, where the PTEG was inserted successfully without interruption of PD, and the feeding started within 24 hours of PTEG insertion [19]. Since then, the reported patient continued both PD and PTEG feeding without complications [19].

Is There a BMI Cutoff for a Patient Who Wishes to Do Peritoneal Dialysis?

The traditional measure of obesity has been by measuring the body mass index (BMI). However, given the age-related changes in the body composition, the increase in fat, and the decrease in muscle mass, BMI may not reflect the proportional changes in body fat or muscle mass [20]. Also, BMI does not give an accurate estimate of the body fat distribution, which is more important when we consider PD [20].

Obesity has a significant impact on the general population; it is considered as one of the risk factors for morbidity and death [21–23]. However, this association varies according to the presence or absence of other medical comorbidities. For example, in patients receiving hemodialysis, higher BMI has been associated with reduced mortality risk [24]. In patients receiving peritoneal dialysis, there have always been concerns about the outcomes, including survival and the risk of PD catheter leak/hernia, residual kidney function decline, and peritonitis and exit site infection. For these reasons, obesity has been viewed as one of the contraindications for PD [25].

Most peritoneal dialysis patients will gain weight in the first year after starting peritoneal dialysis, as was reported by Diaz-Buxo et al.; the average weight gain was 5–7 kilograms (Kg) [26]. This weight gain was attributed to the resolution of

the uremic anorexia and the caloric load (400–800 kcal from the peritoneal dialysis solution) [27]. Several studies have assessed the body composition changes after starting peritoneal dialysis and have shown that there is a highest increase in the total body fat with a significant increase in visceral fat in the first 6 months of the start of PD [28–30]. Kim et al. has studied 148 incident PD patients who experienced weight gain of more or less 3% of total body weight and concluded that there is a correlation between the amount of the weight gain and the rate of decline in residual kidney function (RKF), approximately fourfold higher reduction of RKF with >3% of weight gain [31]. The currently available data about the impact of weight gain on the PD patient's survival has been inconsistent, and we don't know if increase weight gain affects the survival of PD patients. In 2016, Obi et al. studied 15,573 incident PD patients in a cohort study, and they looked at the impact of obesity on dialysis modality longevity, RKF, survival, and peritonitis [32]. It was noted there was a U-shaped correlation between body mass index (BMI) and mortality, with the highest survival rate associated with a BMI range of 30 to <35 kg/m^2 [32]. Also, compared with hemodialysis, PD patients had a lower risk of mortality in the BMI of less than 25 kg/m^2 and between 25 and 35 kg/m^2 and had the same survival rate as matched hemodialysis with BMI ≥ 35 kg/m^2 [32]. More frequent peritonitis-related hospitalization ($p = 0.05$) was seen in obese PD patients in comparison to lean PD patients [32].

Another concern regarding peritoneal dialysis is that obesity may increase the risk of PD-related peritonitis [33]. A cohort study was conducted on PD adult patients in the province of Manitoba during the period 1997–2007 [33]. They studied whether there was any correlation between higher BMI and PD-related infections [33]. After adjusting for all possible confounders, there was no relationship between BMI and peritonitis [33]. However, there was an increased risk for coagulase-negative staphylococci (CNS) among PD patients with high BMI [33]. To reduce the risk of peritonitis in obese PD patients, two-piece extended peritoneal dialysis catheters with remote exit site locations have been compared to the conventional abdominal catheters in obese PD patients [34]. No difference in rates of exit site infection and peritonitis risk was found [34]. Extended catheters may be associated with a higher rate of infection-associated catheter loss particularly if peritonitis is due to gram-positive organisms [34]. Placement of the PD catheter in obese patients might be challenging, and few considerations need to be taken into account: we need to properly estimate the length of the catheter; select the catheter exit site ahead of time; have the patient sitting when the exit site is marked to allow better visualization of the abdomen, including fat rolls; and choose distant exit site or presternal catheter as needed.

We can conclude that body mass index is associated with leaks and hernias, but there is insufficient evidence that higher body mass index is associated with an increased risk of peritonitis or overall mortality. Higher body mass index may be associated with reduced technique survival. Some strategies that can be done to reduce the risk of hernia in obese patients are pre-dialysis assessment of the inguinal, abdominal, and ventral hernias and repair at the time of insertion, purse-string suture at the deep cuff, paramedian incision into the abdominal cavity, low-volume

dialysis at the time of PD initiation, overnight cycler, and keeping day dry if there is sufficient residual kidney solute clearance.

Obese patients are disadvantaged in achieving dialysis adequacy due to inappropriate assessment of dialysis adequacy based on Kt/V of urea. Kt/V which measures how many volumes of distribution of urea are removed by peritoneal dialysis per week has been used in dialysis patients to assess the adequacy of dialysis. Urea is distributed in the *fat-free mass* and given the high fat mass in obese patients; using their total weight to calculate V will overestimate the true volume of distribution of urea. It is possible to determine the Kt/V using the ideal body weight by substituting the ideal for the actual weight into the Watson formula for volume; however, it is unclear if this is the correct strategy. The Watson formula overestimates V in obese patients, potentially leading to a falsely low Kt/V. KDOQI guidelines suggest adjusting clearance to the ideal rather than the actual body weight but acknowledge the uncertainly of determining V in those who are overweight. Unfortunately, there are no randomized trials to guide clinical practice in this area. In the absence of evidence, clinicians should use their clinical judgment in combination with laboratory values to decide if a patient is receiving adequate dialysis and not rely on Kt/V urea.

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Chapter 27
Building an Effective Peritoneal Dialysis Program

Anjay Rastogi, Christina Lopez, and Ramy Hanna

Introduction

The care of end-stage kidney disease (ESKD) patients is extremely complex and costly [1]. The interruption of the patient's psychosocial well-being, ability to work, and overall health have driven the need for extensive supportive infrastructure [2] that serves patients receiving in-center hemodialysis (ICHD) [3]. As Medicare expenses have spiraled upward, an ongoing call for improved efficiency of healthcare delivery to ESKD patients has been placed [4]. The recent "Advancing American Kidney Health" initiative codifies this expert consensus into law by calling for a vast increase in the number of patients receiving dialysis care at home [5, 6].

The need for all major healthcare systems, academic centers, and private practice groups to develop a strong cadre of PD patients is thus clear. In the complex world of ESKD, there is much that needs to be controlled and done. Hence, the concept of the team that is essential to an integrated dialysis program is presented.

Additionally, there are many challenges to maintaining a high-quality, patient-oriented, efficient and effective PD program. These challenges are heavily offset by improvements in patient psychosocial well-being [7], ability to work [8], maintenance of residual kidney function (RKF) [9], and increasing compliance with

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federal and state initiatives. The medical director with the core team of a successful PD program is literally part of the solution to our nation's healthcare crisis.

So how do we define a successful PD program? What metrics do we look at? Recruitment is obviously important, but a truly successful program is a lot more than that. Some of the key metrics for a successful program should include PD retention, quality of life on PD, and transplantation. Infection rates and decreased hospital admissions are critical factors as well [10]. How do we achieve these? Successful PD programs are also not built overnight; it takes a lot of hard work and dedication with consistent support from the key stakeholders. We will be discussing a few key factors that, in our experience, lead to a PD program of excellence.

Recruitment

Patient Selection

Patient recruitment is an essential part of building a successful PD program. Patient selection is important, as PD is a process that has to be undertaken by a trained patient or a patient with a support network. As the race to attract more patients to PD begins, creative solutions will have to be found for patients who would have a more difficult time learning to manage the operation of PD themselves. The best PD candidates are able to handle the activities of daily living (ADLs), easily trainable, and capable of managing the physical operation of PD. Continuous ambulatory peritoneal dialysis (CAPD) requires the ability to manipulate the PD fluid containing bags, and a knowledge of how to operate the cycler is important for those patients using continuous cyclic peritoneal dialysis (CCPD).

A strong support network can allow for patients who may not be able to perform PD on their own. Elderly patients who would benefit from avoiding ICHD for quality of life and avoidance of infection can have PD done by a skilled family member or caregiver. This makes PD a valid option in certain geriatric populations. Home visitation programs have also met with success in nations like Canada and France [11].

Getting patient selection right is critical. Incorrect patient selection will lead to patient dropout. The patient selection has to be a team approach where the referring nephrologist, PD champion, and PD team assess the patient independently and share notes. Any concerns should be addressed as a team. At the end, if it is deemed that the patient will not be a good candidate, it should not be taken as a failure but a success. A patient who is currently not a suitable candidate should be followed for suitability in the future. It is important to keep these patients engaged and reach out to them on a regular basis. In some of the more successful programs, there are few barriers that cannot be overcome by the team. Thinking outside the box might be needed in selected cases to maximize success and to overcome challenges to PD at home. This includes consulting and sharing with other similar programs.

Education

Modality Education for ESKD Patients

It is very important that the modality education be done properly. After the referring nephrologist has done his/her part, the PD champion and PD team should do their own modality education. This modality education has to be very personalized. The cookie cutter approach that is often used by LDOs and MDOs needs to be modified and personalized to the particular patient significantly. The modality education will also lay the groundwork for future outcomes including retention. Modality education should also be used for understanding the patient's unique situation and addressing their concerns, anxieties, and fears. These sessions should be used for assessing if these patients are appropriate for the PD modality [12]. The modality educator has a key role and should be directly appointed and supervised by the PD champion. After the modality education, the notes should be shared with the core PD team.

Modality Education for CKD Patients

Patients with advanced CKD (Kidney Disease Improving Global Outcomes-KDIGO) stages IV and V also make attractive patients for PD recruitment. This will lead to smoother transition to PD when it is needed and more utilization of incremental PD which can lead to a smoother landing and better adjustment to a major lifestyle change [13–16]. To do this effectively, classes must be widely available to explain what dialysis is all about, the differences between HD and PD, and current options. The equivalence of outcomes clinically and the psychosocial benefits of PD and all home dialysis should be explicitly outlined to the patient and their family. The availability of instructional videos, outlines, and translations of these materials in the patient and their family members' language is a must. Again, the nephrologist must provide initial education that is then supported by the nurse educators, dialysis educator, and/or vascular access placement coordinator who is perfectly in line with the materials and follow-up education given to the patient. Consistency is key.

Family Education

Family education starts with the modality and education for the patient and should continue throughout. The involved family members and caregivers should also be a part of this ongoing education. Reviewing unanticipated outcomes and complications is necessary to continue perfecting the ability of the PD program to prevent adverse outcomes. Materials and resources should be made readily available.

Ongoing Patient and Family Education

This is critical. The education should be ongoing and not stop at the modality start. Every opportunity should be used to educate and train the patient. They should always be reminded about issues that can lead to technique failure. If there is a bad outcome like infection, there should be focused retraining. A visit to the home at the end of training, or even before the start of training, is important in order to see the patient in context of their environment. A revisit to the home might be needed. Continual assessment of the patient status is very important as is providing the necessary support. If it is deemed by the core team that the patient might need respite therapy, it should be addressed.

Staff Education

Along with patient education, staff education and enrichment are essential as well. The PD champion should make sure that this is not overlooked and a plan is put in place that is regularly attempted. Teaching materials should be provided. Attendance at conferences should be encouraged. Subscriptions to online tools, journals, and courses should be made available as well. Policies and protocols should be put in place and updated regularly by the staff along with the PD champion. The staff should also participate on the quality improvement projects. Interactions with other programs of excellence should be highly encouraged so there is mutual growth.

PD Access Placement

PD catheter issues are a very common cause of dropout and delayed starts. A strong PD access placement and follow-up team is essential for a successful PD program. Besides the well-trained surgeon and interventionalists, the team should include a well-trained access coordinator. Pre- and post-procedure recommendations and follow-up should be standardized [17]. It is very important that the access team works closely with the PD team. The PD champion has a very important role in building this relationship.

The Team!

To have a successful PD program, you need a team in the true sense of the word, and the team needs a *PD champion* first and foremost. The PD champion is often the medical director or their designee who champions the growth of the PD program, its effectiveness, and the retention and well-being of the PD patients.

It is very important that the right person from the practice or faculty be appointed as the PD champion. This person needs to be given all the support to build a team

and program that is exceptional. Besides the nephrologist, the integral team (also described as the core team) includes the nurse, medical social worker, and renal dietitian among others. The administrative assistants and technicians are additional members that are important. The program managers also play a vital role. Every member of the core team has a vital role and needs to contribute and should be held accountable.

Besides the core team, there are extended teams. These include but are not limited to the outpatient clinics, the access placement team, and the hospital. The teams should also include the transplant program and infectious disease specialist who is aware of the local resistance patterns. The key roles of these various teams are the following:

Outpatient clinics Initiating modality education at the right time and by the right person. Eventually, the PD team will be doing the modality education, but the clinic should facilitate this and make all the referrals in a timely basis. Open and real-time communication with the other teams is critical. Coordination of care is vital and should be the responsibility of the appropriately selected person. Educational materials and resources should be readily available to the patients and their family members. Also, speaking to a PD patient who is as closely matched to the patient being educated should be attempted. This will allay a lot of anxiety. In our program, they are called ambassadors.

Access placement team A properly placed access is vital for successful PD outcomes. It is the responsibility of the PD champion to develop a successful access placement team that includes surgeons, interventional radiologists, and interventional nephrologists. The access needs to be placed in a timely fashion with appropriate follow-up. The PD champion needs to make sure that the access placement team has been provided all resources needed to learn about the techniques and improving outcomes. It is very vital that the communication between the access placement team and the PD team is in real time. We have found it very useful and productive when there are regular face-to-face meetings between the PD and access placement teams. The access team should visit the PD clinic as well. It is also very important to give feedback in real time to the access placement team on how the access is working – good or bad. If there are any complications, they should be addressed in a timely way with clear guidance being provided to the PD team and the patient. An ongoing quality improvement project should be looking at the outcomes of PD catheter placement and appropriate actions taken if there are concerns. Feedback should be provided by the PD champion to the access team and interventions outlined and followed up on as needed.

Hospital team/PD hospital liaison The hospital has a critical role in PD growth and retention. Quite often, the staff in a hospital setting is not well-trained and equipped to deal with PD patients. One of the reasons could be the fact that they don't see too many PD patients, or that not enough resources are provided to train them. This often leads to delays in timely action and inevitable errors. Infection is an important issue that the emergency department and hospital should address immediately, with appropriate attention to latest intraperitoneal antibiotic guide-

lines [18]. PD prescriptions also need to be appropriately adjusted on admission and regularly monitored. The urge to convert PD patients to HD should be prevented where possible, well thought out, and discussed with the patient's dialysis unit's PD champion.

The hospitals also have an important role in identifying appropriate patients for PD. This includes both prevalent and incident patients. For prevalent patients, an open discussion about the potential benefits should be done and, if deemed appropriate, the process to convert them to PD started. For incident patients, urgent PD starts, if appropriate, should be considered. Proper discharge is also the responsibility of the hospital. This includes the right dialysis units and access placements. If the PD catheter cannot be placed inpatient for whatever reasons, the patient should at the minimum be evaluated and cleared for outpatient PD catheter placement with an outpatient date for access placement. The inpatient case management team needs to communicate and work with the PD team to make sure everything flows seamlessly.

Quality control team This is another team which most often is a part of the core team. The job of this team is to follow up outcomes and implement quality improvement projects. The outcomes should be assessed and discussed on a regular basis with the PD team and appropriate interventions made. It is a good idea to have standard operating procedures and protocols. These procedures and protocols should be reviewed and updated on a regular basis. They should be signed and dated by the entire team. To promote active learning, each team member should be asked to present a specific protocol to the rest of the team. These presentations should involve active engagement. The person presenting should do research prior to the presentation for any updates. They should work closely with the PD champion on this. Notes should be taken during the meeting and updates done as needed to the protocols after and reviewed. Every dropout from technique failure should be analyzed, and lessons should be learnt if it was potentially preventable.

Special focus should be placed on PD catheter issues and infection control. The team should be well-versed with the protocols and approach.

Morale building People work for job satisfaction rather than salary. This is also true of a PD program. It is the job of the PD champion to make sure the morale of the staff stays high. A PD champion has to be a true leader and inspire the entire team. Also, making sure the team gets proper treatment from the organization is also the responsibility of the PD champion. It is also important to keep the staff turnover as low as possible. And if a staff member does decide to leave, the reason should be investigated and looked into if it could have been avoided. Morale and team building activities should be highly encouraged. Bonding between team members will lead to a stronger foundation for a program. Team members should be as passionate about PD as the PD champion. They should be in it for the right reasons and they should always be reminded of that. Staff selection is as important if not even more than patient selection. The PD champion should focus on the personal and professional growth of the staff and advancement in their career. This will foster trust and loyalty to the system.

Interactions of the PD Program with the Health Ecosystem

It is the role of the PD champion to serve as an ambassador to their healthcare system and local healthcare providers and hospitals. Educating surgeons, ID physicians, primary care physicians, nurses, hospital staff, patient family members, and patients among others is an all-important role that the successful PD champion must take on. This is how patients are recruited and how teams are formed. Cooperation among nephrologists, surgeons, ID physicians, interventional radiologists, and primary care doctors is key. This will remain an extra role that is specially needed until PD displaces sufficient share of the ESKD population that the medical community will be as familiar with the PD guidelines as we currently are with HD guidelines.

Support from Organizations

For any PD program to be successful, it will need support from the organization. It is quite important that the staffing and space allocation is adequate and we stay one step ahead of the growth. In our experience, there have been times where the growth has outpaced the staff and space, and that has not been good for the program. Planning is key, and regular meetings between the PD leadership and organizations should take place so there are no surprises. There should be a commonality in vision and goals.

Integrated Dialysis Program

There are more and more standalone home programs appearing in the USA. However, the old conventional dialysis units usually consist of ICHD, HHD, and PD programs under one roof. Our program has the pediatric unit as well. Some programs have nocturnal units also. In a successful PD program, there will be true integration of all the existing programs that will work together as a team with a common goal of increasing home dialysis growth and transplantation. The walls have to be literally brought down. The cooperation between the programs occurs at multiple levels. We definitely want to convert the eligible ICHD patients to home dialysis. The staff in ICHD should know how to speak to the patients about the benefits of home dialysis. They should also reach out to the home dialysis staff and connect them with the interested patients. ICHD is also the place to go for respite therapy. They need to make sure the patient goes back to home therapy as soon as possible and feasible. They also need to provide the best dialysis care they can during the respite therapy,

including paying extra attention to the PD catheter and residual kidney function. Volume management will also help ensure patients do not end up with repeated admissions by managing dextrose and icodextrin dwells appropriately [19].

Despite best efforts, there will be patients who will fail PD. For these patients, there should be a planned exit preferably to HHD. For this, planning is needed, including placement of a more permanent HD access and patient education.

The PD team needs to work closely with the ICHD team and provide all the education, resources, and training as possible. Regular meetings between the teams are highly recommended. Also assisting each other as needed is very important. The program managers and PD champion need to participate in these meetings as well.

Transplantation

One of the shortcomings often cited for even highly successful PD programs is not enough emphasis on transplantation. Transplantation still is the modality of choice for majority of patients and should not only be highly encouraged but also facilitated. It should be an active discussion during monthly visits. Active coordination with the transplant program should be happening on an ongoing basis. Transplant education and resources should be provided. Patients and their families should also be educated on living kidney donation. There have been many advances in recent times including paired exchange donation. One of the metrics for a successful PD program is their transplantation rates.

Conclusion

In summary, the secret sauce for a successful PD program is a team approach with strong leadership. All the key stakeholders need to play their part. A truly integrated and comprehensive approach needs to be undertaken. Constant improvement with a dedicated quality team is essential.

Acknowledgments UCLA CORE Kidney Program

Conflicts of Interest Anjay Rastogi is a Medical Director for DaVita Dialysis Unit.

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Chapter 28
The Peritoneal Dialysis Outcomes and Practice Patterns Study

Belinda Stallard, David W. Johnson, Jeffrey Perl, and Simon J. Davies

Introduction

Kidney failure is a leading contributor to the global public health burden with over 2.6 million people requiring kidney replacement therapy (KRT) or kidney transplantation [1]. Peritoneal dialysis (PD) is a form of KRT that is currently utilized by approximately 11% of maintenance dialysis patients worldwide [2] with an average of 20.8 people per million population (pmp) initiating PD each year treated by approximately 1.3 PD centers pmp [3]. PD is a cost-effective treatment [4, 5] which is associated with an initial survival advantage [6, 7] and offers patients a flexible, home-based therapy with increased treatment autonomy [8, 9]. Since the mid-1990s, there have been progressive improvements in patient survival on PD, which have outstripped those observed on HD [10, 11]. Over the same period, there have been concomitant improvements in PD technique survival, with progressively fewer patients transferring to hemodialysis [10]. However, technique survival varies widely both within and between countries, with 3-year rates ranging from 29%

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in Malaysia to 91% in China [2, 12]. This variation is not fully explained by case-mix, suggesting that other factors, such as center practices, may play a role [13–15]. Technique failure has a major disruptive impact on the lives of patients and their caregivers, results in appreciable morbidity and mortality, and has been identified by clinicians and patients as a top research priority [16–18]. Technique failure also incurs considerable cost to healthcare systems, as evidenced by a Canadian study which showed that PD technique failure within the first 3 years resulted in a similar cost burden to patients treated with HD alone, thereby obviating the overall financial benefits that PD provides compared with HD [19]. As technique failure still remains one of the major factors limiting both the utility and utilization of PD as a therapy around the world [2, 12, 20–22], it is imperative that the factors underpinning technique failure are comprehensively identified and, where possible, mitigated.

This chapter will examine the importance of the problem of PD technique failure and provide an overview of the current status and early findings of the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS), the prime objective of which is to identify modifiable practices associated with superior PD technique survival.

The Problem of Technique Failure

One of the key difficulties with technique failure is that there is significant variation in how it is defined in the published literature [23]. In particular, there is marked variation regarding when PD is considered to start and when it is considered to end. Although not often defined at all, some groups define PD to have started with the first exchange (e.g., the *Registre de Dialyse Péritonéale de Langue Française*), while others define it as the end of PD training (Brazilian PD study, BrazPD) [23]. A number of groups, such as USRDS, do not count PD at all unless patients were on that modality at 90 days following dialysis initiation, despite the fact that the first 90 days are a high-risk period for technique failure [24, 25]. Most studies also do not define how long a patient has to be off PD to qualify as a technique failure [23]. A recent Australia and New Zealand Dialysis and Transplant (ANZDATA) registry study explored a range of definitions used to describe PD technique failure and ultimately recommended that PD technique failure be standardly defined as a composite end point of transfer to hemodialysis for at least 30 days or death (either on PD or within 30 days of ceasing PD) [26]. They also recommended a secondary definition using a time window of 180 days, which provides additional information on the likelihood of return to PD [26]. Additional time windows, e.g., 60 days, may be reported. Having a standardized definition of technique failure is critical to benchmarking between centers and countries and to properly elucidating patient-level and center-level characteristics associated with technique failure.

The most commonly recognized patient-related risk factors for technique failure include younger age, higher body mass index, Indigenous race, lower socioeconomic status, and comorbidities (such as diabetes) [15, 27–33]. However, recent studies

have demonstrated that center-level characteristics may play an even more significant role in PD technique failure variability [34]. Schaubel et al. collated data from the Canadian Organ Replacement Register and observed that a dialysis unit's experience in treating PD patients had a significant impact on PD outcomes [35]. Overall, as the cumulative number of patients treated with PD increased and as the percentage of patients initiated on PD increased, mortality and technique failure rates both decreased [35]. Other registry-based studies completed in France, Netherlands, Brazil, Canada, and the United States have similarly shown a correlation between smaller PD center size and higher technique failure rates [35–39]. These findings were further distinguished in a systematic review by Pieper et al. which concluded that larger center volume was associated with an improved technique survival [40]. In an ANZDATA registry study of 9362 patients from 51 centers in Australia, Htay et al. observed sevenfold variation in technique failure across centers which was predominantly accounted for by modifiable, center-level factors (such as PD unit size and proportion of patients treated with PD) rather than patient characteristics [34]. Indeed, center variation in PD technique failure was reduced by 28% after adjusting for patient-specific factors and by a further 53% after adjusting for center-specific factors [34]. Similar findings were observed for rates [27] and outcomes [41] of peritonitis, which is the major cause of PD technique failure after death. These findings suggest the possibility that PD technique failure is strongly influenced by modifiable center characteristics relating to their practice and/or organization.

Another piece of evidence suggesting that PD technique failure is driven by modifiable center characteristics is the evidence that implementation of national quality initiatives has been associated with substantial improvements in technique survival rates. The best example of this is the Australian and New Zealand peritonitis continuous quality improvement (CQI) initiative, which involved generating better evidence to inform peritonitis guidelines, facilitating better translation of evidence and guidelines into clinical practice, and establishing CQI processes at local, state, and national levels through improved outcomes monitoring with quarterly audit and feedback, identification of barriers and enablers through implementation research, improved education targeting early career nephrologists, development of standardized peritonitis pathways, and incentivizing performance improvement [42]. These initiatives were quickly followed by a one-third reduction in peritonitis rates, a one-half reduction in between-center peritonitis rate variation, and a significant improvement in PD technique survival [42].

Due to the cumulative evidence that center-level characteristics are a significant driver for PD technique failure, a better understanding of the modifiable causes of PD technique failure is required. A limitation of the aforementioned studies is that they largely relied on information collected by registries, which lacked sufficient granularity of data (particularly in relation to center organization and practices) to comprehensively address this issue. With this in mind, PDOPPS was established as a global collaboration between the Arbor Research Collaborative for Health and the International Society for Peritoneal Dialysis (ISPD) to understand variation in PD practices and outcomes, identify optimal practices, and ultimately improve outcomes for patients treated with chronic PD [23].

PDOPPS: Design and Rationale

Rationale

Based on the findings of the aforementioned studies, the basic tenet of PDOPPS is that variable (and often poor) PD technique survival rates are driven by variable (and often poor) PD center practices, such that identifying those modifiable practices associated with superior PD outcomes (including PD peritonitis-free survival and technique survival) will help to better inform clinical practice and ultimately patient outcomes.

PDOPPS builds on the successful methodology established by Dialysis Outcomes and Practice Patterns Study (DOPPS), which was originally formed in 1996 to study in-center HD patients and practices [43]. The primary objective of DOPPS was to improve HD patients' morbidity and mortality outcomes, inform policy changes, as well as influence patients' health-related quality of life [43]. DOPPS has helped shape HD practices on a global scale and still remains a leading resource for the nephrology community worldwide with comprehensive data that have influenced clinical practice guidelines for HD [43–49]. DOPPS initially started with 308 HD units from 7 different countries [44] at initiation and then expanded to 21 countries, 580 facilities, and over 30,000 census patients by 2015 [50]. This large prospective cohort study has led to important practice policy changes such as the fistula first policy and strategies for improved management of anemia [51–53], mineral and bone disorders [54, 55], and quality of life among HD patients [56–58]. The program has now been expanded to include patients with chronic kidney disease (CKDopps) [59] and patients receiving peritoneal dialysis (PDOPPS) [23]. All three of these major projects share the common goal of identifying measurable differences in facility practices that will help inform strategies to improve patient outcomes.

Design

The PDOPPS is an international prospective cohort study of PD patients over the age of 18, which began recruitment in 2013. The primary outcome is all-cause PD technique failure, and the secondary outcomes include all-cause mortality, hospitalization rates, PD-related complications, patient-reported outcomes, and cause-specific technique failure [23]. The overall objective is to identify differences in clinical practice between centers to improve PD outcomes as well as to generate scientific hypotheses for the variations found in the study [23].

During the initial phase (Phase 1) that extended from 2013 to 2016, PDOPPS randomly selected at least 20 different PD centers with at least 20 prevalent PD patients from each of the 7 different countries (Australia, New Zealand, Canada, Japan, Thailand, the United Kingdom, the United States) (Fig. 28.1). At study initiation, all centers completed a census of their PD patients from which 20–30 prevalent patients were randomly selected independent of the dialysis unit's size. A maximum

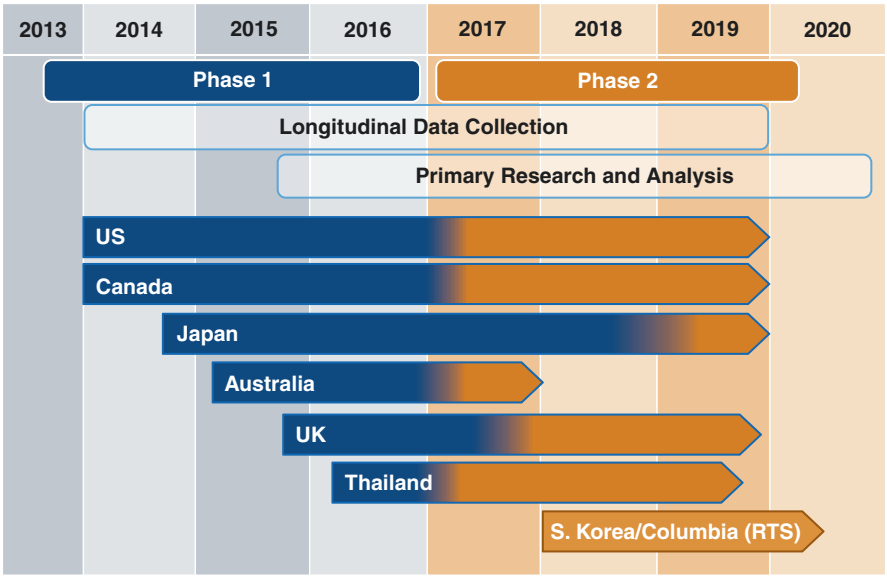

Fig. 28.1 Country participation and timelines for PDOPPS

of 25 incident patients (defined as patients initiating PD within 30 days of the PDOPPS census date and receiving at least one PD treatment at home or a nursing home) were also included. Patients continued to be followed up until kidney transplantation, transfer to a different dialysis unit, permanent hemodialysis transfer (>4 months), kidney function recovery, death, or PDOPPS ends. If patients left the study, they were replaced by randomly chosen patients (on an annual basis) who had entered the dialysis center since the last sampling period [23]. Within each country, national funding was utilized for data collection [23, 60]. All of the original seven countries, except for Australia and New Zealand, and two new countries (South Korea and Colombia) have participated in extended follow-up during phase 2 (2017–2020), during which the cohort has been enriched with incident patients (Fig. 28.1).

Study Data and Collection Instruments

The data collected by PDOPPS using patient and facility questionnaires have been developed by six workgroups in the areas of infection prevention and management, patient support, PD catheter access and function, PD training and education, dialysis prescription and fluid management, and clinical application of PD therapy (Fig. 28.2). These workgroups consist of key international content experts who were carefully selected by the ISPD and Arbor Research Collaborative for Health to ensure diverse representation of disciplines, gender, ethnicity, and geographic regions.

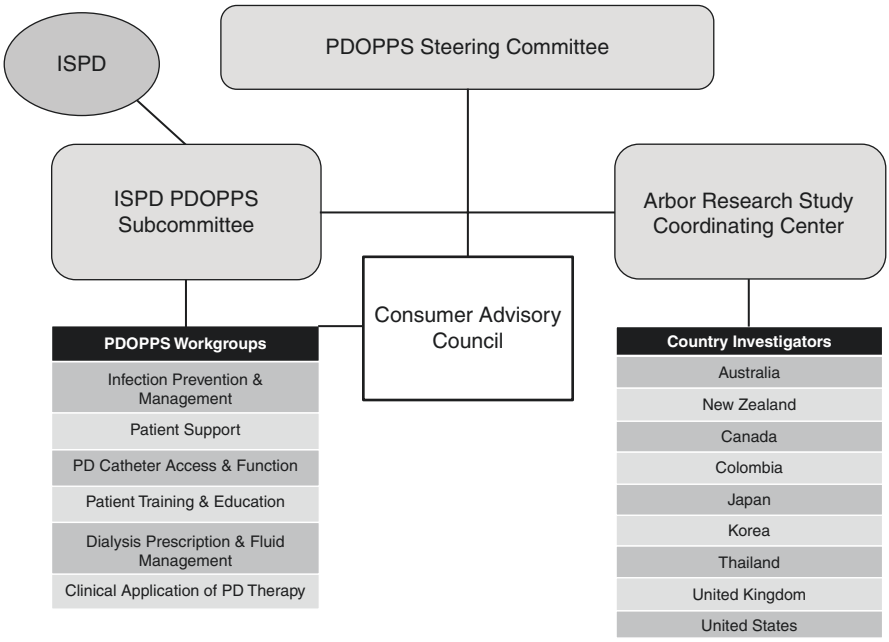

Fig. 28.2 PDOPPS organizational structure

Data collected by PDOPPS are depicted in Fig. 28.3. Demographic data, medical comorbidities and history, PD treatment, PD-related infections, and hospitalizations were collected at study enrolment. PD-related events or treatment changes were collected during follow-up by an interval summary questionnaire which was completed for each patient every 4 months. Furthermore, a standardized questionnaire was completed by patients, which focused on their quality of life and treatment satisfaction and was updated annually. From a center-level perspective, data collection forms were completed by the nurse unit manager and medical director to capture specific unit practices and clinical outcomes. All data were collected using standardized data collection procedures and tools, entered into an online data entry system (PDOPPSLink), and electronically submitted to the data management center at Arbor Research Collaborative for Health [23].

Analysis

Analytic methods used in PDOPPS have been described in detail previously [23]. Associations between practices and outcomes will be analyzed at both patient and center levels. In order to address possible bias introduced by unmeasured patient-level confounders, an instrumental variable analysis will also be applied, as has been done in other published DOPPS research [46]. Facility-based instrument variable

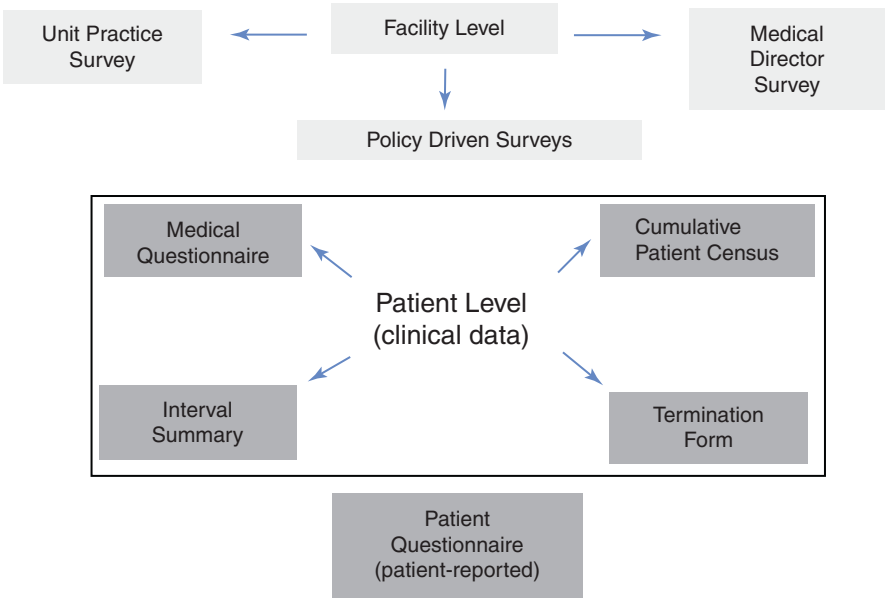

Fig. 28.3 Data collected by PDOPPS

analysis relies on the fact that patients are assigned to the facility's treatment preferences in a "quasi-random" fashion, which is independent of unmeasured patient-level confounders and therefore allows more valid estimates of treatment effects.

Ancillary Studies

PDOPPS provides an important opportunity for investigator-initiated ancillary studies to be conducted. Groups are able submit proposals for analysis of existing PDOPPS data or new data collection in collaboration with PDOPPS. These proposals are reviewed and approved by the PDOPPS Steering Committee. To date, four ancillary studies have been approved:

(a) The "Empowering Patients on Choices for Renal Replacement Therapy Study" (EPOCH-RRT), which aims to compare the effectiveness of hemodialysis and PD with respect to patient-centered outcomes and to develop a decision aid to assist patients with dialysis modality selection
(b) "Biological Determinants of Peritoneal Dialysis Outcomes" (BIO-PD), which aims to identify and validate genetic variants that explain the interindividual variability in peritoneal membrane function in patients undergoing PD
(c) "Optimizing Early Dialysis Catheter Function" (UKCath Study), which aims to establish the determinants of early PD access function, in particular "medical"

versus "surgical" insertion methods and their associated treatment pathways, with the intention of improving PD access outcomes

(d) "Optimizing Prevention of PD-Associated Peritonitis in the US" (OPPUS), which aims to identify patient and PD facility characteristics that are associated with PD peritonitis risk in PD patients and to foster the development and implementation of a standardized peritonitis definition and evidence-based best practice guidelines into dialysis provider organization clinical care pathways and national quality improvement initiatives with the aim of better preventing peritonitis

Current Status of PDOPPS

The initial countries participating in PDOPPS included Australia, New Zealand, Japan, the United Kingdom, Thailand, Canada, and the United States. During phase 1, 7629 patients were recruited from 215 dialysis units across the 7 countries. The study has evolved over time, and now a total of 11,688 patients have been consented for the study. The number of patients enrolled in PDOPPS from each country and the overall facility enrolment summary are summarized in Table 28.1. Additional countries joining PDOPPS in phase 2 include South Korea and Columbia.

Having multiple countries participate in PDOPPS provides a diversity of patients, PD practices, and cultures that can be evaluated throughout the study. In particular, PDOPPS contains a mix of high-income countries (Australia, New Zealand, Canada, Japan, South Korea, the United Kingdom, the United States) and low- and middle-income countries (Colombia, Thailand) from the major regions of the world (North America, South America, Europe, Asia, and Oceania). It also contains a mix of countries with different PD policies including PD-first (Thailand), PD-favored (Canada, the United States), home-based dialysis-first (Australia, New Zealand), and hemodialysis-favored (Japan) approaches [61, 62]. This greatly enhances the

Table 28.1 PDOPPS center and patient enrolments (as of 31 October 2018)

Country	Centers enrolled	Patient enrolment status	
		Census patients	Consented
Australia	19	2097	520
New Zealand	2	341	73
United States	100	8787	3981
Canada	20	3286	925
Japan	32	1664	923
Thailand	22	4644	820
United Kingdom	20	2266	387
Colombia	56	4059	4059
PDOPPS total	271	27,144	11,688

South Korea has not commenced enrolment yet

generalizability of PDOPPS' findings and facilitates comprehensive evaluation of the impact of different practices and policies on PD outcomes. It also allows the examination of unique country practices, such as hybrid dialysis (a combination of PD and HD), which is utilized in approximately one-fifth of patients on PD in Japan but almost not at all in other countries [23, 63]. Moreover, the impact of any policy changes, for example, arising out of the OPPUS project, will be comprehensively evaluated via the PDOPPS platform.

Early Findings from PDOPPS

The findings collated in phase 1 of PDOPPS have thus far resulted in 19 abstracts presented at multiple international conferences and symposia, 15 published studies, and manuscripts in preparation [23, 60, 64, 65]. Some early findings from PDOPPS have been detailed below according to clinical workgroup.

Infection Prevention and Management

The infection prevention and management workgroup recently examined variations in prevention and treatment of PD-related infections in 170 centers caring for more than 11,000 patients in 7 countries [64]. The practices of each PDOPPS country were further compared against practices recommended by the ISPD guidelines, particularly with respect to monitoring the incidence of peritonitis and using prophylactic antimicrobials in the prevention of PD-related infections and empirical treatment of suspected peritonitis. Units consistently recorded and tracked peritonitis episodes in only five countries (Australia, New Zealand, Canada, the United Kingdom, and the United States), while Australia and New Zealand were the only countries in which 100% of PD units recorded and tracked exit site infections. Substantial practice variation was also observed in the use of daily topical antimicrobial prophylaxis (mupirocin or aminoglycoside) by PD units across Australia and New Zealand (ANZ, 94% of units), the United States (88%), Canada (80%), the United Kingdom (71%), Thailand (27%), and Japan (4%). This variation is difficult to understand given the strength of the practice recommendation by the ISPD guidelines (level 1B). Another key finding established was the suboptimal co-prescription of antifungal prophylaxis when PD patients received antibiotic courses to prevent fungal peritonitis, despite this being a level 1B ISPD guideline recommendation. No antifungal prophylaxis was prescribed at all in appreciable proportions of PD centers in ANZ (11%), Canada (45%), the United States (46%), Thailand (77%), the United Kingdom (88%), and Japan (93%). There was also variable administration of prophylactic antibiotics prior to PD catheter insertion despite this having a level 1A ISPD guideline recommendation. The lowest uptake of this guideline was in the

United States (63%), and highest adherence was observed in the United Kingdom and Canada (100%). Considerable differences in facility adherence were also observed in the administration of prophylactic antibiotics prior to other invasive procedures, although these variable uptakes may have been explained by the limited quality and strength of the evidence in this area (levels 2C and 2D). Overall, this study highlighted the significant variations in PD peritonitis prevention and treatment practices among the participating countries, which often deviated from ISPD guideline recommendations.

The group has gone on to examine the association between selected facility practices and peritonitis rates. While the overall peritonitis rate averaged across the seven PDOPPS countries was 0.28 episodes per patient-year, country-specific rates ranged from 0.24 episodes per patient-year in the United States to 0.40 episodes per patient-year in the United Kingdom. Preliminary findings suggest that peritonitis risk is generally not associated with facility size, is lower with APD use, and is higher with failure to use preoperative prophylactic antibiotics prior to PD catheter insertion and possibly failure to use either topical exit site mupirocin or aminoglycoside ointment. These early observations suggest that poor adherence to specific clinical practice guideline recommendations was associated with a higher peritonitis risk.

Patient Support

The PDOPPS patient support workgroup has developed research questions that highlight patient-reported issues. A key focus of the group was functional impairment among PD patients, aiming to identify if there was variation between countries and if this is associated with permanent transfer to hemodialysis or higher mortality rates. Tennankore et al. assessed patient's functional status via two self-reported questionnaires which were combined to create an overall score [65]. The study observed that functional impairment was highly prevalent among patients on PD, with significant differences between the participating PDOPPS countries. Patients in Thailand were shown to have the highest functional impairment, and Japan had the lowest. The study also established that impaired functional status was strongly associated with higher mortality rates; however, functionally impaired patients did not have an increased risk of permanent transfer to HD [65].

In a separate investigation, the workgroup has identified that patients reported a generally favorable perception of PD, with the most commonly reported advantages being home-based treatment and the lack of vascular cannulation, while the most commonly reported disadvantages were a feeling of abdominal fullness and PD fluid storage space requirements. Those patients seeing PD as more disadvantageous were more likely to be depressed, have a lower quality of life, and experience a transition to hemodialysis.

PD Training and Education

Significant variability has been found between countries in the delivery of training to PD patients. Striking differences were seen in the duration of PD training sessions with the majority of patients from Japan (88%) being trained for less than 2 hours and for 2–3 days (39%). In contrast, in Australia, 64% of patients received training sessions lasting up to 6 hours and typically over a 4–5-day period (69%). Interestingly, Japan also appeared to differ in the timing of training with 62% of patients having their training prior to PD catheter insertion, while most other countries confined training to after PD catheter insertion, typically following a period of 2–3 weeks. Canada (84%) and Japan (100%) predominantly trained patients in facilities, while Australia (57%) and the United Kingdom (50%) trained patients using a combination of home and facility. Future studies will evaluate the relationship between PD training practices and outcomes.

Dialysis Prescription and Fluid Management

Early findings from this workgroup have similarly shown that both PD prescriptions and the types of PD utilized were highly variable between the different PDOPPS countries. Most countries had a predominance of automated peritoneal dialysis (APD) use over continuous ambulatory peritoneal dialysis (CAPD) with utilization rates in the United States and Canada being 81% and 71%, respectively. However, in Thailand, the majority of PD patients were treated with CAPD (96%). Among the patients receiving APD, there were a broad number of exchanges that were prescribed to patients such that almost half of the PD patients in the United States and the United Kingdom were prescribed five or more exchanges overnight compared with 39% of patients receiving less than three exchanges in Japan. Similar degrees of national variation in practices were observed in the total dialysis volume prescribed, use of biocompatible solutions (including icodextrin), and the average concentrations of glucose employed.

Conclusion

PDOPPS is the largest and most comprehensive PD study to date. This multinational study has collected data and produced research, which will be extremely valuable to the PD community and help to provide strong evidence for improvements in PD practices. The formation of PDOPPS is unique in that it collaborates with multiple countries to create a diverse body of data for clinical research. Phase 1 has already documented wide variations in clinical practice that cannot be accounted for

by patient factors as well as variation in important outcomes such as infection. The next step (Phase 2) will establish how these variations in practice associate with the primary outcome, technique failure. Future directions for PDOPPS remain vast, and the potential for further research opportunities, protocol establishment, and improvement of national and international guidelines are ongoing, providing an invaluable resource for clinicians, patients, and their caregivers.

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Chapter 29
Peritoneal Dialysis in Developing Countries

Brett Paul Cullis

Introduction

Kidney disease is a major health burden with an estimated 1.1 million deaths worldwide and, according to the Global Burden of Disease Study, the 12th most common cause of death [1]. The risk is significantly increased in low- (LIC) and low middle-income countries (LMIC) where there is a combination of communicable and non-communicable diseases resulting in both acute on chronic kidney disease. Communicable diseases such as malaria and HIV remain significant causes of mortality in their own right but are also the main causes of acute and chronic kidney disease in many tropical countries. In addition to this, throughout Asia, South America and Africa, there is a growing epidemic of diabetes and obesity, and, as a result, the incidence of kidney disease is rising exponentially. Unfortunately, not only is the incidence of CKD increasing in the L/LMICs, but due to the high cost of dialysis provision and limited resources, there is a lack of provision of kidney replacement therapy (KRT) for a large proportion of the population in these countries. The Global Kidney Health Atlas commissioned by the International Society of Nephrology (ISN) sought to examine the current provision of KRT around the world, and although there are missing data from many countries, it has allowed a much better understanding of how dialysis is provided [2]. One of the key findings is the heterogeneity of funding models in LMICs with only 17% of countries providing KRT free of charge and 53% using a mixed model of public and out-of-pocket payment. It is estimated that globally more than half of the people who require KRT will not have access to it and will die from kidney failure [3]. The disparity in the provision of KRT is very much dependant on the country's economic status, and it has been shown that L and LMICs only account for

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approximately 7.2% of the global KRT population, despite making up almost 50% of the world's population [3]. Despite this, there is expected to be a doubling in the number of patients receiving KRT by 2030, and as a result, there needs to be a coordinated plan how to implement this in the most cost-effective manner. What makes this task more complex is the heterogeneity of funding models in different countries. For example, many low-income countries, which do not have the healthcare funding to support a CKD KRT programme, still have haemodialysis facilities (mostly public-private partnerships) which provide dialysis to a very small proportion of the country and at great cost. This is often developed more for political reasons than as part of a coordinated plan for dialysis provision, and these services are also often only supplied to the wealthy or politically connected. Much of this growth is driven by private haemodialysis providers, and hence there is a negative incentive for patients to do PD. In South Africa, for example, there has been a massive upsurge in the number of private dialysis providers, and despite being a country best suited to PD for many reasons, Katz et al. showed that between 2002 and 2008, the number of private paying patients on PD remained static at around 1400, whereas haemodialysis patient numbers doubled from 2040 to 4180 [4]. This increase may be largely due to financial incentives for clinicians to choose HD over PD; however, insufficient postgraduate training in PD management, lack of skilled PD nurses, patient socioeconomic factors as well as perception of suboptimal dialysis and high peritonitis rates are other important factors.

Although transplantation is the optimal form of therapy for eligible patients, it is only a dream for many countries due to the lack of surgeons, physicians and other specialist services, and one has to be realistic that most countries will rely solely on dialysis of some description, as very few patients will ever be transplanted. Despite South Africa falling into the high middle-income bracket, the recent South African Renal Registry report shows that there is a prevalence of 8832 patients on dialysis, and yet there were only 261 transplants in 2016 [5]. It becomes very clear that most patients will never be transplanted in their lifetime, and thus it is imperative when considering dialysis options in these countries that one considers how best to position the different types of dialysis in order to produce the best length and quality of life. What is also clear is that in most L/LMICs, there is a scarcity of skilled nephrologists, vascular access surgeons and surgical facilities resulting in an almost universal use of dialysis catheters for haemodialysis with few if any patients having a fistula or graft. The result is that central venous stenoses and lack of vascular access options occur frequently. It is for these reasons that considering a PD first policy in these countries makes sense as PD will often become a necessity rather than a choice due to lack of haemodialysis access options. As has clearly been shown, "PD first" (with residual kidney function) rather than "PD last" is likely to have the best outcomes both clinically and financially. There are many other potential advantages to PD in these countries which are detailed below; however, significant obstacles also need to be overcome to deliver an effective programme.

It is important to realise that guidelines and best practice recommendations are often written in high-income countries where these options are easily available. However, in most developing countries, medical care is limited to some degree, and

often “best practice” is not feasible. In many cases, makeshift devices and locally mixed solutions save lives despite not being the optimal treatment options, and it is important that these are discussed. The International Society for Peritoneal Dialysis (ISPD) guidelines on PD for AKI have acknowledged this, and in the guidelines, there are two types of recommendation: “optimal” which all units should strive towards and “minimum standards” which are felt to save lives with a risk-benefit ratio which would still favour that they should be attempted in situations where the alternative option is death due to acute kidney injury [6].

Advantages and Disadvantages of Peritoneal Dialysis

In developing countries, the most obvious obstacle to the provision of dialysis is resources, both financial and human. One therefore needs an option that is more cost-effective and requires less nursing and medical staff. It is apparent in many developed countries that chronic peritoneal dialysis is more cost-effective than haemodialysis [7, 8], and although this is true in many developing countries, studies have shown this to vary significantly [8]. One of the confounders is that peritoneal dialysis fluids and connection devices are produced primarily in high-income countries, with little local production. Therefore, these consumables are purchased with foreign currency and then shipped to the countries concerned. Air transport of PD solutions is prohibitively expensive due to volumes and weight of the fluid required. In addition, there are often many official and “unofficial” surcharges at ports of entry into various countries. As the fluid travels by sea, landlocked countries then see increasing cost every time a border is crossed. There are some countries where solutions are produced locally, and this reduces the cost of transport, but often the fluids are made under licence of larger international companies, and as a result, up to 90% of the raw materials still have to be imported, and purchase costs are often similar to those fluids from high-income countries.

When assessing the cost of a dialysis modality, one needs to look at the whole picture as the cost of solutions forms only one constituent. In South Africa, for example, PD and HD consumable costs are almost equivalent. Where the difference occurs is that PD does not require water (often a very scarce resource in developing countries), electricity or maintenance of water treatment plants. Data from the United States (US) shows that erythropoietin-stimulating agents (ESA) and intravenous iron requirements in PD are approximately half that of haemodialysis, and as this often accounts for about one third of dialysis costs, it significantly impacts on overall costs [9]. Finally, if one looks at nursing salaries, these are also significantly reduced. We have demonstrated that in a low-resource environment, we are able to employ 1 peritoneal dialysis nurse to 4.4 haemodialysis nurses for the same number of patients and still achieve excellent results [10].

These cost comparisons would suggest that PD makes financial sense. However, the economic impact to the patient of PD vs HD in LMICs is substantial and should also be considered when choosing a modality. A number of studies have shown that

patients on PD are more likely to be employed compared with HD patients [11–13]. In L/LMICs, there is often only one person supporting a large extended family with a single salary. Therefore, if a breadwinner develops kidney failure and requires dialysis, this can have a devastating effect on the entire family. A modality that allows continued employment is preferable and is most likely going to be PD. Another economic impact of modality is transportation. Developing countries in general have few haemodialysis facilities, and these are centred on the larger cities. The result is that those who need to do haemodialysis often have to travel significant distances to dialysis two to three times per week. The cost of this travel often exceeds any social grant funding the patient may receive and therefore results in further hardship. The long travel times also prevent many of these patients being able to continue in employment with the additional impact this has. PD, on the other hand, is able to offer patients the ability to stay near their home and potentially work during the day.

There are also the health issues that favour PD over HD. In many units, HD is only offered twice a week, and this often results in inadequate dialysis and associated issues with fluid balance, ESA resistance and sepsis. Due to the reasons mentioned above, PD, however, can be delivered at an adequate dose at the patient's home, thus potentially offering superior clearances compared to HD.

Concerns have been raised that despite the theoretical advantages above, it is not possible to do PD in countries where patients live in poor social conditions without running water and electricity and where literacy and education levels are low. These concerns are often unwarranted, and this has been demonstrated in a number of studies. Katz followed up 88 patients in South Africa where only 63% lived in a brick house, the rest in informal housing or shacks with no running water in the house. Despite this, the peritonitis rate was only 1:27 patient-months, and when assessing risk factors for peritonitis, neither housing nor education level was a predictor [14]. In Colombia, it was also shown that the type of housing had no influence on peritonitis rates [15]. There are studies from Taiwan and Brazil however which have shown education level to be a risk factor for peritonitis, and this needs to be addressed especially when selecting training materials and educational approach to training patients [16, 17]. It is known that those without formal education also often lack health literacy, and empowering these patients to manage their care at home may be difficult [18]. As with all studies looking at educational deprivation on health outcomes, it must be borne in mind that this may be a symptom of health risk due to overall social deprivation.

Another major obstacle to the delivery of quality PD in developing countries is the lack of trained nephrologists and specialist PD nurses, with the majority being based in major centres, resulting in poor management of those patients in rural areas. Whereas in Europe and the United States, nephrologist density ranges from 10 to 31 per million population (PMP), in Africa and South East Asia, that number falls to 1 PMP. If one looks at LICs, that number falls to 0.3 PMP. A review of healthcare personnel in developing countries highlighted that at one point, there were more Ethiopian doctors in the United States than there were in Ethiopia. This continuous migration to high-income countries continues unabated. In 2000, it was estimated that more than 25% of doctors in the United States, the United Kingdom

and New Zealand were of foreign origin [19]. It is therefore understandable that for PD to flourish in the developing countries, it is necessary to either train non-nephrologists in PD management. This has been shown to be feasible with the training of PD specialist nurses to manage all aspects of PD with referral of patients with complex medical issues to doctors. We have presented data on the effectiveness of this approach with a PD nurse specialist trained over a 6-month period who managed patients in clinic alone. There was, however, the option of referral to a nephrologist if there were complications, a luxury not necessarily available in many countries. The number of PD patients in the unit increased from 10 to 95 over a 4-year period with a PD penetration of 50%, and a peritonitis rate was 1:25 patient-months [20]. The PD nurse specialist managed approximately 750 visits per year and using a set of protocols is able to manage most eventualities. We feel that this approach may be superior to training medical officers in PD management as in many L/LMICs, non-specialist doctors very seldom remain in a centre for a long period of time, whereas nurse specialists and non-physician clinicians are often more likely to remain in one place.

In summary, PD in developing countries has the potential to offer superior dialysis adequacy with permanent access and less need for specialist nursing and at a lower overall cost. Importantly, patients have the potential to continue to work, spend less time traveling and may overall feel better. There does need to be an understanding that there are significant obstacles that often need to be overcome, and units should consider the best option for them from the models mentioned below.

Peritoneal Dialysis Models in Developing Countries

As previously alluded to, there is marked heterogeneity in the way in which dialysis is offered in developing countries. This is often as a result of piecemeal planning and crisis resolution rather than as a strategic approach taking into account the needs of the entire renal community. Many reviews have looked at the costs of dialysis provision, and in LMICs, this ranges between $4000 and $42000 per annum [21]. It has been suggested that dialysis for CKD should only become an option for a country with a GDP of > $15000, yet despite this, a country such as Malawi with a GDP of $339 and a per capita health expenditure per annum of $93 has two haemodialysis units offering dialysis [22]. This model of care unfortunately only offers care to a very small proportion of the population and is located only in the two major centres, requiring patients to relocate if they live in the rural areas. The cost of dialysis (or proportion thereof) is borne by the patient or family in many LMICs as the government healthcare service does not cover these expenses. In Cameroon, for example, these expenses are estimated to be 30% of the total dialysis costs [23]. One commentator has described dialysis in Africa as “an expensive funeral” as many families use all of their savings to keep a patient alive on dialysis for few months only for them to succumb due to insufficient funds to continue dialysis.

Developing countries therefore need to decide on the most appropriate model of care depending on resources, population density, available infrastructure (water, electricity, etc.) and experience. These models include offering PD for AKI alone and/or for CKD: PD first, PD only or PD + HD.

PD for AKI (See Also Chap. 20)

There is a stark difference in the demographics of the patients developing AKI in developing vs developed countries. In developed countries, AKI predominantly affects the elderly and is found mostly in the intensive care units in patients with multiple-organ failure and often multiple comorbidities. A large multicentre epidemiologic study in developed countries found the median age of patients with AKI to be 67, and in another study, more than 65% of the patients had greater than two associated comorbidities [24, 25]. This is in contrast to what is encountered in developing countries where there is a bimodal distribution of disease, with the highest peak in young patients, who seldom have comorbidities. As a result, if they can be supported through the AKI with dialysis, they are likely to return to long productive lives. A study from Uganda found that 83% of patients with AKI were under the age of 50, and 53% of all patients were either students or employed [26]. It cannot be underestimated the economic contribution that saving these patients brings to a community [26, 27].

If one looks at the costs of PD derived from studies in India and Africa, it is calculated that the cost per life saved is between $350 and $650 [27–30]. This compares very closely with that estimated for the cost per life saved of supplying mosquito nets in Africa [31]. It therefore becomes clear that PD even in low-income countries is economically viable.

The Saving Young Lives (SYL) programme is a partnership among four major nephrology societies: International Society of Nephrology (ISN), International Society for Peritoneal Dialysis (ISPD), International Pediatric Nephrology Association (IPNA) and EuroPD. It was developed to promote and assist the development of acute PD programmes in L/LMICs. Initially through a partnership with the Sustainable Kidney Care Foundation (SKCF), they were able to supply a start-up of fluids and catheters for 2 years to each site; however after 5 years, SKCF funding was not renewed, and SYL now focuses on education and training of physicians and nurses as well as assistance with the logistical obstacles of setting up an acute PD programme. To date, these Saving Young Lives sites have treated over 300 patients (predominantly children) in low-income countries with a survival of approximately 70% [32, 33].

Why acute PD not acute HD? There are a number of benefits of PD over HD in AKI in low-resource environments. Cost is only one of the factors but is significant. As mentioned above, the cost of PD is estimated to be half that of HD and often less. As mentioned above, acute PD is estimated to cost between $350 and $650 per life saved, whereas HD costs may be as high as those in the Democratic Republic of

Congo where it will cost the patient $200 per session [28]. More importantly, it is the lack of electricity, water, reverse osmosis water treatment and nursing expertise in the majority of these countries that makes PD more attractive. HD may be available in the major centres; however with travel times by ambulance calculated in days, these patients will often succumb before they reach the dialysis centre. A treatment such as acute PD that requires very little infrastructure and nurse training can be offered in the most remote centres and therefore makes sense. Other advantages include the fact that PD is a gentle therapy and in critically ill patients may be preferable to intermittent HD (IHD), as continuous extracorporeal therapies are seldom available or are prohibitively expensive. It is our preference to use acute PD for critically ill patients in the ICU who are unstable in preference to IHD.

There have been concerns raised about whether acute PD is a safe alternative to HD as it is thought to be inefficient and therefore not able to clear toxins in hypercatabolic patients. Certainly, the survival seen in the acute PD programmes around the world does not bear this out, and two well-conducted randomised controlled trials have shown that acute PD has similar and in one case superior survival to HD and CRRT [34, 35]. The ISPD guidelines for PD in AKI were published in 2015 and recommended two different target doses of PD. One Kt/V target was felt to be the "optimal" as it was based on the only randomised trial at the time comparing survival between PD and HD. The second was "minimum standard" which was based on clearances extrapolated from a number of larger CRRT and HD trails using standardised Kt/V [6]. The problem with the higher dose is that it requires 36–44 litres of fluid per day which is not feasible in most low-income countries [36]. A subsequent study performed in Thailand compared these two Kt/V targets and showed no difference in survival, thus affirming that lower volumes of fluid (+/− 24 l per day for an adult) are sufficient and certainly far more cost-effective [37].

The Saving Young Lives programme has encountered a number of obstacles to developing PD programmes, with supply of PD fluids and catheters being the most difficult. This is often the result of inefficiencies in the state hospitals in ordering and ensuring a continuous stock level. This results in programmes starting and then faltering after a few months. This has been overcome in a number of ingenious ways, using makeshift devices that would not usually be considered as appropriate but have been lifesaving.

PD Fluids

PD fluids produced commercially adhere to strict microbiological standards and have the advantage of a closed system with less chance of contamination. These fluids are recommended as first line by the ISPD guidelines and SYL. When these fluids are not available, the guidelines give a guide to mixing solutions locally in order to create a suitable solution. This is most easily achieved using modified Ringer's lactate or Hartmann's solution and adding 50% dextrose water. This way with either 30 ml, 50 ml or 90 ml of 50% dextrose added to each litre, one can make similar osmolality solutions to commercially produced ones (1.45%, 2.4%, 4.45%

vs 1.5% 2.5% and 4.25%) [6]. Concerns have been raised that preparing solutions locally would result in inappropriately high incidence of peritonitis. A recent publication from one of the SYL sites in Mbingo, Cameroon, looked at the peritonitis rates in two cohorts of patients. The first were those treated with commercial solutions (provided by SYL), and the second cohort were those treated with locally produced solutions which had to be prepared once the donated solutions had run out. There was no difference in the number of episodes of peritonitis (16%) in each group, although there was a non-significantly shorter time to peritonitis with the locally produced fluid (59 vs 84 days) [38, 39]. It should be noted however that these locally produced solutions are produced in 1-litre bags, and yet for adults, one uses 2 litre exchanges, and as a result, the exchanges need to be modified to account for this. Also there is no closed system, and one needs to create an inflow and outflow route using a three-way tap.

PD Catheters and Access

For acute peritoneal dialysis to be successful, the access device needs to allow rapid inflow and outflow of fluid in order to achieve sufficient clearance. Larger-bore flexible catheters such as the standard Tenckhoff catheter are recommended as the optimal device in the ISPD guidelines. The problem with these catheters is that they are more expensive and require more training to insert than rigid catheters. Rigid catheters consist of a solid plastic outer catheter loaded onto a sharp tip trocar. These catheters are used predominantly throughout South East Asia and to good effect. They are easier to train clinicians to insert and are less expensive to procure; however, they have a much higher incidence of peritonitis and bowel and vessel perforation. The other disadvantage of these catheters is that they have smaller side holes and central lumen and as a result are much more prone to obstruction. In cases where neither of these is available, then improvised catheters have been used, and these include intercostal chest drains, nasogastric tubes with side holes cut in and adult haemodialysis catheters in paediatric patents. Figure 29.1 shows an intercostal drain inserted under local anaesthesia into the peritoneum in a rural hospital to treat a patient with a potassium of 8.2 mmol/l. The patient was dialysed using modified Ringer's lactate and recovered function within 5 days.

If Tenckhoff catheters are the recommended option for acute PD, then there needs to be provision for training of clinicians, few of whom are nephrologists. Many of the doctors in the rural areas are generalists however and therefore often perform caesarean sections and tubal ligations as well as insertion of suprapubic catheters, in which case learning to use the peel-away sheath introducer technique to insert a catheter is often very simple. Commercially produced models for training are prohibitively expensive, and therefore a cheaper portable model needed to be created. Figure 29.2 shows a model using a piece of pork belly suspended over a packing crate. This model costs less than $10 and is suitable for training up to 12 people. It has been used extensively by SYL in our training courses, which have thus far trained over 220 doctors, many of whom train on the model and return to

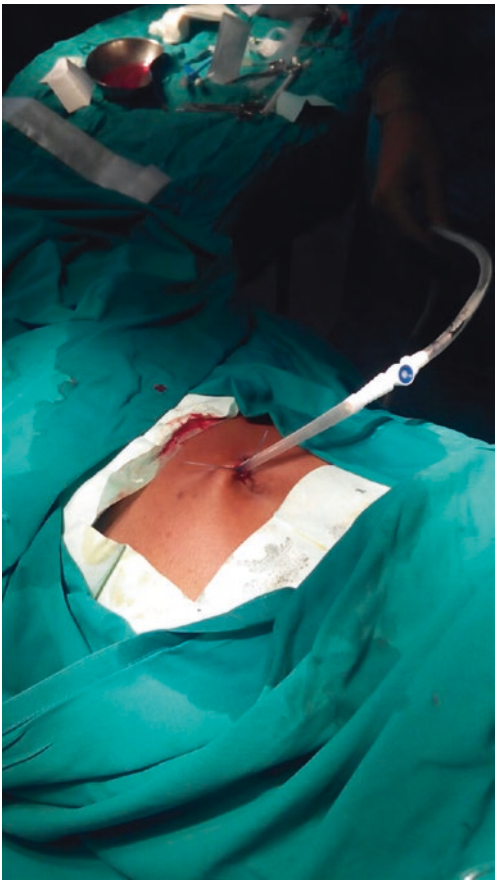

Fig. 29.1 An intercostal drain inserted under local anaesthesia into the peritoneum in a rural hospital to treat a patient with a potassium of 8.2 mmol/l

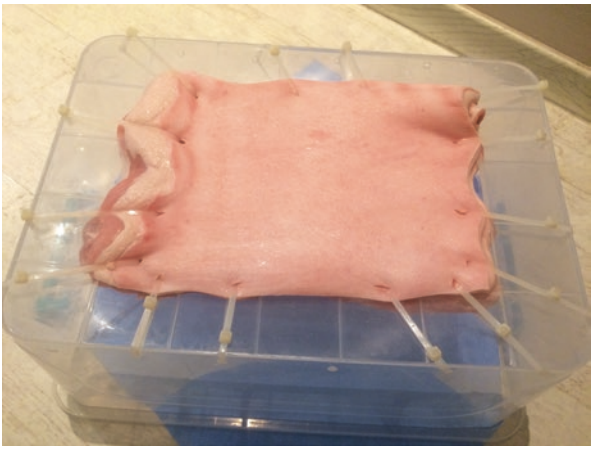

Fig. 29.2 A model using a piece of pork belly suspended over a packing crate

their country to do it alone. These cases though highlight the point that what may be thought to be suboptimal, training a doctor on a pork model for them to attempt it when they get home, can certainly be lifesaving especially when the alternative is death due to AKI.

PD in Chronic Kidney Disease

PD for AKI has the potential to offer lifesaving treatment at a relatively low cost and should be considered by L/LMICs as a standard of care. PD for CKD however is not appropriate in many countries as it diverts much needed resources to a handful of patients, most of whom will not be transplanted and therefore dialysed for life. This funding could be used for other purposes, such as universal HIV treatment, or vaccinations, which would benefit a larger proportion of the population.

In countries with the financial means to provide chronic PD, then this can be successfully achieved albeit with some inventive solutions in difficult situations.

Often in HMIC/LMICs, there is a rationing of dialysis, usually due to the limited number of dialysis stations, nursing staff, etc. In South Africa, as an example, many patients are eligible for, but never receive, dialysis as they have to wait for a dialysis space to be freed up as all units function to capacity. PD is ideal in this situation as it does not rely on physical spaces (only resources). As a result, one can increase the number of patients treated. In our unit with the introduction of a nurse-led PD service, the number of patients treated doubled within the first year from 45 to 90, with the only additional cost (other than consumables) being 2 nursing staff. After 4 years, the PD number increased to 95 with a PD penetrance of 50%. We have now adopted a PD-first policy that has helped ease the pressure on HD resources. However, these patients may eventually need HD and therefore will need to be accommodated there. The PD-first approach has been very successfully implemented in countries such as Hong Kong, Thailand and Mexico, with good outcomes. The results from Thailand show that their outcomes have also improved significantly as the years progressed, and the clinicians became more skilled at treating PD patients. A paper from Cape Town has shown that adopting a PD-first/PD-only approach due to lack of HD resources can be very effective with good outcomes [40].

When resources are limited, it is sometimes necessary to adopt other practices in order to treat the maximum number of patients. In India, for example, patients are encouraged to use 3×2.5 l fluid exchanges per day rather than 4×2 l. As 2-litre and 2.5-litre bags are cost-equivalent, this saves significantly on cost with similar fluid volumes [41].

Patient factors need to be taken into account when setting up a chronic PD unit in a developing country. Often clinicians in high-income countries take for granted simple luxuries which are not available in rural areas such as running water, lighting at night to see for a connection, warming bags using a heater, etc. Below are a number of barriers to PD and how they can be overcome.

Clean Surfaces

Many patients live in informal housing with large numbers of occupants in the household. It is therefore unlikely that they will have a clean room with a sterile surface on which to perform an exchange. This can be overcome by providing a plastic or stainless steel tea tray which can be kept out of the way but easily wiped clean and used for an exchange. A nail on the wall works well as a drip stand.

Water for Washing

Nearly 30% of the world's population have no access to uncontaminated running water. Of those that do, this is usually in the form of a communal tap outside, and therefore washing hands for a peritoneal dialysis exchange can be fraught with difficulty. Our solution has been to supply three stainless steel bowls for washing, moving to the next bowl with each handwash manoeuvre. Another option is to keep water in a plastic container which has a tap attached at the bottom. This is suitable for those with uncontaminated water, whereas those getting their water from a local river are taught how to decontaminate the water with household bleach or water purification tablets. Although not an alternative to handwashing, alcohol spray is helpful for reducing the risk of peritonitis.

Geography

As has been mentioned above, most dialysis units are located in the major centres, and for patients living in distant places, there are a number of issues. Firstly, the time to diagnosis of peritonitis is increased as it may take a patient 2 days to reach the centre before they can be treated. It is also a problem for them to return for intraperitoneal antibiotic doses, and as such, these patients often need to be admitted for the period of their treatment. However, if they show signs of improvement, many are sent home with bags injected with vancomycin which will remain stable for 2–3 weeks.

Living in rural areas makes delivery of fluids very difficult. Often patients have no vehicular access to their houses, and therefore fluids need to be delivered to a local clinic, school or shop and then collected by the patient and carried to the house.

The longer-term solution to the problems of rural patients though is the development of a "wagon wheel" approach where the central hospital is the centre for PD access training and complications, but smaller remote clinic or hospital staff are trained to manage PD patients using protocols. These centres can then administer initial antibiotics for peritonitis, manage fluid balance issues and organise ordering of stock. This has been shown to be effective in Colombia and China and in our unit. We initially trained our referring hospital to perform PD for AKI, which allowed them to understand the principles of PD following which they sent nurses on

secondment to train in chronic PD at our hospital. They now have a functioning nurse-led unit with a clinic and manage eight to ten chronic patients successfully.

The advent of telemedicine and smartphones will revolutionise this issue in the coming years as the ability to send a photo of an exit site, X-ray or PD fluid bag will allow remote patient management to improve dramatically. There are already options for remote patient monitoring in automated PD machines, but the availability of this technology in developing countries might be limited in the short term but may become available in the coming years as costs come down.

Lack of Electricity

In many countries, the ambient temperature is such that warming of bags is not necessary; however, a few practical tricks which patients have developed are to wrap a dialysate bag with a hot water bottle in a blanket. If a hot water bottle is not available, then a plastic cold drink bottle with hot water will suffice. Patients may also sleep with the bag in their bed to warm it for the morning exchange.

A lack of refrigeration facilities is a problem when prescribing ESAs. Solutions to this are to use longer acting agents and administer them when the patient attends clinic once per month. Alternatively, most rural clinics have facilities for refrigeration of vaccines, and this can often be utilised for patients' ESA storage.

Finally, many patients are rapid transporters and may need exchanges more suited to automated PD. In the absence of electricity, this is not an option, and thus other options need to be explored to prevent the need for HD. Icodextrin is very helpful in this scenario. We ask patients to leave the icodextrin in to dwell for 16 hours and then perform manual exchanges 2 hourly in the evening. Another option is the use of icodextrin twice per day in addition to one glucose-containing bag. This often allows adequate ultrafiltration, but may not achieve adequate clearances. As with all these situations, it may be suboptimal but may be the best option available especially if the patient lives in a remote area.

Conclusion

Peritoneal dialysis is ideally suited for the developing world due to its simplicity, cost and ability to penetrate into the remote areas so often inhabited in these countries. Acute PD should be universally offered throughout L/LMICs where it saves lives with minimal investment and staffing.

For a PD programme to be sustainable in those countries with a lack of nephrologists, specialist PD nurses should be trained and empowered to function independently, managing patients with guidelines and protocols with the option of referral to the major centre if complications arise. This way PD can be offered to patients near their homes, allowing them to be able to continue to be employed, care for their families and live a fulfilling life.

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Chapter 30
Advances in Peritoneal Dialysis

Sana F. Khan, Tushar A. Chopra, and Mitchell H. Rosner

Introduction

The first patient treated with peritoneal dialysis (PD) was reported by Ganter in 1923 [1]. Since then, PD has undergone numerous modifications including the development of continuous ambulatory PD by Moncrief and Popovich in 1976, which made PD widely acceptable and effective in treating patients with end-stage kidney disease [2]. Since then, incremental advances in technology such as the development of plastic containment bags, introduction of novel PD catheters, and development of continuous cycling PD (CCPD) have led to a wider acceptance of this kidney replacement modality. However, PD is far from an ideal therapy and continues to be hampered by infectious complications, failure of the peritoneal membrane, and metabolic complications. This chapter focuses on recent advances in PD technology that aim to address some of these issues and ultimately improve outcomes for patients.

Advances in Peritoneal Dialysis Solutions

Biocompatible Solutions

As detailed in Chap. 4, standard peritoneal dialysis (PD) solutions are composed of sterile water, electrolytes, a buffer (either lactate, bicarbonate, or a combination of these), and an osmotic agent. Glucose has been used as an osmotic agent in standard PD solutions for more than five decades. Over time, data demonstrating the local

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peritoneal and systemic effects of glucose-containing peritoneal dialysis fluid has generated concerns regarding metabolic effects of long-term use of these solutions. While glucose is essential for ultrafiltration, its high concentrations are cytotoxic to peritoneal mesothelial cells, resulting in mesothelial cell injury and decreased density and viability of cells [3–5]. Additionally, glucose-based PD solutions contain significant amounts of glucose-derived metabolites, called glucose degradation products (GDPs). These are a consequence of heat sterilization of PD solutions and are also generated over time during storage and exposure to sunlight [6–8]. The generation of GDPs can be decreased by reducing the pH of the PD solution. Both glucose and GDPs have been shown to glycate local proteins to create advanced glycation end products (AGEs). The detrimental effects of AGEs include peritoneal inflammation, fibrosis, neovascularization, increased peritoneal permeability, calcification, and diabetiform neoangiogenesis [5, 9–12]. The metabolic consequences of glucose-based solutions include weight gain, lipid abnormalities, insulin resistance, and worsened glycemic control in diabetic patients (see Chaps. 15 and 16) [13–16].

Standard PD solutions use lactate as a buffer, with the final pH of the solution ranging from 5.0 to 5.5 [17, 18]. The acidic pH of conventional solutions, as well as the lactate buffer, is thought to be detrimental to the peritoneal membrane and local immune function. Impaired bactericidal activity of macrophages has been demonstrated in solutions with acidic pH. Additionally, similar findings have been observed in lactate-based solutions [19, 20].

These factors have led to the development of biocompatible solutions to ameliorate the complications associated with conventional glucose-based solutions. The dialysate is divided into at least two sub-compartments. One compartment contains glucose and electrolytes and has a very low pH, hence slowing the formation of GDPs. The other compartment contains bicarbonate or a bicarbonate-lactate mixture. Prior to dialysis exchange, a connection separating the two compartments is broken, with the final pH of the fluid being close to physiologic levels. The resultant solution is a normal pH, low GDP, bicarbonate containing mixture. Clinically meaningful endpoints for the testing of these novel PD solutions included survival, effect on peritoneal membrane transport, residual kidney function, and frequency of peritonitis. Two observational studies reported superior patient survival among patients using biocompatible dialysate compared to standard solutions; however, the younger age of the group receiving biocompatible dialysate accounted for the mortality difference [21, 22]. Prior to 2012, several small trials demonstrated inconsistent and conflicting results. Several studies [23–26] demonstrated improved preservation of residual kidney function, whereas others did not [27–30]. Similarly, the use of the neutral pH has been associated with lower peritonitis rates in some studies [24, 31, 32], while others are unable to demonstrate a reduction in peritonitis [27, 33]. The effect of biocompatible solutions on peritoneal membrane function was observed to be contrary to expectation, with studies showing diminished ultrafiltration and an increase in peritoneal transport status [23, 27].

The most recent multinational randomized controlled trials are the balANZ and Trio trials. balANZ investigated the effects of biocompatible PD solutions on

dialysis outcomes [34], peritoneal membrane function [35], and peritonitis rates [36], whereas Trio focused on the effect on residual kidney function [37]. balANZ did not demonstrate any difference in technique or patient survival between the two groups [35]. While balANZ did not demonstrate a difference in residual kidney function in the two groups, Trio showed slower rates of decline of residual kidney function [34, 37]. balANZ was also noted to demonstrate a longer time to anuria and first peritonitis episode in the biocompatible group [34]. balANZ reported lower peritonitis rates and decreased ultrafiltration, whereas the opposite results were evident in Trio, with increased peritonitis rates and similar ultrafiltration rates in the two groups [36, 37]. Several factors have been noted to account for the heterogeneity in findings, including relatively small sample size, different compositions of biocompatible solutions used, and differing prevalent rates of peritonitis. Centers with low peritonitis rates would not be able to demonstrate significant decreases in infectious rates compared to centers with higher rates. Additionally, the effect on preservation of residual kidney function would be more prominent in studies with a higher residual kidney function at study initiation [38]. Furthermore, diminished ultrafiltration with biocompatible solutions may be linked to the increased urine output noted in some studies. Given the controversies in this area, a recent meta-analysis of 42 studies compared the effects of biocompatible PD solutions versus conventional PD solutions. This analysis noted better preservation of residual kidney function, urine output, and higher peritoneal solute transport rate in patients who dialyzed with biocompatible PD solutions. Most of the studies included had a follow-up duration of less than 2 years [39]. The use of biocompatible fluids has been associated with a more rapid peritoneal solute transfer rate, accompanied by a decrease in ultrafiltration. It is hypothesized that the reduction in ultrafiltration resulted in a subsequent increase in extracellular fluid volume, which caused an increase in urine output and measured residual kidney function, rather than due to an effect of the low GDP content of biocompatible solutions [40, 41]. In a more recent study investigating long-term changes in peritoneal solute transport, increasing solute transfer rates plateaued after 2 years in patients using biocompatible solutions [42]. Thus far, limited data exists supporting the use of neutral pH biocompatible solutions. The largest study conducted was unable to enroll its total intended patients, whereas others have relatively small sample sizes and short follow-up duration [34, 39]. Since the solutions still contain glucose as the main osmotic agent, it is postulated that reduction in GDP content and increased pH may not alleviate the adverse local and systemic metabolic effects compared to conventional solutions.

Glucose-Sparing Solutions

Given the concerns for peritoneal membrane toxicity of glucose and its metabolites, several studies have aimed to identify an alternative effective osmotic agent. Glycerol, when used as a sole osmotic agent, resulted in increased peritoneal

permeability, decreased duration of ultrafiltration, quick absorption, and elevated triglycerides [43–45]. Colloidal albumin was shown to be an effective agent for ultrafiltration but caused pain on infusion and was cost-prohibitive for use [46–48]. Larger molecular weight compounds such as hydroxyethyl starch and dextran sulfate have been investigated and were complicated by the liver, spleen, and lung accumulation and lower ultrafiltration rates, respectively [49, 50].

Icodextrin and amino acid solutions are non-glucose osmotic agents that have been used in clinical practice since the 1990s. The colloid polymer icodextrin is not metabolized locally and has been shown to maintain a prolonged oncotic gradient, resulting in slow and sustained ultrafiltration [51–54]. It is currently used for a long day dwell in patients undergoing automated peritoneal dialysis, or a long overnight dwell in patients undergoing ambulatory peritoneal dialysis. Studies have shown the ultrafiltration profile of icodextrin to yield greater fluid removal compared to 4.25% dextrose (3.86% glucose) [52, 54, 55]. The use of icodextrin has been shown to result in better fluid balance in patients with poor ultrafiltration rates despite the use of high dextrose-containing solutions [56, 57]. Data from an analysis of anuric patients has shown icodextrin to be associated with fewer functional changes to the peritoneal membrane, resulting in anuric patients being able to be maintained on peritoneal dialysis due to improved fluid balance [58]. Another trial assessing the efficacy of icodextrin in patients with volume overload showed greater ultrafiltration in the icodextrin group compared to the control group utilizing high dextrose-containing solutions [59]. Additionally, icodextrin use has also been associated with preservation of residual kidney function [59–62]. Though the data is of suboptimal quality given small sample size in studies, icodextrin use has also been associated with avoidance of weight gain, improved glycemic control, decreased insulin resistance, improved blood pressure and volume status, decreased left ventricular hypertrophy, and a more favorable lipid profile [63–71]. Lastly, some small studies have demonstrated that icodextrin use has been associated with decreased technique failure and improved patient survival [72–74]. Overall, data is limited given small sample sizes and duration of follow-up. Additionally, long-term implications on peritoneal function have yet to be clarified. Lastly, though certain centers have used icodextrin solutions twice daily in unique situations [75–78], it is currently approved for just one exchange per day, and does not completely eliminate the need for standard glucose-based solutions in the majority of patients.

Amino acid-based dialysate is approved for one exchange per day. Composition of amino acid solutions is noted to be 1.1% essential and nonessential amino acids and has the same osmolarity as 1.5% dextrose (1.36% glucose) solution. Clinical trials have involved small sample sizes and limited duration of follow-up. In a study investigating the effects of amino acid-based solutions for treatment of malnourished patients, one to two glucose-based exchanges were substituted with amino acid solutions, with the aim to have total protein intake 1–1.3 g/kg/day. The malnourished group was shown to have improved nitrogen balance, net protein anabolism, and total protein levels. There was no difference in nutritional status in the group of patients who were not malnourished [79]. Similar clinical outcomes were noted in subsequent studies, with improved nutritional status in malnourished

patients. No difference in patient survival was observed, and there were concerns about adverse effects including nausea and vomiting, elevated urea levels, metabolic acidosis, and increased levels of inflammatory markers [80, 81]. To offset concerns for acidosis, there is some data to suggest that patients are less likely to develop acidosis when amino acid solutions do not contain lysine, arginine, and methionine [82]. Given concerns that loss of nutrients into the dialysate contributes to malnutrition in PD patients, a small study showed that daily losses of amino acids and protein into dialysate are offset by amino acids absorbed from one exchange of 1.1% amino acid solution [83]. Certain studies have also suggested the use of amino acid-based solutions to be associated with lower ultrafiltration and concerns for decrease in dialysis adequacy [84, 85]. Though the use of amino acid-based solutions has shown to be favorable in improving nutritional status of malnourished patients, a clear advantage over glucose-based solutions is yet to be established, especially given the higher cost associated with amino acid solutions. Furthermore, much of the malnutrition in dialysis patients is the result of inflammation, and so it may not be surprising that the use of intraperitoneal amino acids does not significantly improve nutritional status.

The largest multicenter randomized controlled trial investigating the effects of a low-glucose PD regimen in diabetic patients utilized a combination of PD solutions. The study involved both ambulatory PD and automated PD patients. The control group utilized conventional glucose solutions for all exchanges. The two different intervention arms involved a combination of biocompatible low GDP solution, icodextrin (1 long dwell), and amino acid-based solution (1 dwell), IMPENDIA arm, and conventional glucose solution, icodextrin (1 long dwell), and amino acid-based solution (1 dwell), EDEN arm. Given the similar glucose concentration of low GDP biocompatible solutions and standard solutions, both treatment arms were similar in glucose exposure. The results revealed that substitution of two exchanges with glucose-free solutions (icodextrin and amino acid solutions) resulted in reductions in HbA_{1c} and improved triglycerides in the intervention arms. Given these findings, there may be potential cardiovascular benefit in diabetic patients; however, concern for volume overload in the intervention arms warrants attention prior to widespread adoption [86].

Low-Sodium Solutions

The sodium concentration of conventional dialysis solutions is between 130 and 135 mEq/L. As a result, sodium removal via peritoneal dialysis occurs mostly via convective clearance across the peritoneal membrane. Several studies investigating the effect of diffusive clearance of sodium (hence improved volume control) were investigated in the 1990s. These studies evaluated the effects of sodium concentrations ranging between 90 and 126 mEq/L. Overall, it was shown that low-sodium solutions were effective at removing peritoneal sodium, increasing ultrafiltration, and improving volume control. The glucose concentration of solutions was increased

to maintain osmolality and ultrafiltration, hence increasing glucose exposure to the peritoneal membrane [87–89].

More recently, a prospective non-randomized trial compared outcomes of a low-sodium PD solution with increased glucose (compensated) with low-sodium solution with unchanged glucose concentration (uncompensated). The low-sodium solutions were administered in one exchange per day. Although both solutions resulted in increased sodium removal, ultrafiltration was maintained in the compensated group only. Additional effects of compensated glucose low-sodium dialysate were noted to be reduced blood pressure, reduced thirst, and improved fluid status which was measured via bioimpedance [90]. A randomized controlled trial of 108 patients used low-sodium dialysate (125 mEq/L uncompensated) compared with standard dialysate used in all ambulatory PD exchanges. Results showed a marked increase in sodium removal and improved blood pressure control. Continued use of the uncompensated solution was associated with decreased ultrafiltration and concerns for hyponatremia [91]. Although this was a randomized controlled trial, there is still data lacking on the use of low-sodium dialysate in automated PD patients, as well as the effects in anuric patients.

"Bimodal" Solutions

There is some data regarding the effects of using combinations of crystalloid and colloid solutions. Theoretically, the advantages include glucose sparing and enhanced ultrafiltration. An early study using bimodal solutions compared the ultrafiltration profiles of 1.36% glucose, 3.86% glucose, 7.5% icodextrin, and the combination fluid (1.36% glucose/7.5% icodextrin). The ultrafiltration volume was greater than that achieved by icodextrin use alone and was similar to that obtained with 3.86% glucose [92]. An extension of the pilot study reported the use of combination dialysate resulting in increased long dwell ultrafiltration as well as total drain volume compared to icodextrin alone [93]. A different combination solution (2.61% glucose/6.8% icodextrin) was used for a 15-hour dwell in patients with fast peritoneal transport rate. Of note, this bimodal solution was also a low-sodium dialysate (121 mEq/L). Compared to 7.5% icodextrin, the combination solution yielded increased ultrafiltration and peritoneal sodium removal [94]. An extension of the prior study investigated the effects of the same low-sodium bimodal solution over a 4-month follow-up period and showed change from baseline (use of icodextrin alone) in net ultrafiltration and sodium removal [95]. Bimodal ultrafiltration appears to be a potential approach in PD patients with anuria and ultrafiltration failure. The results of the current studies need to be assessed in a randomized controlled trial, so the potential local and systemic advantages of bimodal solutions can be evaluated.

Thus far, glucose remains the main osmotic agent in PD solutions, with icodextrin being used in a once-daily long dwell. There continues to be the search for ideal

alternative PD solutions. The use of hyperbranched polyglycerol, a water-soluble polyether polymer, has been investigated in animal models and has shown to have improved ultrafiltration profile, with decreased peritoneal injury compared to standard solutions [96]. Effects of hyperbranched polyglycerol have been followed for a duration of 3 months only [97]. Further studies are needed to investigate long-term biocompatibility, metabolism, and local and systemic effects of the novel agent.

Bimodal Dialysis and Hybrid Peritoneal Dialysis

Since the early 2000s, there have been reports on the use of combined modalities in PD patients. Hemodialysis (HD) was added onto the PD modality after patients were noted to be doing poorly on PD. Indications included inadequate solute clearance, uremic symptoms, neuropathy, and ultrafiltration complications. The prescription used was one to two sessions of HD and 5–6 days of PD per week. The patients' clinical condition and quality of life showed improvement, and most patients had good tolerance of the combination therapy [98–101]. A retrospective analysis of combination therapy suggested improved survival of patients on PD if hybrid HD therapy was started early [102]. Evaluation of outcomes 12–18 months after initiation of combination therapy revealed improved hemoglobin levels and cardiac function, likely attributed to improved volume control [103]. Another analysis of cardiovascular outcomes revealed decreased acute cardiovascular events and improved systolic function in patients with low ejection fraction [104].

There are several reports of bimodal therapy prescribed to incident end-stage kidney disease patients as well. The first study investigating this modality reported the use of two PD exchanges per day in addition to two, 3-hour HD sessions (without ultrafiltration). There was noted to be adequate solute removal, hemodynamic control, and treatment flexibility in dealing with complications with PD or HD access. There was no change in residual kidney function from baseline and improvement in left ventricular hypertrophy [105]. Another study enrolled patients on combination therapy at dialysis initiation and compared them with patients on PD and HD separately. Patients were followed for 30 months, and the combination therapy group was noted to have preservation of residual kidney function and serum albumin levels compared to the other two groups [106].

Current data on combination therapy suggests several combinations of the number of PD and HD days are possible. PD can be done daily or only on non-HD days. The dialysis regimen is flexible and easily adapted to patients' lifestyle. Dialysis dose prescribed and goal solute clearance appear to need standardization. It is too simplistic to simply add urea kinetics between the two modalities. Furthermore, the presence of two different dialysis accesses may be hard to accept and theoretically increases the risk of infection.

Larger randomized controlled trials are needed, specially investigating outcomes in patients initiated on combination therapy at dialysis initiation. However, hybrid

therapies offer a balance of PD and HD to meet specific patient needs and can be tailored over time in a patient-focused manner.

Remote Patient Monitoring for Peritoneal Dialysis Patients

Remote patient monitoring (RPM) in peritoneal dialysis patients is relatively new and underutilized. It involves digital technologies that collect health data from individuals and transmits the data electronically to healthcare providers in a different location. Communication that can be established remotely includes patient-physician communication, physical exam, biometric monitoring, laboratory, and treatment data monitoring and educational services. PD-specific data that can be analyzed includes types of solutions utilized, therapy duration, ultrafiltration volumes, drain volumes, and alarm types [107, 108]. Systems currently available for RPM include a tablet-based computer system for real-time communication and patient data transmission, videoconferencing equipment installed in patients' homes and connected to similar units in a medical center, as well as a PD cycler-embedded program that allows for transmission of completed treatment data [109–111].

Outcome data on RPM in PD patients is currently limited. A short-term study involving data transmission via videoconferencing equipment involved patients with alternate months of teleconsultations and hospital visits. Most teleconsultations involved modification of treatment and took significantly less time than hospital visits. The hospitalization rate in the intervention group was lower than that in the control group [110]. Another study utilized alerts generated upon patient completion of treatment and symptom-based questionnaires, with follow-up telephone calls or clinic visits. The alerts and interventions allowed for patient self-management and avoidance of hospital admissions [112]. More recently, data sharing via automated peritoneal dialysis was noted to result in more frequent prescription monitoring and fewer clinic visits in incident dialysis patients compared to the control group [111].

RPM has the ability to provide remote support for patients and address several barriers and concerns that result in PD underutilization [113]. Additionally, a simulated study estimated significantly reduced healthcare resource utilization and associated costs as a result of early interventions enabled by RPM [114].

Assisted Peritoneal Dialysis

There appear to be several advantages of PD compared to HD in elderly patients, including maintenance of independence in their home environment, fewer hospital or clinic visits, no need for vascular access, improved hemodynamic tolerance, less

disease burden, and improved preservation of residual kidney function [115]. Barriers to PD for older patients include poor vision, frailty, cognitive dysfunction, physical dependence, and bias from providers against PD [116]. Different models of delivering assisted PD have been developed and implemented to overcome these barriers and to provide elderly and disabled patients the option of choosing PD as a dialysis modality. The French model supports assisted PD, with community nurse-driven phone calls and instructions to start the procedure, followed by nurse visits. Initially, the program was limited to ambulatory PD but now includes automated PD [117]. Patients on automated PD receive two nurse visits to help with connection, disconnection, and management of PD fluid bags [118]. Besides community nurses, there are also models in which family members and healthcare assistants are responsible for patient care [119]. Several assisted PD programs have noted comparable patient survival and technique survival compared to autonomous PD patients [120–122]. Assisted PD patients were also found to have similar rates of all-cause hospitalization compared to in-center HD patients [123]. Peritonitis rates have been noted to be within the limits of guideline recommendations, with some reports of lower peritonitis rates in assisted PD patients compared to autonomous patients [118, 124]. Regarding quality of life, a recent study noted no differences in quality of life between older patients on assisted PD and patients on HD, but treatment satisfaction was noted to be higher in patients on assisted PD [125]. Thus, assisted PD is a valid alternative option for older patients who wish to dialyze at home and maintain their independence and avoid complications associated with in-center HD.

Future Directions

Newer technologies that will allow PD cyclers to make their own solutions on demand will be a breakthrough in decreasing GDPs and allowing for custom glucose formulations that may minimize peritoneal membrane glucose exposure but also maintain ultrafiltration rates. In addition, on-demand fluid production will also decrease storage space requirements for patients which are not insignificant. Finally, devices such as miniature, wearable cyclers may also improve the ability of patients to meet adequacy and fluid removal goals while maintaining independence in their daily activities.

Conclusion

In many respects, PD is performed in a very similar manner as it was done 30 years ago or longer. Advances in PD solutions have included icodextrin and low GDP solutions as well as the availability of solutions with amino acids. However,

outcomes with PD remain suboptimal, and further advances are needed to improve vexing issues such as high peritonitis rates, ultrafiltration failure, metabolic complications, and fibrosis of the peritoneal membrane. It is hoped that further advances in PD technology will lead to demonstrable improvements in its use and outcomes.

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Chapter 31
Nutritional Management of Adult Peritoneal Dialysis Patients

Maria Chan

To sustain life, people with end-stage kidney disease (ESKD) require dialysis to correct metabolic abnormalities and complications associated with the failed kidney function of excretion, homeostatic and hormonal regulation. Complications include consequences of a build-up of uraemic toxins, acid-base, electrolyte and fluid imbalances, as well as an increased cardiovascular risk. Peritoneal dialysis (PD) has been shown to be a cost-effective treatment modality to improve clinical outcomes and quality of life of people with ESKD and a 'PD first' policy has even been adopted in many countries. However, dialysis only partially replaces kidney function and itself introduces many side effects such as high nutrient losses into dialysis fluid and unintentional gain of calories from the dextrose-containing dialysate. Furthermore, protein energy wasting (PEW) is common in the PD population and is associated with increased prevalence of peritonitis, hospitalisation, mortality and morbidity. Therefore, nutritional management is a vital part of multidisciplinary PD management. In this chapter, the rationale and current recommendations of PD nutritional management, such as energy and nutrient requirements, will be discussed, as well as foods and food components. Practical aspects of management will be reviewed with examples of effective interventions and care delivery as cited in the literature.

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Altered Metabolism and Nutrition Abnormalities

Nutrient Losses During Peritoneal Dialysis

There are a number of PD-specific effects on nutrition and metabolism that influence nutrition status.

High protein loss into the peritoneal fluid is a major side effect of PD. The average daily protein loss in CAPD is approximately 6–8 g with high individual variability [1]. This amount is similar to the amount of protein found in a large egg or matchbox-sized portion of cooked lean beef (~30 g). APD is associated with slightly higher average protein loss than CAPD, approximately 10 g/day. Free amino acid loss is small in CAPD and is approximately 1.2 ± 0.7 g in APD. Metabolic balance studies indicate at least ~1.1 g/kg IBW/day and adequate energy to achieve nitrogen balance [2]. Other factors affecting protein loss are tonicity of the dialysate, duration of the dwell and high peritoneal transport status. Consequently, hyperlipidaemia associated with weight gain and pre-existing cardiovascular comorbidity [3] and hypoalbuminemia are common and are associated with mortality. In addition, there are significant losses of water-soluble vitamins and minerals, such as vitamins B and C and folate. Fat-soluble vitamin loss appears low, except vitamin D, which is protein-bound and lost in the PD effluent [4, 5].

Caloric Gain from Dextrose in Dialysate

Dextrose absorption from dialysate varies between 10 and 180 g/day [6]. Higher absorption is related to higher strength of the dialysis fluid, larger volume, longer dwell time and higher transport rate (high transporters). Approximately 60–76% and 40–50% dextrose is absorbed in CAPD and APD, respectively, due to longer or shorter dwell time. Dextrose provides ~3.4 kcal/g; caloric gain can be calculated by:

$$\begin{aligned}&\text{Number of exchanges} \times \text{volume}(\text{L}) \times \text{strength}(\text{g of dextrose / L}) \\ &\quad \times 3.4\,\text{kcal}(\text{per g of dextrose}) \times \%\text{absorption rate.}\end{aligned} \quad [7]$$

For example, a CAPD patient on four exchanges of 2-l bags with 2.5% dextrose is estimated to gain ~476 kcal/day, similar to that obtained from ~27 teaspoons of sugar. A 2-litrebag of 4.25% dextrose-containing dialysate provides ~200 kcal or energy from ~12 teaspoons of sugar.

Typically, approximately 300–500 kcal/day is gained from dextrose-containing dialysate [8]. While caloric gain helps spare protein to maintain nitrogen balance, patients who have undesirable weight gain and hyperlipidaemia will have increased cardiovascular risk [3, 9].

The absorption rate of icodextrin is much lower than that of dextrose, at approximately 25% [6]. A typical 2-litrebag of 7.5% icodextrin in an 8-hour dwell provides ~150 kcal. In a randomised, controlled trial (RCT), patients using icodextrin were less likely to gain body weight and fat mass compared with standard dextrose-containing dialysate [10].

Gastrointestinal Disorders

Prevalence of gastrointestinal (GI) symptoms is high in PD patients [11], e.g. nausea, vomiting, bloating, early satiety, anorexia, constipation, diarrhoea or heartburn, leading to reduced intake [12, 13]. The filling of dialysate may lead to abdominal distension, a sense of fullness by interfering with gastric emptying and intestinal motility; the dextrose itself may inhibit food intake and cause a disturbed hunger profile [14]. The dialysate dwell may delay gastric emptying if not drained, especially in subjects of smaller body size [15]. In one study, when patients were asked to consume meals with or without the filling of dialysate, no significant difference in energy and nutrients was observed [16]. In another study, glucose from dialysate did not suppress appetite, did provide a significant level of caloric intake and did not exert negative effects on obesity or patient survival [17].

These studies showed a large individual variation in the presence of GI symptoms, which may not be caused solely by the mechanical presence of dialysate; the variation may be due to uraemia, other hormonal factors or regulatory peptides [18].

Peritoneal Solute Transport Rate

A high peritoneal solute transport rate has been linked with factors such as hypoalbuminemia, malnutrition, inflammation and atherosclerosis syndrome, known to be associated with increased risk of death [19]. However, the evidence is inconsistent, and morbidity is more likely to be related to fluid reabsorption and volume overload rather than nutritional factors or PEW [20].

Residual Kidney Function

Decline in residual kidney function (RKF) is associated with the severity of PEW, suboptimal energy and nutrient intake [21]. Therefore, every effort should be made to preserve RKF.

Peritonitis

Peritonitis is a common complication in PD, with protein loss approximately twice the usual level. Losses remain high for 3–13 weeks, even after returning to baseline and symptoms subsiding [1]. In short and uncomplicated peritonitis, intake of at least 1 g/kg IBW/day protein and 25 kcal/kg IBW/day could maintain neutral or positive balance [22]. However, the presence of acute symptoms, such as abdominal pain, reduced appetite, nausea and vomiting, can reduce intake further. In addition to malnutrition [23], peritonitis is associated with chronic inflammation [24] and

mortality [25]. Significant predictors of peritonitis include poor nutrition as assessed by subjective global assessment (SGA), nutrition risk index (NRI), low serum albumin and low energy intake [26].

Therefore, nutrition intervention is needed to prevent and manage peritonitis.

Protein Energy Wasting

Protein energy wasting is reported in 28–54% of PD patients in an international study [27]; it is associated with morbidity, mortality, peritonitis rate and poor quality of life in incident and prevalent PD patients [23, 28–30]. Sarcopenia or frailty is common in PD, closely related to PEW and associated with high morbidity [31].

In addition to PD-related factors, other factors contributing to PEW may include old age [32], medications or psychosocial issues such as loneliness, depression, poor literacy and numeracy to follow dietary recommendations [33].

Goals for Nutritional Management

To achieve desirable clinical and patient-centred outcomes, the goals of nutritional interventions are to attain optimal nutritional, correct abnormalities and reduce risk factors associated with chronic uraemia and PD procedures as summarised in Table 31.1.

Nutritional Requirements for Patients Undergoing Peritoneal Dialysis

Dietary requirements of PD patients have been systematically reviewed to provide guiding principles for best practice. The most commonly cited guidelines are from the Kidney Disease Outcomes Quality Initiative (KDOQI)™ [34], the International Society of Renal Nutrition and Metabolism [35], the British Dietetic Association [36] and evidence-based practice group guidelines from Europe [37], America [38] and Australia and New Zealand [39]. Table 31.2 summarises the current recommendations. This information is then translated into food-based recommendations for individuals according to age, gender and physical activity levels. Dietary requirements

Table 31.1 Goals of nutritional management of peritoneal dialysis

To maintain optimal nutritional status
To alleviate uremic symptoms and symptoms related to PD
To correct electrolyte, metabolic and fluid imbalances
To prevent complications, e.g. peritonitis
To reduce cardiovascular risk
To improve quality of life and patient-centred outcomes

Table 31.2 Recommended energy, protein and mineral intakes for peritoneal dialysis patients

Energy and nutrients	Recommendation
Energy	*Including calories from dialysate*: ~30 kcal/kg IBW/d for ≥60 year ~35 kcal/kg IBW/d for ≤60 year Or *Oral* dietary prescription (average): ~25 kcal/kg IBW/d for ≥60 year ~30 kcal/kg IBW/d for ≤60 year Or To attain/maintain IBW. Adequate to maintain nitrogen balance. Depending on physical activity level and baseline nutritional status.
Protein	1.0–1.3 g/kg IBW/d Peritonitis ~1.5 g/kg IBW/d
Sodium	80–100 mmol/d, no added salt diet
Potassium	Restriction is not usually required A higher intake is required if hypokalaemia is present. 40–70 mmol/d if restriction is required
Phosphorous	800–1000 mg/d ± phosphate binders with foods and snacks if restriction is required
Fluids	Previous day's output +500 mL/d if restriction is required and depending on balance
Vitamins and minerals	Encourage an adequate diet to meet requirements. Water-soluble vitamins (Vit B and C) supplementation near the RDI levels, depending on intake. Individualised supplementation of folate, vitamin B_{12} and iron for anaemia management. Individualised supplementation of Vit D and calcium for bone management. Routine soluble vitamin supplementation (except Vit D) is not recommended.

Abbreviations: *IBW* ideal body weight, *RDI* recommended daily intake, *Vit* vitamin
Please also refer to the new KDOQI and Academy of Nutrition and Dietetics Clinical Practice Guideline for Nutrition in Chronic Kidney Disease to be released in 2020 [40]. There are a few small variations from current recommendations

may vary between regions due to ethnicity, body size/composition, food habits, lifestyle, etc. The new KDOQI and Academy of Nutrition and Dietetics Clinical Practice Guideline for Nutrition in Chronic Kidney Disease will be released in 2020, and there will be updated recommendations for energy, protein and various nutrients [40].

Energy

Resting energy expenditure of PD patients is similar to that of haemodialysis patients, non-dialysis-dependent patients or the general population [41]. Therefore, all guidelines include recommendations that for stable patients in the absence of concurrent illnesses or inflammation, total energy requirements are ~35 kcal/kg

IBW/day for ≤60 year old or ~ 30 kcal/kg IBW/day for >60 year old, as recommended by the World Health Organization (WHO) [42]. In adequately dialysed patients, the oral energy prescription would be 300–500 kcal/day less than the total energy requirements, accounting for dextrose absorption. All levels are to be adjusted according to the individual dialysis prescription, initial nutrition state, body weight and physical activity level to attain a healthy body weight.

Protein

The recommended daily intake (RDI) of protein for healthy adults [42] and non-dialysed CKD patients [34] is approximately 0.8 g/kg IBW/day with adequate energy intake. In view of the high protein loss associated with PD, evidence-based guidelines recommend PD patients to have a high protein intake of 1.0–1.3 g/kg IBW/day. During acute illnesses, including peritonitis, an even higher protein intake of ~1.5 g/kg IBW/day is recommended [39, 43].

In some Asian countries, studies have shown a 'lower' protein intake could attain optimal nutrition status and survival [44, 45]. With careful monitoring, a lower protein intake ~0.66 g/kg/day (total weekly Kt/v of 1.25, residual kidney Kt/v ~ 0.09) using two exchanges per day could maintain neutral nitrogen balance and reasonable nutritional status in patients with limited economic capacity [46]. The researchers relate the lower protein requirement to small body size and lower membrane transport.

Sodium and Fluids

In patients with diminishing RKF, sodium and fluid restrictions are required for better blood pressure control [47]. A 'no added salt' diet (80–100 mmol/day sodium) and fluid allowance 'previous day's urine output + ~500mL' are recommended [39]. Anecdotally, in non-adherent patients, hypertonic dialysate is required to remove excess sodium and fluids, and this excess caloric intake may lead to an undesirable gain of body fat.

Potassium

Due to the continuous nature of PD, dietary restriction of potassium is uncommon, and PD patients can have a relatively liberal intake. However, 22–60% of PD patients develop hypokalaemia, which is associated with poor dietary protein or food intake and poor nutritional status rather than dialysis factors, such as RKF or glucose load [48, 49]. Furthermore, hypokalaemic PD patients have a higher prevalence of peritonitis, due to a pathogenic mechanism linking malnutrition and hypokalaemia [50], and higher mortality [48].

Phosphorous

Hyperphosphataemia is common in PD and predicts cardiovascular and all-cause mortality. A PD diet is high in protein, which is also naturally high in phosphorous. The current recommendation is for an optimal serum phosphate level that can be achieved by individualised dialysis prescription, dietary modifications of 800–1000 mg/day [39] and phosphate binders. Not all phosphorous is absorbed from foods in the same way; phytate-bound phosphorous in plant foods has a low absorption rate (20–40%), as compared with phosphorous from animal (40–60%) or food additives (~90%) [51]. Education is key to management of serum phosphate levels.

Vitamins and Minerals

Peritoneal dialysis removes water-soluble vitamins and protein-bound, fat-soluble vitamin D. Compounded by reduced dietary intake, altered metabolism and availability, micronutrient deficiency is common in PD patients. Due to large individual variation in dietary intake, baseline nutritional status, inconsistent data from prevalence and efficacy studies, it is very challenging to make generalised recommendations for vitamin and mineral supplementation [5].

Food-Based and Dietary Pattern Recommendations

In addition to the prescription of energy and nutrient levels as discussed above, optimal intake of all other essential vitamins and minerals must be considered, as well as food components, e.g. dietary fibre, pre- and probiotics, antioxidants and flavonoids. 'Food synergy' is an important concept that encompasses the coordinated effects of all biological constituents of food and nutrients on health [52]. Furthermore, dietary patterns synergise the additive effects of foods and food constituents on health; significant effects have been observed in the Dietary Approaches to Stop Hypertension (DASH) diet [53] and the Mediterranean diet [54], which both emphasise plant-based eating of fruit, vegetables, legumes, nuts, plus quality lean animal protein, oily fish and low-fat dairy. There is limited data in PD (and haemodialysis) patients; recommendations are therefore deduced from that of the general [55] and non-dialysis-dependent CKD populations [56, 57].

In clinical practice, nutritional prescription is translated into food-based knowledge about quantity and quality that individuals need to consume from the basic core food groups. Table 31.3 summarises recommended food choices for people on PD, based on a combination of healthy eating guidelines, DASH- and Mediterranean-style eating and PD dietary recommendations.

Table 31.3 Recommended food choice for people on peritoneal dialysis

Food *General recommendation for people on PD*	Main nutrient	Important food components				Potential benefits for PD *Deduced from general and CV health, non-dialysis CKD studies* PD denotes information from PD studies
		Dietary fibre	Pre- and probiotics	Antioxidants	Flavonoid/ isoflavones	
Core food groups						
Bread, cereals and grain products *(Wholemeal/whole grain products)*	CHO (unrefined), PO_4, Vit Bs and E	✓	✓	✓		↓ constipation (**PD and I**) *Others:* *↓ CRP levels (E)* *↓ myocardial infarction risk (E)* *Low GI:* *↑ insulin sensitivity (I)* *↓ mortality (E)*
Fruit **Vegetables** *(choose a variety of coloured vegetables in season)*	Vit A, C and K Vit A, C and K, mg, folate, iron in green leafy veg	✓	✓	✓	✓	↓ constipation (**PD and I**) *Others:* *↓ BP (I)* *↓ CRP (I)* *↓ inflammation and oxidative stress (E)* *↓ acidosis (I)* *↓ CV and all-cause mortality (E)* *Low GI:* *↑ insulin sensitivity (I)*
Meat and meat alternatives **Including eggs, plant-based proteins, e.g. dried beans, legumes, nuts and seeds** *Lean cuts of meat, skinless poultry, fish; vegetarian proteins (unsalted)*	Iodine, iron, PO_4,protein, Vit Bs and B_{12} and zinc Omega-3 fatty acids and Vit D (in oily fish) N-6 fatty acids and Vit E (in nuts)	Plant-based proteins ✓	Plant-based proteins ✓	Plant-based proteins ✓	Plant-based proteins ✓	Soya protein: ↓plasma coagulation factor IX activity (**PD and I**) Low AGE products: Altered gut microbiome, which may reduce CV risk (**PD and I**) *Others:* *Plant-based protein:* *↓ serum lipids (I)* *↓ CRP (I)* *Fatty fish:* *↓ CV and all-cause mortality (E)* *↓ risk MI, IHD, stroke (E)*

Milk and dairy and /or alternatives *(fat-reduced varieties if needing to lose weight)*	Calcium, PO_4, protein, Vit B_2, A and D		✓	✓		Limited data in PD ↑ *muscle and bone (I)*
Fat *(mono- or polyunsaturated fats. Limit saturated fats and trans-fats)*	Essential fatty acids, fat-soluble vitamins			✓	✓	Limited data in PD ↓ *serum lipids (I)* ↓ *markers of oxidative stress*
Other foods and dietary patterns						
Alcohol *(limit): moderate*	Alcohol			✓		Limited data in kidney health
Salt/sodium *(limit to 80–100 mmol/d, Avoid processed and salted foods)*	Sodium					↓ BP (**PD and I**) ↓ extracellular fluid volume (**PD and I**)
Sugars *(limit or optimal level for energy)*	CHO (refined)					– –
Healthy dietary patterns *(that emphasise plant-based foods, good quality animal protein, low sugar)*	From all core food groups	✓	✓	✓	✓	Limited data in PD *Others:* ↓ *BP (I)* ↑ *serum albumin (I)* ↓ *serum lipid (I)* ↓ *inflammation (I)*

Abbreviations: *BP* blood pressure, *CHD* coronary heart disease, *CHO* carbohydrates, *CKD* chronic kidney disease, *CRP* C-reactive protein, *(E)* epidemiology study, *EFV* extracellular fluid volume, *GI* Glycaemic index, *(I)* intervention study, *IS* insulin sensitivity, *K* potassium, *Mg* magnesium, *MI* myocardial infarction, *Na* sodium, *(PD)* information from PD specific study, *PO_4* phosphorous, *Vit* vitamin

Effective Nutritional Management

Nutrition interventions are known to improve nutritional status and reduce complications as reported in intervention studies as well as quality improvement initiatives from day-to-day clinical practice.

Protein Energy Wasting: Nutritional Status

Nutritional support can be delivered with a combination of dietary counselling, food and food fortifications, use of oral nutrition supplements (ONSs), enteral feeding and use of intraperitoneal amino acid dialysate. The effectiveness of nutritional support depends on the cause and severity of the problem, presence of inflammation and other comorbidities, individual adherence, aging [32] and psychosocial situation [58]. Common outcome measures are weight, body composition, biochemical parameters (albumin, C-reactive protein) and presence of malnutrition, measured using SGA.

While nutrition counselling alone may be challenging to improve outcomes [59], it has been shown to improve nutrition status [60]; the effect is more significant with food fortification using egg albumin powder [61] or whey protein [62]. The use of an ONS, in liquid formula or protein bar, improves body weight and nutritional status [63]. Although the effectiveness of ONSs has been questioned [64], it is important to consider a holistic approach to nutritional support rather than to administer a standard dose of supplement without considering the baseline intake and total nutrition requirements of an individual. A similar explanation is given to inconsistent data on the use of intraperitoneal amino acid-containing dialysate, which typically provides 1.1% (~22 g) amino acids in a 2-litre dialysate bag [65]. The effect was promising when combined with sufficient oral nutrition intake [65] as compared with no or limited effect if an amino acid dialysate was given alone [66]. Furthermore, there are two types of malnutrition: type I is predominantly caused by poor protein and energy intake, while type II characterizes malnutrition secondary to inflammation and is also associated with atherosclerosis, which is known as MIA syndrome [67]. Type I and type II can co-exist. In type II malnutrition, treating the underlining cause of inflammation and atherosclerosis is important, although not always feasible. This may explain the limiting effect of ONS and/or intraperitoneal amino acids alone in some malnourished PD patients.

Sodium and Fluids

Strict sodium/salt and fluid restrictions result in better management of volume control, leading to healthier blood pressure levels [47, 68], reduction in antihypertensive

medication use and more precise cardiovascular protection as measured by left ventricular mass index (LVMI) and left atrial index (LAI) [69].

Minerals

Structured dietetic intervention in a multidisciplinary clinic decreased the proportion of PD patients with abnormal serum potassium (hyper- and hypokalaemia) from 28.6% to 13.1% [70]. The reduction of hypokalaemia episodes also led to reduced potassium supplementation. Counselling on diet and phosphate binder adherence [71] was associated with lower serum phosphate levels in a 12-month RCT on providing practical tips for food preparation, which resulted in lower serum phosphate and reduced phosphate binder use [72].

Cardiovascular Health

Inclusion of 14 g of soy protein for 8 weeks in a RCT reduced coagulation factor IX activity, a risk factor for thrombosis [73]. In a small RCT, adopting cooking methods to reduce advanced glycation end products (AGEs), such as boiling, steaming instead of frying and grilling on high heat, altered the gut microbiome, which is related to reduced CV risk [74].

Gut Health

A higher fibre intake from either food or fibre supplement can address constipation issues and minimise laxative use with no adverse effect on potassium, phosphate or fluid balance [75].

Summary

There is a lack of high-grade evidence in all aspects of nutrition intervention in PD. Inconsistency in findings is largely due to study designs, small sample sizes, varied baseline dietary intake and nutritional status. In addition, it is challenging to implement or study PD diets as it involves multiple nutrient modifications and many confounding factors. Before higher grades of evidence are available, priority should be given to implement best practice for dietary prescription and food choice, as well as searching for the best care delivery methods to improve outcomes.

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Chapter 32
The Role of Peritoneal Dialysis in Pandemics and Natural Disasters

Bourne Auguste

Introduction

The frequency of natural disasters around the globe has steadily increased over the last several decades. This surge in disasters is attributable to rapidly growing populations in high-risk areas along with climate change that has increased the vulnerability of coastal regions due to rising sea levels [1]. The infrastructural damage and disruption to social systems during disasters have significant implications for the sustained delivery of care. Vulnerable populations, especially those on dialysis, can be significantly affected by these catastrophic events, and their life-sustaining treatment may be delayed for a variety of reasons. Infrastructural damage related to earthquakes, hurricanes, flooding, and other natural disasters can disrupt water and electrical supply that are essential components in providing hemodialysis [HD] for patients.

The Renal Disaster Relief Task Force [RDRTF] of the International Society of Nephrology was developed in 1988 after the Armenian earthquake [2]. This earthquake resulted in more than 35,000 deaths with over 350 people requiring acute dialysis for acute kidney injury related to crush injuries [3, 4]. RDRTF continues to play an important role around the globe in providing recommendations for kidney replacement therapy [KRT] in disaster zones. However, many of the recommendations have favored using HD in these situations, especially in the management of crush injuries. Unfortunately, the global prevalence of HD coupled with an underutilization of acute peritoneal dialysis [PD] has led to missed opportunities for practitioners in capitalizing on the benefits of PD in austere environments.

Similarly, pandemics, which are large-scale outbreaks of infectious disease occurring across many countries, can lead to social and economic disruptions,

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negatively impacting dialysis care [5]. These disruptions may arise due to containment and mitigation strategies against disease spread. The impact of these disruptions can be devastating by increasing morbidity and mortality for dialysis patients. There is now mounting evidence that the frequency of pandemics has increased over the last century that has been primarily driven by higher population densities and globalization [5, 6]. Additionally, the increasing threat of polymicrobial antibiotic resistance is another imminent risk factor for future pandemics [5].

In this chapter, experiences from various PD programs around the globe in the face of natural disasters will be highlighted. Additionally, the benefits and drawbacks of PD during the COVID-19 pandemic, at the time of this writing, and future pandemics will be discussed. These experiences and lessons learned may better inform renal programs about strategies to maintain and increase PD adoption in times of crisis.

Earthquakes

Earthquakes can lead to extensive infrastructural damage and crush injuries within the population. Chronic HD patients are commonly displaced following an earthquake and transferred to other centers to provide them with this life-sustaining therapy [7–9]. An estimated 90% of earthquakes and most destructive ones occur in the basin of the Pacific Ocean in an area called the "Ring of Fire" [10, 11]. Countries within that region (Fig. 32.1) have historically had devastating destruction to their

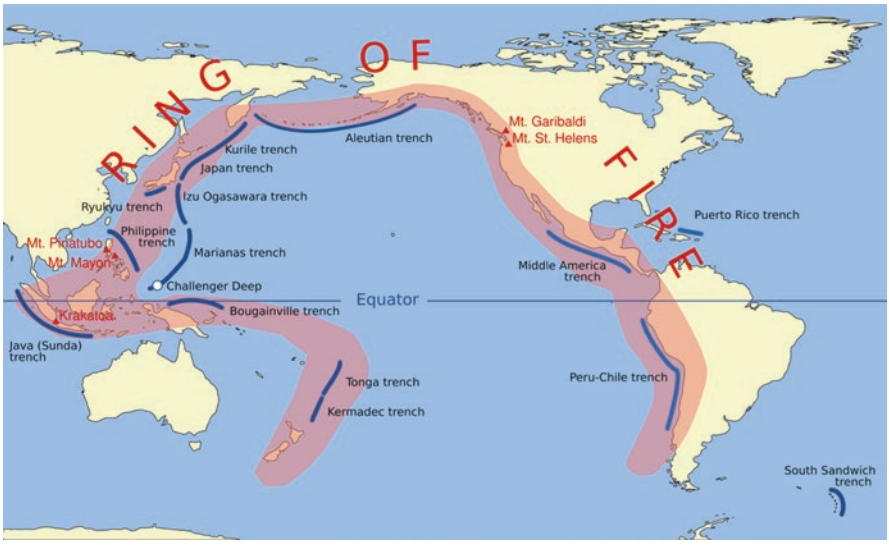

Fig. 32.1 Ring of fire in the basin of the Pacific Ocean showing high-risk regions for earthquakes and volcanic eruptions (Source: Gringer (https://en.wikipedia.org/wiki/Ring_of_Fire), "Pacific Ring of Fire", marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki:Template:PD-self)

infrastructure over several decades related to earthquakes, volcanic eruptions, and tsunamis.

In January of 1995, an earthquake damaged the Japanese city of Kobe killing over 5000 people [12]. The earthquake caused significant damage, disrupting water supply, electricity, gas, and telephone services. There was also damage to highways and roads leading to transportation paralysis within the city [12, 13]. Collectively, these factors affected many HD and medical facilities, and as a result, HD could not be offered to patients in Kobe [12]. HD patients were treated with potassium exchange resins until an available treatment facility had been identified. Approximately 1668 HD patients had to be transferred to neighboring facilities in Osaka and Hyogo, which were not affected by the earthquake. The majority of patients received HD within 3 days of the disaster at neighboring centers, with some not receiving treatment for up to 7 days [12, 13]. Although no HD patients died due to delay in access to treatment, widespread disruptions in HD occurred across Japan in an effort to urgently accommodate displaced individuals [12].

In contrast, no PD patients were transferred to other dialysis centers for care as the resources required to support these patients immediately following the disaster was significantly fewer than that needed for HD patients. For example, many of the PD patients who were on automated therapy with a cycler prior to the earthquake were subsequently transitioned to manual exchanges, which did not require electricity, in its aftermath [13]. Although some patients had their homes destroyed by the disaster, they were still able to perform manual PD at other locations and evacuation sites [13]. This demonstrates that PD places minimal demands on the healthcare system, particularly in times of disaster.

Another earthquake struck off the Japanese coast of Tohoku in March of 2011. This was the largest earthquake in the recorded history of Japan, registering 9.1 on the Richter scale, resulting in large tsunamis and 15,899 confirmed deaths [14, 15]. Tsunamis resulted in widespread infrastructural damage, including the Fukushima Daiichi nuclear power plant and causing a nuclear reactor explosion with the release of radioactive materials [16–18]. Mandatory evacuation orders were put in place that extended up to a 20-km radius from the nuclear power plant. Consequently, 161 centers had to transfer chronic dialysis patients to other facilities to accommodate treatment for the 10, 906 displaced patients [9, 16–19].

On the other hand, the experiences of PD patients in the three affected prefectures in Japan (Iwate, Miyagi, and Fukushima) were quite different from that of the HD patients. Although some PD patients lost their homes and supplies in the tsunami, many were still able to perform manual exchange PD in evacuation centers [19]. Patients who performed cycler-based therapy before the disaster were subsequently reverted back to automated PD once the power supply had been restored [19].

The Japanese experiences highlight that the delivery of PD is not as heavily reliant on social infrastructure such as transportation to and from a dialysis center, reliable water supply, and electricity as compared to HD. Furthermore, patients can perform PD independently or with very little support from others. Lastly, PD can be performed at home or in evacuation sites without the need for transfer of patients to other dialysis centers to receive treatment. The displacement of dialysis patients

following earthquakes may last several weeks or in some cases may be permanent [7, 19]. Therefore, future disaster preparedness strategies should aim to increase more widespread adoption of PD and consider it as an initial modality for replacement therapy for ESRD patients in high-risk regions.

Tropical Cyclones and Flooding

Asian countries along the Pacific Ocean are commonly battered by typhoons, but there is limited literature examining their impact on the care provided to dialysis patients. However, the experiences of US centers in caring for dialysis patients during hurricanes have been more readily reported in the literature [7]. Over the last two decades, numerous hurricanes (Katrina, Sandy, Rita, and Wilma) have resulted in widespread infrastructural damage, leading to a significant impact on patient care. According to the 2016 US census, nearly 60 million Americans lived along the Atlantic and Gulf Coast regions, placing them in the destructive path of hurricanes [20].

Hurricane Katrina resulted in extensive destruction along the US Gulf Coast and severely damaged the city of New Orleans. The flooding associated with Katrina after the levees were breached caused many dialysis centers to close temporarily and in some cases permanently [21, 22]. A total of 5849 patients were affected by Hurricane Katrina in 2005 with 92 dialysis centers being closed for at least 1 week [21]. Although many patients made evacuation plans prior to the storm, several arrived in neighboring communities and centers that lacked preparation to accommodate this influx of HD patients [21, 22]. In the aftermath of Katrina, many US renal programs in collaboration with the Kidney Community Emergency Response Coalition have improved their disaster preparedness strategies at the local and state levels [23]. However, disaster preparedness among patients is quite variable and tends to be poorer among prevalent HD patients. Observational data from six regional dialysis centers in North Carolina demonstrated a lack of disaster preparedness irrespective of sociodemographic characteristics [24]. Data from that study also revealed that PD patients were better prepared for disasters as compared to hemodialysis patients [24].

The reported experiences of a small PD program in New Orleans leading up to Hurricane Katrina and its immediate aftermath revealed that many patients evacuated before the storm arrived. Among the patients who did not evacuate, two patients required hospitalization for volume overload and peritonitis, respectively [25]. Despite the ability to perform manual exchanges in the absence of a power supply, extensive flooding did not allow for safe PD without the risk of contamination. Many of the evacuated PD patients arranged for at least a 1-week supply of solutions [25]. Additionally, some patients contacted suppliers directly after the storm to arrange delivery at their new locations. Patients communicated with the PD nurse after the hurricane and were able to have many of their questions around prescriptions and other concerns addressed directly.

The aforementioned experiences underscore that performing PD in certain disaster scenarios may have some limitations, particularly in the face of extensive flooding. Although a published experience highlighted the benefits of PD after flooding in the Indian district of Leh in 2010 [26]; PD was done in patients with access to supplies and without an imminent risk of contamination during therapy. Therefore, in situations where advanced disaster preparedness and early evacuation can be undertaken, patients should take heed to avoid delay in treatment in the aftermath of a disaster. Furthermore, advanced disaster preparedness strategies should include having at least a 1-week supply of solutions and arranging for advanced delivery of additional supplies to the planned evacuated location.

COVID-19 and Future Pandemics

In December 2019, an outbreak with the novel SARS-CoV-2 virus (COVID-19) began in Wuhan, China. On January 30, 2020, it was then declared a public health emergency of international concern and then later called a pandemic on March 11, 2020, by the World Health Organization [27, 28]. As of the end of April 2020, more than 3.08 million cases of COVID-19 have been reported in 210 countries around the globe, resulting in more than 215,000 deaths thus far. The symptoms of COVID-19 can be non-specific, but the most common presentations are fever along with respiratory tract symptoms. However, emerging data around the globe indicates that patients who are asymptomatic may also shed the virus without being aware. This carries significant risk for vulnerable and immunocompromised patients, particularly those on chronic in-center HD who congregate in close proximity multiple times per week [29–31]. Therefore, as the risk of future pandemics increases, viable alternative strategies need to be considered.

Early data has suggested that acute kidney injury occurs in 5–15% of patients infected with COVID-19 [32, 33]. This has increased the burden on resources to provide kidney replacement therapy in the form of hemodialysis for patients both in the inpatient and outpatient setting. Some dialysis centers have decreased the intermittent HD hours from 4 to 3 hours per session and have also considered reducing sessions per week in an effort to mitigate the risk of disease spread, conserve personal protective equipment, and avoid burnout among healthcare providers [34, 35]. Patients with COVID-19 can also have severe acute respiratory distress syndrome (ARDS) that requires lung-protective ventilation strategies with prone patient positioning [36]. Unfortunately, due to the nature of this disease, both acute and maintenance PD have some major drawbacks in this population. There is a high chance of peri-catheter dialysate fluid leak along with limitations of small fill volumes due to the impaired respiratory reserve capacity.

The primary advantage of PD in this situation is that it can free up resources by being used in non-COVID-19 patients who have had acute kidney injury or progression of their kidney disease that need dialysis. Patients can be managed with PD,

which can free up HD resources and staff who are required for the more critically ill patients. Additionally, PD can be used as a means to limit disease spread during a pandemic by eliminating the close proximity of patients within a confined area that occurs within an HD unit. Similarly, infected PD patients can still be supported with PD both at home and if hospitalized provided that protective measures can be instituted. This is supported by a reported experience in Hong Kong during the SARS-coronavirus global outbreak in 2003 where PD was safely performed for patients who tested positive for the virus with appropriate infection control measures put in place [37].

PD can be performed independently at home or with very little support, and this would minimize the exposure to nursing staff along with other patients in a dialysis program. A "PD-first approach" for chronic kidney disease patients during pandemics would also reduce the demand for HD resources in terms of nursing staff, particularly if there are staffing shortages due to infection. Additionally, infected dialysis patients who do not require hospitalization can maintain self-isolation practices and continue to receive treatment regularly without putting other individuals at risk by travelling to and from dialysis units several times per week.

Conclusions

As the global population grows, the risk of natural disasters and future pandemics will continue to rise. Therefore, renal programs in high-risk regions should consider adopting a "PD-first policy" where feasible in the face of disasters and pandemics. PD is a viable modality to support patients with end-stage kidney disease [ESKD] in austere environments. Natural disasters along with pandemics place tremendous strain on dialysis supplies and human resources; PD can serve as an outlet to reduce this burden. Firstly, PD can be performed in the absence of an electrical power and water supply. Secondly, many patients can perform PD in their own home and do not need to rely on transportation services which may be disrupted during a disaster. Thirdly, PD is technically simpler to perform compared to HD, and patients can do it independently or with very little assistance at home. Patients can also perform PD at evacuation sites without needing to be transferred to another dialysis center, ultimately easing the strain on surrounding facilitates providing respite care. Lastly, in terms of future pandemics, the independent nature of PD is a significant advantage in reducing the risk of disease spread through isolation practices.

In adopting robust disaster preparedness plans, renal programs should move away from an HD-centric approach in planning for future austere environments. Programs should continue to promote PD in eligible patients not only to provide patients with more choice but to prepare in the event of future disasters.

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Correction to: Nutritional Management of Adult Peritoneal Dialysis Patients

Maria Chan

Correction to: Chapter 31 in: A. Rastogi et al. (eds.), Applied Peritoneal Dialysis,
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An error was found on Chapter title in Chapter 31 in the original publication and the same is now corrected.

Chapter title changed from - Nutritional Management of Adult Peritoneal Dialysis Patients Abstract

To chapter title - Nutritional Management of Adult Peritoneal Dialysis Patients

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