Yong-Lim Kim
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Editors

The Essentials of Clinical Dialysis

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Preface

Over the past half century, dialysis has developed and progressed as a therapeutic replacement of renal function. Correct understanding of a patient condition and providing needed treatment forms the core of patient care, just as locating a vessel is critical in sailing. Further, optimal care of patients with end-stage renal disease requires a thorough grasp of different treatment options related to dialysis. This book guides readers through all the relevant options with great readability.

Intended to be an introductory material for dialysis specialists, this book was written to provide latest insights and guidelines with much simplicity and clarity. Illustrations would further enhance reader understanding.

While dialysis patterns might differ from country to country depending on national healthcare policies, this book focuses on universal treatment methods across the world. Some countries might not have access to dialysis consumables or peritoneal dialysis fluids that are mentioned in this book.

Lastly, my sincere gratitude goes to all those authors who took part in writing this book for the hard work and dedication.

Daegu, South Korea — Yong-Lim Kim
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Part I

Preparation of Dialysis

Dialysis Indication and Initiation Time for Dialysis

1

Norio Hanafusa

1.1 Background

1.1.1 Kidney Functions

Kidneys have many functions to maintain internal milieu of aqueous phase. These include maintenance of hydration status, electrolyte concentration, and acid-base status and excretion of endogenous or exogenous wastes. Moreover, kidneys also produce several hormones.

On the other hand, some chronic kidney disease (CKD) patients eventually develop end-stage renal disease (ESRD), which requires some artificial support for the kidney functions. In general, most of kidney functions deteriorate in same paces as the glomerular filtration rate (GFR) declines in the patients. Therefore, many nephrologists consider the indication of dialysis initiation by estimated GFR (eGFR) values (van de Luijtgaarden et al. 2012).

The exact measurement of GFR involves complicated processes. Thus, in patients with earlier stage of CKD, eGFR calculated from creatinine or cystatin-C, age, gender, and race (Levey et al. 1999, 2006, 2009) is widely used to determine CKD staging (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). However, creatinine has a limitation that the serum levels are influenced by muscle mass or the amount of meat that the patients ate as their foods. Therefore, the patients with reduced muscle mass or appetite which is prevalent among older population experienced lower serum creatinine levels compared to those who have the same GFR but sufficient muscle mass (Grootendorst et al. 2011). Actually, those who have higher production or urinary excretion of creatinine tended to demonstrate lower eGFR compare to creatinine clearance (Beddhu et al. 2003). Therefore, eGFR can potentially underestimate the actual GFR among such population, vice versa.

The significance of measured GFR can be illustrated by the following evidences. A study from NECOSAD (The Netherlands Cooperative Study on the Adequacy of Dialysis), a cohort of incident dialysis population performed in the Netherlands, demonstrated that eGFR overestimated measured GFR (mGFR; mean of creatinine and urea clearance) by 0.8 mL/min/1.73 m^2, and the limits of agreements were −4.1 to 5.6 mL/min/1.73 m^2. In this study, higher measured clearance was not associated with the worse outcome, while higher eGFR was associated with worse outcome. Moreover, eGFR was shown to relate with the muscle mass (Grootendorst et al. 2011).

A meta-analysis indicated the significance of measured GFR and demonstrated that higher measured GFR related to better survival (adjusted

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HR 0.801), although the higher eGFR related to worse outcome (AHR 1.038) (Susantitaphong et al. 2012).

Taken together, measured clearance might be helpful to consider the indication of dialysis initiation, although the measurement itself requires collection of urine.

Several investigations employed the average of creatinine and urea clearances (Dombros et al. 2005). The author considers the direct measurement of clearances is required to test the patient's true kidney function not from the estimation.

1.1.2 Historical Perspectives of the Timing of Dialysis Initiation

Historically, the earlier initiation of dialysis treatment was recommended, because the early initiation of dialysis shortens the period during which the patients experience uremic circumstances. Such early initiation of dialysis was considered to improve survival or quality of life by preventing uremic complications (Dombros et al. 2005; Bonomini et al. 1985; Perrone et al. 1992; Churchill 1997; Tattersall et al. 1995; Hakim and Lazarus 1995). Bonomini et al. investigated the outcome of 390 incident patients. Among them, 82 patients started dialysis early (mean creatinine clearance of 11 mL/min), because they manifested uremic symptoms refractory for medication, were unable to follow low-protein diet, or adopted early dialysis voluntarily. On the other hand, remaining 308 patients were treated by low-protein diet conservatively for 24–53 months and then started their dialysis therapy at the time of their Ccr of 2.1–4.8 mL/min. They found that the patients in early-start group experienced higher survival and full-time working rate and lower hospitalization rate compared to those in late-start group (Bonomini et al. 1985). Thus they concluded that early start of dialysis is beneficial for patients' conditions after start of dialysis therapy.

From such evidences, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guideline recommended early start of dialysis therapy in terms of GFR. The guideline published in 2006 told the value of eGFR from where dialysis therapy is considered should be 15 mL/min/1.73 m^2 (Initiative NKFKDOQ 2006), while the guideline in 1997 told 10.5 mL/min/1.73 m^2 (National Kidney Foundation (NKF-DOQI) 1997). As a result, the eGFR at the initiation of dialysis therapy had been becoming higher in the United States. In 1996, only 19% of the patients started their dialysis with their eGFR more than 10 mL/min/1.73 m^2, but 45% of incident patients started dialysis with eGFR more than 10 mL/min/1.73 m^2 in the year 2005 and (Rosansky et al. 2009). O'Hare, et al. demonstrated that the dialysis started earlier by 147 days from 1997 to 2007. The differences were more pronounced for older population. The patients 75-year-old or more started dialysis earlier by 233 days during the past 10 years (O'Hare et al. 2011). Also in Canada, the similar trend had been observed (Clark et al. 2011).

1.2 Current Considerations About Dialysis Initiation

1.2.1 Early Dialysis Initiation Is Not Favorable

However, many evidences, most of them are epidemiological and observational studies, against early initiation have been published since late 1990s. For example, the results from Dialysis Morbidity Mortality Study Wave II in the United States demonstrated that HR for survival was 1.14 ($p = 0.002$) per 5 mL/min/1.73 m^2 of higher eGFR at the initiation (Beddhu et al. 2003). Similarly, the results from Centers for Medicare and Medicaid Services indicated that the patients who started dialysis with eGFR more than 10 mL/min/1.73 m^2 experienced significantly poorer survival (HR 1.42) compare to those with eGFR less than 5 mL/min/1.73 m^2 (Kazmi et al. 2005).

Also from European countries, many studies showed that higher eGFR at the initiation related to worse outcome. The results from the registry of European Renal Association and European

Dialysis Therapy Association investigated the relationship between eGFR at the initiation and subsequent survival. They found that higher eGFR was associated worse survival (HR 1.02, 95%CI: 1.01–1.04 per 1 mL/min/1.73 m^2 higher eGFR) (Stel et al. 2009).

Moreover, in Asian countries, similar findings have been obtained. In Japan, the averaged eGFR is lower than other countries. The results of the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) indicated that mean eGFR was 6.52 mL/min/1.73 m^2 and only 10.6% of total population started their dialysis treatment with eGFR more than 10 mL/min/1.73 m^2 in 2007 (Yamagata et al. 2012a). Among such population, Yamagata et al. demonstrated that the patients with eGFR more than 8 mL/min/1.73 m^2 experienced worse 1-year survival compared to those with eGFR between 4 and 6 mL/min/1.73 m^2. HR for eGFR of 8–10 mL/min/1.73 m^2 group was 2.20 (95%CI 1.52–3.17) after adjustment. Moreover, they found that eGFR less than 2 mL/min/1.73 m^2 tended to be associated with worse survival (HR 3.40, 95%CI 0.98–11.8) (Yamagata et al. 2012a). Hwang et al. investigated the data of Taiwan and also found that lowest quintile of eGFR (eGFR <3.29 mL/min/1.73 m^2) at initiation of dialysis was associated with better subsequent 1-year survival (Hwang et al. 2010).

Meta-analyses published to date also demonstrated that earlier dialysis initiation was associated with worse outcomes (Susantitaphong et al. 2012; Pan et al. 2012; Slinin et al. 2015). One meta-analysis investigated the results of 15 observational studies. They found that 1 mL/min/1.73 m^2 higher eGFR was associated with higher mortality [HR 1.037, 95%CI 1.030–1.045], and the results did not differ after adjustment of nutritional markers (Susantitaphong et al. 2012). Another meta-analysis investigated ten observational studies and one randomized control trial which will be discussed later. They also found that early dialysis initiation related to higher mortality [OR 1.33, 95%CI 1.18–1.49] (Pan et al. 2012). Recently, another meta-analysis of 19 trials was performed to form an evidence for NKF KDOQI guideline. In this meta-analysis again, the patients with estimated creatinine clearance (eClcr) of 10–14 mL/min/1.73 m^2 did not experience better survival compared to those with eClcr of 5–7 mL/min/1.73 m^2 (Slinin et al. 2015). Moreover, a meta-analysis that investigated such relationship only among diabetic patients also failed to demonstrate the superiority of early dialysis initiation (Nacak et al. 2016).

From these results, across races or ethnicities, the concept that early dialysis initiation can lead to better clinical outcome after dialysis initiation is now questioned. However, the observational studies cannot eliminate biases such as immortal-time bias, lead-time bias (Sjolander et al. 2011), or others (Mehrotra et al. 2013). Therefore, randomized control trials had been anticipated to investigate the timing of dialysis initiation and subsequent clinical outcomes.

1.2.2 The Initiating Dialysis Early and Late (IDEAL) Study

Under such circumstances, the Initiating Dialysis Early and Late (IDEAL) study was planned (Cooper et al. 2004) and performed (Cooper et al. 2010). IDEAL study is the only randomized control trial to investigate the timing of dialysis ever. The study recruited 828 CKD patients (mean age of 60.4 years old and 355 of them were diabetic) with their eGFR of 10–15 mL/min/1.73 m^2 by Cockcroft-Gault equation. The patients were randomized into two groups; one group started dialysis at eGFR of 10–14 mL/min/1.73 m^2 (early-start group), and the other started at eGFR of 5–7 mL/min/1.73 m^2 (late-start group). Primary endpoint was set as all-cause mortality. The time period from randomization to actual initiation of dialysis was 1.80 (95%CI 1.60–2.23) months for early-start group and 7.40 (95%CI 6.23–8.27) months for late-start group. During the median follow-up period of 3.59 years, 152 patients (of 404 patients, 37.6%) in early-start group and 155 patients (of 424 patients, 36.6%) in late-start group were deceased. The HR of death for early-start group was 1.04 (95%CI 0.83–1.30, $p = 0.75$) compared to late-start group. Other endpoints of cardiovascular disease,

infection, or other complications were also comparable between two groups. Therefore, this study did not demonstrate the superiority of early start and failed to show the advantage of late start at the same time. However, some limitations have been pointed out for this study. The most important is 75.9% of the patients in late-start group started their dialysis before their eGFR reached 7.0 mL/min/1.73 m^2 due to mostly uremia (72.7% of those started earlier in late-start group), while 18.6% in early-start group started their dialysis eGFR below 10 mL/min/1.73 m^2. Such high proportion of protocol violation makes this study difficult to be assessed. Nonetheless, IDEAL study told us that the timing of starting dialysis cannot be determined solely by eGFR. Thus close monitoring the uremic symptoms of the patients including other conditions is warranted for determining the initiation of dialysis.

Moreover, several post hoc analyses have been published about IDEAL study. One of the studies compared the medical costs and quality of life between two groups. The study demonstrated that the medical costs were higher among the patients who were allocated to the early-start group, while the quality of life did not differ between the groups (Harris et al. 2011). Another study investigated the effect of timing only among the planned hemodialysis patients. This study again did not show the advantage of early initiation (Collins et al. 2011). These facts also discouraged the advantage of early initiation of dialysis treatment.

1.3 Factors To Be Considered for the Initiation of Dialysis

1.3.1 Uremic Symptoms

As discussed above, there is little evidence by which we can set the specific eGFR value for dialysis initiation, although many nephrologists rely on the eGFR value in decision-making to start dialysis treatment, especially for the uncomplicated patients (van de Luijtgaarden et al. 2012). Therefore, during the process of actual dialysis initiation, we should consider the entire clinical picture of the patients and should make clinical judgment (Weiner and Stevens 2011). In Japan, the guideline published in 1991 demonstrated a systematic list of the signs or symptoms observed in uremia (Kawaguchi and Mimura 1991), and these criteria were also utilized by the current Japanese guideline on initiating hemodialysis (Watanabe et al. 2015). Table 1.1 shows these uremic symptoms demonstrated by this guideline. Table 1.2 indicates the symptoms and signs of uremia described in NKF KDOQI hemodialysis adequacy guideline 2015 update (National Kidney Foundation 2015). DOPPS data demonstrated that higher mortality can be observed soon after hemodialysis initiation (Bradbury et al. 2007). Specifically, the incident hemodialysis patients experience higher mortality due to heart failure. Therefore, overhydration can be related to worse outcomes among the uremic symptoms. The fact was also evidenced by the study on JRDR. Yamagata et al. investigated the relationship between the symptom at the initiation of dialysis and subsequent survival. They found that congestive heart failure, intractable edema, oliguria, and unrecovered acute exacerbation of renal function were related to higher mortality, and HR for them were 1.87 (95%CI 1.47–2.38), 1.91 (95%CI 1.44–2.54),

Table 1.1 Uremic signs and symptoms listed in the Japanese guideline in 1991

Category	Signs and symptoms
Fluid accumulation	Anasarca, severe low proteinemia, lung congestion
Electrolyte disturbance	Refractory electrolyte and/or acid-base disturbances
Gastrointestinal symptoms	Nausea, vomiting, appetite loss, diarrhea, or others
Circulatory abnormalities	Severe hypertension, heart failure, pericarditis
Neurological symptoms	Central and/or peripheral nervous disorders, psychosis
Hematological symptoms	Severe anemia, bleeding diathesis
Visual disturbance	Uremic retinopathy, diabetic retinopathy

Adapted from Kawaguchi and Mimura (1991)

Table 1.2 Uremic symptoms and signs described in NKF KDOQI guideline in 2015

Symptoms
Fatigue
Lethargy
Confusion
Anorexia
Nausea
Alterations in senses of smell and taste
Cramps
Restless legs
Sleep disturbances
Pruritus
Signs
Seizures/change in seizure threshold
Amenorrhea
Reduced core body temperature
Protein-energy wasting
Insulin resistance
Heightened catabolism
Serositis (pleuritis, pericarditis)
Hiccups
Platelet dysfunction
Somnolence

Adapted from National Kidney Foundation (2015)

1.64 (95%CI 1.19–2.25), and 2.74 (95%CI 1.94–3.88), respectively (Yamagata et al. 2012b). Another study investigated the association of signs and symptoms with early dialysis initiation among nursing home residents (Kurella Tamura et al. 2010). They evaluated seven clinical signs and symptoms: dependence in activities, cognitive impairment, edema, dyspnea, nutritional problems, vomiting, and body size. They found that the patients who manifested more signs and symptoms significantly more likely start dialysis at their eGFR of 15 mL/min/1.73 m^2 or higher (OR 1.16 per symptom, 95%CI 1.06–1.28).

1.3.2 Nutritional Indications

Deterioration of nutritional status has been one of the reasons for dialysis initiation. Certainly, most of guidelines (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013; National Kidney Foundation (NKF-DOQI) 1997; Watanabe et al. 2015; National Kidney Foundation 2015; European Best Practice Guidelines Expert Group on Hemodialysis ERA 2002; Tattersall et al. 2011; The CARI guidelines 2005a; Warwick et al. 2014; Churchill et al. 1999) in their statements recommended dialysis initiation when the patients experience the deterioration of nutritional status that can be attributable to uremia. However, the actual descriptions about malnutrition to make nephrologists consider dialysis initiation are diverse. The early guidelines, NKF KDOQI 1997 and CSN 1999, recommended normalized protein equivalent of nitrogen appearance (nPNA) to use and to initiate dialysis if nPNA falls below 0.8 g/kg/day spontaneously (National Kidney Foundation (NKF-DOQI) 1997; Churchill et al. 1999). CNS 1999 guideline mentioned subjective global assessment as an index of malnutrition (Churchill et al. 1999). The latest NKF KDOQI 2015 guideline mentioned protein-energy wasting as one of the signs to be monitored closely (National Kidney Foundation 2015). On the other hand, other guidelines did not specifically tell about the indices to monitor in their statements (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013; Watanabe et al. 2015; European Best Practice Guidelines Expert Group on Hemodialysis ERA 2002; Tattersall et al. 2011; The CARI guidelines 2005a; Warwick et al. 2014). Although the guidelines told that malnutrition is one of the signs to initiate dialysis, the detailed criteria for dialysis initiation remain to be investigated. Therefore, the nutritional status of CKD patients should be assessed globally from such indices as SGA, lean body mass, serum albumin, PNA, or other indices (Kalantar-Zadeh et al. 2001).

Nonetheless, the proportion of the patients who have PEW are quite high, and it can be related to subsequent worse survival (de Mutsert et al. 2008). Therefore, the nutritional management on the advanced CKD, especially those preventing PEW, is required to attain better clinical outcomes. Once the patients develop decline in nutritional status that is resistant for dietary therapy, we should start dialysis therapy properly.

1.3.3 Comorbidities

Obviously, the compelling reasons for dialysis initiations such as overhydration or congestive heart failure independent of patients' GFR worsen the prognoses afterward. Several studies have elucidated this point. A study from France investigated the association of eGFR at the initiation of dialysis with subsequent survival. The higher mortality was observed among those with higher eGFR by crude model (HR 1.40, 95%CI 1.36–1.45). However, the association was attenuated (HR 1.08, 95%CI 1.04–1.12) by adjustment for comorbidities, mobility, and nutritional status as well as age and gender. The fact indicated that age or comorbidities affected the association of higher eGFR and mortality partly but not entirely (Lassalle et al. 2010). Moreover, the frailty among CKD population comes to draw attentions. Among the incident dialysis population, the proportion of the patients with frailty was reportedly as high as 73%. The frail population significantly related to higher eGFR at dialysis initiation and poorer survival (Bao et al. 2012). These evidences remind us that the patients who started dialysis early might be forced to start early by compelling reasons due to comorbidities. To elucidate this association, Rosansky et al. investigate the effects of eGFR at initiation only among the "healthiest" population with serum albumin ≥3.5 g/dl. But they found that the association of higher eGFR and worse outcome was not changed even among such healthiest population (Rosansky et al. 2011). Another study on older population was also performed on the United States Renal Data System (USRDS) database. They investigated the association of eGFR values at initiation and subsequent survival for up to 3 years. The results indicated that higher eGFR (≥ 10 mL/min/1.73 m^2) was associated with poorer prognosis even after rigorous adjustment for patients' health status and it was consistent across subgroups (Crews et al. 2014). Therefore, comorbidities can affect the outcome but not entirely.

1.3.4 Speed of Decline of Renal Function

Recently, the rate of decline of renal function reportedly associates with the incidence of ESRD among pre-dialysis CKD population (Kovesdy et al. 2016). The rate of decline in eGFR before dialysis initiation has been reported to relate with the survival after start of dialysis therapy. O'Hare et al. investigated the trajectories of eGFR decline and subsequent clinical outcome among incident dialysis patients. They reported that steeper eGFR decline was associated with higher mortalities during the first year of dialysis and higher probabilities of hospitalization or diagnoses of AKI (O'Hare et al. 2012). Similarly, several studies demonstrated that abrupt (Hsu et al. 2016) or even faster (Browne et al. 2014; Ramspek et al. 2016) decline of eGFR was associated with higher mortality during short (Hsu et al. 2016) or longer periods (Browne et al. 2014; Ramspek et al. 2016). Interestingly, a study from NECOSAD demonstrated such relationship could only be observed with mGFR but not with eGFR (Ramspek et al. 2016). CKD is one of the major risk factors for AKI requiring dialysis (Hsu et al. 2008). Thus we can imagine that such abrupt or steeper renal function decline is related to the acute on chronic renal failure. We should pay special attentions for patients who experience faster decline of renal function to prevent vicious cycles worsening clinical outcomes.

1.3.5 Facility Characteristics

Clinical practice patterns of facilities might be associated with the timing of initiation. Margaret et al. investigated eGFR values for veterans who initiated within versus outside the Veteran Affairs (VA) medical centers. They found that the patients less likely started dialysis at eGFR ≥10.5 mL/min/1.73 m^2 within the VA medical centers compared to outside of the VA facilities (Yu et al. 2015). This observation was confirmed by another study which investigated the average eGFR at initiation of dialysis within 804 health service areas

in the United States. The study found that there was wide variety in mean eGFR values and only 11% of variation was explained by the patient characteristics (Scialla et al. 2014). On the other hand, a Canadian study investigates the proportion of the patients with eGFR of 10.5 mL/min/1.73 m^2 or more at the initiation of dialysis across the regions. They found that a large heterogeneity existed for the proportion by regions investigated. However, only 3.1% of variabilities could be attributed to the facility, while remaining 96.9% was attributed to patient factors (Sood et al. 2014).

1.3.6 Other Clinical Indicators

Many researchers have developed clinical scores that predict mortality after initiation of dialysis. For this purpose, Charlson's comorbidity index (CCI) (Charlson et al. 1987) has historically been used. However, this index was developed for the patients on admission to predict 1-year survival and was not developed for the incident dialysis population. Park et al. developed modified CCI from the Korean incident dialysis population of 24,738 patients, and they found that the index had improved predictive power of 6-month, 1-year, and 2-year survival compared to the original CCI (Park et al. 2015). Doi et al. also developed an equation to predict 1-year mortality among incident dialysis population. They found that eGFR, albumin, calcium, modified CCI, performance status, and ESA use were associated with the survival (Doi et al. 2015). These indices clearly indicate that we should pay attentions not only to the patients' laboratory data or clinical symptoms but also the comorbidities of the patients. Thereby, they provide the opportunity to improve the outcomes of the incident patients.

1.4 Published Guidelines

From the evidences above described, many guidelines have been published regarding the timing of initiation of dialysis (Table 1.3).

Table 1.3 The indications of dialysis initiation described in each guideline (National Kidney Foundation 2015; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013; Working Group Committee for Preparation of Guidelines for Peritoneal Dialysis Japanese Society for Dialysis Therapy, Japanese Society for Dialysis Therapy 2010; Watanabe et al. 2015; Tattersall et al. 2011; The CARI guidelines 2005a, 2005b; Warwick et al. 2014; Churchill et al. 1999)

		The first-line indications of dialysis	Renal function from which dialysis is indicated	Renal function for dialysis initiation without uremic symptom
NKF KDOQI	2015	Signs and/or symptoms associated with uremia Evidences of protein-energy wasting Inability to safely manage metabolic abnormalities and/or volume overload with medical therapy	Not specified	No specific GFR
KDIGO	2012	Symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus) Inability to control volume status or blood pressure Progressive deterioration in nutritional status refractory to dietary intervention Cognitive impairment	Not specified but conditions requiring dialysis initiation often but not invariably occur in the GFR range between 5 and 10 mL/min/1.73 m^2	Not specified
JSDT	2009	Signs or symptoms of uremia resistant to medical treatment	GFR < 15.0 mL/min/1.73 m^2	GFR < 6.0 mL/min/1.73 m^2

(continued)

Table 1.3 (continued)

		The first-line indications of dialysis	Renal function from which dialysis is indicated	Renal function for dialysis initiation without uremic symptom
	2013	Uremic signs and symptoms (see Table 1.1) Malnutrition Deterioration of ADL	GFR < 15.0 mL/min/1.73 m^2 Maximal pre-dialysis medication should be undertaken until GFR < 8	GFR < 2 mL/min/1.73 m^2
EBPG	2011	Symptoms or signs of uremia Inability to control hydration status or blood pressure Progressive deterioration in nutritional status	GFR <15 mL/min/1.73 m^2 (majority of the patients will be symptomatic in the range 9–6 mL/min/1.73 m^2)	No specific GFR but asymptomatic patients may benefit from a delay in starting dialysis in order to allow preparation, planning, and permanent access creation rather than using temporary access In high-risk patients or the patients who cannot be monitored uremic symptoms closely, a planned start to dialysis while still asymptomatic may be preferred
KHA-CARI	2005	Evidence of uremia or its complications such as malnutrition	GFR falls below approximately 10 mL/min/1.73 m^2 (occasionally, patients may require to initiate dialysis at a higher GFR)	GFR falls below approximately 6 mL/min/1.73 m^2
UK	2013	Careful discussion with the patient of the risks and benefits of RRT Symptoms and signs of renal failure Deterioration of nutritional status Comorbidity Functional status Physical, psychological, and social consequences of starting dialysis	CKD stage 5 (eGFR <15 mL/min/1.73 m^2)	Not specified
CSN	1999	Symptoms or signs of uremia Evidence of malnutrition nPNA < 0.8 g/kg/d or clinical malnutrition by SGA, dialysis initiation is recommended	GFR is less than 12 mL/min	GFR is less than 6 mL/min

NKF KDOQI, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guideline; *KDIGO*, Kidney Disease: Improving Global Outcomes; *JSDT*, the Japanese Society for Dialysis Therapy guidelines; *EBPG*, European Best Practice Guidelines; *KHA-CARI*, Kidney Health Australia Caring for Australasians with Renal Impairment; *UK*, the Renal Association guidelines in the United Kingdom; *CSN*, the Canadian Society of Nephrology; *GFR*, glomerular filtration rate; *ADL*, activity of daily living; *CKD*, chronic kidney disease; *RRT*, renal replacement therapy; *nPNA*, normalized protein equivalent of nitrogen appearance; *SGA*, subjective global assessment

1.4.1 NKF KDOQI Guidelines

Since 1997, the National Kidney Foundation in the United States has published guidelines periodically. The timing of initiation of dialysis therapy has been one of the most important topics of this guideline.

In the guidelines for peritoneal dialysis adequacy published in 1997, the description about the timing for initiating dialysis was included (National Kidney Foundation (NKF-DOQI) 1997). The guideline employed two parameters of renal urea clearance and normalized urea appearance, the proxy of protein intake. The

patients should be advised to initiate dialysis when the weekly renal Kt/Vurea falls below 2.0, which is equivalent to urea clearance of 7 mL/min, creatinine clearance of 9–14 mL/min/1.73 m^2, and GFR of 10.5 mL/min/1.73 m^2. Dialysis should also be started when nPNA spontaneously falls below 0.8 g/kg/day despite of intervention by a registered dietitian.

However, in 2006 the update version of hemodialysis adequacy guidelines recommended higher GFR values to consider dialysis initiation (National Kidney Foundation Kidney Disease Outcome Quality Initiative 2006). The guideline says when patients reach stage 5 CKS (eGFR <15 mL/min/1.73 m^2), nephrologist should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy. Particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5.

The current version was published in 2015 (National Kidney Foundation 2015). This version changed the description about the timing of dialysis initiation dramatically. They underscore the importance of signs and symptoms and removed the concrete value of GFR for considering dialysis initiation. The guideline says: The decision to initiate maintenance dialysis should be based primarily upon an assessment of signs and/or symptoms associated with uremia, evidences of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy rather than on a specific level of kidney function in the absence of such signs and symptoms. The rationale for this recommendation emphasized two points. One is that dialysis initiation should not base solely on measurements of kidney function especially in asymptomatic patients. The other is that dialysis initiation should not be denied to patients with signs or symptoms which can be managed by dialysis, simply because the GFR is considered too high.

1.4.2 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline

Kidney Disease: Improving Global Outcomes (KDIGO) published CKD guideline in 2013 (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). The guideline describes the timing of renal replacement therapy (RRT) initiation. This guideline was also made after the results of IDEAL study were published. Therefore, the appearance of signs or symptoms was emphasized. It says that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, and pruritus), inability to control volume status or blood pressure, a progressive deterioration in nutritional status refractory to dietary intervention, or cognitive impairment. The guideline only mentions GFR by saying that these conditions often but not invariably occur in the GFR range between 5 and 10 mL/min/1.73 m^2.

1.4.3 Japanese Guidelines

Historically, in 1972 the Ministry of Health and Welfare in Japan started covering dialysis therapy by healthcare insurance. At that time, the committee in the Ministry determined criteria for dialysis therapy. The criteria determined that dialysis therapy is indicated when uremic symptoms are refractory for medical treatments and deteriorate patients' daily activities. The concrete indices included clinical symptoms (oliguria or nocturnal polyuria, insomnia and/or headache, nausea and/or vomiting, renal anemia, severe hypertension, and hypervolemia), decreased renal function (i.e., creatinine clearance $\leq$10 mL/min or serum creatinine $\geq$8 mg/dl), and deterioration in daily activities. Thereafter the criteria have been used for 20 years. However, the changes in patients' characteristics required the revision of these criteria.

Therefore, a committee for the Ministry of Health and Welfare was organized, and the committee made a new guideline in 1991 (Kawaguchi and Mimura 1991). The guideline was based on the previous criteria and adopts a scoring system shown in Table 1.4. The patients who are diabetic, old, or young were considered to have higher priority for initiating dialysis treatment. The validity of this guideline was confirmed by the committee itself and also by the data from JRDR later. The guideline had been widely used in considering dialysis

Table 1.4 The scoring system adopted in the Japanese guideline in 1991

Factors	Scores
1. Uremic signs and symptoms	
Numbers of observed signs and/or symptoms listed in Table 1.1	
≥ 3	30
2	20
1	10
2. Renal function	
Serum creatinine [mg/dl] (creatinine clearance [mL/min])	
≥ 8 (<10)	30
≥ 5, <8 (≥10, <20)	20
≥ 3, <5 (≥20, <30)	10
3. Disturbance of activities in daily living	
Bedridden due to uremic symptoms	30
Severely disturbed	20
Moderately disturbed and find difficulties in commuting, schooling, or daily works	10
4. Younger (<10 years old), older (≥ 65 years old), or with systemic vasculitis	10

When the summations of each score become 60 or more, the dialysis initiation is considered. Adapted from Kawaguchi and Mimura (1991)

initiation as well as the qualification for beneficiary of medical care for persons with disability.

In 2009 the Japanese Society for Dialysis Therapy (JSDT) published a guideline concerning peritoneal dialysis (the English version was published in 2010) (Working Group Committee for Preparation of Guidelines for Peritoneal Dialysis Japanese Society for Dialysis Therapy, Japanese Society for Dialysis Therapy 2010). In the guideline, they stated the timing of peritoneal dialysis initiation. Initiation of dialysis must be considered in patients with stage 5 CKD (GFR < 15.0 mL/min/1.73 m^2) if they have signs or symptoms of uremia resistant to medical treatment. And also, initiation of dialysis is recommended before GFR reaches 6.0 mL/min/1.73 m^2. This guideline sets higher eGFR target to initiate dialysis, because it was made before publication of the results of IDEAL study, and PD requires more residual renal function than HD does.

As for hemodialysis initiation, another committee was formed within JSDT and published a new guideline on hemodialysis initiation. The Japanese version was published in 2013 and the English version was published in 2015 (Watanabe et al. 2015). This guideline has several specific points. First, the renal function was recommended to be assessed by GFR instead of creatinine values. Second, considerations about signs and symptoms, malnutrition, and deterioration of ADL were emphasized. Third, the GFR values at which consider the dialysis initiation were set 15, 8, and 2. The GFR of 15 mL/min/1.73 m^2 is the value from which dialysis becomes an option of therapies for ESRD. The GFR of 8 mL/min/1.73 m^2 is the value above which the prognosis of the patient is considered worse and until which dialysis therapy might be deferred, if no compelling indications. The GFR of 2 mL/min/1.73 m^2 is the value for initiation of dialysis treatment even if the patients without any uremic symptoms. Forth, the importance of early referral, proper timing of access creation, and comprehensive pre-dialysis management was emphasized. The guideline indicated the flow of consideration about dialysis initiation (Fig. 1.1).

1.4.4 European Best Practice Guidelines (EBPG)

In 2002, the previous version of European Best Practice Guideline (EBPG) was published (European Best Practice Guidelines Expert Group on Hemodialysis ERA 2002). This version told that dialysis should be instituted whenever the GFR is <15 mL/min and there is one or more of the following: symptoms or signs of uremia, inability to control hydration status or blood pressure, or a progressive deterioration in nutritional status. In any case, dialysis should be started before the GFR has fallen to 6 mL/min/1.73 m^2, even without symptoms.

In 2011, the update version after IDEAL study was published (Tattersall et al. 2011). The recommendations in 2002 were not significantly changed, but the absolute eGFR value of 6 mL/min/1.73 m^2 at which dialysis therapy should start was made vaguer. The guideline tells as follows—in patients with a GFR <15 mL/min/1.73 m^2, dialysis should be considered when there is one or more of the following: symptoms or signs of uremia, inability to control hydration status or blood

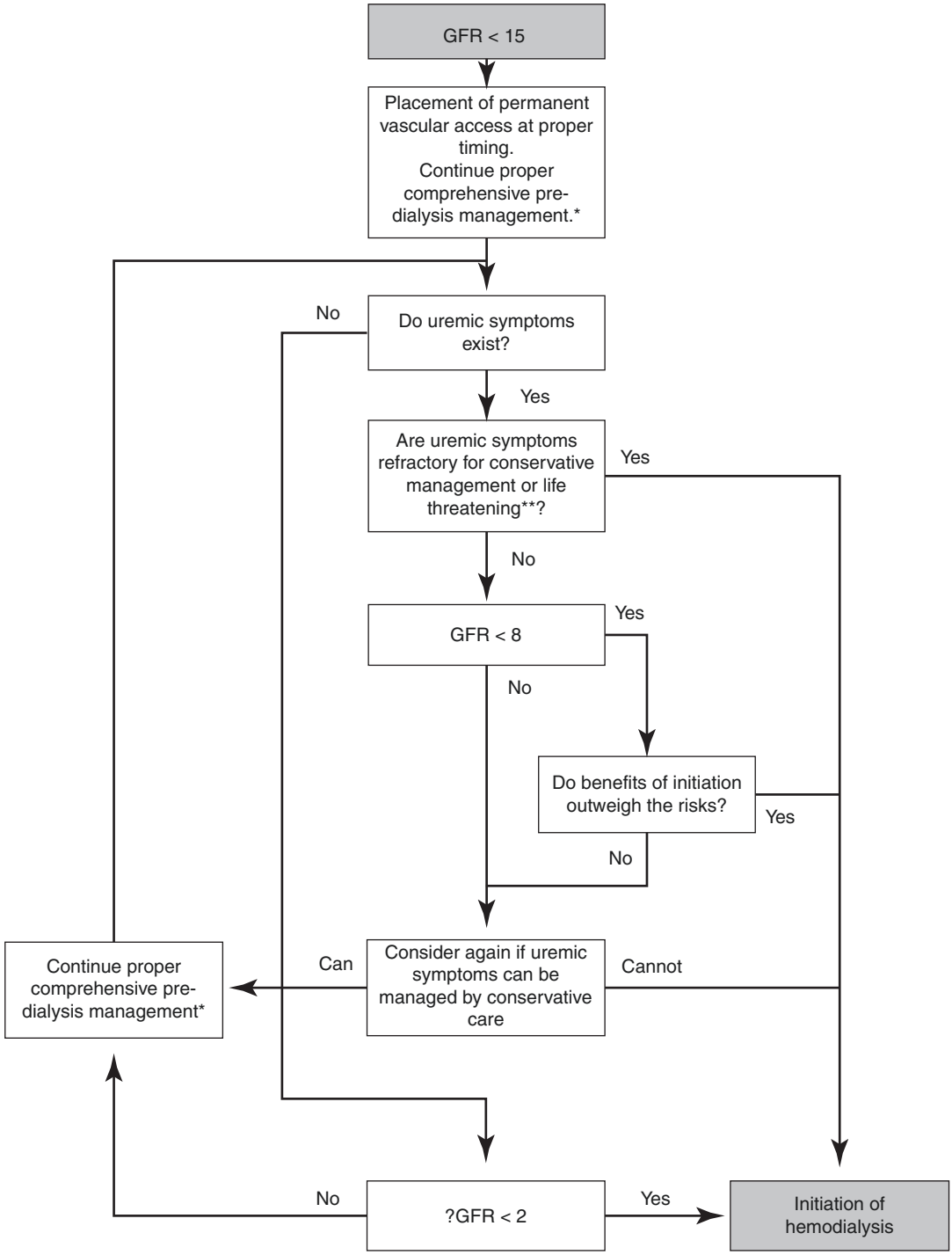

Fig. 1.1 Flow of considering the indication of dialysis initiation described in JSDT guideline in 2013. When the GFR falls below 15 mL/min/1.73 m^2, the option of dialysis can be considered. However, comprehensive pre-dialysis management should be undertaken as long as possible, unless uremic symptoms are refractory for conservative management or life-threatening. Once GFR falls below 8 mL/min/1.73 m^2, initiation of dialysis is considered, when the benefits of initiation outweigh the risks or uremic symptoms cannot be managed conservatively. When GFR falls below 2 mL/min/1.73 m^2, even if the patient is asymptomatic, dialysis should be initiated. Abbreviation: GFR, glomerular filtration rate. Adopted from reference (Watanabe et al. 2015)

pressure, or a progressive deterioration in nutritional status (majority of the patients will be symptomatic in the range 9–6 mL/min/1.73 m^2). In high-risk patients, e.g., diabetics and those whose renal function is deteriorating more rapidly than eGFR 4 mL/min/year, a planned start to dialysis while still asymptomatic may be preferred, if close monitoring is not feasible or if uremic symptoms may be difficult to be detected. Asymptomatic patients presenting with advanced CKD may benefit from a delay in starting dialysis in order to allow preparation, planning, and permanent access creation rather than using temporary access.

1.4.5 Kidney Health Australia Caring for Australasians with Renal Impairment (KHA-CARI Guidelines) (Australia)

Kidney Health Australia Caring for Australasians with Renal Impairment (KHA-CARI) Guidelines also have been published for wide ranges of kidney diseases. The guidelines for dialysis initiation, "Level of renal function at which to initiate dialysis" (The CARI Guidelines 2005b) and "Other criteria for starting dialysis" (The CARI guidelines 2005a), were published online in 2005. In these guidelines, the timing of starting dialysis therapy was recommended both from the GFR levels and signs or symptoms relating uremia.

As for the renal function (The CARI Guidelines 2005b), they set two GFR levels. One is 10 mL/min/1.73 m^2. The patients are commenced dialysis when GFR falls below approximately 10 mL/min/1.73 m^2, if there is evidence of uremia or its complications such as malnutrition. Occasionally, patients may require to initiate dialysis at a higher GFR. The other is 6 mL/min/1.73 m^2. Even if there is no evidence of uremia or its complications including malnutrition, the patients are commenced dialysis when GFR falls below approximately 6 mL/min/1.73 m^2.

As for the signs and symptoms (The CARI guidelines 2005a), the stress was placed on the presence of malnutrition, which is suspected due to uremia and is not responsive to dietary intervention or correction of other reversible causes. The patients are commenced dialysis at first indication of such malnutrition. On the other hand, the existence or appearance of "absolute indications," described below is no longer valid for indications for dialysis initiation, and their presence suggests delayed initiation. In this case, the absolute indicators are pericarditis, fluid overload, and hypertension poorly responsive to non-dialytic treatment, hyperkalemia, acidosis, advanced uremic encephalopathy and/or neuropathy, significant bleeding diathesis, severe nausea, and vomiting. Similarly, traditional "relative indications" may not be useful, because they are largely subjective and may be due to intercurrent diseases. These relative indicators include anorexia, profound fatigue and weakness, impaired cognition, memory and attention span, severe pruritus, depression, and poor interpersonal relationship.

1.4.6 United Kingdom (The Renal Association)

The Renal Association in the United Kingdom has periodically published the guidelines concerning CKD or ESRD. The current version of the guideline about dialysis initiation, "Planning, initiation & withdrawal of Renal Replacement Therapy," was published online in 2014 (Warwick et al. 2014). This guideline covers wide-range of the field including education or referral to nephrologists, initiating RRT, and withdrawal.

In the section about initiation, the guideline recommends that the decision to start RRT in patients with CKD stage 5 (eGFR <15 mL/min/1.73 m^2) should be based on a careful discussion with the patient of the risks and benefits of RRT taking into account the patient's symptoms and signs of renal failure, nutritional status, comorbidity, functional status, and the physical, psychological, and social consequences of starting dialysis in that individual.

Moreover, the guideline underscores RRT starts in a controlled manner, with established permanent access and without hospitalization. Thus, CKD stage 4–5 patients or CKD stage 3 with rapid progression should be referred to a

nephrologist. And most patients with eGFR <30 mL/min/1.73 m^2 and declining should receive timely and personalized information about RRT options. All patients with severe CKD (stage 5 and progressive stage 4) should be offered an education program about CKD and ESRD options with their families or carers. Such multistep approaches are intended for appropriate dialysis initiation.

1.4.7 The Canadian Society of Nephrology

Canadian Society of Nephrology also published the guideline about dialysis initiation, although it was published in 1999 (Churchill et al. 1999). The guideline recommended that symptoms or signs of uremia or evidence of malnutrition should be investigated, when the GFR is less than 12 mL/min. If there is evidence of uremia or if the PNA is less than 0.8 g/kg/d or if there is clinical malnutrition determined by SGA, dialysis initiation is recommended. When the GFR is less than 6 mL/min, dialysis initiation is recommended without symptoms. Above all, the guideline described that all decisions should be based on discussion of the biochemical and nutritional data with the patient and family with the social impact of the decisions into account.

1.5 Pre-dialysis Care

The significance of pre-dialysis care, especially by multidisciplinary team, has been demonstrated. An Italian study investigated the efficacy of these multidisciplinary teams of doctor, nurse, and dietician on the CKD stage 5 patients. Patients' age was the median of 72 years old, 19% of the population was diabetic, and eGFR was 9.5 mL/min/1.73 m^2 at baseline. Among them 62% of the population started dialysis at their eGFR of 6.1 ± 1.9 mL/min/1.73 m^2 after 13.9 ± 15.6 months. Moreover, the patients with eGFR lower than median (5.7 mL/min/1.73 m^2) experienced better survival after initiation (Dattolo et al. 2015). Such multidisciplinary care also reportedly reduces the medical costs during the first 6 months of dialysis (Yu et al. 2014). Another study demonstrated that dietitian care more than 12 months before initiation of dialysis was associated with better 1-year survival after start of dialysis (Slinin et al. 2011).

As well as the timing of dialysis initiation itself, the timing when the patients were referred to nephrologist is also important for the prognosis after start of dialysis.

Many studies have investigated the timing of referral and subsequent clinical outcomes by comparing two groups, i.e., early referral and late referral groups. Most of them studied the timings in terms of survival after initiation of dialysis, while some others also investigated other comorbidities such as infection, hospitalization, or anemia management. In general, early referral was shown to be associated with better clinical outcomes. However, most importantly, the definitions of early and late referral were diverse, and conclusive timing of early referral might be difficult to be made.

Hasegawa et al. investigated the frequency, and the timing of pre-dialysis nephrology visits was associated with the 1-year survival after dialysis initiation. The patients who had more chance to receive nephrology clinics experienced better survival thereafter (Hasegawa et al. 2009).

Other meta-analysis investigated the timing of referral and its consequences on clinical outcomes including 63,887 patients from 40 cohort studies. The study found that early referral was significantly associated with reduced 3-month mortality, hospitalization periods, and catheter use for vascular access. Improved blood pressure control and higher proportion of ESA use were found in the early referral group (Smart et al. 2014).

What makes the early referral better in clinical outcomes? Mendelssohn et al. investigated this point. They studied the relationship between the timing of referral and survival by the groups with or without vascular access at the initiation of dialysis therapy. They found that the patients with vascular access and referred early exhibited the best survival, while the patients referred early but without vascular access demonstrated similar survival to the patients who were

referred late (Mendelssohn et al. 2011). Another study indicated the efficacy of predialysis education program. The program includes explanations of RRT, preparation of access placement, and referral to surgeons who will create an access. The patients who received such program experienced higher rate of existence of vascular access and better 90-day survival after initiation of dialysis treatment (Lacson et al. 2011). The fact indicated that the advantage of early referral might derive from the early creation of vascular access and avoidance of temporary vascular access which may relate to worse outcomes.

However, there are several barriers for these appropriate early referral or optimal dialysis initiation. From England National Health Service database, an important finding was obtained. In the study, the late referral was defined as referral to nephrologist less than 90 days prior to the initiation of dialysis, and the proportion of such patients was high and about 34% of total population. Moreover, 49% of those who were referred late experienced some medical contacts log before the referral. Thus appropriate monitoring renal function at such occasions might have led to the referral at more appropriate timing (Blunt et al. 2015). Another issue is suboptimal initiation of dialysis might occur after referral to the nephrologists. Hugh et al. demonstrated that 56.4% of patients started dialysis suboptimally, and 65% of them were not attempted to create permanent vascular access before initiation even among the patients who referred to nephrologist for more than 12 months (Hughes et al. 2013). Similarly, Al-Jaishi et al. demonstrated that only 39% of non-late referral (nephrologist referral ≥3 months of initiation) patients had been created permanent access before dialysis initiation (Al-Jaishi et al. 2015). The former study investigated the reasons for these delays. It demonstrated that the reasons were patient-related delays 31%, acute on CKD 31%, surgical delay 16%, and late decision-making 11% (Hughes et al. 2013). We should be aware of these factors among early referral patients and make sure to take a proper pathway to dialysis initiation.

1.5.1 Vascular Access Existence of Initiation of Dialysis

Above mentioned, proper permanent vascular access placement relates to better survival after initiation of dialysis treatment not only in shorter period of time (Chesser and Baker 1999) but also in longer period of time (Lorenzo et al. 2004). The former study demonstrated the existence of permanent vascular access related to better survival during 90 days after initiation of dialysis treatment (Chesser and Baker 1999), while the latter indicated that patients with arteriovenous fistula exhibited better outcome of 1 and 2-year survival after dialysis initiation (Lorenzo et al. 2004). Such relationship does not only apply to the younger generation. Kawanishi et al. demonstrated that catheter use was more prevalent among the older population. Even such older population as ≥70 years old experienced worse adverse outcome compared to arteriovenous fistula (AVF) or arteriovenous graft (AVG) (Kawanishi et al. 2015). Besides clinical outcomes, economic benefits are also demonstrated. The patients who were created vascular access after dialysis initiation experienced higher medical costs and longer hospitalization periods than those with vascular access at the time of initiation (Wu et al. 2009).

A recent study demonstrated an interesting result that the patients with advance CKD who were created vascular access experienced slower decline of renal functions (Sumida et al. 2016). The authors concluded that such favorable effects may be due to patients' improved adherence, intensified nephrologist care, or other physiological mechanism to be investigated. On the other hand, there is a conflicting result that the patients who created vascular access during stage 4 of CKD exhibited the worse survival compared to others (Hiremath et al. 2011).

DOPPS data investigated the timing of first cannulation of vascular access after creation from the view point of subsequent access survival (Rayner et al. 2003). The study indicated that the incidence of access failure was significantly higher, if the first cannulation was made within 14 days after creation. Recently, Hod et al. investigated the time period from creation of AVF to

dialysis initiation retrospectively among older patients in USRDS database. They found that the AVF success rate (dialysis initiation with AVF initially placed) increased with the periods longer. They concluded that dialysis initiation at 6–9 months after creation of AVF experienced the highest AVF success rate, although the mean number of procedures for access intervention per patients became also higher at this time (Oliver et al. 2012).

Above all, the timely placement of proper vascular access requires adequate pre-dialysis nephrologist care.

1.6 Post-dialysis Initiation Management

1.6.1 Early Mortality

Several studies have demonstrated that the early mortality is high among dialysis population. Chan et al. investigated the mortality and hospitalization during the first 90 days of dialysis among more than 300,000 incident patients in the United States (Chan et al. 2011). They found that the relative risks of death and hospitalization during the first 2 weeks were 2.72 (95%CI 2.50–2.94) and 1.95 (95%CI 1.92–2.01), respectively, compared to those of the patients who survived the first 1 year. Age (>65 years old), catheter use for vascular access, higher comorbid conditions, and lower serum albumin were major factors that related with higher mortality within the first 2 weeks. DOPPS demonstrated that the mortality soon after initiation up to 120 days was high, especially among older (≥ 65 years old) patients (Robinson et al. 2014). Similar results were obtained from other studies (Saggi et al. 2012; Lukowsky et al. 2012). One of them indicated that inadequate preparation of the patients for dialysis treatment was related to higher mortality during these transitional periods (Saggi et al. 2012). Therefore, the early referral to nephrologists and proper pre-dialysis care with multidisciplinary teams are again warranted to improve the early survival among the dialysis patients.

1.6.2 Importance of Pre-dialytic Care and Conservative Management

The numbers of older dialysis patients are rapidly growing especially in developed countries. It is often possible that these patients cannot enjoy the survival benefits from initiation of dialysis treatment. Therefore, conservative management for far advanced CKD has become the topics of debate recently. Several studies compared the survival between conservative management and dialysis initiation and found that the patients with very elderly (usually more than 80 years old) and/or with many comorbidities experience comparable survival between these two therapies (Williams 2012; Verberne et al. 2016). A meta-analysis compared these two modalities on 13 studies (O'Connor and Kumar 2012). They found that even the patients who were implemented conservative management survived at least 6 months (range 6.3 to 23.4 months). Although the survival benefit of dialysis decreased with comorbidities, the patients managed conservatively experienced a high symptom burden to require further palliative cares (O'Connor and Kumar 2012).

For more practical approach, the delay of initiation of dialysis treatment with multidisciplinary teams and close monitoring, especially appropriate dietary therapies, have been proposed. Brunori et al. from Italy demonstrated importance of pre-dialysis nephrology care on advanced CKD patients. They recruited old CKD patients (more than 70 years old) without dialysis, and their eGFRs were between 5 and 7 mL/min/1.73 m^2. They allocated the patients into two groups; one received dialysis therapy soon after allocation, while the other received intensive pre-dialysis care including very low-protein diet with supplementation of keto acids and essential amino acids. The patients allocated the dietary management group could defer their dialysis treatment by the median period of 10.7 months. Moreover, the survival between the two groups was comparable, and the dietary group exhibited even better survival by per protocol analysis after adjustment of baseline unbalances (Brunori et al.

2007). This result indicates the possibility that pre-dialysis care for far advanced CKD patients provided with supplemented very low-protein diet and close monitoring could safely retard dialysis initiation. Thus the patients can enjoy the period free from dialysis treatment and can receive moratorium during which preparation for dialysis treatment can be made such as proper access creation or selection of the most appropriate modality.

1.6.3 Incremental Dialysis

We discussed the timing of dialysis initiation above and the controversy on it. A concept has been proposed since late 1990s about gradual increase in dialysis dose after initiation of dialysis. At first, this method was applied to peritoneal dialysis patients who had still enough residual renal function and did not require full dose of peritoneal dialysis (Burkart 1998; Golper 1998). It is described that advantages of this approach were reduced medical costs, glucose exposure, protein loss, membrane fatigue, and greater patient acceptance. However, the close monitoring of residual renal function, frequent prescription changes, potentially reduced removal of middle molecules, and uncertainty about clinical outcomes were considered its disadvantages (The CARI guidelines 2005c).

On the other hand, the efficacy of less frequent hemodialysis at the initiation on the patients with sufficient residual renal functions has been investigated. Recently, Obi et al. demonstrated the association of twice-weekly hemodialysis and preservation of residual renal function (Obi et al. 2016). Many studies have demonstrated that preservation of residual renal function related to better survival among hemodialysis patients (Wang and Lai 2006; Vilar et al. 2009) as well as peritoneal dialysis patients (Shemin et al. 2000; Termorshuizen et al. 2003). Another investigator group also demonstrated the similar results. They combined incremental dialysis and supplemented very low-protein diet and found that the patients who received such incremental dialysis therapy experienced better preservation of residual renal function, reduced accumulation of uremic solute, and less hospitalization compared to the patients in control group (Caria et al. 2014). Therefore, incremental hemodialysis for the incident hemodialysis patients at lower frequency might potentially offer clinical benefits. However, no randomized control trials have been performed to compare incremental dialysis and conventional thrice-weekly hemodialysis treatment. Therefore, there remains the possibility of selection or survival biases that patients with much residual renal function remained incremental dialysis. Kalantar-zadeh et al. publicized and proposed criteria for incremental dialysis (Table 1.5) (Kalantar-Zadeh et al. 2014). Above all, future randomized control trials are required to compare incremental dialysis with or without dietary protein restriction and conventional thrice-weekly hemodialysis in terms of hard outcomes such as survival or cause-specific mortality as well as preservation of residual renal function. The results will provide concrete evidences about such infrequent hemodialysis at the initiation.

Table 1.5 Treatment criteria for twice-weekly HD

1.	Good RKF with urine output >0.5 L/d
2.	Limited fluid retention between two consecutive HD treatments with fluid gain <2.5 kg (or <5% of ideal dry weight) without HD for 3–4 d
3.	Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant fluid overload
4.	Suitable body size relative to RKF; patients with larger body size may be suitable for 2x/wk. HD if not hypercatabolic
5.	Hyperkalemia (K > 5.5 mEq/L) is infrequent or readily manageable
6.	Hyperphosphatemia (P > 5.5 mg/dL) is infrequent or readily manageable
7.	Good nutritional status without florid hypercatabolic state
8.	Lack of profound anemia (Hb > 8 g/dL) and appropriate responsiveness to anemia therapy
9.	Infrequent hospitalization and easily manageable comorbid conditions
10.	Satisfactory health-related quality of life

Lack of systolic dysfunction (ejection fraction >40%) and no major coronary intervention over the previous 3 months. *Hb* hemoglobin, *HD* hemodialysis, *K* potassium, *P* phosphorus, *RKF* residual kidney function

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Modality Selection

2

Sun-Hee Park

2.1 Introduction

The incidence and prevalence of chronic kidney diseases (CKD) are increasing worldwide because of population aging, increasing life expectancy, and the increased prevalence of diabetes mellitus (Coresh et al. 2007). The global CKD prevalence in the general population is estimated to be 11–13% on the basis of observational studies (Hill et al. 2016). When CKD progresses to end-stage renal disease (ESRD), the failing kidney requires functional replacement, and the so-called renal replacement therapy (RRT) is needed to ensure patient survival. Three RRT options are available at present: transplantation, hemodialysis (HD), and peritoneal dialysis (PD). However, the choice of transplantation for RRT is affected by other factors such as availability of a living donor and cultural beliefs. Thus, the choice is usually one of the two dialysis modalities, which have been compared in this chapter.

The global population undergoing dialysis is continuously increasing, and over two million people worldwide receive dialysis or kidney transplants at the end of 2010 (Couser et al. 2011). The percentage increase in the prevalence of dialysis between 2000 and 2013 is the highest in Thailand (839.3%) and the lowest in Sweden (28.5%) (Saran et al. 2016). In general, HD is used more commonly than PD. In-center HD remains the most common type of RRT in most countries, accounting for 78–97% of dialysis modalities used for ESRD. However, the ratio of HD to PD varies considerably among countries (Lameire and Van Biesen 2010). The variable penetration of each dialysis modality is attributed not only to the medical condition of the patients but also to the resources and demand for dialysis or reimbursement policy, both of which differ substantially in various healthcare systems. The proportion of patients on PD is increasing in developing countries but not in developed countries (Jain et al. 2012). The use of PD is the highest in Hong Kong (72%), while the use of home HD is the highest in Australia and New Zealand (9.3% and 18.4% in 2013, respectively) (Saran et al. 2016). This is because in some countries, healthcare policies support the use of PD or home HD, for example, the "PD-first policy" in Hong Kong and the "Home dialysis-first" policy in Australia and New Zealand (Liu et al. 2015). Dialysis therapy consumes a large proportion of the health budget, and the reimbursement policy varies widely among countries (Vanholder et al. 2012, 2016). Although the cost of dialysis therapy varies across countries, PD is usually less expensive than HD (Klarenbach et al. 2014).

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Thus, healthcare policy or budget and the reimbursement policies in each country strongly affect modality selection.

It is commonly accepted that before they develop ESRD, patients with advanced CKD should be thoroughly educated about RRT modalities in order to minimize complications that may occur in the case of emergency initiation of dialysis or to maximize the treatment outcomes. They need to be informed about the benefits and risks of each modality to determine which RRT option is appropriate for them. Pre-dialysis care, timely education, and preparation for dialysis are the central aspects for improving outcomes, as they are associated with reduced need for hospitalization, reduced use of central venous catheters, and a higher proportion of starting home dialysis (Bargman 2015).

In this chapter, we will describe (1) the current options for dialysis therapies for patients with ESRD, along with a comparison of survival outcomes between HD and PD; (2) the factors that influence the choice of dialysis modality in ESRD patients and medical or socioeconomic eligibility for a specific dialysis modality; (3) selection of the dialysis modality and outcomes in special subgroups of patients, particularly the elderly and patients with diabetes mellitus; and (4) the value of decision-making aids for the selection of dialysis modality.

2.2 Current Options, Characteristics of Dialysis Modalities, and Clinical Outcomes

2.2.1 Types and Characteristics of Dialysis Modalities

Many ESRD patients are treated with either HD or PD. The characteristics of the dialysis modality differ according to the setting where the dialysis takes place, the frequency of dialysis per week, the session duration, and the equipment needed. In-center HD, usually performed thrice a week and typically lasting 3–5 h, is the most prevalent type of dialysis for ESRD patients. Other HD modes, such as in-center nocturnal HD or short daily HD, are also available in some countries. Frequent HD or extended-duration HD such as nocturnal HD can be performed at home. Short daily HD is typically performed 5–6 days per week, with each session lasting 2–3 h depending on body size and equipment. Nocturnal HD is usually performed 5–7 days per week for 6–10 h depending on patients' sleep patterns. For continuous ambulatory peritoneal dialysis (CAPD), manual exchanges are done approximately four times daily, with each exchange lasting about 30 min. In automated PD, the patients use a machine to perform the exchanges at night for about 8–10 h as they sleep while on the machine, and it provides greater daytime freedom compared to CAPD. The dialysis modalities and their characteristics are presented in Table 2.1.

HD and PD have different profiles of advantages or disadvantages (Table 2.2). HD depends on machines to remove uremic toxins and fluid and has a higher efficiency profile than that of PD. Because creating vascular access is essential for HD, this modality may not be useful for patients with severe atherosclerosis or poor vascular condition. In addition, anticoagulation therapy is needed during the extracorporeal circulation in dialysis, and patients may experience uncontrolled bleeding. For in-center HD, patients or family members do not need to participate in the delivery of HD, so it is appropriate for patients who are dependent on physicians or those lacking a support system. However, transportation to a hospital or HD center is needed for in-center HD. In addition, it is easier to monitor adherence with treatment, for example, injection of parenteral erythropoietin. However, the schedules are usually inflexible, and traveling to the place of dialysis is sometimes difficult. Some patients receiving in-center HD suffer from post-dialysis fatigue and exhaustion and feel difficulties in working on HD days. Moreover, myocardial stunning occurs during dialysis with aggressive ultrafiltration (Nie et al. 2016). In contrast, vascular access or anticoagulation therapy is not needed with PD, and the "lost time" to starting dialysis after catheter placement is less compared to that for HD, for which needs several weeks of maturation time for vascular access. PD has a lower risk

Table 2.1 Types of dialysis and typical characteristics of each dialysis modality

	In-center HD or home HD			PD	
	CHD (mainly in-center)	SDHD	NHD	CAPD	APD
Location	At a hospital/ satellite dialysis unit	At a hospital/ satellite dialysis unit or home	At a hospital/ satellite dialysis unit or home	Home or work, but any clean place possible	Home, but any clean place possible
Typical number of session per week	3	5–7	5–7	Every day	Every day
Typical number of session per day	1	1	1	4–5	1
Typical length of sessions (hours)	4	1.5–3	6–8 (modifiable as prescription)	4–6 (modifiable as prescription)	8–10 (modifiable as prescription)
Operating person	Staff at a hospital	Staff at a hospital or trained patient/ family	Staff at a hospital or trained patient/ family	Trained patient or family member	Trained patient or family member
Necessity	A traditional dialysis machine and dialysate	A traditional dialysis machine and dialysate or portable dialysis machine	A traditional dialysis machine and dialysate or portable dialysis machine	Dialysis fluid	A machine and dialysis fluid
Access	Any vascular access (catheter, AVF, or AVG)	Any vascular access (catheter, AVF, or AVG)	Any vascular access (catheter, AVF, or AVG)	Peritoneal catheter	Peritoneal catheter

CHD conventional hemodialysis, *SDHD* short daily hemodialysis, *NHD* nocturnal hemodialysis, *CAPD* continuous ambulatory peritoneal dialysis, *APD* automated peritoneal dialysis, *AVF* arteriovenous fistula, *AVG* arteriovenous graft

of bacteremia due to its characters of "needleless," and PD has a better hemodynamic stability. PD usually preserves residual renal function better than HD does, and it can be used as a bridge to transplantation (Moist et al. 2000; Sezer et al. 2011). In addition, PD is originally a "home therapy" and provides more flexible schedules and more independence. Therefore, PD is more attractive for patients who want to keep working or studying or for those who have children at home. However, the efficacy of PD for removing uremic toxins and fluids is lower than that of HD, especially in patients with large body size or lower peritoneal membrane transport characteristics. In addition, it is not possible to precisely predict the peritoneal ultrafiltration volume in PD. Further, the clinical challenges of PD include complications such as peritonitis, catheter-related mechanical complications, and metabolic complications such as weight gain, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. Lastly, patients on PD have no "off days," which can be exhausting for both patients and family members.

2.2.2 Comparison of Survival Outcomes by Dialysis Modality

While selecting a dialysis modality, patients want to determine the most ideal or appropriate options for RRT that could enhance their survival by quantity as well as quality. Since current data on the survival of dialysis patients are limited by study design or heterogeneity, it is not easy for individual patients to make a scientific decision on the basis of the survival outcomes reported in the literatures (Choi et al. 2013a).

Table 2.2 Advantages and disadvantages of hemodialysis and peritoneal dialysis

	Advantages	Disadvantages
Hemodialysis[a]	Higher efficiency in uremic toxin and fluid removal	Dependent on the machine
		Anticoagulation and increased risk of bleeding
	Better monitoring of adherence with treatments	Inflexible schedules
		Transportation to a dialysis center
		Post-dialysis fatigue or exhaustion
Peritoneal dialysis	No vascular access	Lower efficiency in uremic toxin and fluid removal[b]
	No anticoagulation	
	Better hemodynamic stability	Difficult prediction of precise ultrafiltration volume
	Flexible schedules	
	Better preservation of residual renal function	Metabolic complication of glucose-based peritoneal fluid
		Exhaustion due to no "off-day"
	More independence	Room for supplies

[a]Hemodialysis: in-center HD
[b]In patients with large body surface area or lower peritoneal transport characteristics

Randomized controlled trials (RCTs) are the most ideal study design to compare clinical outcomes by dialysis modality. However, in real clinical practice, it is difficult to perform RCTs focusing on modality selection. The one RCT published thus far had to be terminated prematurely because over 90% of eligible patients did not agree to randomization (Korevaar et al. 2003). Educated or informed patients usually have their own preferences regarding dialysis modality, and random allocation that goes against these preferences is a significant challenge to RCTs. Another RCT was completed in China, but the results have not been reported yet (ClinicalTrials.gov identifier: NCT01413074). Because of the many obstacles in RCTs, observational cohort studies were used instead to compare clinical outcomes by dialysis modality. However, the survival data obtained through observational studies have several limitations, including population heterogeneity, selection bias, and discordance in the method of adjustment for various measured or unmeasured confounding factors (Merchant et al. 2015). In observational studies, statistical techniques can be used to adjust for differences in patient characteristics or comorbidity profiles between groups. In particular, the recent application of more sophisticated statistical matching techniques, such as propensity score matching or marginal structural models, has enabled comparison of clinical outcomes by dialysis modality in a more scientific manner with observational studies (Austin 2009; Suarez et al. 2011).

Observational cohort studies using national registry-based data have shown inconsistent results. For example, some studies found no differences in mortality risk between PD and HD by using the US Renal Data System (USRDS) data (20) or Canadian dialysis population data (21), while the study conducted with data from a Danish registry showed consistent survival advantages of PD over HD (Heaf and Wehberg 2014). This discrepancy is partly attributed to selection bias or differences in patient characteristics and/or the degree of adjustments. In addition, whether or not these data exclude data of the first 90 days of dialysis could also affect the results. The survival advantage of PD over HD observed from day 0 data was no longer observed on analysis of data from 90 days after initiation (Quinn et al. 2011), and it has been proposed that acutely ill patients might be disproportionately included to HD in that case. Along the same lines, the initial survival advantage of PD over HD is associated with the higher risk of central venous catheter for HD in the initial period (Perl et al. 2011). The type of vascular access could thus be an important component of the association between modality and survival.

A study using marginal structural model analysis showed that the earlier survival advantage of PD relative to HD for 24 months is independent of known confounders (Lukowsky et al. 2013).

Further, a recent analysis of Australia and New Zealand Dialysis and Transplant (ANZDATA) registry data found that the crossover point of survival between PD and HD was nearly 1 year after the initiation of dialysis: up to 1 year from the start of dialysis, PD had a survival advantage over HD, but its mortality risk was higher than that of HD after 1 year (McDonald et al. 2009). From the same registry with dialysis patients on various dialysis modalities including facility HD and home HD and PD, a survival advantage of home HD was observed. In the same report, adjusted mortality of PD overall was significantly higher compared to facility HD, while mortality of PD was significantly lower until 12 months of follow-up (Marshall et al. 2011). A national prospective cohort study in Korea has consistently shown earlier survival advantage of PD over HD (Choi et al. 2013b), but in this case, the survival advantage persists until 42 months after dialysis initiation from day 90 after initiation (Jung et al. 2015).

The survival outcomes from these cohort studies vary by subgroup. Age, presence of diabetes, and comorbidities, particularly cardiovascular disease (CVD), influence the effect of dialysis modality on survival: younger, nondiabetic patients with no additional comorbidities had a lower risk of death with PD than with HD, but older patients with diabetes had a higher risk of death with PD than with HD (Mehrotra et al. 2011; McDonald et al. 2009).

In addition, in a more contemporary cohort, some changes in relative mortality risk were observed between HD and PD (Mehrotra et al. 2011). Data from the USRDS show that the survival trend is similar between patients starting dialysis with PD or HD. A similar result from Canadian cohort has demonstrated that the survival difference between PD and HD was decreased in a recent dialysis cohort using stratified analysis by dialysis initiation period (Yeates et al. 2012). In addition, improvement of outcomes has been founded in subgroup of patients; the attenuated risk of death in the older diabetic patients was compared to the earlier cohorts (Mehrotra et al. 2011; Heaf and Wehberg 2014).

A summary of the outcomes of recent studies comparing survival between HD and PD is presented in Fig. 2.1. Overall, despite the initial survival advantage of PD over HD, the long-term survival rate is similar between these modalities. Therefore, survival rate cannot be used as a parameter in decision-making on dialysis modality selection.

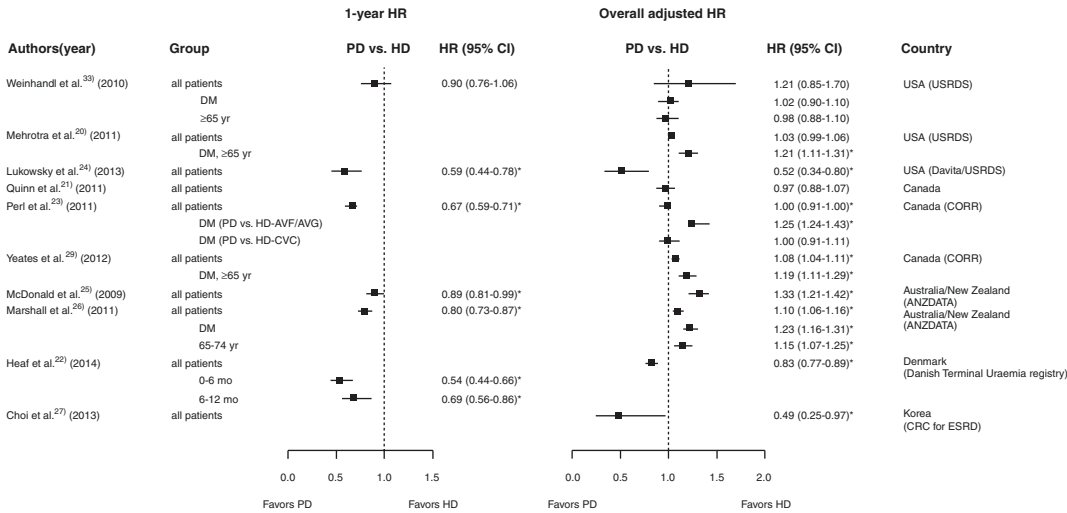

Fig. 2.1 Outcomes of recent studies comparing survival of hemodialysis and peritoneal dialysis patients. *HR* hazard ratio, *CI* 95% confidence interval, *DM* diabetes mellitus, *USRDS* the US Renal Data System, *CORR* the Canadian Organ Replacement Register, *ANZDATA* the Australia and New Zealand Dialysis and Transplant, and *CRC for ESRD* Clinical Research Center for End Stage Renal Disease *$p < 0.05$

2.2.3 Comparisons of Other Clinical Outcomes by Dialysis Modalities

CVD is the most common cause of death in dialysis patients, accounting for about 40% of deaths in dialysis patients in Western countries. The association of dialysis modality and cardiovascular mortality or risk has not been clearly evaluated. In an earlier observational study, periodic dialysis in HD is associated with sudden and cardiac death after weekend (Bleyer et al. 1999). In addition, abrupt hemodynamic shifts and the rapid loss of residual renal function in HD may be associated with the increased cardiovascular risk in HD (Moist et al. 2000). On the other hand, repeated glucose exposure and systemic absorption and the subsequent metabolic derangements including insulin resistance, hypertriglyceridemia, and metabolic syndrome in PD also increase CVD risk, although the lower fluctuations in body fluid and electrolyte concentration potentially reduce it (Johnson et al. 2007). Analysis of ANZDATA registry data showed that PD is associated with a higher risk of CVD death than HD (Johnson et al. 2009a). A retrospective matched-pair cohort in the USA showed that HD is associated with better survival among subgroups with cardiovascular disease than PD (Weinhandl et al. 2010). In addition, a nationwide population-based study in Korea showed that the relative risk for major cardiac and cerebrovascular events after dialysis is higher in PD than HD after covariate-adjusted analysis (Kim et al. 2015).

Infection is the second leading cause of death in dialysis patients. The overall infection rates are similar between PD and HD, but studies have shown that cases of serious bloodstream infection are lower in PD than in HD (Saran et al. 2016). However, analysis of ANZDATA registry data showed PD has an increased risk of infection-related death than HD has, and this was mainly related to increased risk for death by bacterial and fungal peritonitis (Johnson et al. 2009b). Additionally, analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis cohort also showed that compared to HD, PD carried a higher overall infection risk attributable to dialysis technique-related infection. However, during the first 6 months, the incidence rate of infection is higher with HD than PD (van Diepen et al. 2014). A Canadian retrospective study showed that PD was associated with a higher risk of infection-related hospitalization than HD (Lafrance et al. 2012), although subsequent analysis of the same group showed that PD is not associated with a higher mortality or all-cause overall readmission after the initial infection-related hospitalization (Laurin et al. 2015).

Generally, there is still paucity of evidence supporting the effect of dialysis modality on CVD outcome or fatal infectious complications, and the differences in CVD- or infection-related mortality between modalities are not usually considered a major determinant in modality selection.

2.3 Factors Influencing Decision-Making in Dialysis Modality Selection

The selection of dialysis modality is affected by many different factors: medical factors include comorbidities, previous abdominal surgery, and patient tolerability to volume shifts, while nonmedical factors include patient preference, their home situation such as family support or self-perceived burden on their family, socioeconomic factors such as accessibility of the dialysis center, financial factors such as the method of reimbursement, and cultural factors (Wauters and Uehlinger 2004).

Medically, HD is contraindicated in cases in which it is difficult to create a vascular access and relatively contraindicated in patients who cannot tolerate volume shifts, whereas PD is contraindicated in cases of peritoneal adhesion, large mesenteric resection, large abdominal hernia, peritoneal defects such as peritoneal-pleural communications, and severe chronic obstructive airway disorders. Regarding comorbidities, patients who select PD have variable degree of comorbidities in different cohorts: less comorbidities have been found in the US, Canadian, and Korean cohorts but higher comorbidities have been found in the Australian and New Zealand cohorts (Mehrotra et al. 2011; Perl et al. 2011; McDonald et al. 2009;

Choi et al. 2013b). Because most patients do not have any medical contraindications to HD or PD, they are usually free to choose to either modality.

Patients who choose PD as the initial dialysis modality are usually independent, prefer therapy at home and flexible schedules, have the ability to continue work or traveling while on dialysis, and have the ability to care for their children. However, patients not choosing PD as a dialysis modality have concerns about indwelling catheter in the abdomen, concerns about sterility or fear about getting an infection related to the self-procedure, and concerns about storage space for dialysis supplies (Morton et al. 2010). On the other hand, patients who choose HD as a dialysis modality usually want physicians to take care of them and prefer planned schedules or free day without dialysis and the convenience of HD. On the other hand, patients not choosing HD have needle phobia, fear of cross infection during extracorporeal circulation.

A recent data investigating the influence of behavioral stage of change on dialysis modality decision-making showed that people who have higher dialysis knowledge tended to act rather than just think. In other words, knowledge about dialysis helps patients decide on dialysis modality (Prakash et al. 2015). Figure 2.2 presents a conceptual framework within which patients function while selecting a dialysis modality.

In addition to the patient preference, physician reimbursement incentive, funding policy, and the type of provider also influence the choice of dialysis modality. Reimbursement for dialysis is a major factor involved in the selection process, not only for patients but also for healthcare providers. With the introduction of a capitation fee in the late 1990s, the use of PD reduced continuously in Ontario, Canada (Mendelssohn et al. 2004). However, in recent years, several Asian countries, including Hong Kong, Vietnam, Taiwan, and Thailand, as well as New Zealand

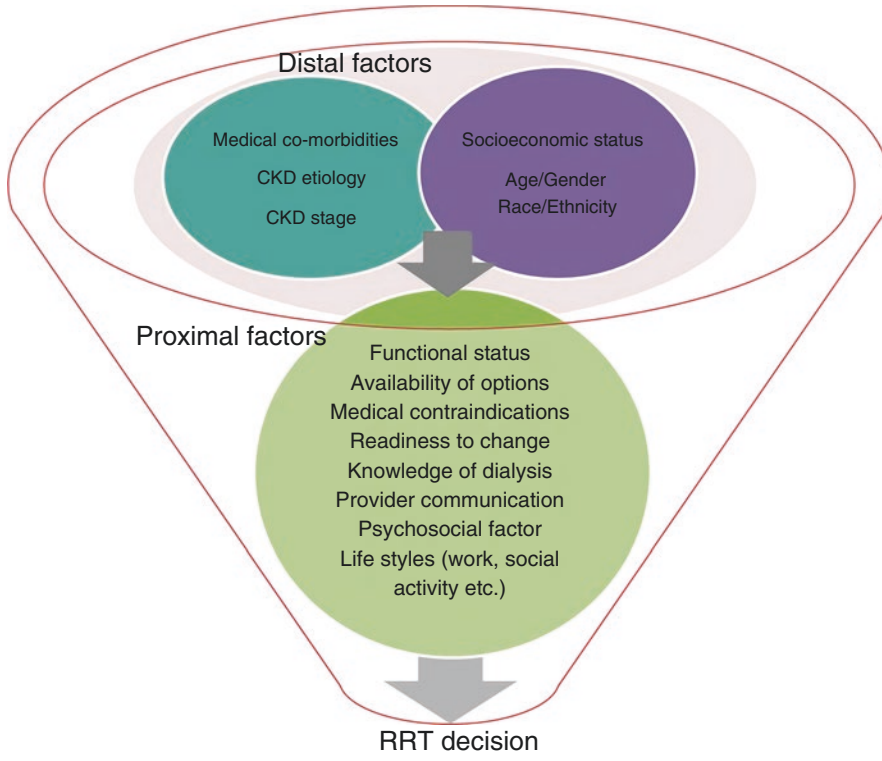

Fig. 2.2 Conceptual model for dialysis decision-making. *CKD* chronic kidney disease, *RRT* renal replacement therapy [adapted from Prakash et al. (2015)]

and Australia, have introduced reimbursement policies for PD, whereby the use of this modality has increased (Kwong and Li 2015). In addition, US data have shown that the new bundled prospective payment system (PPS) provided a financial incentive for increased use of PD (Hornberger and Hirth 2012), and consequently, under the Medicare bundled PPS, an increasing proportion of patients who are receiving PD and home HD rather than in-center HD are expected to be able to save on dialysis costs (Liu et al. 2014). In fact, the use of PD has increased since the introduction of bundled PPS (Saran et al. 2016). In contrast, without changes in the payment systems, PD use has steadily declined since 2007, as reported in a European observational study based on registry data, despite the initial survival advantages of PD (van de Luijtgaarden et al. 2016). A previous European study also showed that the type of provider, whether public or private, affects PD use (De Vecchi et al. 1999). A similar finding was also reported on the basis of US data, in that, the ownership pattern of the dialysis unit was found to affect PD use in the USA (Mehrotra et al. 2009). Overall, the analysis of the cost and incentive mechanism for low-cost dialysis modality has shown that the proportion of profit dialysis centers is associated with the utilization rate of low-cost dialysis (Cleemput and De Laet 2013).

The cost of ESRD care has increased worldwide, and the annual cost of HD in the USA continues to increase (Saran et al. 2016; Manns et al. 2007), because of the increasing prevalence of ESRD. Therefore, it is vital to understand the cost effectiveness of dialysis treatment in order to ensure appropriate use of resources and provide stable healthcare. Between the two dialysis modalities, PD is usually less expensive and more cost effective than HD, in most countries (Chang et al. 2016; de Wit et al. 1998; Lee et al. 2002). Several studies from Western Europe and North America have shown that healthcare costs for HD are about 30–50% higher than those for PD (Karopadi et al. 2013). However, in developing countries, PD is considered more expensive than HD because of the high-cost supplies and relatively lower cost of labor, but actually, PD is less expensive than HD (Hooi et al. 2005; Lo 2002). Despite these advantages (Neil et al. 2009), PD penetration is still considerably lower than HD penetration, except in some countries; at the end of 2014, only an estimated 11% of dialysis patients were treated with PD globally. Considering the outcome data and feasibility, PD seems to be an underutilized modality (Jiwakanon et al. 2010). Therefore, potential bias that could interfere with the choice of dialysis modality should be prevented at the individual physician level, and structural healthcare policies should be introduced for global equity in provision of both dialysis modalities at national levels.

2.4 Selection of Dialysis Modalities for Special Subgroups

Most patients do not have any contraindications for one dialysis modality over the other. Several studies have shown that most patients are medically eligible for PD (Jager et al. 2004). However, in special subgroups of patients, physicians focus on patient characteristics and consider the specific benefits or risks of HD or PD.

2.4.1 Dialysis in the Elderly

The number of elderly patients who need RRT has recently increased (Saran et al. 2016). Given the reduced life expectancy of many elderly patients and the lack of evidence supporting the usefulness of dialysis in improving life expectancy, it is more difficult to decide whether or not to start dialysis, to find the appropriate time for dialysis initiation, and to select the dialysis modality. Therefore, in these cases, it is very important to discuss dialysis decisions with patients and their families.

In elderly patients, PD is beneficial because of its cardiovascular stability and because patients do not need to travel to and from the dialysis canter. In addition, PD does not require repeated vascular puncture: the veins of some elderly patients are often unsuitable for the repeated puncture required in HD. However, PD is risky for some elderly

patients, especially those with impaired vision and decreased mental activity, because these impair the self-performance of the dialysis procedure (Dimkovic and Oreopoulos 2000). In addition, patients of advanced age have decreased manual dexterity, have difficulty in ambulating, are unable to perform exchanges by themselves, and may lack social support, because of which PD tends to be a more difficult option for them. Connection assist-devices or cyclers are alternative solution in such case, and assisted PD is another option (Saran et al. 2016; Segall et al. 2017).

Assisted PD is a type of home-care assistance that can allow more patients to receive PD at home. There are two models of assisted PD: automated PD with two daily nurse visits and automatic PD or CAPD with a home health assistant or family member trained as an assistant, which requires another one visit from a trained nurse. The assisted PD program is cost-saving despite the additional cost for caregivers (Brown et al. 2007; Couchoud et al. 2015a).

On the other hand, among the elderly, the survival rate of PD patients is generally lower than that of HD patients. Consistent results have been obtained from both direct comparative studies in elderly populations and subgroup analysis of the elderly subgroup from a larger study. Data on Medicare beneficiaries in the USA have shown that in patients aged over 65 years who start dialysis, PD is associated with higher mortality during the first 90 days as well as thereafter until 1 year (Winkelmayer et al. 2002). These differences in mortality between HD and PD were also observed in patients with diabetes. Registry data from France similarly showed that compared to planned HD, PD had a higher mortality risk for elderly patients (Couchoud et al. 2007). This study also found that PD was the most commonly selected modality among patients from the oldest group, aged ≥85 years. A recent meta-analysis including a Korean data consistently showed that the risk of death in elderly patients was higher in PD than HD group (Han et al. 2015). Lastly, a subgroup analysis from a larger study showed that elderly PD patients have a higher risk for death than elderly HD patients in cohort studies from Denmark, the Netherlands, and the USA (Heaf et al. 2002; Jaar et al. 2005; Liem et al. 2007; Vonesh et al. 2004). Nonetheless, current observational studies on survival data are not a strong reference for decision-making regarding the dialysis modality among elderly patients.

There are other concerns regarding using PD in the elderly. The higher risk of malnutrition and infection leads to greater mortality in the elderly. Infectious diseases are one of the main causes of death in ESRD patients, and previous studies have shown a higher risk of infection-related mortality in PD than HD (Johnson et al. 2009b). Although an older study has shown a higher risk of peritonitis in elderly patients (Holley et al. 1994), a recent study has shown that infection rate is similar to non-elderly PD patients (Ho-dac-Pannekeet 2006; Li et al. 2007).

Another consideration in modality selection for elderly patients is the aspect of quality of life (QOL). Many elderly patients value QOL over quantity. Several studies on QOL were not restricted to elderly patients, and most have shown equivalent or better QOL with PD than conventional HD. A systematic review found that PD patients mostly rate their QOL higher than HD patients (Boateng and East 2011). The mental health component was comparable in both groups of patients, but HD patients reported a higher QOL in terms of the physical dimension. Thus, regarding QOL it is difficult to find any significant difference between HD and PD in general. In a cross-sectional study with patients aged over 65 years, the unadjusted QOL did not differ between HD and PD, and no differences were observed in physical component scores. However, PD patients had marginally but significantly better mental component scores (Brown et al. 2010). In a short summary, there seem to be no differences in QOL between PD and HD among the elderly.

2.4.2 Dialysis in Diabetic Patients

Diabetic patients with ESRD have a higher mortality rate compared to nondiabetics, partially because of the higher burden of CVD in the former. A potential advantage of PD in patients

with diabetes is that because this is a continuous therapy, and these patients therefore have less dialysis-induced hypotension, coronary ischemia, arrhythmia, and better blood pressure control. In addition, PD does not require systemic heparinization and therefore is beneficial for patients with significant diabetic retinopathy and retinal hemorrhage (Tokuyama et al. 2000). PD is more effective in preserving residual renal function, which is extremely important in the case of patients with diabetes. However, PD may have harmful metabolic effects in these patients. Glucose adsorbed during PD leads to weight gain, hyperglycemia, hypertriglyceridemia systemically, and morphological and functional deterioration of the peritoneal membrane locally. However, in terms of infection rate, there are no consistent evidences to show that diabetics have more peritonitis or exit site infections. Further, no evidence indicates that the incidence of encapsulating peritoneal sclerosis is higher in diabetics.

On the other hand, studies comparing the outcomes between PD and HD have produced varying results. Some have found that PD is better for this subgroup of patients, while others favor HD. Still others show no statistical difference in survival between PD and HD patients with diabetes (Couchoud et al. 2015b). In general, nondiabetics and younger diabetics between aged 18 to 44 years have superior or equivalent survival rates with PD than HD. In the USA, patients with ESRD and diabetes aged >45 years have better survival with HD than PD, but in Canada and Denmark, no difference in survival has been found between PD and HD in this subgroup (Vonesh et al. 2006). Therefore, PD does not seem to be contraindicated in diabetic patients.

Glycemic control is an important predictor of mortality in both HD and PD patients (Oomichi et al. 2006), suggesting the great significance of glycemic control in diabetic dialysis patients. Therefore, special consideration is required while taking care of diabetic PD patients: limited use of hypertonic glucose-based PD solutions and use of icodextrin which leads to avoid hyperglycemia and hyperinsulinemia during long-dwell (Gokal et al. 2002) and greater ultrafiltration efficiency can be ensured (Holmes and Mujais 2006). In an RCT, the use of icodextrin was found to be associated with improved metabolic control and volume status in diabetic PD patients (Paniagua et al. 2009), and a glucose-sparing regimen improves glycemic control (Li et al. 2015).

In summary, for diabetic dialysis patients, evidence is not available to support either HD or PD. Therefore, patients should be provided balanced information during decision-making regarding choice of modality, and modality selection should be based on patient's preference. In addition, maintaining the target hemoglobin A1C (HbA1C) below 7.5%, avoiding the use of hypertonic glucose-based PD solutions, maintaining euvolemia through effective ultrafiltration, and exercising to maintain the appropriate body weight should be recommended.

2.5 The Use of a Dialysis Decision Aid for Modality Choice

Pre-dialysis education programs are usually recommended for ESRD patients who need help with decision-making on dialysis start, dialysis modality, and other treatment options. Consideration of patient's preference in treatment planning is known to improve health outcomes (Dahlerus et al. 2016). Patients' decision depends on many factors including clinical indications, availability of resources for dialysis, and the benefits or potential risks of each treatment modality. An interview-based survey has shown that patients do not struggle with the decision until they become symptomatic (Winterbottom et al. 2014). Further, patients generally want to stick with their initial decision because they want to maintain the status quo. A systematic review has reported that the requirements of patients with advanced CKD and their families are not satisfied, and the timing of information for decision is not appropriate (Morton et al. 2010). Patient decision aids are a useful option for evidence-based decision-making. Several decision aids are available for CKD decision-making: for dialysis, there are *Making the right choices for you-the dialysis decision aid booklet* (Yorkshire

Dialysis Decision Aid [YoDDA]; UK) (Schatell 2015), *My Kidney, My choice* (Australia), *Kidney Failure: What type of dialysis should I have?* (US) (Schatell 2015), *Chronic kidney disease: Treatment options* (UK), *My life, My Dialysis Choice* (US), *The American Match-D tool Home Dialysis Central, Method to Assess Treatment Choices for Home Dialysis (MATCH-D)*, and http://homedialysis.org/match-d.

The YoDDA booklet contains information about how to manage CKD (conservative care and RRT) and the two dialysis modalities (HD, in-center HD and home HD; PD, CAPD and automated PD), a questionnaire to help people think about important considerations of their life now and in the future, and a final glossary for patients.

A recent prospective study has shown that using YoDDA as part of pre-dialysis education was useful for patients with declining kidney function and supported dialysis decision-making taking patient lifestyle into consideration (Winterbottom et al. 2016).

Another decision aid, *My kidneys, My choice*, developed in Australia, aims to enhance shared decision-making by prioritizing patient lifestyle. A small survey has shown that for routine education, this decision aid has high patient acceptance and usability. It was found to be a useful adjunct to the original pre-dialysis education program and minimized staff variations in pre-dialysis education (Fortnum et al. 2015).

In summary, the use of decision aids helps patients with decision-making by providing adequate information about CKD and treatment options in the context of their lifestyle more effectively and therefore enables patient-centered dialysis decision-making.

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Part II

Hemodialysis

The Basics of Vascular Access Construction and Its Timing

3

Seiji Ohira†

Key Points

1. Vascular access (VA) is essential for performing hemodialysis.
2. At present, the native artery-vein anastomosis or arteriovenous fistula (AVF) is the most frequently used having far superior patency; however, it can become a burden to cardiac function, which must be carefully considered especially in the elderly patients.
3. In the case that native vasculature, especially veins, are not available for AVF construction, synthetic grafts (AVG) must be used instead.
4. Stenosis is prone to develop close to the anastomosis in AVF and at the anastomosis of the vein and graft or close to the anastomosis in AVG. It must be remembered that PTA (percutaneous transluminal angioplasty) is now the first choice to repair AVF- and AVG-stenosis.
5. In the case that AVF or AVG have clearly become a burden to cardiac function, arterial superficialization or intravascular indwelled catheters must be adopted for use as vascular access. Surgical repairs for high-flow AVF or AVG with clinical problems must be needed at times in order to reduce the VA-flow.

3.1 Introduction

Renal replacement therapies (RRT) for end-stage renal disease (ESRD) include (1) dialysis (hemodialysis, peritoneal dialysis), (2) renal transplant (cadaveric, living), and (3) conservative treatment (dietary, antihypertensive drugs, diuretics).

In Japan, 95% of these patients choose and are started on hemodialysis (HD). According to the Japanese Society for Dialysis Therapy (JSDT), as of December 2012, there were 309,946 patients on maintenance dialysis. Realizing that 97% of these are HD patients makes it easy to recognize that it is extremely important for the dialysis staff thoroughly understand VA as it is vital for hemodialysis.

The construction and restoration of the VA are the specialty of the physician, but the preoperative preservation of the superficial veins and postoperative observation and management of the VA and the cannulation of the VA and care after cannulation are tasks entrusted to nurses and clinical engineers. The tasks related to the VA make up an important part of team medical care.

3.1.1 Informed Consent Related to the Construction and Restoration of VA

When the diagnosis of ESRD has been determined and it has reached the point where RRT cannot be avoided, the physician should explain

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to the patient the importance and choices available for RRT. If possible, the nurse should also be present, adding to the explanation. If the patient has understood and agreed to maintenance hemodialysis (HD), there should be further discussion about HD and the required VA. Subjects to be explained to the patient at the time of VA construction are shown in Table 3.1. The explanation should not be concluded in a single session, but divided into multiple sessions in order to gain the patient's understanding and acceptance. Complications, subject (10) from Table 3.1, are shown in Table 3.2 and cover a wide range of topics. It isn't appropriate to give an explanation that will create anxiety or discourage the patient before the initiation of HD. What is needed from the dialysis staff is to be keenly aware of the conditions of the patient's VA and to provide details of the restoration method when it becomes necessary. Figure 3.1 shows the patency rates of a distal forearm AVF by age, gender, and diabetic renal failure. It is necessary to be aware that even properly constructed and properly cannulated AVFs will, in time, show damage and lose function, requiring measures for restoration.

Table 3.1 Subjects to be explained to the patient at the time of VA construction

1.	The purpose of VA construction
2.	The method of VA construction (surgical procedure) and pre-surgical examinations
3.	Introduction to the surgeon and assistant
4.	Method of anesthesia
5.	Time of operation
6.	What to be careful after surgery
7.	Actual method of the use of the VA (actual cannulation)
8.	Patency rates for various VAs
9.	Importance of periodic examinations of VA function and form
10.	Expected VA-related complications
11.	Methods of restoration for complications above
12.	Others

It is not advisable to discuss all subjects in one setting giving them the all the same level of importance. It is best to choose the necessary subjects based upon the patient's disposition and condition, dividing the explanation into several discussions with repeated question and answer sessions

Table 3.2 Complications associated with VA construction

1.	Inadequate blood flow
2.	Stenosis (narrowing of the arterial or venous lumen)
3.	Thrombosis (disruption or occlusion of VA blood flow)
4.	Infection of cannulation site
5.	Aneurysm at the cannulation site
6.	Venous hypertension (sore thumb or sore hand syndrome)
7.	Steal syndrome (ischemic injury)
8.	Excessive blood flow, increased stress on cardiac function (high-output failure)
9.	Recirculation
10.	Limited cannulation area, complications in the cannulation area
11.	Others

After a period of use, all VAs will show wear. The patient needs to understand this, and when it becomes necessary, restoration of the VA should be explained to the patient

3.1.2 When to Construct the VA

According to the 2011 Edition of VA Guideline (VA-GL) of the JSDT (Japanese Society for Dialysis Therapy 2011), in Chap. 2, GL-5, it is recommended as expert opinion that "VA construction should be considered when eGFR is less than 15 mL/min/1.73 m^2 (CKD stages 4 and 5) as well as taking into account clinical conditions." In addition, "In patients with diabetic nephropathy, who have a tendency to show overhydration, VA construction should be considered at a higher eGFR." The 2011 Edition of the VA-GL also states that "Anticipating the start of hemodialysis from the results of various laboratory tests and clinical symptoms, ideally the AVF should be constructed at least 2–4 weeks before the initial puncture. In the case of an AVG, the time from construction to initial puncture should be 3–4 weeks." Also from the JSDT, it is noted in the Clinical Guideline for Hemodialysis Initiation for Maintenance Hemodialysis (Japanese Society for Dialysis Therapy 2013) in Statement 5 that "It is recommended that arteriovenous fistula (AVF) and arteriovenous graft (AVG) be created at least 1 month prior to the initiation from the viewpoint of expected lifespan after hemodialysis initiation." Care should be taken to assure that

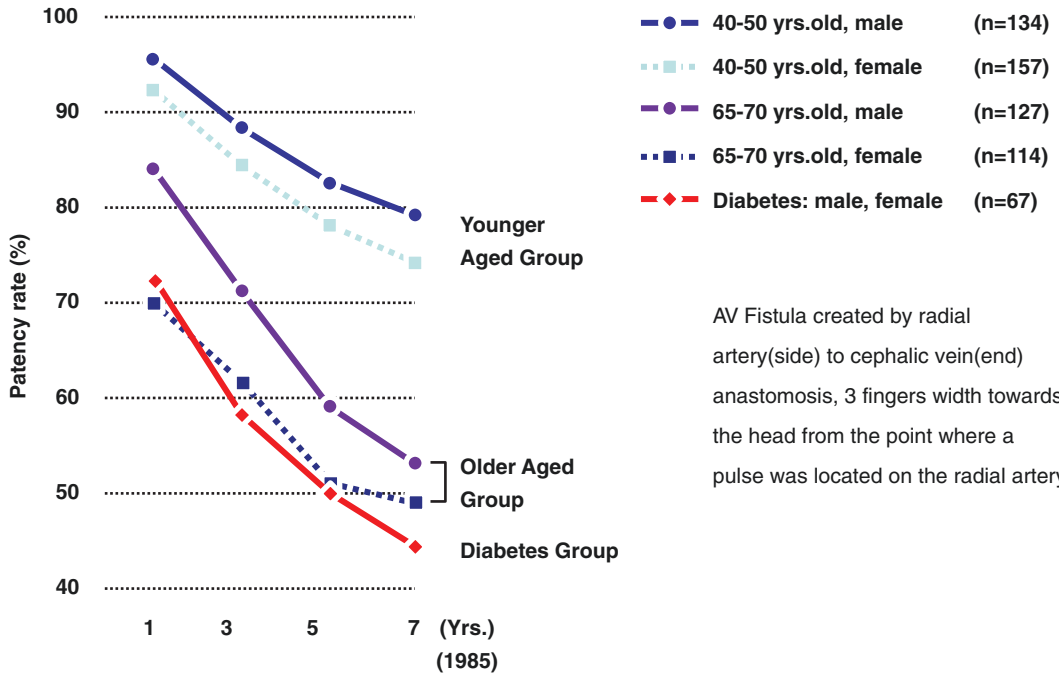


Fig. 3.1 Patency rates for initial shunt in the distal forearm. The patency rate for the older age group and diabetes group is clearly poorer than that of the younger age group

the initiation of dialysis is not too early or too late taking into account renal function and symptoms, with the best indicator being that the constructed AVF or AVG are matured (dilated) at the time of cannulation.

The nephrologist should allow the patient to be examined by a VA surgeon beforehand so that the surgeon has ample time prior to surgery to make a thorough examination of the arteries and veins for use in the proposed VA.

3.1.3 Basics of VA Construction

3.1.3.1 Selecting the Type of VA

If the situation requires emergency HD, then HD must be initiated with an intravascular indwelled catheter. Except for this situation, as a rule AVF or the next best choice, AVG, should be the type of VA chosen in cases where there is ample time of 1 month or more before the proposed initiation of HD. Whichever the choice, it is essential to examine in detail the arteries and subcutaneous veins of the arm of the patient. A frequently used AVF in the distal forearm is typically constructed with a radial artery and cephalic vein side (A) to end (V) anastomosis. Because there are more variations in the veins than arteries in the arm, it becomes necessary to predict which vein will dilate with the anastomosis of the previously mentioned AVF (Fig. 3.2). Although there are fewer variations in the arteries compared to the veins, the pulse of the radial artery in the distal forearm may not be palpable due to arteriosclerosis in elderly patients. In such a case, there is little arterial blood flow, and creation of an AVF in the distal forearm will be difficult. Not limited to just the elderly, it is vital to choose the type of VA taking into consideration the condition of the arteries and veins in addition to any accompanying symptoms as well as the remaining life expectancy as shown in Fig. 3.3.

3.1.3.2 VA Construction (Surgery)

Whatever the type of VA, the factors having the most effect on short-term and long-term results (patency) are (1) the patient's vascular condition (age, gender, underlying disease, cardiovascular

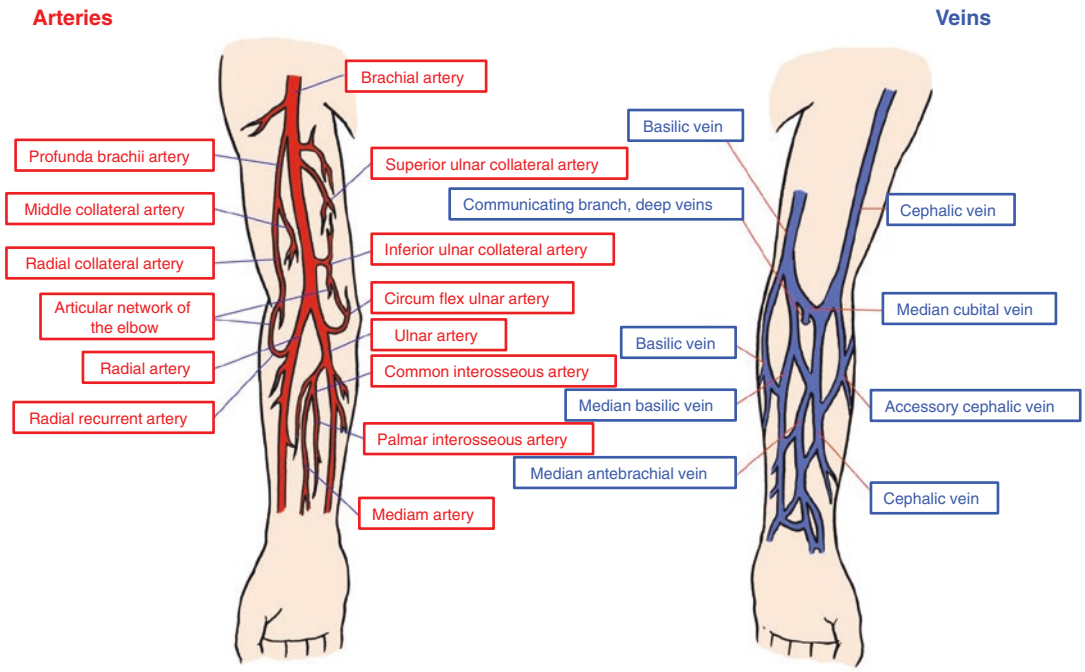
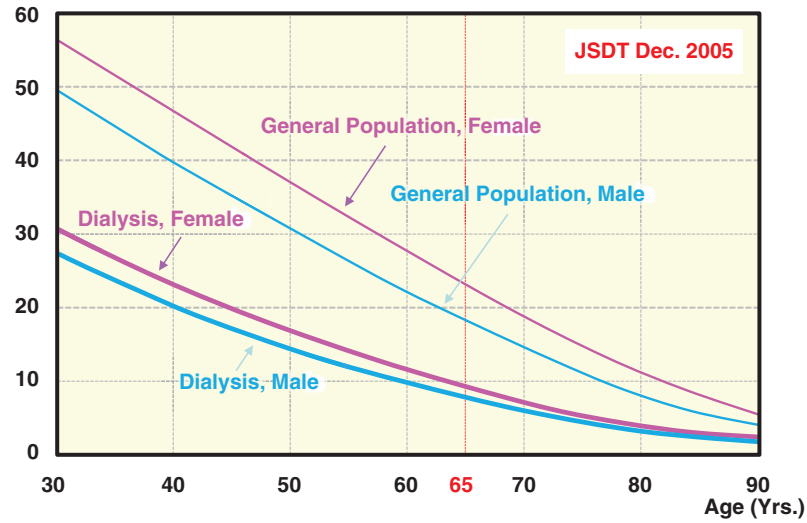


Fig. 3.2 Arteries and veins of the upper limb. During the construction, management, and restoration of AVF/AVGs, it is necessary to remember the names of the arteries and veins in the upper limb and to make a detailed record. Variations are more frequent in veins than arteries



Average age of patients on dialysis : M : 65.4 yrs. F : 67.4yrs.
Average age of patients at year's end : M : 63.2 yrs. F : 65.0yrs.

Fig. 3.3 Average remaining life expectancy of dialysis patients based on age. The remaining life expectancy of dialysis patients is roughly half compared to persons the same age in the general population

complications, blood pressure, degree of obesity, degree of anemia, etc.) and (2) the surgeon's skill (selection of location, choice of vessels, diameter and type of anastomosis, surgical experience, etc.). With regard to the patient's vascular condition, these conditions cannot be changed; therefore, the best choice of VA and location will need to be made in accordance with the patient's vasculature. With regard to the skill of the surgeon, thorough education and practical training are necessary for the physician before they can be considered proficient. A German vascular surgeon (Hehrlein 1995) aptly stated, "The best way to reduce early thrombosis is to hire a skilled surgeon."

Anesthesia of VA Construction

The purpose of anesthesia is to relieve the patient of uneasiness and pain during the operation. First, it should be recognized that chronic kidney failure patients are at high risk with regard to anesthesia. A work-up of their overall condition, especially a thorough examination of their cardiac function and blood pressure, should be performed. Local anesthesia is sufficient for the anastomosis of the AVF using native vasculature; however, in some cases, due to the aggressiveness of the surgery or disposition of the patient, sedation may be added. If the area of the surgery is in the middle of the limb or near to the trunk, a nerve block or general anesthesia will be chosen. Monitoring of the patient's respiration, blood pressure, and body temperature is required during and after the surgery.

Poor Fistula Maturation

Throughout the world, the advancing age of maintenance hemodialysis patients is remarkable. Not only arteriosclerosis but phlebosclerosis often coexists in the elderly (Lee et al. 2011). Even if the radial artery and cephalic vein of the AVF in the distal forearm are properly anastomotized and blood flows from artery to vein and if arteriosclerosis or phlebosclerosis in excess of a certain level exists, the vessels won't dilate, blood flow will not increase with time, and maturation of the AVF is delayed or can't be expected. Therefore, it is particularly important to verify the degree of sclerosis in artery and vein through examination prior to surgery and precisely determine the location of anastomosis in elderly patients.

3.1.3.3 VA Care Immediately Following Construction

Because AVF and AVG are surgical procedures to shunt arterial blood flow to the vein, peripheral ischemia is inevitable. Normally, because peripheral ischemia (reduced blood flow to the periphery) is compensated for by collateral circulation, the patient will only complain of a slight coldness and in time become accustomed to it. However, although rare, some patients will complain of marked coldness and continual sharp pain immediately following surgery. In this case, managing it not only with analgesics but relieving the ischemia (including closing the anastomosis) must be considered. The observation of the blood vessel sounds, the strength and characteristics of thrill, and the dilation of the vein immediately following construction of the AVF or AVG are important; however, attention to the symptoms of peripheral ischemia is also necessary (Fig. 3.4).

3.1.3.4 Care Until Cannulation

Guidance should be provided regarding (1) the presence and degree of peripheral ischemia, (2) listening to blood vessel sounds and thrill and palpation (strength and characteristics) of the arterialized vein, (3) the presence of infection at the surgical site, and (4) limitations of joint flexion and the degree of movement of the limb where AVF/AVG construction took place. Holding the joint medial to the shunt in a bent position for prolonged periods of time prevents blood flow through the shunt and leads to thrombosis (occlusion) and should be avoided. (5) Of course, the degree of dilation of the arterialized vein should be closely observed.

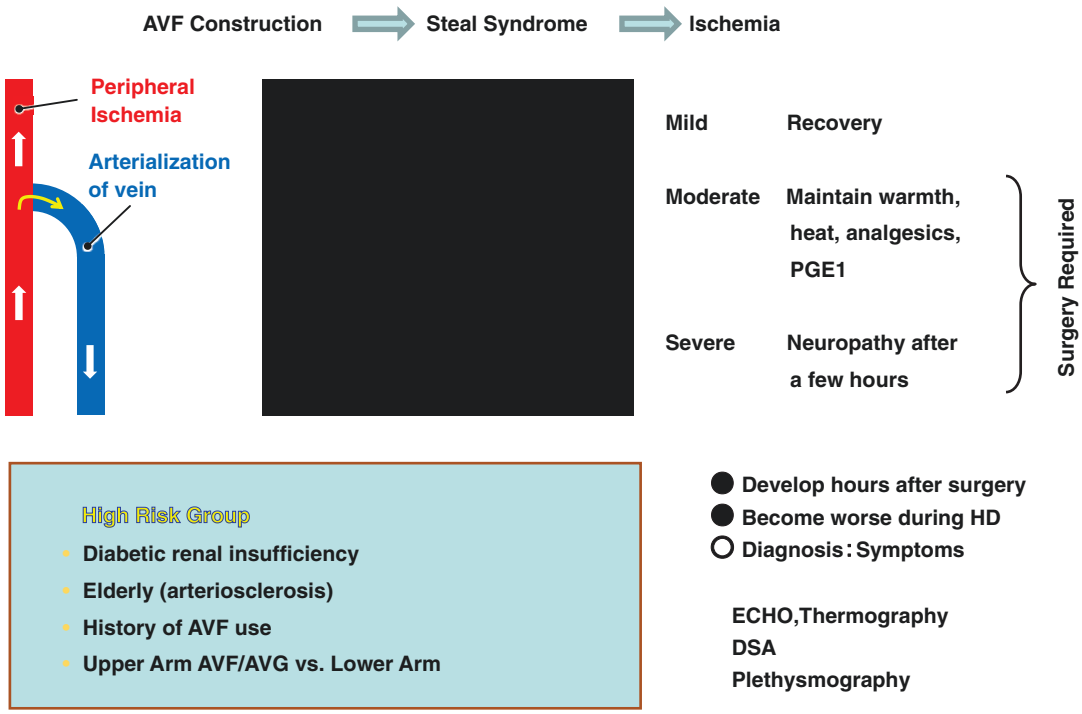


Fig. 3.4 Peripheral ischemia following shunt construction. A shunt where a portion of arterial blood flow is directed to the vein formed by an arterial side to venous end anastomosis reduces peripheral blood flow (ischemia). Observation is necessary to determine whether or not ischemia causes any major clinical symptoms after construction of the shunt

3.1.3.5 Initiation of Cannulation

Many patients experience a high degree of apprehension toward the initiation of HD. To ease that apprehension, it is necessary to treat them kindly and thoughtfully from the time the patient is led to the bed to have their blood pressure measured after having been weighed. Properly perform cannulation by (1) thoroughly sterilizing the skin, (2) determining the location of the puncture, and (3) using the appropriate needle for the patient's VA. For patients extremely apprehensive of pain, use an extra-small gauge needle with additional local anesthesia or pre-application of an analgesic such as a lidocaine patch (Penles®). Cannulation difficulties: the arterialized vein can be difficult to cannulate because (1) of insufficient dilation, (2) it is too deep, or (3) it is tortuous and lacks continual straight length. It is vital to construct an easily cannulated AVF in which following the anastomosis of the artery and vein, the arterialized vein is sufficiently dilated. However, due to the condition of the patient's damaged vessels, reconstruction can be difficult in many cases. In these situations, echo-guided needle cannulation is useful, and acquisition of this technique is especially important with the current rapid increase in elderly patients.

3.1.3.6 Precautions During HD

Observe and record whether or not the prescribed blood flow rate (200–300 mL/min) can be achieved from the VA, whether the venous pressure is within the permitted range, whether there is discomfort or pain in the limb with the VA, and whether peripheral ischemia symptoms become worse, and note any changes in blood pressure, heart rate, or breathing. The prevention of dialysis needle deviation is important and requires vigilance during hemodialysis treatment. If it is not immediately noticed, a large amount of blood could be lost, leading to a very serious situation. In a survey performed by the Japanese Association of Dialysis Physicians (Shinoda et al. 2016), from the 1755 dialysis facilities responding, there were 432 serious accidents reported for the year 2013, and of

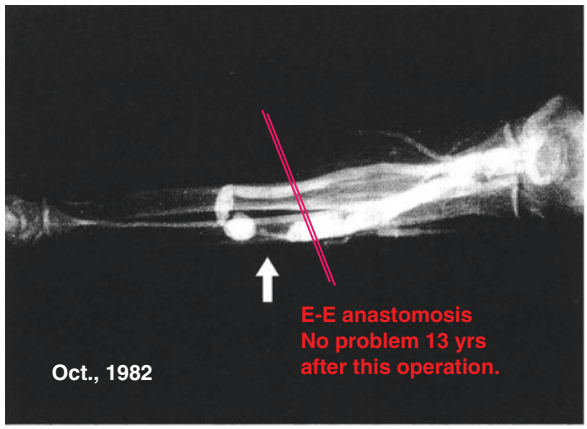
these, 167 (38.7%) were dislodged needles. Among these dislodgement accidents, 35.6% were life threatening or required hospitalization, with the top ranking reason being self-dislodgement by patients with dementia. Deviations of the dialysis needle can be caused by (1) improperly secured needles, (2) unusual movement by the patient, and (3) inappropriate pulling; however, one should bear in mind that with the recognized increase in the number of elderly hemodialysis patients with dementia, the prevention of self-dislodgement by will be a problem in the future.

3.1.3.7 Procedures Following Dialysis Needle Removal

When HD is completed, withdraw the needle and apply hemostatic techniques. The needle was placed into a vein, but because of the anastomosis, there is arterial blood flow and the vein has become arterialized. Because of this, if hemostasis is not properly performed, a surprisingly large amount of bleeding can occur. Hemostatic techniques must be applied in a sterile manner. It is vital that this be conveyed to the patient.

3.1.3.8 Long-Term Observation and Management of AVF and AVG (Ohira 2011)

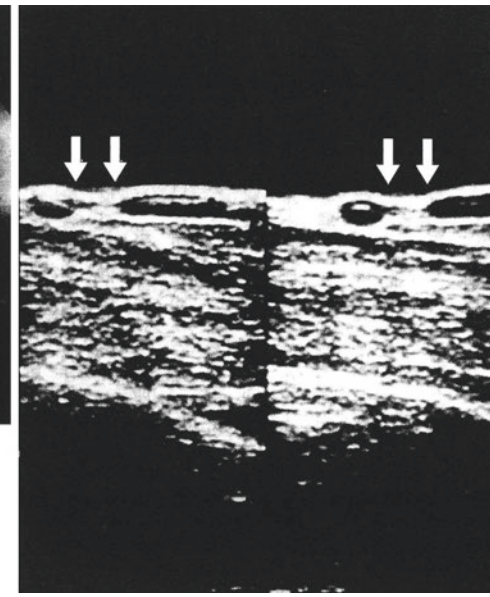
At every HD session, observe the following: (1) cannulation, (2) blood flow rate, (3) venous pressure, (4) patient complaints following cannulation, and (5) hemostatic characteristics after needle removal. In the case that venous stenosis is suspected, take the appropriate steps of performing ultrasound and angiographic examinations and consider methods for restoration (Figs. 3.5 and 3.6). As the period of hemodialysis is extended, the condition of the arteries and veins used in the VA as well as others throughout the body deteriorate. Because of this, the construction or restoration of the AVF, the most preferable type essential for maintenance hemodialysis, becomes difficult and the retention rate gradually decreases, and as shown in JSDT statistical data, there is an increase in AVG and arterial superficialization (Table 3.3). Glazer et al. emphasize that prolonging the patency and limiting the complications of a functioning hemodialysis (HD) access require a multidisciplinary approach (Glazer et al. 2015) (Fig. 3.7).



Angiography revealed a segmental stenosis just proximal to AV anastomosis

68 y/o male with Hx of 9 yrs HD

If there exist multiple segmental stenoses, then PTA method must be the first choice.



Echo showed a segmental stenosis consistent with angiogram

Fig. 3.5 Segmental stenosis: surgical repair or PTA repair? Segmental stenosis was diagnosed by angiography (*left*) and echo (*right*), both of which showed consistent findings

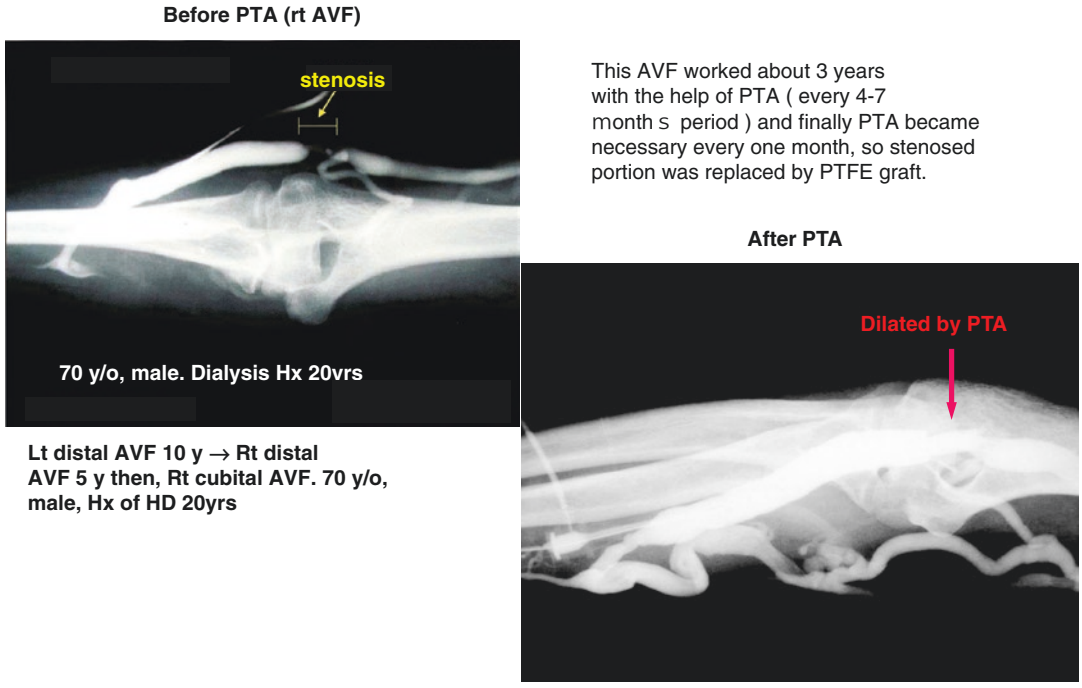


Fig. 3.6 AVF stenosis and its repair by PTA (percutaneous transluminal angioplasty). Right cubital AVF revealed stenosis at the cubital area which was treated successfully by PTA. Repairs by PTA became frequent, so the repeated stenosed portion was replaced by PTFE graft

Table 3.3 The ratio of VA types based on dialysis duration (Japanese Society of Dialysis Therapy Dec., 2009)

Duration	Pts no	AVF	AVG	Artery superficialized	Artery direct punt	Catheter		Others	Single needle
						Long	Short		
˂2 years	40,948	89.9%	5.6%	1.6%	0.1%	0.8%	1.5%	0.1%	0.3%
2–5 years	45,326	91.0	6.4	1.6	0.1	0.4	0.1	0.1	0.2
5–10 years	44,136	90.2	7.3	1.7	0.1	0.4	0.1	0.1	0.1
10–15 years	21,149	89.1	8.1	1.9	0.2	0.4	0.1	0.1	0.1
15–20 years	10,428	87.6	9.2	2.2	0.2	0.5	0.1	0.1	0.2
20–25 years	5481	86.2	10.0	2.6	0.2	0.5	0.2	0.1	0.2
˂25 years	4776	81.3	12.5	4.3	0.3	1.0	0.2	0.2	0.3
Total	172,244	89.7%	7.1%	1.8%	0.1%	0.5%	0.5%	0.1%	0.2%
		154,450	12,234	3146	228	899	777	186	324

cf. Dec. 1998年: AVF 91.4%, AVG 4.8%
There is an increase in AVG, and arterial superficialization as a period of hemodialysis is extended

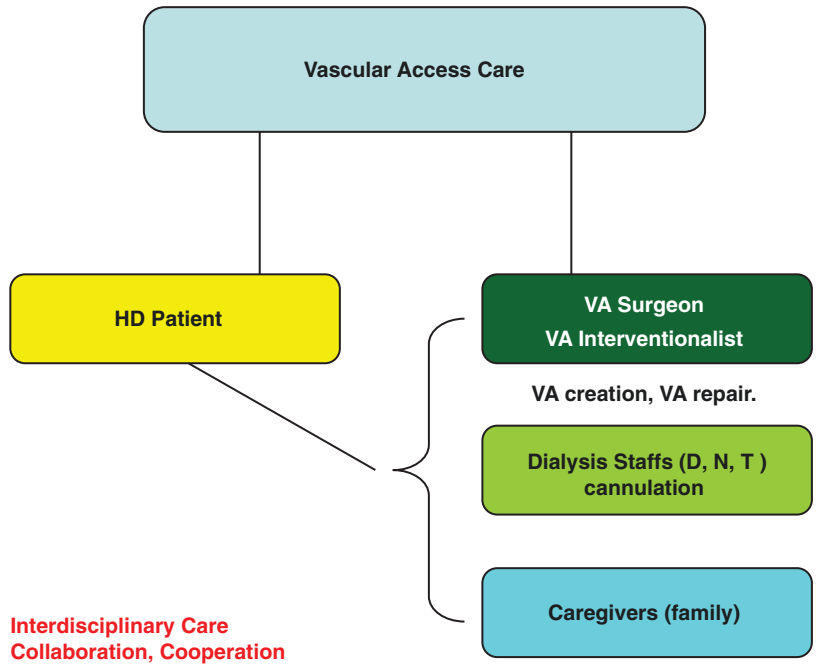


Fig. 3.7 Collaboration in vascular access care. Vascular access care requires interdisciplinary care. Namely, cooperation between vascular surgeon, dialysis staffs (doctor, nurse, technician), dialysis patient, and caregiver (family)

Conclusion

In maintenance hemodialysis, the patient's blood is withdrawn from the patient's artery, and after the blood has been filtered by the dialyzer, it is returned to the patient's blood vessels by a process. This process is known as vascular access (VA). This process relies on the vasculature and is essential for hemodialysis treatment. It is said that VA is the dialysis patient's lifeline, but it is also their Achilles' heel. The job of constructing, observing, and maintaining a VA and if necessary restoring it is considered one of the most important aspects in dialysis medical care where physician, nurse, and clinical engineer work together as a team. It is strongly desired that the members of the dialysis staff each acquire adequate VA-related knowledge and practical skills that are associated with their occupational field.

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Hemodialysis Procedure and Prescription

4

Won Kim

4.1 Hemodialysis Procedure

The hemodialysis process requires a dialysis machine, a dialyzer, dialysate, and blood circuit (Fig. 4.1). Hemodialysis can be performed by physicians, nurses, and technicians in a dialysis center. In general, in-center hemodialysis takes between 3 and 5 h (the average is 4 h) and is conducted three times a week. Patients are seated in a comfortable chair or bed to receive dialysis treatment and can watch movies, read, rest, or socialize with neighboring patients during treatment. When new patients arrive at the center, they will learn the routine of having their vital signs measured (weight, blood pressure, heart rate, and temperature). A nurse or dialysis technician cleans the access site and prepares the hemodialysis machine. This process can vary for different dialysis machines and circuits.

4.1.1 Preparation of Items

- Arterial and venous blood tubes (or blood tube set).
- Dialyzer.
- Two needles (15, 16, or 17 G) for hemodialysis.
- Normal saline 1 L and infusion solution set.
- Heparin.
- Syringes (e.g., 5, 10, 20, or 30 mL) for heparin administration.
- Dressing set (2% chlorhexidine with 70% propyl alcohol, 70% alcohol, and/or 10% povidone-iodine sponge), sterilization drape.

4.1.2 Anticoagulation

Hemodialysis requires extracorporeal blood flow. Some form of anticoagulation is required to prevent thrombosis in the extracorporeal blood circuit (dialyzer and arterial/venous blood tubes) during the procedure. Anticoagulation protocols used in hemodialysis differ according to dialysis center. Anticoagulants used in hemodialysis are unfractionated heparin, low-molecular-weight heparin, regional anticoagulation with citrate or protamine reversal, direct thrombin inhibitor, antiplatelet agents, prostacyclin, heparinoids, and heparin-protamine. Strategies to decrease the risk of bleeding include using low-dose heparin and the fast-flow no-heparin method. The most commonly used anticoagulant is heparin. Each dialysis center may have its own heparin protocol. A commonly used heparin protocol in routine hemodialysis consists of an initial dose of heparin administered as a bolus at the start of the hemodialysis treatment and

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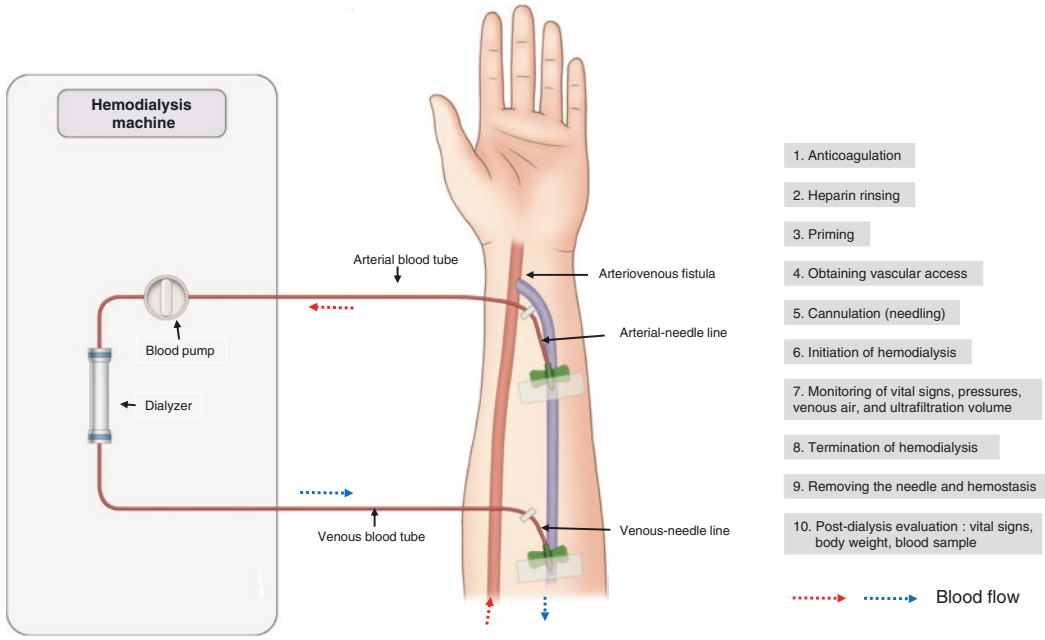

Fig. 4.1 Schematic demonstration of hemodialysis prescription

a continuous dose of heparin administered during hemodialysis to maintain suitable anticoagulation (Hemodialysis Adequacy 2006). An initial dose of heparin (10–50 units/kg, usually 50 units/kg) is bolus injected just after needle insertion into the arteriovenous fistula or through a central venous catheter (Santos and Peixoto 2008). A continuous dose of heparin (500–1500 units/h, usually 1000 units/h) is administered during the session of hemodialysis. A strategy to maintain the patency of the extracorporeal circuit and to minimize bleeding risk is needed in anticoagulation.

4.1.3 Heparin Rinsing

Rinsing is a process of washing the extracorporeal circuit with rinsing solution. After setting up the hemodialysis machine with the arterial/venous blood tubes and dialyzer, 2000–5000 units (usually 3000 unit) of heparin in 1 L of normal saline is infused into the extracorporeal circuit. Then, the heparinized saline is flushed from the extracorporeal lines with unheparinized normal saline prior to the start of the dialysis treatment. Because the heparin is not administered to the patient during the rinsing process, it can be used in the rinsing process of a heparin-free protocol, which is indicated for patients with a high risk of bleeding. However, heparin should not be used in the rinsing sequence for a patient with heparin-induced thrombocytopenia. This rinsing process is optional, and thus this process can be omitted.

4.1.4 Priming

- Because the dialyzer and arterial/venous blood tubes are filled with air or foreign materials (e.g., sterilant), performing the priming process with normal saline is essential to remove such materials from the extracorporeal circuit. Therefore, after priming, there should be no air within the extracorporeal circuit.
- Set up the hemodialysis machine with the arterial/venous blood tubes and dialyzer.
- After connecting the venous or arterial blood tube to normal saline, start the blood pump at a low rate (50–100 mL/min). The nurse or technician operates the machine to fill the extracorporeal circuit with normal saline. In some dialysis machines, the priming process

is automatically completed by a computerized program. After connecting between arterial and venous blood tube ends, recirculation process is performed in the extracorporeal circuit. During recirculation, remnant air bubble can be removed from arterial/venous blood tubes and dialyzer. However, the recirculation process is optional and can be omitted.

4.1.5 Obtaining Vascular Access

4.1.5.1 Patients with Central Venous Catheter

- The operator washes his or her hands and assesses the condition of the hemodialysis machine. After priming the extracorporeal circuit, heparin should be prepared for initial bolus (10–50 units/kg) and maintenance (500–1500 units/h) administration.
- The operator is recommended to wear clean gloves. After opening the dressing set and preparing the items to be used, the gauze and tape previously used for dressing are removed. The catheter insertion site should be inspected for the color, blood clots, swelling, and pus discharge.
- Antiseptics including 2% chlorhexidine with 70% alcohol or 70% alcohol and/or 10% povidone-iodine can be used for disinfection, and the catheter insertion site is sterilized, starting from the center and moving outward in a circular pattern. After removing the heparin cap at the end of the catheter, disinfect the both ends of catheter. After disinfection, the catheter tip must be handled with aseptic techniques and minimum exposure to air.
- After the antiseptics have dried, the catheter insertion site and both suture sites are fixed with gauze.
- The patency of the catheter lumen is verified using normal saline (e.g., 20 mL in a 20-mL syringe). If flushing is unsuccessful, obstruction is suspected.
- Blood sample should be taken immediately after obtaining vascular access to prevent dilution by fluid.
- The prepared heparin (10–50 units/kg) is injected into the venous end of the catheter.

4.1.5.2 Patients with Arteriovenous Fistula or Graft

- The operator washes his or her hands and prepares the items to be used for hemodialysis.
- Any abnormalities of vascular access should be inspected by checking thrill, bruit, and pulsation.
- The operator wears gloves to sterilize the arterial and venous areas of the arteriovenous fistula puncture site by rubbing a 2% chlorhexidine gluconate with 70% isopropyl alcohol or 70% alcohol and/or 10% povidone-iodine-soaked cotton ball in a circular pattern with a diameter up to 5 cm. Wait 3 min to allow it to dry if you use povidone-iodine.
- The area to be sterilized is secured by spreading the sterilization wrap below the patient's arm to the arteriovenous fistula site.

4.1.6 Cannulation (Needling)

1. The operator should verify the absence of abnormalities in the patient's vascular access (thrill, bruit, pulsation, redness, or swelling of arteriovenous fistula or graft) and inspect arteriovenous fistula for a cannulation site.
2. Three types of cannulation techniques:
   (a) Rope-ladder technique: The cannulation site should be at least 5–10 mm from the previous puncture site to promote proper healing.
   (b) Buttonhole technique: This technique can be used only in the arteriovenous fistula. If there is a limited number of puncture sites available, insert the needle into the same site, and create a hole by the repeated needle insertion. This method may also be less painful.
   (c) Area puncture technique: One or two areas of vascular access are repeatedly used for cannulation. Thus, repeated puncturing of the same site can weaken the blood vessel walls and produce aneurysm or pseudoaneurysm.
3. The operator should wear sterile gloves.
4. Apply a tourniquet to facilitate needle insertion and prevent damage to the inside of the

vessel. Even if the blood vessel appears thick enough, a rubber band is recommended to prevent damage of blood vessel.

5. Needles can be inserted into the vessel with an angle at 20–35° for arteriovenous fistula and at 45° for arteriovenous graft using a needle because steep angles during needle insertion can cause injury at the site of vascular access. Thus, this procedure should be cautious. If flashback of blood occurs, the needle must be inserted with a less steep needle angle:
   (a) For arterial sites, needle insertion should be at least 3 cm away from the arteriovenous anastomosis. For venous sites, cannulation site should be at least 5 cm away from the arterial needling site in order to minimize access recirculation.
   (b) Blood sample should be taken immediately after access cannulation to prevent dilution by fluid.
   (c) The syringe containing heparin with normal saline is connected to the venous needle line to remove the air and is then clamped to prevent an air embolism.
   (d) Hemodialysis session will start 3 min after injection of the initial heparin into the venous needle line in order to allow the heparin to mix in the body.

4.1.7 Complications of Cannulation

4.1.7.1 Infiltration

- An infiltration is made if the needle makes more than one hole with going into the fistula and out the other side. If infiltration occurs before the heparin injection, the needle should be removed, and two fingers should be used to press an area at least 2.5-cm wide. If infiltration occurs after the heparin injection, perform dialysis without removing the needle if the hematoma size does not increase. If the hematoma size increases, remove the needle and apply an ice bag on the area.
- When puncturing the venous site, the puncture should be made above the infiltration area whenever possible. If the puncture must be below the infiltration area, it should be 5 cm below it to prevent clots from being trapped in the needle.

4.1.7.2 Thrombosis or Stenosis of Vascular Access

- Vascular access thrombosis is highly associated with dehydration and hypotension caused by excessive hemodialysis, slow blood flow from venous stenosis, hematoma due to inexperienced puncturing, excessive pressure during hemostasis after hemodialysis, sleeping on one's arm, improper blood vessel selection, and initial use of immature blood vessels. Intimal proliferation is the main cause of stenosis, though vascular intimal damage from repeated puncturing and deficiency in the puncture technique are also causes.

4.1.8 Initiating Hemodialysis

- The inlet of the patient's arterial needle line should be connected to the end of the arterial line of the blood tube.
- The blood pump should be started with low flow rate (usually 50 mL/min) and gradually increase (to 100 mL/min) until the entire blood circuit is filled with blood. At first time, the blood circuit is filled with priming fluid. After starting blood pump, the priming fluid inside of blood circuit is replaced by blood. During this procedure, the priming fluid is disposed through the other end of blood circuit.
- After the extracorporeal circuit is filled with blood, the blood pump should be turned off, and the inlet of the patient's venous needle line and the end of venous blood tube are connected to each other.
- The blood pump is turned on after the lines are connected. At this time, the hemodialysis starts at a blood flow rate of 100 mL/min and is gradually increased to the patient's target blood flow rate. If the blood flow rate is increased too quickly, symptoms such as hypotension, sweating, and chest discomfort can occur.

4.1.9 Monitoring of Parameters

4.1.9.1 Body Weight

- Patient weight should be measured before and after hemodialysis to ensure that the target weight loss is being achieved. Dry weight refers to the post-dialysis weight when all or most of the excess body fluid has been eliminated.

4.1.9.2 Vital Signs

- It is important to assess the changes of blood pressure from the previous state of the individual patient during hemodialysis. Treatment may be required for systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg. If a patient's pulse rate increases, it may relate with anemia, ischemic heart disease, and hypotension. In many cases, body temperature may increase during hemodialysis due to high dialysate temperature or an infectious condition. Peripheral vasoconstriction as a result of hypovolemia leads to reduced dissipation of heat from the skin.

4.1.9.3 Pressure Monitors on the Arterial Blood Line

- Pressure can be monitored in the arterial blood line between patient's vascular access (arterial) and the blood pump (pre-pump pressure monitor). Pressure in the arterial blood line usually ranges from −80 to −200 mmHg. When the blood volume is insufficient from the vascular access, the pressure in the arterial line (pre-pump pressure) could decrease, which causes an alarm to sound.
- There are many causes of decreased pressure in arterial line: improper positioning of catheter, the presence of thrombus or fibrin clot inside of the catheter, abnormal position of the arterial needle, inadequately inserted needle, needle touching the blood vessel wall, hypotension, stenosis of the arterial anastomosis, twisting of the arterial line, and blood vessel collapse due to elevation of patient's arm.
- Management of decreased pressure in arterial line includes fluid administration, repositioning or reinsertion of the arterial needle, extension of the time with reducing blood flow rate, and revascularization of the stenotic vascular access.

4.1.9.4 Pressure Monitors on the Venous Blood Line

- Pressure can be monitored in the venous blood line between the blood pump and vascular access (venous side) (post-pump pressure monitor). Normal pressure in the venous blood line is between 50 and 250 mmHg.
- Causes of increased pressure in venous blood line are high arterial pressure, using a small-caliber needle, a clot in the venous line filter, stenosis or cramping in the venous side of the vascular access, improper insertion of the venous needle, and a twisted venous line.
- When a clot is suspected in the venous line or filter, the dialyzer is washed with saline. If a clot is found in the dialyzer, the venous line is exchanged for a new one, and dialysis is continued after adjusting the heparin dose.
- Obstruction in the venous needle or in a venous-side vessel can be assessed by checking for resistance while washing the needle with saline after separating the venous line from the blood pump, which has been temporarily turned off.

4.1.9.5 Venous Air Trap and Detector

- The air trap is used to prevent air embolism when returning the blood back to the patient. Thus, the air detector should be turned on at all times during dialysis.

4.1.9.6 Food and Water Intake During Dialysis

- Food intake during hemodialysis is not usually recommended. Pulmonary aspiration can be induced by hypotension or vomiting, while the food is being digested. But access to the amount of food and water intake during dialysis and the same amount of water should be removed during hemodialysis to achieve the desired post-dialysis dry weight.

4.1.10 Termination of Hemodialysis

- Heparin infusion should be discontinued usually 30 min prior to terminating hemodialysis in patients with arteriovenous fistula or graft for the proper hemostasis after removing needles from vascular access.
- Blood from the extracorporeal circuit should be returned to the patient's body using normal saline. If the patient's blood pressure is low upon termination of hemodialysis, more normal saline can be administered.

4.1.11 Removing the Needle and Hemostasis

- If pressure is applied to the vascular puncture site to control bleeding before the needle is completely removed, there may be vascular injury caused by the tip of the needle, which can result in significant bleeding and delayed hemostasis. Vascular injury can be avoided by removing the needle at the same angle and in the same direction as it was inserted.
- Hemostasis should be performed with sterile gauze, applying constant pressure for 10–15 min. Adequate pressure should be applied to the puncture site after removing the needles for proper hemostasis without clotting the vessels. If there is clotting in the vessel, there is no thrill and pulsation. After the operator sterilizes the site with disinfectant (e.g., povidone/iodine), sterile gauze should be applied to the puncture site. The patient can remove the gauze after 6–8 h.
- Post-dialysis thrill and bruit are always assessed. A swollen fistula can be treated by applying a cold compress on that day and a hot compress on the next day. Compresses should be applied for 20–30 min, with a 1-h interval between applications.

4.1.12 Post-dialysis Evaluation

1. Vital signs: Blood pressures in supine and standing positions, temperature, heart rate, and respiratory rate
2. Changes of body weight:
   - The patient body weight should be measured before and after hemodialysis, and calculate the changes of bodyweight during hemodialysis. There may be a difference between calculated ultrafiltration volume and measured pre- to post- weight change, because of failure to account for the volume of administered fluid to the patient during hemodialysis, hyperalimentation, or oral fluid ingestion.
3. Post-dialysis blood values for hemodialysis adequacy:
   - The method and timing of obtaining the blood sample may have an effect on concentrations of urea, potassium, and bicarbonate (rebound effect) at the end of hemodialysis.
   - Adequacy of dialysis, access recirculation, and cardiopulmonary recirculation based on urea nitrogen measurement can be affected by the method and timing of blood sampling. According to the KDOQI guideline, the post-dialysis blood sample for hemodialysis adequacy should be drawn after decreasing the blood flow rate (100 mL/min for 15 s) or stopping the dialysate flow rate (3 min) (Hemodialysis Adequacy 2006).

4.2 Hemodialysis Prescription

4.2.1 Rationale for Hemodialysis Prescription

Hemodialysis is a treatment that removes waste products (uremic toxins) and extra fluid and balances electrolytes (sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphate, etc.) in patients with decreased renal function. To maintain physiologic state in hemodialysis patients and improve their quality of life, proper guidelines regarding many factors should be followed. In this chapter, prescriptions involved in the regulation of the blood flow rate, dialysate flow rate, dialysate sodium, potassium, calcium, magnesium, temperature, and the selection of a dialyzer are described.

4.2.2 Basic Mechanisms Applied to Hemodialysis Prescription

4.2.2.1 Diffusion

Diffusion is the movement of a solute from a high-concentrated compartment to a low-concentrated compartment through a semipermeable membrane (Fig. 4.2a). In hemodialysis, some solutes are removed from the blood compartment by diffusion (e.g., urea and creatinine), while others are added (e.g., bicarbonate in patients with metabolic acidosis and calcium in patients with hypocalcemia). The clinical significance of diffusion during dialysis is that low-molecular-weight substances, such as urea, creatinine, endotoxin fragments, uric acid, and ammonia, can be removed. Large molecules, such as albumin, red blood cells, and bacteria, cannot pass through the semipermeable membrane. Thus, the amount of diffusion depends on the degree of each solute's concentration gradient between compartments and the molecular weight, electrical charge, and lipid solubility of the solutes. Other factors that determine diffusion are surface area, pore size, and numbers of pores (mass transfer coefficient to the solute) in the

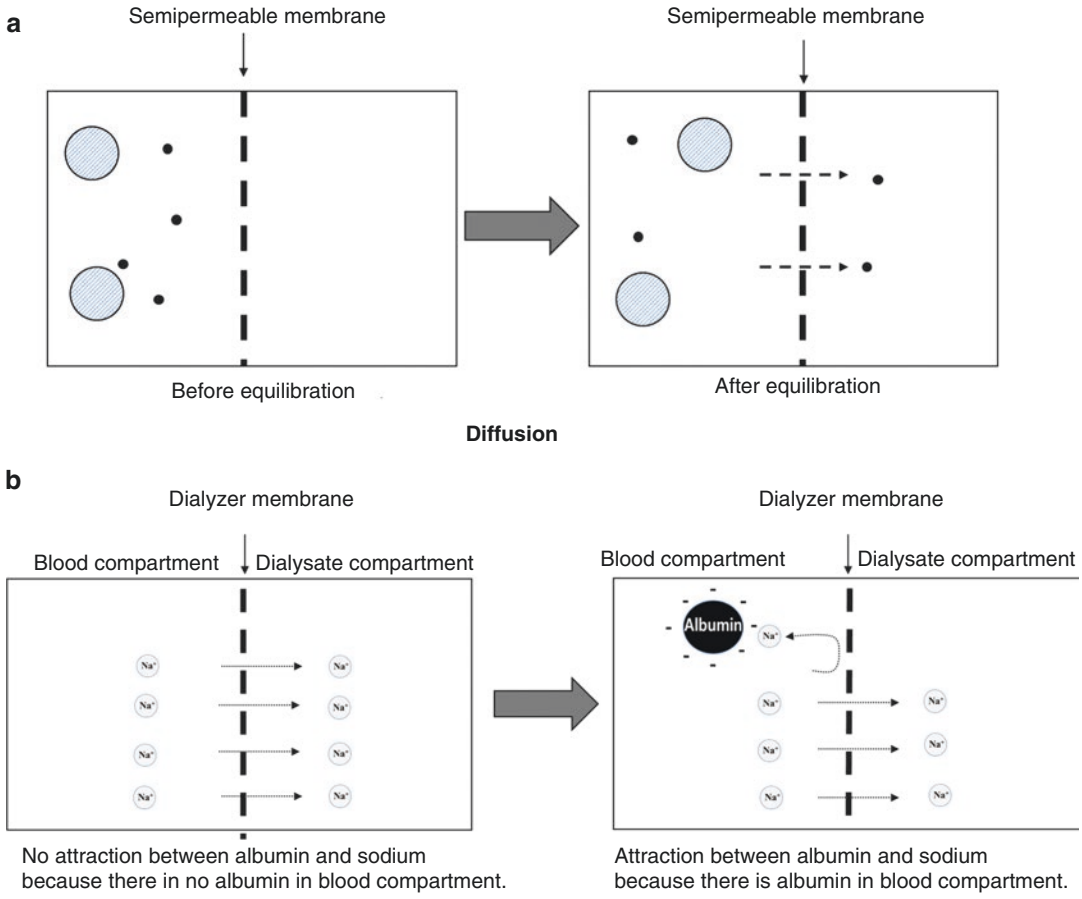

Fig. 4.2 Diffusion and the Gibbs-Donnan effect. (**a**) Diffusion is the movement of small molecules through a semipermeable membrane because of the concentration gradient of small molecules between the two compartments. Large molecules cannot cross the semipermeable membrane. The *small black circles* indicate small molecules, such as urea. The *large circles* indicate large molecules, such as albumin. (**b**) The Gibbs-Donnan effect occurs when nondiffusible albumin (an anion) attracts diffusible sodium (cation) in the blood compartment of the dialyzer and the attracted sodium crosses the dialyzer membrane less readily than sodium without albumin. *Arrows* indicate the diffusion of sodium

dialyzer membrane. Maximizing diffusion during dialysis requires a dialysate flow in the direction opposite the blood flow (counter current), a higher concentration gradient between the blood and dialysate compartments, a large surface area, and a high-flux membrane.

In hemodialysis, the diffusion of sodium ions is partially inhibited by nondiffusible protein in the blood compartment of dialyzer. Because positively charged sodium ions (cations) are attracted by large negatively charged proteins (anions) in the blood compartment of the dialyzer (Gibbs-Donnan effect), sodium will not cross the membrane as readily as small anions (Fig. 4.2b). This effect lowers sodium diffusion through the dialyzer membrane by 4–5% and varies with blood pH during hemodialysis (Santos and Peixoto 2008).

An error occurs when measuring plasma and dialysate sodium concentrations. Plasma consists of water (93% of the plasma volume) and nonaqueous components such as lipids and proteins (7% of the plasma volume). Water represents nearly 100% of the dialysate volume. Sodium is distributed only in the water component of plasma and dialysate. Over time, the plasma sodium level becomes 6–7 mEq/L higher than that of the dialysate. In practice, overestimation of plasma sodium and suppressed diffusion via the Gibbs-Donnan effect compensate for each other.

4.2.2.2 Ultrafiltration

When hydrostatic pressure changes in one compartment, water passes through a semipermeable membrane from the high-hydrostatic-pressure compartment to the low-hydrostatic-pressure compartment. That movement results in ultrafiltration (Fig. 4.3). Ultrafiltration is positively related to the pressure gradient between the blood and dialysate compartments, which is generated by a difference in the hydrostatic, osmotic, or oncotic pressure gradient. During hemodialysis, the hydrostatic pressure gradient produced by the blood pump induces ultrafiltration. Clinically, ultrafiltration is a critical mechanism for removing excessive fluid from a patient during hemodialysis. Decreased oncotic pressure in the blood compartment caused by pre-dilution can increase ultrafiltration during continuous renal replacement therapy.

4.2.2.3 Convection

During the movement of water, small molecules can pass through the semipermeable membrane.

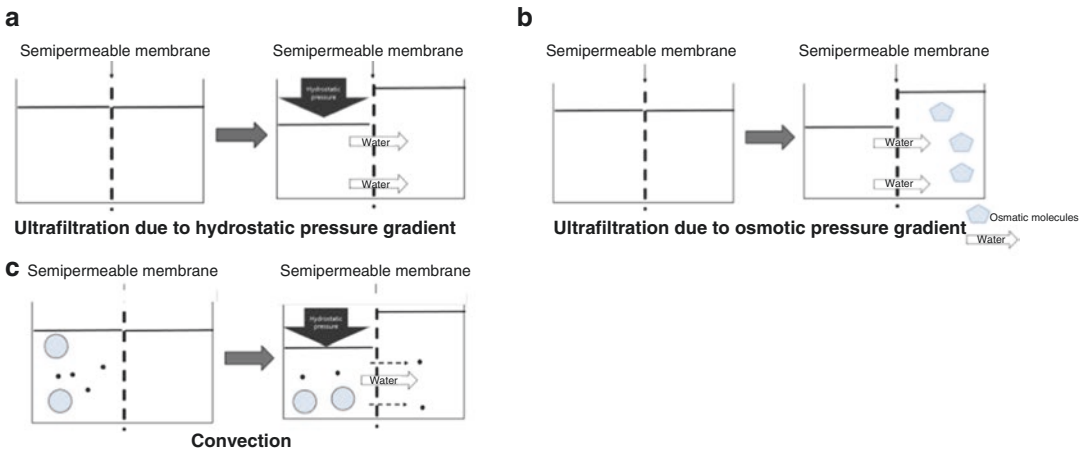

Fig. 4.3 Ultrafiltration and convection. (**a** and **b**) Ultrafiltration is the movement of water through a semipermeable membrane because of the hydrostatic (**a**) or osmotic (**b**) pressure gradient between the two compartments. The *large pentagons* indicate osmotic molecules, such as sodium or glucose and *open arrows* indicate the movement of fluid (water). (**c**) Convection is the movement of small molecules through a semipermeable membrane during fluid movement. The *small black circles* indicate small molecules, such as urea, and *open arrows* indicate the movement of fluid (water)

Convection is the movement of small molecules through a semipermeable membrane during fluid movement even when the solute concentration is the same in both compartments. Because convection can co-occur with ultrafiltration, the transport of small molecules might not be related to the concentration gradient of the solute (diffusion).

Some higher-weighted molecules, including β2-microglobulin, can be removed by convection. Convective removal of higher-molecular-weight solutes can be significant when using high-flux dialyzers (Fig. 4.3).

4.2.3 Parameters Related to Hemodialysis Prescription

Hemodialysis prescription is an integral area in nephrology. Many parameters should be considered in prescribing hemodialysis, and all hemodialysis prescriptions must be modified to account for the individualized conditions of each patient. In particular, each hemodialysis patient's electrolytes should be screened, and the dialysis protocol for each patient should correct any underlying or associated conditions. The parameters commonly used during chronic hemodialysis prescription are ultrafiltration; dialysis time and frequency; dialysate sodium, potassium, calcium, bicarbonate, magnesium, temperature, and glucose; the type of dialyzer; blood flow rate; and dialysate flow rate (Table 4.1). Prescriptions in hemodialysis may require a comprehensive approach based on medications, laboratory test findings, and patient conditions.

Table 4.1 Compositions of normal serum and dialysate for hemodialysis

	Normal serum level	Dialysate level
Sodium (mEq/L)	135–145	135–140
Potassium (mEq/L)	3.5–5.0	2.0–4.0
Calcium (mmoL/L)	1.12–1.32	1.25–1.50
Chloride (mEq/L)	102–109	98–124
Bicarbonate (mEq/L)	24	32–39
Magnesium (mmoL/L)	0.7–1.0	0.5–0.75
Glucose (mg/dL)	70–150	100–200, 0
pH	7.4	7.1–7.3

4.2.3.1 Adequacy of Hemodialysis

Brief Summary of Hemodialysis Adequacy

- A target single-pool Kt/V of 1.4 per hemodialysis session for patients treated thrice weekly is recommended.
- The minimum delivered single-pool Kt/V is 1.2 per session for thrice weekly hemodialysis patients.

Small solute (urea) clearance is the best method for measuring hemodialysis adequacy, and Kt/V is the most commonly used measure. A target single-pool Kt/V of 1.4 and a minimum delivered single-pool Kt/V of 1.2 per hemodialysis session are recommended for patients treated thrice weekly. Adequacy of hemodialysis is described more in detail in the "Adequacy of hemodialysis" chapter.

4.2.3.2 Ultrafiltration (Amount of Fluid Removal)

Summary of Ultrafiltration Prescriptions

- Determination of ultrafiltration volume from body weight before and after hemodialysis based on dry weight.
- Ultrafiltration rate higher than 13 mL/kg per hour is not recommended due to increased mortality rate.
- Diet education for dialysis patients: Low-sodium diet.
- For patients with severe hypervolemia, additional prescription with more frequent or longer hemodialysis may be needed for volume control.
- (Optional) Measurement of body fluid composition by bioimpedance analysis can be used for proper evaluation of volume status.

- (Optional) Automatically regulating ultrafiltration volume based on blood volume monitoring via a biofeedback system significantly reduces the frequency of hypotensive episodes.

The amount of fluid removed by ultrafiltration varies according to patient condition, with a range of 0–4 L per hemodialysis session. Fluid removal might not be needed in a patient with adequate urine volume and no edema. Those prescribing ultrafiltration should consider: (1) cardiac function, (2) volume status before hemodialysis, (3) number of antihypertensive drugs, and (4) vascular or autonomic response. A large volume of fluid removal can cause muscle cramps, nausea, vomiting, hypotension, decrease in residual renal function, or cardiac damage (Table 4.2). One report demonstrated that a 1 L increase in ultrafiltration was associated with a 5.1-fold increased risk of hemodialysis-induced cardiac injury (Burton et al. 2009). An ultrafiltration rate higher than 13 mL/kg per hour significantly increased the all-cause of mortality rate in the US-based Hemodialysis (HEMO) Study (Flythe et al. 2011). Therefore, an ultrafiltration rate lower than 13 mL/kg per hour is warranted during hemodialysis. To maintain hemodynamics in physiologic state, minimizing the ultrafiltration rate is recommended.

To decrease both the amount of fluid removed during hemodialysis and interdialytic weight gain, patients must be educated to reduce their sodium and water intake. The KDOQI Clinical Practice Guideline for Hemodialysis Adequacy (2015 update) recommends sodium intake reduction to control hypervolemia and left ventricular hypertrophy (<6 g/day) (KDOQI Clinical Practice Guideline for Hemodialysis Adequacy 2015). Any ultrafiltration prescription should include the amount of fluid the patients received during priming of the circuit before starting hemodialysis or returning of blood from the extracorporeal circuit to the patient's body at the end of hemodialysis.

Table 4.2 The effects of high and low ultrafiltration rates

Effects of a low ultrafiltration rate
• Hypertension
• Volume overload
Effects of a high ultrafiltration rate
• Hypotension
• Muscle cramps
• Fatigue
• Generalized malaise
• Decrease of residual renal function
• Cardiac damage (myocardial stunning)
• Increased mortality

Dry weight is a patient's body weight after hemodialysis, when excess fluid has been removed. Dry weight has been used as a target body weight after hemodialysis. The correct dry weight for a patient is determined using clinical subjective estimates, including no edema on physical examination and no intradialytic hypotension or muscle cramps. Because no equation can accurately estimate the dry weight of every patient, it can be determined by trial and error. If the dry weight is set too high, excess fluid in the body can cause pulmonary congestion and edema after hemodialysis. On the other hand, low blood pressure and muscle cramps are linked to a low dry body weight. It is highly recommended for hypervolemic patients to reduce the dry weight over time. It is also important to accomplish the change gradually (over several weeks or even longer) while assessing the patient's tolerance of the change both during and after hemodialysis in patients with maintaining hemodialysis. Additional prescriptions with more frequent or longer hemodialysis may be needed for volume control in patients with severe hypervolemia.

Many factors are involved in the changes of body weight. A patient's body weight usually increases due to generalized edema, ascites, and pleural effusion. However, patients can lose body weight through malnutrition, hyperglycemia, and insulin resistance. Thus, accurate assessment of volume state is important. A body composition monitor with bioimpedance has been used to evaluate hydration status and body constituents exactly and noninvasively. Studies suggest that bioimpedance analysis-guided fluid assessments may ameliorate volume overload and increased blood pressure (CADTH Rapid Response Reports 2015; Abbas et al. 2015).

Changes of blood volume during hemodialysis are determined by ultrafiltration and plasma refill-

ing (blood volume change = ultrafiltration volume − plasma refilling). Plasma refilling during hemodialysis is fluid movement from the interstitium to intravascular space, driven mainly by the plasma oncotic pressure gradient. Therefore, the change of ultrafiltration volume during hemodialysis might not be the same as the blood volume change. If the rate of ultrafiltration exceeds the plasma refilling rate during hemodialysis, volume deficiency results in intradialytic hypotension. The plasma refilling calculation with online measurement of blood and ultrafiltration volume is clinically important to prevent hypervolemia. Noninvasive monitoring of relative blood volume during hemodialysis allows operators to make real-time interventions in ultrafiltration. Blood volume can be indirectly estimated using an optical or ultrasonic measurement of red blood cells (e.g., HEMO$^{CONTROL®}$ in Baxter company, BVM® in FMC company, Hemox® in Belco company, Crit-Line®). However, current blood volume monitoring systems have several limitations: (1) they can detect only relative changes in blood volume, not absolute blood volume, and (2) inflammation, food intake, and fluid administration can induce measurement errors (Dasselaar et al. 2012).

Automatically regulating ultrafiltration volume based on blood volume monitoring via a biofeedback system significantly reduces the frequency of hypotensive episodes (Dasselaar et al. 2012). It can be helpful to control an individualized prescription of blood volume and to prevent the complications related with rapid change of ultrafiltration rate.

4.2.3.3 Dialysis Time and Frequency

Summary of Dialysis Time and Frequency Prescriptions

- Conventional hemodialysis: three sessions per week, 4 h per session.
- Short, frequent hemodialysis (five to seven sessions per week, <3 h per session) is also recommended.
- Diet education: Low-water and low-sodium diet if interdialytic weight gain is high.

The optimal length for a hemodialysis session for patients treated thrice weekly remains undetermined. The duration of a hemodialysis session is generally about 4 h, ranging between 2.5 and 5 h. The KDOQI Clinical Practice Guideline for Hemodialysis Adequacy (2015 update) recommends at least 3 h per session for thrice weekly hemodialysis patients with low residual renal function (<2 mL/min) (KDOQI Clinical Practice Guideline for Hemodialysis Adequacy 2015). This guideline also suggests that patients with large interdialytic weight gain, high ultrafiltration rates, poorly controlled blood pressure, difficulty achieving dry weight, or poor metabolic control might need longer hemodialysis times (KDOQI Clinical Practice Guideline for Hemodialysis Adequacy 2015).

For conventional hemodialysis patient, hemodialysis frequency is generally three to four sessions per week. Recently, the KDOQI Clinical Practice Guideline for Hemodialysis Adequacy (2015 update) recommended short, frequent, in-center hemodialysis (outpatient treatment of less than 3 h per session for five to seven sessions per week) as an alternative to conventional treatment (KDOQI Clinical Practice Guideline for Hemodialysis Adequacy 2015). Short, frequent hemodialysis can improve quality of life, decrease left ventricular hypertrophy, improve control of intradialytic blood pressure, and benefit phosphorus metabolism (Culleton et al. 2007; Chertow et al. 2010; Rocco et al. 2011). However, it also causes complications, such as the need for more frequent vascular access repair (angioplasties, thrombectomies, and surgical procedures) and hypotensive events. Thus, this modality should be practiced only in patients not at risk for vascular access problems or intradialytic hypotension.

Increasing the duration or frequency of hemodialysis sessions can increase solute clearance. Increasing the session time or adding more sessions can help patients reach their target Kt/V. However, optimal duration or frequency of hemodialysis should be customized based on the patient conditions, including adequacy of dialysis. When a patient with chronic kidney disease begins hemodialysis, the first session should be short (1 or 2 h), and the session time should gradually

increase over 3 or 4 days to prevent dialysis disequilibrium syndrome. For a hemodialysis patient with significant residual renal function, the dose of hemodialysis can be reduced. As residual renal function tends to decrease overtime, the KDOQI Clinical Practice Guideline for Hemodialysis Adequacy (2015 update) suggests frequent monitoring of residual renal function for adequacy of hemodialysis (KDOQI Clinical Practice Guideline for Hemodialysis Adequacy 2015).

4.2.3.4 Dialysate Sodium

Summary of Dialysate Sodium Prescriptions

- Recommended dialysate sodium: 135–140 mEq/L.
- Sodium level of dialysate should be equal to that of patient serum in order to achieve a neutral sodium balance during hemodialysis.
- High dialysate sodium (>140 mEq/L) can be used in patients with:
  - Hyponatremia
  - Volume deficiency
  - Intradialytic hypotension
- Low dialysate sodium (<135 mEq/L) can be used in patients with:
  - Hypernatremia
  - Increased interdialytic weight gain
  - Interdialytic hypertension
- Individualized dialysate sodium concentration according to each patient's stable pre-dialysis plasma sodium level (sodium set point) has a beneficial effect.
- (Optional) A real-time monitoring system of dialysate and blood conductivity has been used to help an individualized prescription of dialysate sodium.
- Diet education: Decreased salt diet (<6 g/day).

Adequate sodium balance (zero balance) during hemodialysis is critical to maintain body fluid and minimize ultrafiltration rates. Sodium and water overload during hemodialysis can lead to increased cardiovascular morbidity and hospitalizations. The dialysate sodium prescription can ameliorate sodium overload and its related complications in hemodialysis patients. A dialysate sodium concentration with a range from 135 to 140 mEq/L is commonly prescribed depending on patient condition. To achieve a neutral sodium balance during hemodialysis, the sodium level of the dialysate should be equal to that of patient's serum.

The dialysate sodium concentration influences plasma sodium level via diffusion and convection. Higher dialysate sodium concentration than serum sodium of patient increases movement of sodium from dialysate to the patient's blood. Thus, a high dialysate sodium concentration (>145 mEq/L) increases serum sodium level and potentiates thirst, interdialytic fluid ingestion, and weight gain after dialysis (Table 4.3). It has been demonstrated that increasing dialysate sodium by 2 mEq/L correlates with 0.17% of interdialytic weight gain (Hecking et al. 2012). High dialysate sodium concentrations should be avoided, especially in patients with hypertension or increased interdialytic weight gain. However, high dialysate sodium (>140 mEq/L) can be used in patients with hyponatremia, volume deficiency, or intradialytic hypotension.

Lower dialysate sodium concentration than serum sodium of patient increases sodium movement from the patient's blood to dialysate. A low dialysate sodium concentration (130–135 mEq/L) decreases serum sodium level and results in a decrease in plasma osmolarity. A decreased serum sodium level can cause volume deficiency and intradialytic hypotension (Table 4.3).

Table 4.3 The effects of high and low dialysate sodium concentrations

Effects of a low dialysate sodium concentration
• Intradialytic hypotension
• Cramping
• Headache
• Decreased plasma osmolarity and cellular over hydration (disequilibrium syndrome)
Effects of a high dialysate sodium concentration
• Intradialytic and interdialytic hypertension
• Increased thirst and interdialytic ingestion of water
• Increased weight gain and risk of volume overload
• Increased post-dialysis serum sodium

Therefore, low dialysate sodium concentration can ameliorate interdialytic weight gain and high blood pressure.

When a fixed dialysate sodium concentration is used for patients with variable serum sodium level during hemodialysis, the amount of sodium removed varies with serum level. Actually, total body sodium is regulated by the sodium distribution volume in the body, the amount of interdialytic sodium intake, urinary sodium excretion through residual kidney function, extrarenal sodium loss in the interdialytic period, the sodium gradient through the dialyzer, and ultrafiltration. Thus, the prescription for dialysate sodium can vary or customized to maintain a zero sodium balance during hemodialysis.

Individualized dialysate sodium prescription based on patient volume status, serum sodium level, changes in blood pressure, and other associated morbidities is an ideal strategy to avoid complications related with dysnatremia. To help individualized dialysate sodium prescriptions, "sodium set point" was introduced. It has been reported that conventional thrice weekly hemodialysis patients develop a unique and constant pre-dialysis serum sodium level over time. It is called as sodium set point. Individualized prescriptions for dialysate sodium concentrations made using a patient's sodium set point can decrease interdialytic weight gain in nortensive and hypertensive patients during hemodialysis (Eftimovska-Otovic et al. 2016). It has been demonstrated that hemodialysis with a sodium set point may have a beneficial effect on serum sodium regulation, interdialytic weight gain, and intradialytic hypotension (Basile and Lomonte 2016).

Serial measurement of dialysate and serum sodium concentration during hemodialysis is important in a customized prescription of dialysate sodium, but it is nearly impossible in practice. Thus, monitoring of conductivity has been used instead of continuous measurement of sodium level in blood and dialysate. The conductivity of a solution is related to the concentrations of ions. Blood and dialysate conductivity reflect the plasma and dialysate sodium concentrations, respectively. One mS/cm of dialysate conductivity is equivalent to approximately 10 mmoL/L of dialysate sodium. Using a continuous monitoring equipment for dialysate sodium concentration via real-time monitoring of dialysate conductivity can keep the patient's serum sodium at a target level, which might decrease the rate of disequilibrium syndrome, intradialytic hypotension, and cardiovascular instability. Many dialysis machines offer continuous monitoring system for dialysate or serum sodium. However, limitation is that conductivity measures are affected by a patient's acid-base status, temperature, and protein binding with anions such as sulfate and phosphate (Raimann et al. 2011).

The sodium level of the dialysate can vary during the course of the hemodialysis (sodium profiling). In sodium profiling, an initially high concentration of dialysate sodium is gradually reduced to a low concentration (e.g., 150 mEq/L in the first 1 h, 145 mEq/L for 1 h, 135 mEq/L for 1 h, and 130 mEq/L for the last 1 h). Theoretically, there can be a constant plasma sodium level in the physiologic range during hemodialysis. However, due to a tendency for sodium accumulation during hemodialysis, recent trends do not usually use dialysate sodium profiling.

Hemodialysis patients should consume a low-salt diet (<6 g/day) to prevent left ventricular hypertrophy and hypertension. In patients with severe and chronic hyponatremia (<125 mEq/L) or hypernatremia (>155 mEq/L), rapid correction of dysnatremia (>12 mEq/L per day) via hemodialysis can induce osmotic demyelination. Therefore, correction of dysnatremia should be limited to 0.5 mEq/L per hour with regular measurements (every 0.5 or 1 h). The optimal dialysate sodium level for daytime (quotidian) or nocturnal hemodialysis patients is not well known.

In dialysis patients, especially when they are beginning hemodialysis, low serum osmolality induces a water shift from blood to the intracellular compartment of brain cells. Increased intracranial pressure from sodium change partially contributes to the neurologic symptoms of altered mentality, focal neurological deficits, and papilledema (dialysis disequilibrium syndrome). Using a higher dialysate concentration of sodium may decrease the risk of dialysis disequilibrium syndrome for naïve hemodialysis patients.

4.2.3.5 Dialysate Potassium

Summary of Dialysate Potassium Prescriptions

- Dialysate potassium should be individualized but is generally in the following ranges:
  - If a patient's serum potassium >5.5 mEq/L → dialysate potassium is 2.0–3.0 mEq/L.
  - If a patient's serum potassium 3.5–5.5 mEq/L → dialysate potassium is 3.0 mEq/L.
  - If a patient's serum potassium <3.5 mEq/L → dialysate potassium is 3.0–4.0 mEq/L.
  - EKG monitoring is warranted if severe pre-dialysis hyperkalemia (K > 5.5), severe pre-dialysis hypokalemia (K < 3.5), or arrhythmia occur when using low dialysate potassium (<2.5 mEq/L).
  - Measurement of serum potassium concentration every 1 or 2 h if cardiac toxicity is suspected due to hyperkalemia or hypokalemia.
- Diet education: Low-potassium diet for patients with recurrent hyperkalemia.
- Underlying correctable factors:
  - Hyperkalemia (metabolic acidosis, drugs such as ARB, ACE inhibitors, nonsteroidal anti-inflammatory drugs, and β-blockers)
  - Hypokalemia (furosemide)
  - Cardiac toxicity (hypomagnesemia, hypocalcemia, QT interval – prolonging drugs such as macrolides or fluoroquinolones)
- (Optional) Dialysate potassium profiling with a constant plasma-dialysate potassium gradient can be used for severe hyperkalemic patients.

Pre-dialysis hyperkalemia or hypokalemia is associated with increased risk of sudden cardiac death in hemodialysis patients (Hung and Hakim 2015). Changes in serum potassium level per unit time are critical in cardiac complications, in addition to the absolute level of serum potassium. The risk of cardiac complications increase if hyperkalemia is overcorrected or if the serum potassium level is rapidly changed during hemodialysis. Therefore, it is important to keep serum potassium level within the normal range with minimal change during hemodialysis and in the interdialytic period. Many factors, such as excessive or poor nutritional potassium intake, certain medications, and decreased excretion of potassium through the kidneys, are linked to dyskalemia during hemodialysis. Therefore, diet education and careful prescription of medications are also needed to prevent or treat dyskalemia. However, in practice, keeping potassium serum level in the normal range is difficult in hemodialysis patients.

No consensus has been reached about the optimal dialysate potassium level or removal rate for potassium during hemodialysis. Generally, the recommended dialysate potassium range is from 2 to 3 mEq/L. A dialysate potassium concentration of 0 mEq/L is not recommended. Very low-potassium dialysate concentrations (1.0 mEq/L) can be used for hyperkalemic patients. However, the lower limit of dialysate potassium in hyperkalemic patients was suggested to be 2.0 mEq/L (Thornley-Brown and Saha 2015). In patients with predialysis serum potassium < 5 mEq/L, a low-potassium dialysate concentration (<2–3 mEq/L) is not recommended because of increased risk of sudden cardiac death (Table 4.4) (Tucker and Moledina 2016). Thus,

Table 4.4 The effects of higher and lower dialysate potassium concentrations

Effects of a low dialysate potassium concentration
• Risk of hypokalemia through overcorrection of hyperkalemia
• Risk of cardiac arrhythmia (e.g., ventricular ectopy) because of rapid decrease in serum potassium
Effects of a high dialysate potassium concentration
• Risk of hyperkalemia
• Risk of cardiac arrhythmia because of rapid increase in serum potassium

a dialysate potassium concentration between 3.0 mEq/L and 4.0 mEq can be used for patients with pre-dialysis hypokalemia.

In patients with severe predialytic hyperkalemia (K > 6.5), predialytic hypokalemia (2.5 < mEq/L), or arrhythmia, electrocardiographic monitoring might be needed. In cases of cardiac arrhythmia or risk of cardiac toxicity from dyskalemia during hemodialysis, the serum potassium level should be measured every 1–2 h. A low-potassium diet should be recommended to prevent recurrent hyperkalemia.

Nephrologist should screen for the factors underlying hyperkalemia, including metabolic acidosis, angiotensin II receptor blockers, angiotensin II-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, β-blockers, and a low dialysate bicarbonate level (metabolic acidosis). The serum potassium level will decrease after correction of the metabolic acidosis, because potassium in the blood will shift into the cells. Thus, a higher concentration of dialysate potassium can be required during correction of metabolic acidosis. Furosemide can contribute to hypokalemia. Digoxin toxicity increases in hypokalemia during hemodialysis; thus, the serum potassium level should be kept in the normal range when digoxin is administered. Other cardiac risk factors, including hypomagnesemia, hypocalcemia, and QT interval-prolonging drugs such as macrolides and fluoroquinolones, should be avoided. The serum potassium level can increase after hemodialysis as potassium shifts from cells to serum. This rebound hyperkalemia following hemodialysis can cause sudden cardiac arrest.

When a fixed concentration of dialysate potassium is used, different potassium removal rates can result in increased incidence of complications due to rapid changes in serum potassium concentration. Therefore, individualized prescriptions might be necessary. As part of the personalized prescription for dialysate potassium in hyperkalemic patients, dialysate potassium profiling has been suggested. Potassium profiling (using higher potassium dialysate in the first part of hemodialysis and lowering the concentration during the session) to maintain a constant plasma-dialysate potassium gradient reduces premature ventricular complexes (Redaelli et al. 1996; Santoro et al. 2008). A significant limitation of such an automatic system is that it needs special equipment and programs for dialysate potassium profiling. Thus, it cannot be commonly used. After treatment with low-potassium dialysate, patients with persistent hyperkalemia might need increased dialysis times or frequencies, treatment for constipation, or provision of oral potassium-binding resins.

4.2.3.6 Dialysate Calcium

Summary of Dialysate Calcium Prescriptions

- Recommended ionized dialysate calcium: 1.25–1.5 mmoL/L (2.5–3.0 mEq/L)
- High dialysate calcium (1.5–1.75 mmoL/L or 3.0–3.5 mEq/L) can be used for:
  - Hypocalcemia
  - Patients using cinacalcet
  - Parathyroidectomy patients (hungry bone syndrome)
- Low dialysate calcium (<1.25 mmoL/L or <2.5 mEq/L) can be used for:
  - Hypercalcemia
  - Adynamic bone disease

Abnormal calcium balance can cause vascular or soft tissue calcification, mineral bone disorder, electroinstability of cardiac muscle cells, and hyperparathyroidism in patients with chronic kidney disease. Predialytic plasma-ionized calcium screening should be performed to evaluate the calcium state of dialysis patients. Maintaining intradialytic and interdialytic serum calcium levels in normal range is important, but debate remains about the optimal dialysate calcium level. The range for ionized dialysate calcium concentrations is generally held to be 1.25–1.5 mmoL/L (2.5–3.0 mEq/L) (National Kidney Foundation 2003; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group 2009).

Because the dialysate calcium level is positively correlated with serum level, a higher concentration

Table 4.5 The effects of high and low dialysate calcium concentrations

Effects of a low dialysate calcium concentration
• Hypocalcemia
• Intradialytic hypotension
• Risk of heart failure exacerbation and prolonged QTc interval
• Stimulation of parathyroid hormone secretion
Effects of a high dialysate calcium concentration
• Hypercalcemia
• Risk of vascular and soft tissue calcification
• Suppression of parathyroid hormone secretion
• Reduction in vitamin D analogue dose

of dialysate calcium than patient's serum calcium can increase the serum calcium level and decrease the serum phosphate level and parathyroid hormone secretion (Table 4.5). Thus, hemodialysis patients with hypocalcemia or a negative calcium balance can be treated with high-calcium dialysate (1.5–1.75 mmoL/L; 3.0–3.5 mEq/L). High-calcium dialysate is also temporarily prescribed to patients with symptomatic hypocalcemia following parathyroidectomy (hungry bone syndrome) and to control parathyroid hormone in hyperparathyroidism (Langote et al. 2015). However, treatment with a high concentration of dialysate calcium carries the risk of vascular calcification, cardiovascular death in patients with calcium-based phosphate binder, over suppression of parathyroid hormone, adynamic bone disease, and hypercalcemia (Table 4.5).

A dialysate calcium concentration less than 1.25 mmoL/L (2.5 mEq/L) could cause increased risk of sudden cardiac death (Pun et al. 2013). Therefore, low dialysate calcium should be prescribed with care, most often to prevent vascular or soft tissue calcification and hypercalcemia due to secondary hyperparathyroidism. It can also be used in adynamic bone disease with non-calcium-based phosphate binder (Lezaic et al. 2007). The adverse effects of a low dialysate calcium concentration are possible hypotension during hemodialysis and malignant arrhythmia caused by a prolonged QTc interval, which can warrant EKG monitoring.

4.2.3.7 Dialysate Bicarbonate

Summary of Dialysate Bicarbonate Prescriptions

- Typical dialysate bicarbonate: 35 mmoL/L.
- Suggested target serum bicarbonate before hemodialysis: 22–24 mmoL/L (18–23 mmoL/L).
- If pre-dialysis serum bicarbonate is low (<20 mEq/L):
  - Evaluate other factors related to metabolic acidosis (high-protein intake, ketoacidosis, lactic acidosis, diarrhea, etc.) or compensatory state of respiratory alkalosis.
  - Use an alkali supplement with a high dialysate bicarbonate concentration (35 mmoL/L) with oral sodium bicarbonate.
  - In patients with very low pre-dialysis serum bicarbonate (<10 mEq/L), avoid rapid administration of bicarbonate to prevent the complications that accompany rapid correction of severe metabolic acidosis.
- If pre-dialysis serum bicarbonate is high (>27 mEq/L):
  - Malnutrition with poor dietary protein intake is one of the causes of pre-dialysis metabolic alkalosis.
  - Check other factors related to metabolic alkalosis or compensatory state of respiratory acidosis.
  - Decrease the dialysate bicarbonate concentration according to acid-base state and correct the cause of metabolic alkalosis or compensatory state of respiratory acidosis.
- Suggested target serum bicarbonate after hemodialysis: <28 mmoL/L (20–28 mmoL/L)

- If post-dialysis serum bicarbonate is high (>28 mEq/L):
  - Check factors related to metabolic alkalosis or compensatory state of respiratory acidosis.
  - In metabolic alkalosis, reduce alkali administration by individualizing the dialysate bicarbonate concentration.
  - In compensatory state of respiratory acidosis, carefully adjust dialysate bicarbonate concentration according to blood pH.

Table 4.6 The effects of high and low dialysate bicarbonate concentrations

Effects of a low dialysate bicarbonate concentration
• Metabolic acidosis (pre-dialysis low blood bicarbonate level)
• Chronic kidney disease-mineral and bone disorder
Effects of a high dialysate bicarbonate concentration
• Post-dialysis metabolic alkalosis (high post-dialysis serum bicarbonate level)
• Risk of hypocalcemia: Tetany
• Risk of hypoxia and decreased cardiac function
• Risk of hypokalemia

The daily acids produced by metabolism can be neutralized by the body's buffer system. The blood bicarbonate buffer system plays a critical role in regulating the hydrogen concentration in blood. Because chronic kidney disease patients have trouble in reclaiming bicarbonate from the kidneys, their blood bicarbonate levels tend to decrease, and organic and inorganic acids, including sulfate and phosphate, tend to accumulate. Metabolic acidosis is a complicated state in hemodialysis patients with negative effects on nutrition and chronic kidney disease-mineral and bone disorder (Table 4.6). During hemodialysis, increasing the concentration of dialysate bicarbonate above the serum bicarbonate level is an important way to supply bicarbonate (in metabolic acidosis) through diffusion. However, over-correcting metabolic acidosis is also harmful during and after hemodialysis. Thus, the dialysate bicarbonate concentration should neutralize blood bicarbonate before and after hemodialysis to prevent the adverse effects of both metabolic acidosis and alkalosis. Especially, hypokalemia with metabolic alkalosis significantly increases the risk of cardiac arrest. Acetate was used as an alkali source. However, because acetate had deleterious effects such as hypotension, headaches, nausea and vomiting, and hypoxemia, bicarbonate has been used in place of acetate.

As chronic kidney disease is the most common cause of simple metabolic acidosis in hemodialysis patients, the range of pre-hemodialysis serum bicarbonate is 17–27 mmoL/L in established hemodialysis patients (John 2010). The suggested target pre-dialysis serum bicarbonate level is 22–24 mEq/L (Basile et al. 2016; Locatelli et al. 2015). Many studies have shown declining outcomes in hemodialysis patients with pre-dialysis metabolic acidosis (Bommer et al. 2004). Thus, it is reasonable to maintain the pre-dialysis serum bicarbonate in the near-normal range. Maintaining a pre-dialysis bicarbonate concentration of 22–24 mEq/L might decrease the mortality associated with severe metabolic acidosis. Because the blood bicarbonate level is affected by many factors, such as a high-protein diet, acid loss from the gastrointestinal tract, residual renal function, respiratory function (respiratory acidosis or alkalosis), and nutritional status, bicarbonate prescriptions should be individualized according to acid-base state. Especially in patients with poor nutrition, pre-dialysis serum bicarbonate level can be high with increased the mortality rate. A dialysate bicarbonate concentration of 35 mEq/L is usually prescribed for maintenance hemodialysis patients. Many hemodialysis centers use a dialysate bicarbonate concentration of 32–39 mEq/L.

If pre-dialysis bicarbonate is low (<20 mEq/L), patients need alkali administration via a high dialysate bicarbonate concentration (>35 mEq/L) with oral sodium bicarbonate in interdialytic period.

If the pre-dialysis bicarbonate is very low (<10 mEq/L), larger amount of alkali administration may be needed to increase transfer of bicarbonate to blood. However, the rate of bicarbonate supplementation should be decreased to prevent complications from too rapidly correcting severe metabolic acidosis. Rapid correction or overcorrection of metabolic acidosis may increase the risks of hypocalcemia (tetany), hypoxia, decreased cardiac function and hypokalemia. Bicarbonate flux depends on the bicarbonate concentration gradient between blood and dialysate, the surface area and efficiency of the dialyzer membrane, and the blood flow rate. To prevent complications from excessively rapid correction of serum bicarbonate, reduce the bicarbonate concentration in the dialysate and the blood flow rate while monitoring the serum bicarbonate. Clinicians should evaluate the other factors associated with metabolic acidosis (high-protein intake, gastrointestinal bicarbonate loss, ketoacidosis, lactic acidosis, etc.) or compensated state of respiratory alkalosis (central nervous system stimulation, hypoxemia, drugs, cardiac failure, mechanical ventilation, etc.).

If pre-dialysis bicarbonate is high (>27 mEq/L), malnutrition with poor dietary protein intake is one of the causes of pre-dialysis metabolic alkalosis, because low protein intake results in decreased production of hydrogen ion. Clinicians also evaluate the other causes of metabolic alkalosis (upper gastrointestinal acid loss due to persistent vomiting or nasogastric suction, excess exogenous bicarbonate loads, loop diuretics, etc.) or compensated state of respiratory acidosis (airway obstructive or parenchymal lung disease, drugs that act on the central nervous system, etc.). To decrease the serum bicarbonate level, correct the cause of the metabolic alkalosis and/or respiratory acidosis. The dialysate bicarbonate concentration should be reduced based on the acid-base state.

The post-dialysis bicarbonate level is also important because metabolic alkalosis (overcorrected metabolic acidosis) can aggravate cardiovascular function, hypocalcemia and hypokalemia during hemodialysis (Table 4.6). The suggested target bicarbonate level after hemodialysis is less than 28 mEq/L. Increased serum level of bicarbonate after hemodialysis is related to metabolic alkalosis or a compensated state of respiratory acidosis. A massive flux of bicarbonate from dialysate to blood results in an increase of serum bicarbonate level (post-dialysis metabolic alkalosis; >28 mEq/L), which induces hypokalemia as the potassium shifts from blood to cells. Hypokalemia increases susceptibility to arrhythmia and leads to hypotension and hemodynamic instability. Additional concern about high bicarbonate-containing dialysate is tetany caused by hypocalcemia (Kaye et al. 1997). Thus, to reduce the complication during alkali administration, individualizing dialysate bicarbonate concentration is recommended. In respiratory acidosis, blood bicarbonate increases to compensate for CO_2 retention, thereby maintaining blood pH in the normal range. Because a rapid change in blood bicarbonate level can aggravate the body's acid-base state, careful adjustment of dialysate bicarbonate concentration according to blood pH is required.

In patients with a mixed acid-base disorder, careful interpretation of acid-base state is essential. Identifying the underlying cause of the acid-base disorder should be performed firstly, and dialysate bicarbonate should be prescribed based on arterial blood pH.

4.2.3.8 Dialysate Magnesium

Summary of dialysate magnesium prescriptions

- Ionized dialysate magnesium: 0.5 mmoL/L (1.0 mEq/L).
- Dialysate magnesium concentration less than 0.5 mmoL/L (1.0 mEq/L) is not usually recommended.
- Low dialysate magnesium (<0.5 mmoL/L or <1.0 mEq/L) can be used in hypermagnesemia.
- High dialysate magnesium (<1.25 mmoL/L or <3.0 mEq/L) can be used in severe hypomagnesemia with malnutrition.

Magnesium is an abundant intracellular cation with a physiologic role in the neuromuscular, bone, and cardiovascular systems. Normal serum magnesium levels are in the range of 0.7–1.0 mmoL/L (1.4–2.0 mEq/L; 1.7–2.4 mg/dL). Because magnesium is primarily excreted from the kidneys, the serum level of magnesium in hemodialysis patients usually increases. However, because total body magnesium is also regulated by the intestines, bones, and drugs (vitamin D increases intestinal absorption; proton pump inhibitors decrease intestinal absorption; sevelamer hydrochloride increases serum magnesium), serum magnesium level of hemodialysis patient can be normal or below normal (Mitsopoulos et al. 2005; Alhosaini et al. 2014; Schmulen et al. 1980). Therefore, regular measurement of serum magnesium is needed.

A dialysate magnesium level of 0.5 mmoL/L (1.0 mEq/L) is commonly used, with the ordinary range from 0.5 to 2.0 mEq/L. A dialysate magnesium concentration less than 0.5 mmoL/L (1.0 mEq/L) is not usually recommended. Because hypomagnesemia can cause low cardiac contractility and hypotension, a low concentration of dialysate of magnesium should be avoided in patients with hypomagnesemia.

Because the magnesium level in dialysate is positively correlated with that in serum, a low concentration of dialysate magnesium (<0.5 mmoL/L; <1.0 mEq/L) can decrease serum magnesium level during hemodialysis via both diffusive and convective processes (Table 4.7). Thus, hemodialysis patients with hypermagnesemia or a positive magnesium balance can be treated with low-magnesium dialysate (<0.5 mmoL/L or <1.0 mEq/L).

High-magnesium dialysate (<1.25 mmoL/L or <3.0 mEq/L) can be used for severe hypomagnesemia patient with malnutrition or old age. Magnesium-containing cathartics are not recommended for hypermagnesemia patients.

Table 4.7 The effects of dialysate magnesium concentration

Effects of a low dialysate magnesium concentration
• Hypotension
• Muscle cramps (due to hypomagnesemia; <0.25 mmoL/L)
Effects of a high dialysate magnesium concentration
• QT interval prolongation (due to hypermagnesemia)
• Cardiac conduction defects (bradycardia, atrioventricular block) (>4–5 mg/dL)
• Decrease in neuromuscular effects (muscle weakness, suppressed deep tendon reflex) (>4–5 mg/dL)

4.2.3.9 Dialysate Temperature

Summary of dialysate temperature prescriptions

- Dialysate temperature: 36.5 °C (35–37 °C).
- Low-temperature dialysate can be used in patients with intradialytic hypotension.
- (Optional) Cooled dialysate (0.5 °C below the core body temperature) may have a beneficial effect on hemodynamic tolerability.

The dialysate temperature is usually set to 36.5 °C (35–37 °C). High or low dialysate temperature can change the core body temperature of the dialysis patient. Increased core body temperature caused by overheated dialysate (>37 °C) results in vasodilatation, increased peripheral blood flow, and sweating. Very high dialysate temperature (>47 °C) results in protein denaturation or hemolysis. Cold dialysate temperature (35.7–36.5 °C) contributes to shivering and increased peripheral vascular resistance and arterial blood pressure (Table 4.8). Some studies showed that a low dialysis temperature (35.7–

Table 4.8 The effects of high and low dialysate temperatures

Effects of a low dialysate temperature
• Shivering
• Cardiovascular instability
• Decreased incidence of intradialytic hypotension
Effects of a high dialysate temperature
• Intradialytic hypotension
• Increased sweating
• Increased peripheral blood flow
• Protein denaturation (>45 °C)
• Hemolysis (>45 °C)

36.5 °C) is linked to decreased incidence of intradialytic hypotension, an increase in post-dialysis mean arterial pressure, and a protective effect against dialysis-associated cardiomyopathy (Toth-Manikowski and Sozio 2016; Odudu et al. 2015). Cooled dialysate (automatic regulation of dialysate temperature at 0.5 °C below the core body temperature) has a beneficial effect on hemodynamic tolerability and ischemic brain injury (Eldehni et al. 2015). As some of modern hemodialysis machines has an equipment to control of dialysate temperature, automatic cooling dialysate may be an effective and less expensive strategy to maintain hemodynamic stability and organ injury.

4.2.3.10 Dialysate Glucose

Summary of dialysate glucose prescriptions

- Commonly used dialysate glucose: 100–200 mg/dL (5.5–11.1 mmoL/L) or no glucose.
- Dialysate glucose (100–200 mg/dL) is usually used to decrease the risk for hypoglycemia and disequilibrium syndrome.

Dialysate glucose concentrations of 100–200 mg/dL (5.5–11.1 mmoL/L) are usually used as a physiologic dialysate glucose concentration to decrease the risk of hypoglycemia and disequilibrium syndrome. Glucose-free dialysate is used in some hemodialysis center.

4.2.3.11 Dialyzer

Summary of dialyzer prescriptions

- Biocompatible membranes or at least, low-flux synthetic or modified cellulose membranes should be used

Dialyzers can be classified as biocompatible or bio-incompatible, depending on whether they abnormally activate the immune system or an inflammatory response (e.g., complement activation). Dialyzers can also be sorted into cellulo se (unmodified cellulose, including cuprophane), modified cellulose, and synthetic based on the membrane material. Because free hydroxyl groups in unmodified cellulose membranes can activate an inflammatory reaction, unmodified cellulose membranes are known to be bio-incompatible. Bio-incompatible membrane including unmodified cellulose membranes is not recommended. It has been suggested that modified cellulose membranes (cellulose acetate/cellulose diacetate) may be associated with increased mortality and morbidity compared with more biocompatible synthetic membranes. Therefore, synthetic dialyzer membranes are recommended today. Dialyzers are also categorized as high-flux or low-flux according to the rate at which they remove large molecules, such as β2-microglobulin (molecular weight: 11,800 D). A high-flux dialyzer can clear larger molecules than the low-flux dialyzers used in conventional hemodialysis and has a high ultrafiltration rate (e.g., ultrafiltration co-efficiency >20 mL/mmHg per hour). Thus, most dialysis centers try to use high-flux dialyzers to improve middle-and high-molecular-weight clearance and prevent abnormal immune activation.

Recently, the KDOQI Clinical Practice Guideline for Hemodialysis Adequacy (2015 update) recommended high- or low-flux membrane with biocompatible material (KDOQI Clinical Practice Guideline for Hemodialysis Adequacy 2015). The evidence supports the use of biocompatible, low-flux synthetic or modified cellulose membranes. In large, randomized clinical trials, including HEMO and the European Membrane Permeability Outcome (MPO) study, overall mortality did not differ significantly between high-flux and low-flux groups. However, the subgroup of patients undergoing long-term hemodialysis (>3.7 years) in HEMO and the subgroup of patients with a low serum albumin level (<40 g/L) in MPO experienced a mortality ben-

efit from high-flux dialyzers. Because some studies showed decreased mortality after using high-flux dialyzers, many dialysis centers now recommend that patients are placed on high-flux and synthetic dialyzer membrane.

4.2.3.12 Blood Flow Rate

Summary of blood flow rate prescriptions

- A blood flow rate of 300 mL/min is acceptable
- Increasing the blood flow rate maximizes the delivered dose of hemodialysis (Kt/V)

A blood flow rate of 300 mL/min is acceptable, but the rate can range from 200 to 800 mL/min. The blood flow rate should be at least 200 mL/min. Blood flow rate is positively correlated with solute removal. Thus, increasing the blood flow rate helps maximize the delivered dose of hemodialysis (Kt/V) in addition to maximizing its efficiency. Sometimes, it can be difficult to achieve the blood flow rate (400–450 mL/min) because some fistulas and catheters cannot tolerate high blood flow. Patients just initiating hemodialysis should start with a lower blood flow rate (100–200 mL/min) that is gradually increased during the first three or four sessions.

4.2.3.13 Dialysate Flow Rate

Summary of dialysate flow rate prescription

- Dialysate flow rate is typically 500 mL/min.
- Dialysate flow rates higher than 600 mL/min may offer limited or no benefit.

Dialysate flow rates in hemodialysis can range from 200 to 800 mL/min, and they are typically 500 mL/min. Increasing the dialysate flow rate from 500 to 800 mL/min may increase in Kt/V. However, recent several researches have suggested that dialysate flow rates higher than 600 mL/min may offer limited or no benefit (Albalate et al. 2015; Ward et al. 2011). The dialysate flow rate is usually 2.0-fold higher than the blood flow rate (Watanabe et al. 2015).

4.2.4 Hemodialysis Prescriptions in Patients with Residual Renal Function

Residual renal function may provide some benefits to patients on maintenance hemodialysis. Preservation of residual renal function contributes to increase patient's survival, nutrition, anemia, and quality of life (Termorshuizen et al. 2004). Although there is no consensus about exact hemodialysis prescription to preserve residual renal function, several suggested strategies have been suggested.

As hemodialysis with ultrafiltration may induce renal injury, personalized prescription with minimal ultrafiltration, but, an adequate dose of hemodialysis is needed, especially for the patient who is starting hemodialysis for the first time or has residual renal function. As an individualized therapy, the dose of hemodialysis is adjusted based on residual renal function in incremental hemodialysis (Park et al. 2016). Incremental hemodialysis has been suggested as a kind of hemodialysis prescription with increasing the dialysis dose according to residual renal function (e.g., once-weekly or twice-weekly hemodialysis). Using high-flux and biocompatible membrane can provide greater preservation of residual renal function. Intradialytic hypotension or acute kidney injury can aggravate residual renal function. So far, they should be avoided. To achieve adequacy of hemodialysis, monitoring residual renal function is critical for hemodialysis patients. One report suggested that monitoring residual renal function with residual renal urea clearance and urine volume should be performed every month to four times in the first year (Mathew et al. 2016).

Other factors not related with hemodialysis may affect the residual renal function; nephrotoxic agents (radiocontrast, nonsteroidal anti-inflammatory drug, aminoglycoside), high blood pressure, high-protein diet. Thus, control of blood pressure and a low protein-diet are required to preserve residual renal function. Peritoneal dialysis can be recommended because this modality preserve the residual renal function.

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Technological Aspect for Hemodialysis

5

Yoshihiro Tange and Shingo Takesawa

5.1 Introduction

Recent progress in artificial kidney has increased the removal of uremic toxins. However, these improvements are not ideal to prevent chronic kidney disease (CKD)-related complications and improve mortality. The fundamental concept for selection of dialysis membrane is based on solute removal capability and biocompatibility. Theory of hemodialysis (HD) is known as some chemical engineering phenomenon. Small molecular weight (MW), such as urea and creatinine (Cr), are strongly affected by diffusion (Shinaberger 2001). On the other hand, low molecular weight proteins such as β_2-microglobulin (BMG: MW 11.8 kDa) (Gejyo et al. 1985) and α_1-microglobulin (AMG: MW 33 kDa) are affected by filtration.

Hemodiafiltration (HDF) is a combination of diffusion and filtration and, therefore, can separate small molecules from large molecules (Fig.5.1). Diffusion and filtration are significantly important to remove solutes using dialysis membranes. In addition, some membrane materials can adsorp proteins. Therefore, diffusion, filtration, and adsorption are key for solute removal.

What solutes should be removed is significantly important from the point of view of technological aspect introduced in this chapter.

Small molecular weight (molecular weight less than 1000) are strongly affected by diffusion. Large molecular weights (molecular weight over 5000) are strongly affected by filtration. Solute permeability is affected by membrane pore size (Fig. 5.2).

As reference, diffusive coefficient values are plotted in this figure (Klein et al. 1976, 1979; Colton et al. 1971; Pitts et al. 1978; Holland et al. 1978). Small molecular weight solutes are affected by diffusion, whereas large molecular weight solutes tend to be lower than small molecules.

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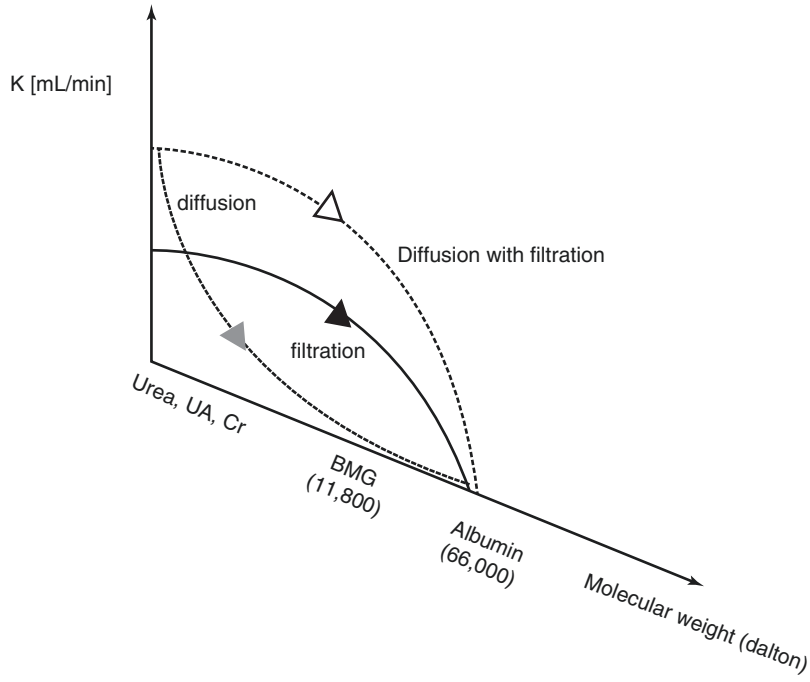

Fig. 5.1 Relationship between molecular weight and clearance (*K*)

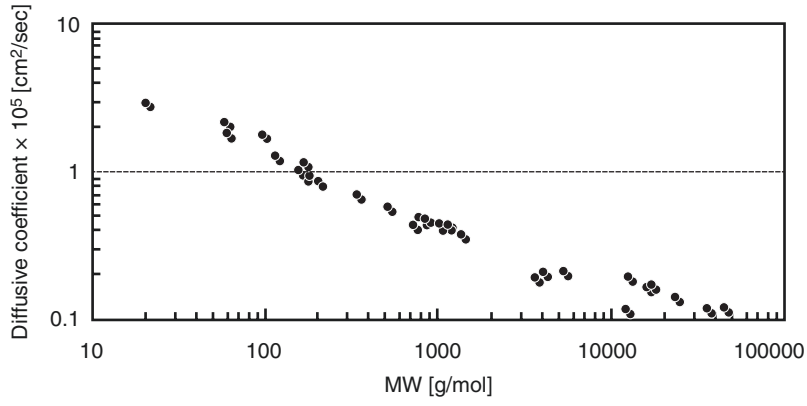

Fig. 5.2 Relationship between molecular weight and diffusive coefficient.

5.2 Theatrical

5.2.1 Dialyzer Performance: Clearance (*K*)

Clearance (*K*) can calculate from the blood sample of inlet and outlet dialyzer. In the case of small molecules, blood flow (Q_B) is used for *K*. On the other hand, low molecular weight proteins, such as BMG, calculation *K* should use plasma flow rate (Q_P), because low molecular weight proteins cannot pass through the red blood cell wall. Therefore, *K* of small molecules is not over the Q_B. Low molecules should use not Q_B but Q_P. As the *K* is defined by Eq. (5.1),

$$K = \frac{\dot{m}}{C_{Bi}} \tag{5.1}$$

$$\dot{m} = \left(\text{inlet amount}\right) - \left(\text{outlet amount}\right) \tag{5.2}$$

Therefore,

$$K\left[\text{mL}/\text{min}\right] = \frac{C_{Bi} \times Q_{Bi} - C_{Bo} \times Q_{Bo}}{C_{Bi}} \tag{5.3}$$

Dialysis efficiency: Reduction ratio (R) and removal amount (M)

$$R[\%] = \frac{C_{B(0)} - C_{B(t)}}{C_{B(0)}} \times 100 \quad (5.4)$$

where

$\dot{m}$: The amount to be removed per minute

C_{Bi}: inlet of concentration (g/L)
C_{Bo}: outlet of concentration (g/L)
$C_{B(0)}$: concentration at zero minutes (g/L)
$C_{B(t)}$: concentration at t minutes (g/L)
Q_{Bi}: inlet of blood flow rate (mL/min)
Q_{Bo}: outlet of blood flow rate (mL/min)

$$M[\mathrm{g}] = C_{Do} \times (Q_D + Q_F) \quad (5.5)$$

R and M are strongly affected by patient's body weight, that is, R becomes higher in patients with small body weight, whereas M becomes higher in patients with large body weight. M also proves to be proportional to the initial concentration in the blood ($C_B(0)$).

Directly comparing M does not make sense because higher M implies larger removal or higher concentration. After that, the ratio of M to $C_B(0)$, $M/C_B(0)$, was introduced for comparison. In terms of clear space (CS), or the removal space by treatment (Akihiro Yamashita et al. 1982), the patient's side and dialyzer side both can be evaluated. The dimension of CS is "L." CS occurs when $M/C_B(0)$ shows a body fluid volume at which the concentration of solute of interest becomes zero. CS has been used to evaluate for treatment (Kashiwagi et al. 2013; Nagaoka et al. 2011).

$$\mathrm{CS}[L] = \frac{M}{C_B(0)} \quad (5.6)$$

5.3 Solute Removal Characteristics by Dialyzer

There are some materials used as dialyzers, which recently can be of three types, namely, low flux, high flux, and super flux. The solute removal characteristics of these dialyzers are different. When compared, low-flux and super-flux dialyzers are completely different (Fig. 5.3).

R and K of KF-15 (EVAL) and APS-15E (PS) were calculated clinically. KF, low-flux; and APS, super-flux. K was measured for 1 h after the start of HD treatment. Q_B and Q_D were set at 200 and 500 mL/min, respectively, and Q_F was 10 mL/min/m^2.

5.4 Kinetic Modeling for Blood Purification in Critical Care

From an in vitro study, solute removal experiment was reported (Mineshima 2015). In continuous hemodialysis (CHD) experiments, the Q_D should be required at least twice the Q_B for sufficient removal of small molecular substances. In the continuous hemodiafiltration (CHDF) experiments, the Q_F is about one-fourth of Q_B value, and the Q_D should be set up at least twice the Q_B value.

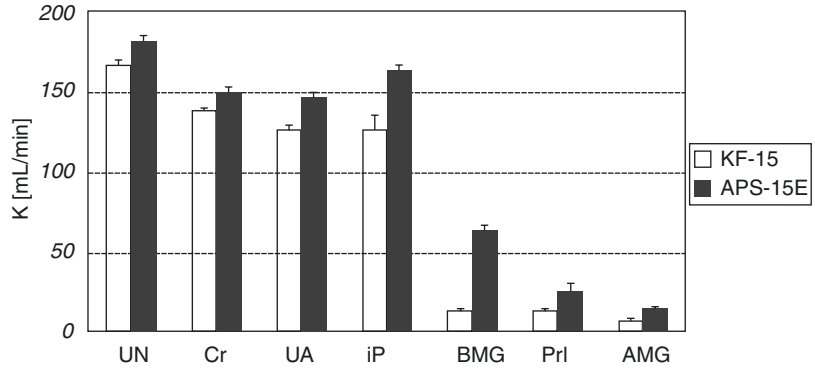

Fig. 5.3 Comparison in reduction ratio and clearance between low-flux and super-flux dialysis membrane

5.5 Dialyzer Reuse

To save medical costs, dialyzer reuse is practically universal in all the developing countries of Asia (Prasad and Jha 2015). However, the reuse practice is not standardized. Dialyzer reuse is an efficient cost-saving method that allows the use of more efficient and expensive biocompatible synthetic membranes, thereby providing high-quality dialysis to individuals living in countries with limited medical resources without compromising the safety or effectiveness of the treatment (Dhrolia et al. 2014). There was evidence of a higher relative risk of hospitalization (but not mortality) for dialyzer reuse compared with single-use dialysis (Manns et al. 2002). Chemicals such as sodium hypochlorite, peracetic acid, etc, are used for disinfection.

5.6 Evaluation for HD Treatment in Clinical

Comparing different membrane materials is difficult since few membranes adsorp some proteins. Evaluation of dialysis membrane was shown as clearance (*K*), reduction ratio (*R*), removal amount (*M*), and clear space (CS).

We evaluated BMG of *R* and *M* for three different membranes, namely, polysulfone (PS), polymethylmethacrylate (PMMA), and cellulose triacetate (CTA), in five patients under the same hemodialysis conditions. Membrane characteristics are completely different in every dialyzer. Therefore, it is required to evaluate dialyzers. Especially, PMMA can strongly adsorp BMG; therefore evaluation using spent dialysate such as CS and *M* is difficult. PMMA membrane can adsorp high molecular weight pathogenic substances that cannot be removed by other dialysis membranes, such as cytokines (Yamashita and Tomisawa 2010). However, the precise adsorption mechanism remains unknown and needs to be elucidated for potentially achieving more efficient removal of these pathogenic substances (Ooishi et al. 2014). In this case, evaluation from patient's blood side such as *K* and *R* is effective.

Comparison between BMG *R* and removal amount of BMG using PS (PS-1.9 H), CTA (FB-210U), and PMMA (BG-2.1 U) in five patients. Condition of this evaluation is the same. PMMA has a strong adsorption for BMG. Therefore, BMG does not appear in spent dialysate. However, *R* for BMG shows high. PMMA membrane has strong adsorption compared to another membrane. In this case, *K* and *R* are effective to evaluate dialyzers (Fig. 5.4).

New dialysis membrane has large pore radius. However, proteins such as albumin come into contact and/or plug the dialysis membrane. It is called fouling. In this case, albumin leakage appears higher only in the early stage of treatment (Fig. 5.5).

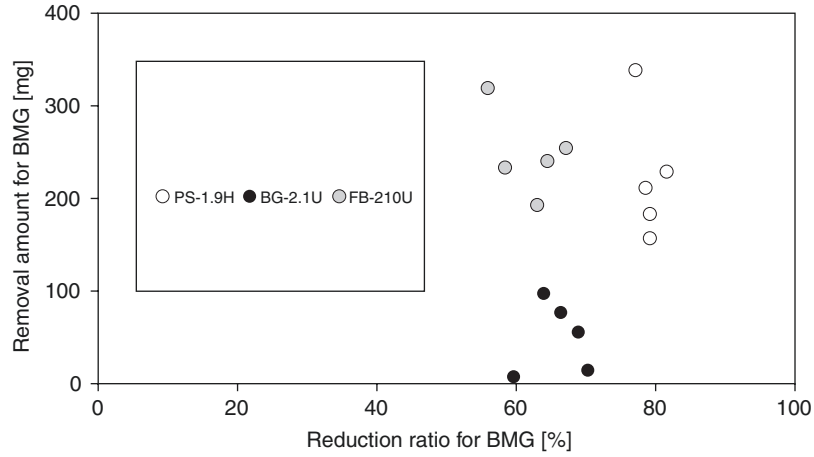

Fig. 5.4 Relationship between BMG reduction ratio and removal amount

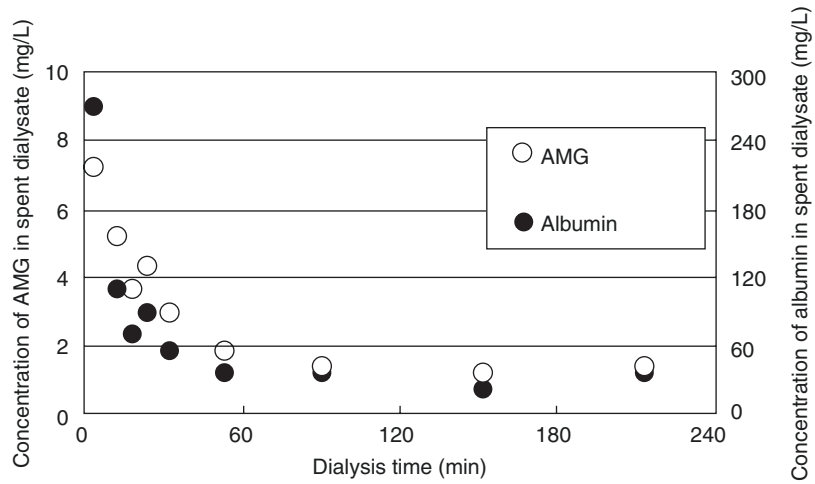

Fig. 5.5 Changes in albumin leakage during hemodialysis

5.7 Internal Filtration

High-flux membrane can be used in not only diffusion but also filtration. Blood flow through the inlet becomes higher than the dialysis fluid flow. On the other hand, blood flow through the outlet becomes lower than that at the dialysis fluid side. In high-flux dialysis membrane, filtration occurs from the dialysate flow to the bloodstream. It is called back filtration. Low molecular weight proteins can be removed by internal filtration (Dellanna et al. 1996), which can be estimated by the Doppler ultrasound method (Mineshima 2011; Sato et al. 2003).

5.8 Biocompatibility and Quality for Dialysis Fluid

Endotoxin (ET) is a component of the outer membranes of Gram-negative bacteria, which are released upon death of these bacteria. ET causes some symptoms during HD. Purification of dialysis fluids is important when high-flux membrane is used because back filtration or back diffusion can occur (Hoenich et al. 2009). It is known that ET leaks in high-flux membranes. In 2000s, our group studied about SC of ET in various dialysis membranes in simulated circulation model (Shinkai et al. 2001). As a result, dialysis membranes leaked ET (Fig. 5.6). This is the reason why purification of dialysis fluid should be ET-free when using high-flux dialysis membrane.

Yamamoto et al. demonstrated in vitro that dilution and pH change of dialysate facilitate indoxyl sulfate (IS) dissociate from albumin (Yamamoto et al. 2013). The pre-dilution mode can dilute the blood before hemodiafilter in online HDF therapy. This method also facilitates the dissociation of IS from albumin by dilution and removal of dissociated IS (MW = 213) by diffusion. H2 application to HD solutions appears to ameliorate inflammatory reactions and improve BP control. This bioactive system could provide a novel therapeutic option for uremia control (Nakayama et al. 2010). We focused on IS and developed a dialysate containing high dissolved hydrogen. We examined in vitro whether it is possible to separate IS from albumin. IS can be easily separated by dilution. This study demonstrated that hydrogen water promoted IS to dissociate from albumin during HD therapy. More beneficial effects would be expected in the combination of pre-dilution mode online HDF with hydrogen water (Tange et al. 2015).

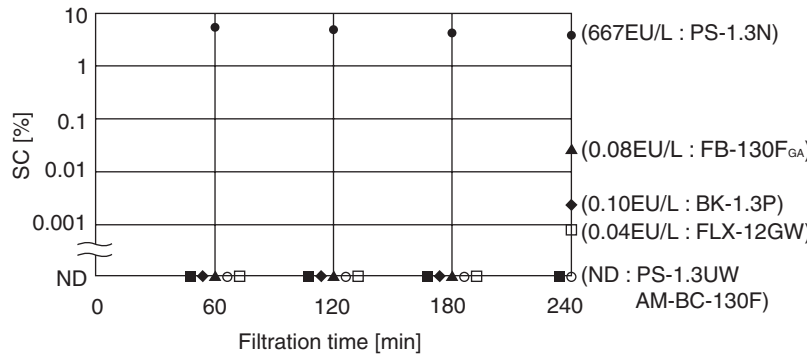

Fig. 5.6 Changes in sieving coefficient of endotoxin in various membranes

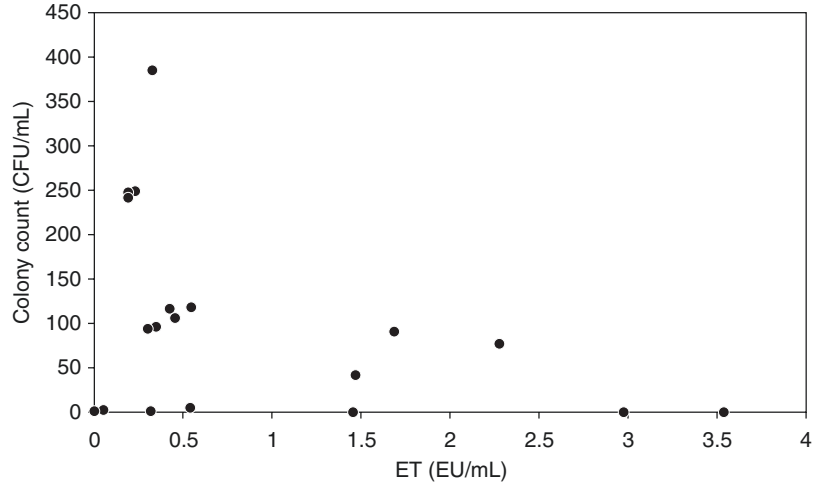

Fig. 5.7 Relationship between ET and bacteria colony count using R_2A sheet

5.9 New Treatment Mode Using Ultrapure Dialysis Fluid

To manage ET and bacteria for dialysis fluid, online hemodiafiltration (HDF) was admitted in Japan. There is no correlation between ET values and bacteria count (Fig. 5.7). Therefore, evaluation water purification should be both ET and bacteria count. To safely control ultrapure dialysis fluid, supplemental fluid can be used as priming solution instead of saline. Moreover, to enhance back filtration, intermitted infusion HDF can be applied as new HDF mode from Japan (Mineshima and Eguchi 2013). To use ultrapure dialysis, fluid can reduce medical cost and enhance solute removal efficacy.

There are no correlation between ET and colony counts. Therefore, to evaluate water quality, both ET and bacterial count are necessary.

Conclusion

Solute removal capability and biocompatibility are significantly required for selection of dialysis membrane. Evaluation for dialysis membrane from blood side and/or spent dialysis fluid has some formula. The combination of both sides is strongly needed to select for dialysis membranes. Moreover, from the viewpoint of dialysis fluid, water purification contributes to complication in hemodialysis patients.

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Flux of Dialysis Membrane: Benefit and Risk

6

Tadashi Tomo

6.1 Introduction

Hemodialysis is a process of purifying the blood of patients with acute or chronic renal failure. It removes uremic toxins from the blood through a diffusion process and supplies a buffer, such as bicarbonate, and necessary electrolytes through a semipermeable membrane.

Hemodialysis was first applied to humans in 1945 by Kolff et al. Since then, a significant progress has been made on the dialysis membrane as an artificial kidney, and there has been an effort to remove middle molecules and protein-bound molecules as well as small water-soluble molecules such as urea nitrogen and creatinine.

In addition to conventional hemodialysis, filtration blood purification therapy such as hemodiafiltration or hemofiltration with high-volume replacement fluid became available, so there has been a need to develop blood purification membrane with high water permeability.

On the other hand, the increased permeability of dialysis membrane to solutes and water enhances backfiltration or back diffusion from dialysate to blood. Therefore, purification of dialysis fluid is essential to avoid contamination of blood with endotoxin fragments and bacterial DNA fragments.

Here, we review the clinical effects and risks of high-flux dialysis membrane.

6.2 Flux of Dialysis Membrane

Traditionally, the term "flux" referred to water permeability. Currently, the term usually refers to both water and solute permeability. In general, "high-flux membrane" refers to the membrane with high permeability to solutes such as middle molecules and protein-bound molecules as well as to water.

6.3 Advances in Membrane Materials and Improvement in Flux (Water and Solute Permeability)

Kiil-type dialyzer and coil-type dialyzer were used before, but they were replaced by hollow fiber-type dialyzer (or plate-type dialyzer). In this article, the membrane materials that had been used for Kiil-type dialyzer and coil-type dialyzer are not addressed.

Hollow fiber membrane materials are made of cellulose (plant-based materials such as regenerated cellulose and cellulose triacetate) and synthetic

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polymers (polyacrylonitrile, polymethyl methacrylate, polysulfone, polyether sulfone, ethylene vinyl alcohol copolymer, polyester polymer alloy, and polyamide).

The materials for cellulose-type membranes have gradually changed from cuprammonium rayon to cellulose diacetate to cellulose triacetate. The materials for synthetic polymer membranes have changed from polyacrylonitrile or polymethyl methacrylate to polysulfone types (polysulfone and polyether sulfone).

6.4 Changes in Targeted Uremic Toxins

The uremic toxins that can be removed by renal replacement therapy such as hemodialysis have been significantly changed. There has been an effort to remove middle molecules as well as small water-soluble molecules such as urea nitrogen and creatinine. In Japan, Shimojo et al. found that β2-microglobulin was a cause of dialysis amyloidosis. In response to this, dialyzers that can remove β2-microglobulin have been developed (Gejyo et al. 1986).

In 2006 "a functional classification of dialyzer for the medical fee reimbursement" was developed in Japan. In this classification system, the function of dialyzer is classified according to the levels of clearance of β2-microglobulin, and medical fee for the use of dialyzer is set based on the function. The dialyzers that can remove more β2-microglobulin became expensive. Under the medical imbursement system in Japan, there is a tendency that the dialyzers that can remove more β2-microglobulin are increasingly used (Nakai et al. 2010).

The molecular weight of β2-microglobulin is 11,800 Da. A study has reported that there are uremic toxins with a molecular weight exceeding 11,800 Da (Vanholder et al. 2008). In Japan, many dialyzers that can remove middle molecules such as α1-microglobulin have been developed. Those with higher permeability to proteins including albumin have also been developed.

6.5 Water Flux of Membrane

Here, we look at water flux of membranes. During the era when cuprammonium rayon was mainly used as a membrane material, it was difficult to improve water permeability of the membrane. After the introduction of synthetic polymer membranes such as polysulfone and polyether sulfone, the water permeability of membranes dramatically increased. As a result, hemodiafiltration with higher-volume replacement fluid (16 L or more in post-dilution HDF and 60 L or more in pre-dilution HDF per one session (4 h)) became available (Masakane 2016).

6.6 Risks Associated with High-Flux Membranes

6.6.1 Backfiltration of Pyrogens

Backfiltration and back diffusion of dialysate are the major risks associated with high-flux membranes. In blood purification therapy such as dialysis, diffusion of uremic toxins from blood to dialysate occurs, and, simultaneously, diffusion of uremic toxins from dialysate to blood can also occur. The increased permeability of membranes (solutes and water) enhances back diffusion and backfiltration. If the dialysate is contaminated, it is expected that pyrogens in the dialysate such as endotoxin fragments and bacterial DNA fragments enter into blood. The pyrogens stimulate neutrophils and monocytes and enhance production of free radicals and inflammatory cytokines, leading to microinflammation and subsequent development of dialysis-related complications. Therefore, biological contamination of the dialysate must be avoided especially when high-flux dialysis membrane is used (Fig. 6.1).

Traditional cellulose-type membranes are known to have a lower adsorption capacity for pyrogens. On the other hand, synthetic polymer membranes also have a higher adsorption capacity for pyrogens, which may contribute to prevent back diffusion and backfiltration of pyrogens. However, even in the synthetic

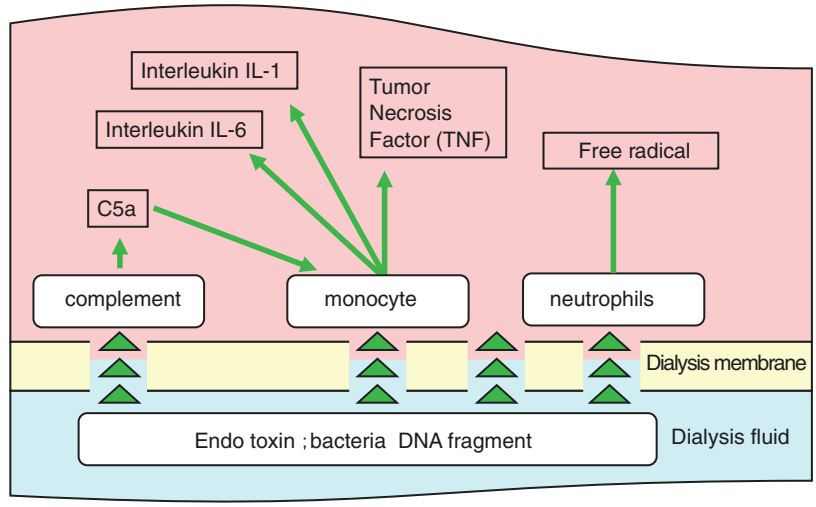

Fig. 6.1 Backfiltration, back diffusion of pyrogen, activation of complement, monocyte, neutrophils

Table 6.1 JSDT Standard on microbiological management of fluids for hemodialysis 2008

• Dialysis water (reverse osmosis (RO) water)	
Bacteria: <100 CFU/mL	Endotoxin: <0.050 EU/mL
• Standard dialysis fluid	
Bacteria: <100 CFU/mL	Endotoxin: <0.050 EU/mL
• Ultrapure dialysis fluid	
Bacteria: <0.1 CFU/mL Endotoxin: <0.001 EU/mL (less than the detection limit)	
Note: The action level shall be set depending on the quality condition of each facility, typically at 50% of the maximum allowable level, except for the endotoxin level of ultra-pure dialysis fluid	
• Online prepared substitution fluid	
Sterile and non-pyrogenic Bacteria: $<10^{-6}$ CFU/mL	Endotoxin: <0.001 EU/mL (less than the detection limit)

polymer membranes with a higher adsorption capacity, it is difficult to block back diffusion and backfiltration of pyrogens because the mean membrane pore size is large.

In 2008, the Japanese Society for Diabetes Therapy published "Standard on Microbiological Management of Fluids for Hemodialysis and Related Therapies," which is the most strict standard in the world (Kawanishi et al. 2009) (Table 6.1).

6.6.2 Loss of Necessary Elements such as Albumin in the Body

In dialysis therapy for patients with end-stage kidney disease (ESKD), there has been an effort to remove middle molecules and protein-bound molecules as well as small water-soluble molecules (Vanholder et al. 2008). To remove protein-bound molecules, the membrane with larger pore size is needed, but it also removes necessary elements such as albumin. Therefore, there is a risk of loss of necessary elements in the body (Fournier et al. 2015).

6.7 Does High-Flux Membrane Contribute to Improving Survival?

The flux (solute and water permeability) of membrane has been increased to remove uremic toxins with larger molecule toxins. Here, we look at the effect of high-flux membrane on survival of dialysis patients.

The membrane permeability outcome (MPO) study, a 3-year observational study, investigated the effect of membrane type on patient survival by comparing the survival rates between dialysis patients using high-flux membrane (mean UFR, 44.7 mL/min) and those using low-flux membrane (mean UFR, 9.8 mL/min). The study also compared the survival rates between the two groups according to the presence/absence of diabetes mellitus and hypoalbuminemia (≤4 g/dL or >4 g/dL). Overall, there was no significant difference in survival rates between the two groups. However, subanalysis showed that patients with diabetes and patients with hypoalbuminemia had significantly higher survival rates in the high-flux group compared with the low-flux group. In addition, the blood concentration of β2-microglobulin was significantly lower in the high-flux group compared with the low-flux group (Locatelli et al. 2009).

On the other hand, the Dialysis Outcomes and Practice Patterns Study (DOPPS) investigated the effects of biocompatibility and flux of membrane on survival rates and reported that there were no significant effects on survival rates (Yokoyama et al. 2008).

A meta-analysis of 33 studies (3820 patients) based on the Cochrane database revealed that the cardiovascular death rate was 15% lower in the high-flux group than in the low-flux group, although all-cause mortality did not differ significantly between the two groups (Palmer et al. 2012).

Further studies are required to confirm the effect of high-flux membrane on survival of dialysis patients.

6.8 Summary

The solute permeability of dialysis membrane has significantly improved. This is largely attributable to an effort to remove not only small water-soluble molecules but also middle molecules and protein-bound molecules as well. Furthermore, with increasing water permeability of the membrane, hemodiafiltration with high-volume replacement fluid has become available.

However, the increased flux (solute and water permeability) of membrane enhances backfiltration and back diffusion from dialysate to blood. If the dialysate is contaminated, the pyrogen enters into the blood and can cause microinflammation. Therefore, dialysate purification is essential for strict management.

Because there is no ample evidence of the effect of high-flux membrane on survival of hemodialysis patients, further studies are needed.

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Anticoagulation

7

Naoki Kimata and Kenichi Kokubo

7.1 Anticoagulation for Hemodialysis

Naoki Kimata

7.1.1 Introduction

Anticoagulation in hemodialysis is targeted to prevent activation of coagulation cascade. Adequate anticoagulation procedures rely on the basic knowledge of hemostasis and the coagulation cascade. This chapter focuses on the principles of anticoagulation and the currently available main anticoagulants used in routine hemodialysis procedures.

7.1.2 Unfractionated Heparin (UFH)

UFH is the most common anticoagulant used for maintenance hemodialysis in the world. The reasons for the spread, as it is easy to administer, has a short half-life and low cost. UFH preparations constitute a mixture of anionic glycosaminoglycans of varying molecular size from 3000–35,000 Da. The main action of heparin on the coagulation system is by binding to antithrombin III and enhancing its activity 1000–4000-fold. Antithrombin inactivates thrombin, factor Xa, and to a lesser extent factors IXa, XIa, and XIIa (Fig. 7.1).

Application of heparin during hemodialysis requires an initial loading dose and followed by a maintenance dose. Although the heparin dosage has not been standardized in the United States and Japan, the European best practice guidelines for HD recommend administering 50 IU/kg UFH into the arterial access needle for an initial loading dose. The maintenance dose of heparin is 800–1500 IU/h, given via constant infusion into the arterial line using an infusion pump (EBPG Expert Group on Haemodialysis 2002a). Alternatively, the maintenance dose can be given as repeated bolus injection. During intermittent HD, the patient is systemically anticoagulated. This maintenance infusion is stopped 30–60 min before the end of treatment to reduce bleeding times from fistula puncture sites, if needed (Kessler et al. 2015; Fischer 2007).

In UFH dose adjustment, activated coagulation time (ACT: 80–120 s) or activated partial thromboplastin time (aPTT: 24–40 s) adjusts to 1.5–2.0 times above normal range.

In patients at high risk of bleeding, UFH still is the most frequently used agent for anticoagulation in the world. The earliest approach was regional heparinization of the dialysis circuit.

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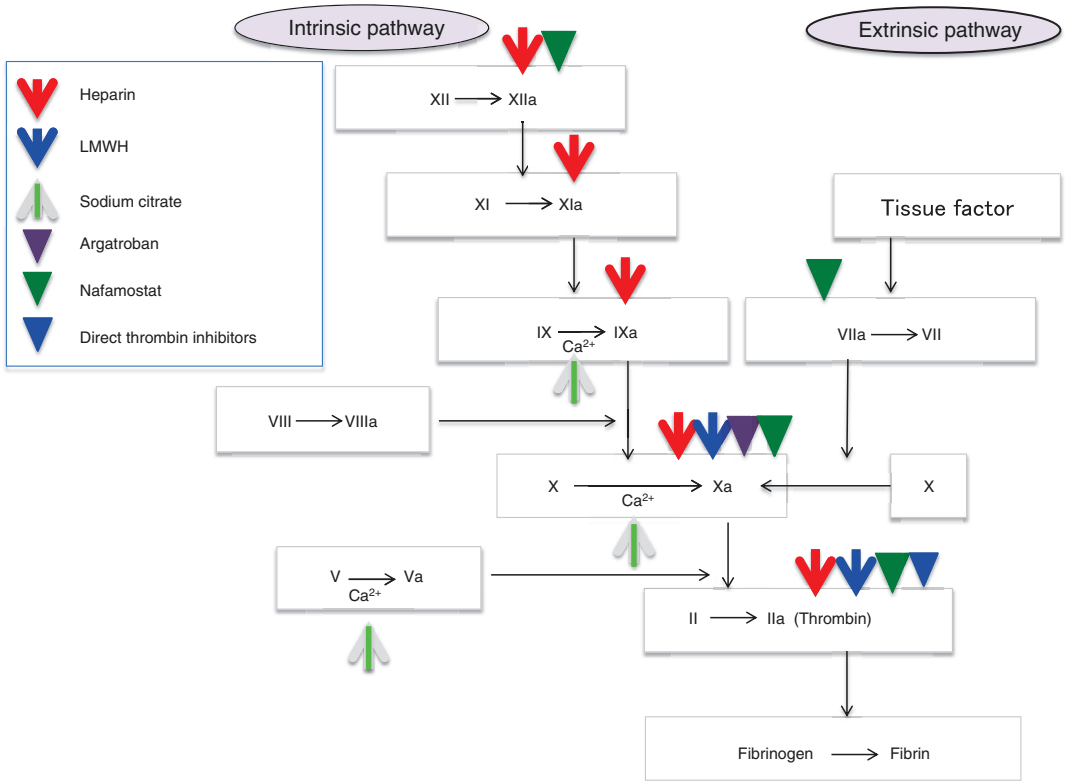

Fig. 7.1 Targets of anticoagulants within the coagulation cascade

Based on the ability of protamine to neutralize the anticoagulant effect of heparin, this technically complex method has been abandoned to other methods such as use of low-dose heparin or heparin-free dialysis (Kessler et al. 2015; http://www.uptodate.com/contents/hemodialysis-anticoagulation).

The heparin-free hemodialysis protocol requires pretreating both the dialyzer and blood lines with 2000–5000 units of heparin contained in a liter of normal saline. The heparinized saline is flushed from the extracorporeal lines prior to the start of the dialysis treatment so that heparin is not administered to the patient. Extracorporeal blood flows are rapidly increased to 250–500 mL/min and maintained throughout the treatment, and 25–30 mL saline flushes are administered every 15–30 min into the arterial tubing line (http://www.uptodate.com/contents/hemodialysis-anticoagulation).

The minimum-dose heparin hemodialysis protocol usually involves boluses of 500 units of heparin every 30 min to keep the activated clotting time >150 but <200 s. Alternately, a continuous infusion of heparin with frequent activated clotting time (ACT) monitoring can be used to achieve the same degree of anticoagulation (http://www.uptodate.com/contents/hemodialysis-anticoagulation).

Side effects of heparin are increased bleeding risk, heparin-induced thrombocytopenia (HIT), hypertriglyceridemia, anaphylaxis, hyperkalemia, and possibly bone mineral disease. HIT is a life-threatening complication associated with heparin treatment, where antibodies to heparin–platelet complexes can lead to platelet activation and aggregation. The diagnosis of HIT is primarily based on the course of reduction in platelet count and/or the development of thromboembolic event during treatment with heparin. HIT may develop

in two distinct forms, type I and type II. HIT type I is a nonimmune heparin-associated thrombocytopenia, within the first 2–3 days of heparin therapy. Direct heparin-induced degranulation of platelets can result in a modest reduction in platelet count (<100,000/mL). Platelet count increases subsequently even though heparin use is continued. HIT type II which is an immune-mediated disease may present from 4 to 10 days after initiating heparin therapy. There is antibody formation against the complex of heparin and platelet factor (Fischer 2007; http://www.uptodate.com/contents/hemodialysis-anticoagulation).

If HIT is suspected, any form of heparin including LMWH or heparin flushes have to be stopped, including any "heparin lock" solutions for dialysis or other catheters. Furthermore, the European best practice guideline recommends the use of therapeutic doses of an alternative nonheparin anticoagulant in patients with strong suspicion of HIT. Candidates are the direct thrombin inhibitors lepirudin, argatroban, or bivaluridin or the antithrombin-dependent factor Xa inhibitors, danaparoid, or fondaparinux (EBPG Expert Group on Haemodialysis 2002b). Furthermore, nafamostat mesilate is selected in Japan.

7.1.3 Low-Molecular-Weight Heparin (LMWH)

LMWH is recommended over UFH as anticoagulation in the European best practice guidelines for hemodialysis. Nevertheless, LMWH is used in Europe and Japan; in contrast the use of LMWH remains limited in the United States.

LMWH is produced by chemical or enzymatic cleavage of UFH to molecular size from 4000 to 8000 Da. Commonly used LMWH are dalteparin, tinzaparin, enoxaparin, nadroparin, parnaparin, reviparin, and others.

LMWH shows a stronger affinity to inhibit factor Xa and low specificity to thrombin, because most of the molecules do not contain enough saccharide units to bind both ATIII and thrombin and have different actions in terms of their anti-IIa activity compared with blocking factor Xa activation (Fig. 7.1). However, action of LMWH depends on the length of the polysaccharide chain, and, hence, all LMWHs do not show the same inhibitory profile. In common practice, doses are adjusted by monitoring measurement of anti-factor Xa activity (aPTT and ACT are unreliable) or clotting of the extracorporeal circuit, and most are effective when given as a single bolus dose at the start of a standard 4-h session.

Benefits of LMWH include higher bioavailability (less nonspecific binding to platelets and plasma proteins), improved lipid profile, reduced risk of hyperkalemia and osteoporosis, and lower incidence of HIT type II. Additional benefits of LMWH are expected to be high-bleeding-risk patients in Japan, but meta-analysis found no decreased risk of bleeding compared with UFH when it is used for anticoagulation in long-term hemodialysis (Kessler et al. 2015).

7.1.4 Direct Thrombin Inhibitors

Direct thrombin inhibitors are anticoagulants that bind directly to thrombin and do not require natural cofactors to inhibit the clotting cascade. Instead, they directly bind to and block thrombin, the final key enzyme within the coagulation process inducing the conversion of soluble fibrinogen to insoluble fibrin (Fischer 2007).

Argatroban is a synthetic peptide derived from arginine, with a molecular weight of 527 Da and acts as a reversible direct thrombin inhibitor by binding to the thrombin active site. Argatroban does not require the cofactor antithrombin III for antithrombotic activity (Fig. 7.1). For hemodialysis, a loading dose of 10 mg/h, followed by a maintenance infusion of 2 μg/kg/min or 5–20 mg/h, is titrated to achieve an aPTT of 1.5–2.5. To prevent excessive bleeding from fistula needle sites, the infusion should be stopped 30 min before the end of the dialysis session.

Lepirudin is a recombinant form of the natural anticoagulant hirudin, with a molecular weight of 6.9 Da. It has been administered as a single bolus

at the start of hemodialysis or as a continuous infusion. However, lepirudin use has been limited because of a prolonged half-life in dialysis patients of >35 h, leading to bleeding complications with repetitive use.

7.1.5 Regional Anticoagulation

Regional anticoagulation is not necessarily the mainstream of anticoagulation therapy for hemodialysis. The earliest approach to anticoagulation for patients at high risk of bleeding was regional heparinization of the dialysis circuit. Based on the ability of protamine to neutralize the anticoagulant effect of heparin, this technically complex method has been abandoned to other methods such as use of low-dose heparin or heparin-free dialysis (Kessler et al. 2015).

In regional citrate anticoagulation, sodium citrate is administered in the arterial line to bind calcium, an important cofactor in the coagulation cascade, to inhibiting coagulation of the circuit (Fig. 7.1). The ability of the blood coagulation is restored by the use of a calcium infusion administered via the venous line. However, regional anticoagulation with citrate and calcium infusions is too tedious and expensive for routine use and thus often is limited to the intensive care setting.

7.1.6 Nafamostat Mesilate (NM)

NM is the most common anticoagulant used for the patients at high risk of bleeding in Japan. NM is a serine protease inhibitor with a half-life of 5–8 min, acts predominantly as a regional anticoagulant by inhibiting thrombin, factor Xa and factor XIIa, and also has effects on the kinin system, fibrinolysis, and platelet activation (Fig. 7.1). The maintenance dose of NM is 20–40 mg/h, given via constant infusion into the arterial line using an infusion pump, and no initial bolus is needed. In NM dose adjustment, ACT or aPTT adjusts to 1.5–2.0 times above normal range. Rarely, most important side effects of NM are anaphylactoid reactions. Severe anaphylactic shock develops immediately after the treatment has started. In addition, it is important to observe the patient, 5–10 min after the treatment has been started.

7.1.7 Dose of Anticoagulant and Dialysis Vintage

Figure 7.2 shows the relationship between total dose of anticoagulant per session and dialysis vintage in Japan. Total dose of UFH and LMWH has increased with increasing the dialysis vintage (Fig. 7.2a). In addition, the trend is also similar in terms of total anticoagulant dose per body weight (Fig. 7.2b).

By contrast, Fig. 7.3 shows the association between total dose of UFH/LMWH per session and patient age in Japan. Total dose of UFH and LMWH has decreased with increasing the patient age (Fig. 7.3a). However, total anticoagulant dose per body weight was very similar in patients divided into 15-year-age groups (Fig. 7.3b).

In Japan, the mean age of maintenance dialysis patients has been increasing since 1982, and there has been a notable increase in the patients aged ≥65 years (Patient Registration Committee, 2005). At the end of 2012, the patients aged ≥65 years proportion was 65.5%, clearly showing aging among Japanese patients undergoing dialysis. Similarly, at the end of 2012, the mean age of incident dialysis patients in Japan was 68.4 years (Kimata et al. 2015).

UFH/LMWH per session may be low as the proportion of elderly people in patients with dialysis less than 2 years has increased. However, dose of anticoagulant was increased with increasing the dialysis vintage. In general, most outpatient dialysis units do not regularly measure anticoagulation parameters, unless there is an issue with dialyzer clotting or prolonged bleeding following dialysis. However, it may be necessary for regular evaluation of anticoagulation dose.

7.1.8 Coagulation Due to Other Causes

Thrombosis in blood tubing, drip chambers, and dialysis membrane occur as a result of activation

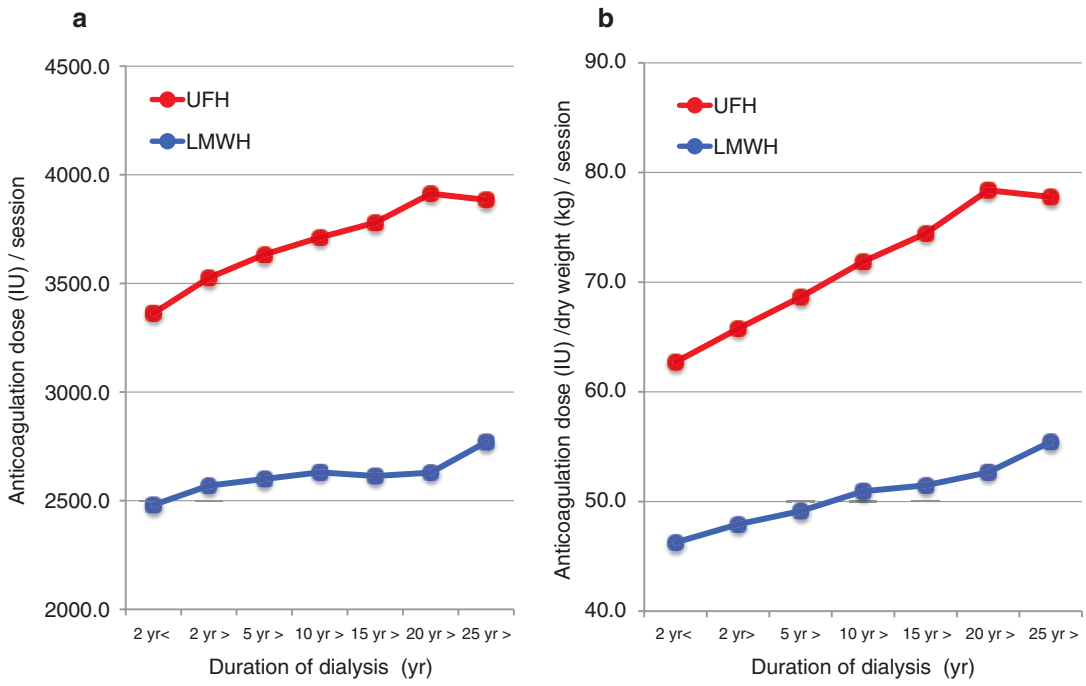

Fig. 7.2 Association between total dose of UFH/LMWH per session and dialysis vintage in Japan

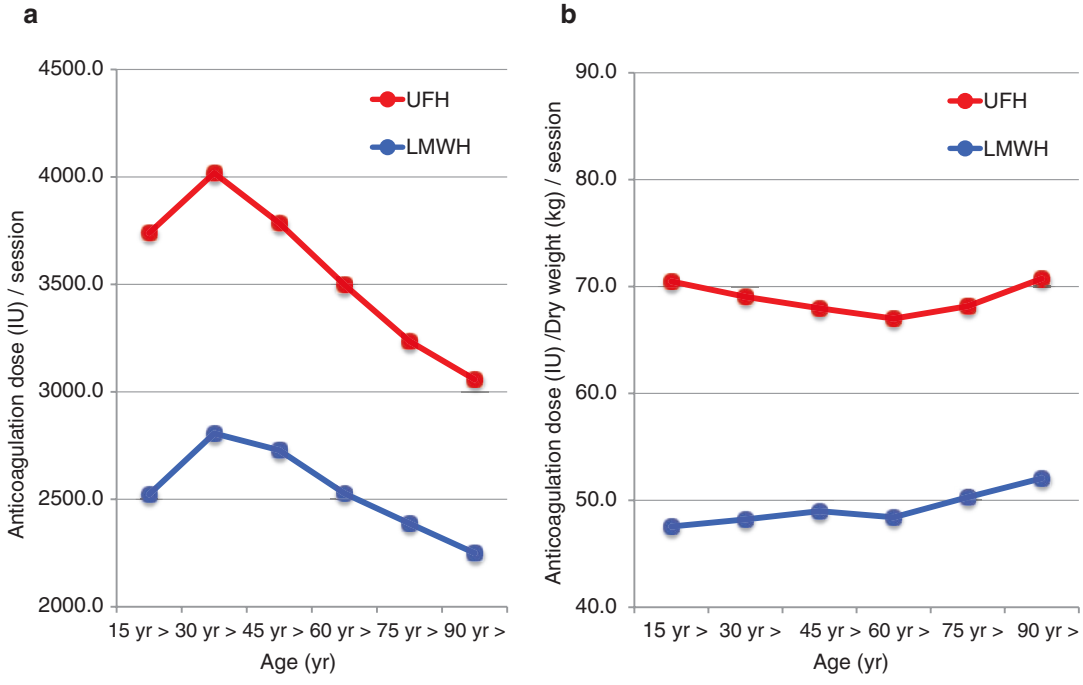

Fig. 7.3 Association between total dose of UFH/LMWH per session and patient age in Japan

of platelets and coagulation cascade. Thrombus formation was macroscopically roughly classified into two types (white thrombus or red thrombus). While the appearance of red thrombus formation is a common phenomenon in every hemodialysis unit, the occurrence of white thrombus in the dialysis tubing is relatively rare (Watnick et al. 2008).

White thrombus was found in 8 out of 486 patients (1.64%) in 3 months of our observation. During rinse back at the end of dialysis, white particulate matter measuring 1–3 mm was found firmly adherent to the blood tubing line, and 3–5 mm was found in the drip chamber or/and needle cannula site.

Electron microscopy of the core of white thrombus was CD61-positive platelet-rich thrombus with a small amount of fibrin, and red thrombus had aggregated erythrocytes in the core of the clots. Additionally, the core of the red thrombus was occupied with the red blood cell and fibrin. Suburb of the core was highly consists with erythrocytes, leukocyte, and fibrinogen (Fig. 7.4) (Kimata et al. 2008).

From the clinical records, white thrombus was found postoperatively more frequently than red thrombus. Besides, most of the phenomenon of white thrombus will calm down after a lapse of more than 4 days after surgery. In contrast, red thrombus was frequently found in cases of low blood-flow rate (<100 mL/min), high ultrafiltration rate, high hematocrit, and access recirculation. Red thrombus is almost resolved with an increase in heparin dose. However, the white thrombus occurred regardless of the type of dialyzer or blood tubing and did not resolve with an

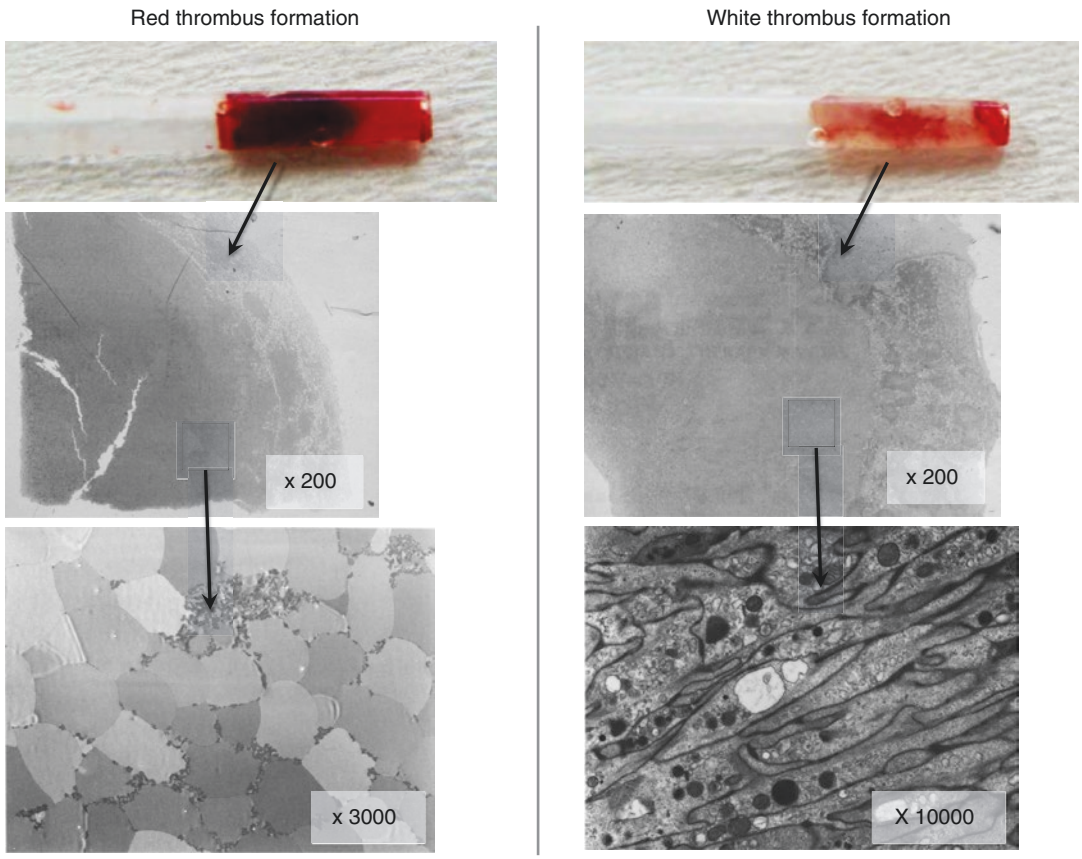

Fig. 7.4 Two types of thrombus formation in hemodialysis blood tubing lines

increase in heparin dose. The internal use of aspirin was the most effective for suppressing the white thrombus (Kimata et al. 2008).

7.1.9 Summary

UFH is the most commonly used anticoagulant because it is inexpensive and has a short half-life. Nevertheless, the dosage has not been standardized in the United States and Japan. Anticoagulation for patients at HIT, alternatives from UFH, includes direct thrombin inhibitors (argatroban and lepirudin), regional anticoagulation (citrate and nafamostat mesilate), and anticoagulation-free treatment with frequent saline flushes. Furthermore, despite changing the anticoagulant dosage or anticoagulant type, in cases of repeating the circuit coagulation, sometimes white thrombus (platelet-derived thrombus) is involved. In that case, it should be considered an antiplatelet medication, such as aspirin.

7.2 Anticoagulation in Patients on Hemodialysis

Kenichi Kokubo

7.2.1 Anticoagulation in Hemodialysis Patients

During hemodialysis, blood from the body is circulated through a blood circuit outside the body (extracorporeal circulation). During the extracorporeal circulation, the blood comes in contact with artificial surfaces, such as the blood circuit and dialysis membrane, which triggers the coagulation cascade. Therefore, anticoagulation is indispensable during hemodialysis.

The first anticoagulant tried to use during hemodialysis in humans was hirudin, by Haas in 1924 (Haas 1925). In 1928, Haas tried to use heparin during batch-type hemodialysis treatment (Haas 1928). This was the first use of heparin in humans during blood purification therapy (Paskalev 2001). In 1937, Thalhimer succeeded in removing urea in dogs by extracorporeal circulation using heparin (Thalhimer 1937; Cameron 2000). In 1945, Kolff et al. were the first to succeed in rescuing patients with acute renal failure by hemodialysis (Kolff et al. 1944); they also used heparin as the anticoagulant.

Heparin was discovered in 1916 from the extracts of the dog's liver with anticoagulant activity (Howell and Holt 1918); ever since, it has been used as an anticoagulant to suppress blood coagulation during extracorporeal blood circulation. This discovery became the basis for the development of anticoagulant therapy required during extracorporeal circulation, such as during hemodialysis and during open heart surgery under cardiopulmonary bypass using an extracorporeal membrane oxygenator.

At present, while heparin remains the mainly used anticoagulant in blood purification therapy, several new anticoagulants with different mechanisms of action have also been developed and used as anticoagulants during extracorporeal circulation. The currently used anticoagulants include low-molecular-weight heparin, which is fractionated heparin composed of low-molecular-weight molecules, and synthetic anticoagulants such as nafamostat mesilate and argatroban hydrate. In this chapter, we review the mechanisms of blood coagulation and the biological reactions that occur when the coagulation cascade is triggered by the blood coming in contact with external materials as well as the mechanisms of actions and usage of the anticoagulants used during hemodialysis.

7.2.2 Mechanisms of Blood Coagulation and Coagulability Monitoring

7.2.2.1 Coagulation Cascade

Coagulation in the living body has a very important action: to stop bleeding. During hemodialysis, which requires extracorporeal circulation of blood, it is necessary to prevent triggering of the blood coagulation cascade when the blood comes in contact with the extracorporeal circulation circuit and dialysis membrane. Blood coagulation can occur via an intrinsic pathway (also known as the contact activation pathway), which is triggered by contact with a foreign surface and

begins with the activation of coagulation factors contained in the blood, and an extrinsic pathway, which is triggered by damage of blood vessels and tissues. The intrinsic pathway is called so because all the elements necessary for its activation of this pathway are present within the normal blood, and the extrinsic pathway is called so because it is activated by extravascular factors, like tissue factor. More than 40 types of blood coagulation factors are known, including those involved in the intrinsic and extrinsic pathways, factors with anticoagulant effect, and factors that are related to fibrinolysis. Under physiological conditions, the anticoagulant factors dominate, preventing blood from clotting.

In the intrinsic and extrinsic pathways (Fig. 7.5), the last steps of coagulation are shared, wherein active factor X (factor Xa) enzymatically converts prothrombin (inactive form of thrombin) to the active thrombin; subsequently, polymerization of fibrinogen to form fibrin fibers is initiated; and plasma and blood cells are captured within the matrix of the fibrin fibers to form a thrombus. In the initial steps of the intrinsic pathway, when the blood comes in contact with a foreign surface, e.g., an extracorporeal circulation circuit or dialysis membrane, factor XII in the blood is activated first, followed by sequential activation of factor XII, factor XI, and factor X. In the extrinsic pathway, tissue factor activates factor VII, and activated factor VII causes activation of factor V and activated factor V causes activation of factor X. The activated forms of these factors are serine proteinases. The anticoagulants used during extracorporeal circulation exert their anticoagulant actions by blocking the actions of some serine proteinases in the coagulation cascade.

7.2.2.2 Biological Reactions That Occur When the Coagulation Cascade Is Triggered By Contact with Dialysis Membrane

Anaphylactic-like shock is well-known to occur when a dialysis membrane made of polyacrylonitrile material with a strong negative charge (AN

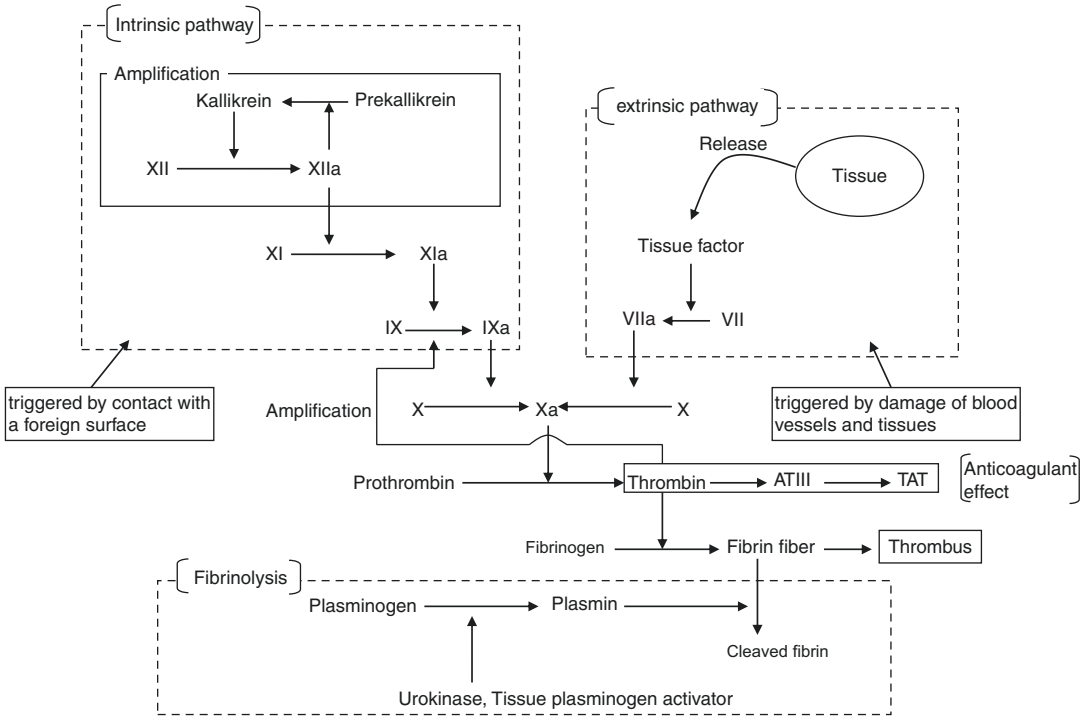

Fig. 7.5 Coagulation and fibrinolysis cascade

69 membrane, made from the copolymer of acrylonitrile and sodium methallyl sulfonate) is used for hemodialysis in patients taking angiotensin-converting enzyme (ACE) inhibitors. Therefore, use of the AN69 membrane is contraindicated in patients taking ACE inhibitors.

Anaphylaxis is an acute allergic reaction mediated by IgE antibodies and is classified as type I allergy. It is the prototype of an excessive immune response that can be elicited by foreign antigens such as bee venom, a variety of foods, drugs, etc. The inciting allergen binds to the IgE expressed on the surfaces of mast cells and basophils, which results in degranulation of these cells and the release of histamine, platelet-activating factors, etc., which leads to capillary dilatation. These events could lead to shock and circulatory/respiratory failure, the so-called anaphylactic-like shock. A condition similar to anaphylaxis can also occur without the involvement of IgE; under which circumstance, the reaction is called anaphylactic-like reaction; and this is probably the type of reaction that occurs when a dialysis membrane with a strong negative charge is used in patients taking ACE inhibitors.

As described in Sect. 7.2.2.1, coagulation that occurs via the intrinsic pathway starts with the activation of coagulation factor XII. This activation can occur especially easily when a dialysis membrane with a strong negative charge is used. Kallikrein is produced from prekallikrein by activated factor XII, which further promotes activation of factor XII to amplify the intrinsic coagulation pathway. At the same time, kallikrein cleaves kininogens into bradykinin, which is a very strong pain-producing substance that enhances vascular permeability, induces the generation of nitric oxide, relaxes smooth muscle, dilates blood vessels, and causes lowering of the blood pressure. Accumulation of large amounts of bradykinin in the blood could thus cause anaphylactic-like shock (Fig. 7.6).

In general, the produced bradykinin is degraded by kininase II (also known as angiotensin-converting enzyme, or ACE). However, in patients taking ACE inhibitors, which are commonly used antihypertensive agents, this action of kininase II is inhibited. Therefore, when a negatively charged membrane is used for dialysis in patients taking ACE

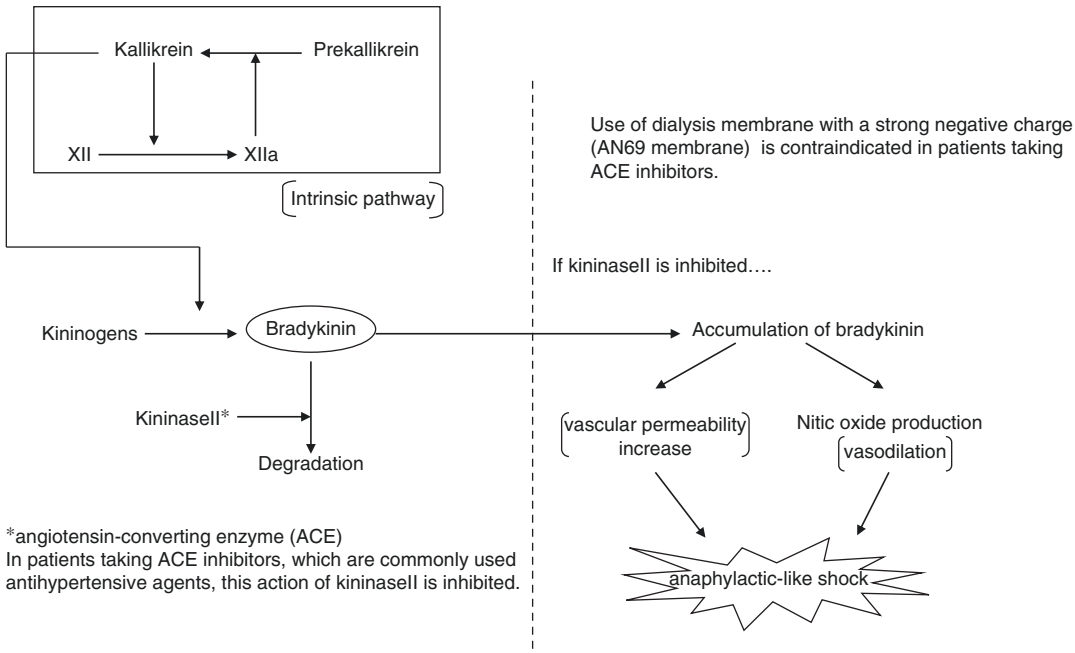

Fig. 7.6 Biological reactions that occur when the coagulation cascade is triggered by contact with dialysis membrane

inhibitors, bradykinin is likely to accumulate in the blood, causing anaphylactic-like symptoms. Therefore, the use of AN69 membranes is contraindicated in patients taking ACE inhibitors. Therefore, either the dialyzer membrane used or the medication should be changed in such patients to carry our hemodialysis. Adsorbents made of dextran sulfate used for LDL apheresis also have a strong negative charge; therefore, use of these membranes is also contraindicated in patients taking ACE inhibitors.

7.2.2.3 Coagulability Monitoring

Since activated clotting time (ACT) can be easily measured within a short time, it is widely used as a test for monitoring blood coagulability during extracorporeal circulation. However, since the ACT can be influenced by the platelet count and hematocrit (Ht), values are likely to vary depending on the technical procedure used. Although activated partial thromboplastin time (APTT) represents a better measure of the heparin activity than ACT, measurement of APTT takes much time, and real-time monitoring is not possible. In patients with enhanced fibrinolytic activity, the APTT is prolonged and the heparin activity cannot be reliably monitored.

The target values of coagulability during extracorporeal circulation are 150–200 s (s) for ACT and 60–70 s for APTT. When heparin is administered continuously at 20 U/(kg/h), the ACT and APTT values are mostly usually in this range, but it may be necessary to adjust the dose depending on the values, as these may differ greatly depending on the patient's condition and individual differences. Several tests may be performed for coagulability monitoring, as briefly explained below.

1. Activated Clotting Time (ACT)

   ACT is a measure of the time taken for clot formation via the intrinsic coagulation pathway, starting from activation of factor XII to the formation of fibrin. Kaolin or celite is added as an activating agent to the collected whole blood, and the clotting time is measured. It is widely used for coagulability monitoring in patients undergoing therapies involving extracorporeal blood circulation receiving heparin. The reference value in normal humans is 100–120 s.
2. Prothrombin Time (PT)

   PT is a measure of the time taken for clot formation via the extrinsic pathway, starting from activation of factor VII by tissue factor (TF) to the formation of fibrin. Calcium and tissue thromboplastin are added to the collected plasma, and the clotting time is measured. In addition to being used as a screening test for coagulation activity via the extrinsic pathway, it is also used to monitor the progression of liver cirrhosis. To check for changes in the blood coagulability by anticoagulant therapy, the use of INR (international normalized ratio) is recommended. The reference values are 11–12 s for PT and 0.8–1.2 for INR.
3. Activated Partial Thromboplastin Time (APTT)

   APTT is a measure of the time taken for clot formation via the intrinsic pathway, which is measured after the addition of contact activating factors such as partial thromboplastin, calcium, kaolin, and celite or ellagic acid to the collected plasma. It is used as a screening test for coagulation activity via the intrinsic coagulation pathway. The reference value is 24.6–32 s.

7.2.3 Mechanisms of Actions and Usage of Each Anticoagulant During Hemodialysis Treatment

7.2.3.1 Unfractionated Heparin (UFH)

1. Mechanism of Action

   Heparin, a sulfate polysaccharide with a molecular weight of about 3000–25,000 derived from the porcine small intestine, is currently the mainly used anticoagulant drug (Fig. 7.7). In regard to its basic structure, it is a highly sulfated glycosaminoglycan composed of multiple repeats of uronic acid and glucosamine. It is also called unfractionated heparin (UFH) to distinguish it from

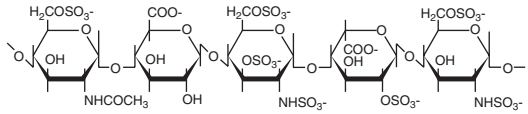

Fig. 7.7 Basic chemical structure of UFH

fractionated heparin developed later. It activates antithrombin by binding to antithrombin III (AT III) and changing its structure. Antithrombin III inhibits thrombin, factor Xa (active form of factor X), and other serine proteases by binding to their active site. Thrombin has a higher affinity for the heparin-antithrombin III complex than factor Xa.

The half-life of UFH is about 1 h. The blood coagulability during UFH administration is monitored by the ACT. The dose of heparin is adjusted so as to increase the ACT to about 1.5–2 times the normal. In regard to the adverse effects, heparin is known to have unfavorable effects on the lipid metabolism and calcium metabolism.

Heparin-induced thrombocytopenia (HIT) may occur in patients receiving heparin. HIT is a disease state in which autoantibodies against heparin are formed, and therefore thrombus formation together with thrombocytopenia can occur with the use of heparin. In HIT, an autoantibody against a complex of platelet factor 4 (PF 4) and heparin acts as an antigen after administration of heparin. The antibody binds to the PF4-heparin complex, which binds to the platelet surface receptor to activate platelets. This leads to a hypercoagulable state, resulting in platelet consumption and reduction in the number of platelets as well as thrombus formation. At this time, production of thrombin is also accelerated, which also causes exacerbation of HIT.

HIT has been observed to be more likely to occur in dialysis patients with diabetic nephropathy and various arteriosclerotic vascular complications. The appearance of HIT account for about 0.5–5% of patients taking heparin. Although the appearance rate is related to the type and amount of heparin used and the duration of administration period, close attention should be paid, as it might occur even with only flushing of an indwelling catheter with a small amount of heparin.

2. Usage

During procedures involving extracorporeal circulation, heparin is administered as a continuous infusion at about 500–1500 U/h (at 10–25 U/(kg/h). It is usually sufficient to use variations of 500, 750, 1000, and 1250 U/h to accommodate individualized needs. In some facilities, heparin is administered at the initial dose of about 1000–2000 U (20–50 U/kg) at the beginning of extracorporeal circulation. The optimal dosage differs among patients; therefore, the dose needs to be adjusted according to the individual needs of patients. The state of the residual blood clot in the dialyzer after treatment, the blood coagulation time (e.g., activated coagulation time, ACT), or the activated partial thromboplastin time (APTT) can be examined to adjust the dose of heparin. Normally, the dose of heparin is adjusted so that the ACT is about 150–200 s or the APTT is 60–70 s.

Because UFH has a strong bleeding-promoting effect, special attention should be paid during the perioperative period and in cases with hemorrhagic complications.

7.2.3.2 Low-Molecular-Weight Heparin (LMWH)

1. Mechanism of Action

Low-molecular-weight heparin (LMWH) is a heparin composed of molecules with a lower molecular weight (3000–8000) fractionated from UFH (Fig. 7.8). Unlike UFH, its action on factor IIa (thrombin) is weak, while its inhibitory effect on factor Xa is strong. In general, since the coagulation time in the body is mainly prolonged by the anti-IIa action and only slightly prolonged by the anti-Xa action, prolongation of the coagulation time by LMWH in the body can be suppressed to a mild degree, while the coagulation in extracorporeal circulation is strongly inhibited by the anti-Xa action. Therefore, LMWH can be used for patients with mild hemorrhagic complications. The half-life is about 2–3 h, which is longer than that of UFH, and a stable effect

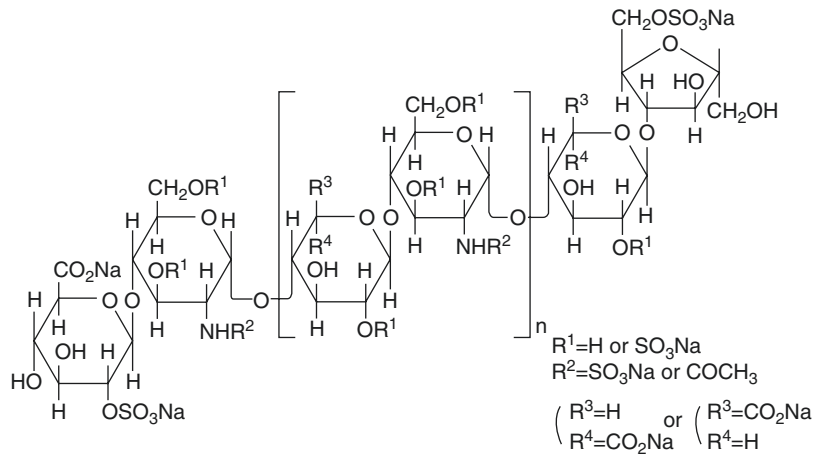

Fig. 7.8 Basic chemical structure of LMWH

can be easily obtained with fewer doses. Its effects on lipid metabolism and calcium metabolism are also less than those of UFH.

The anticoagulant activity of LMWH cannot be monitored by ACT, but by whole-blood Xa clotting time. However, since it takes relatively long to obtain the results of measurement of the whole-blood Xa coagulation time, it is difficult to adjust the dose of LMWH during treatment by monitoring the blood coagulability.

2. Usage

Since the half-life of LMWH in the blood is as long as 180–240 min, heparin is administered as a continuous infusion at the rate of about 500–750 lU/h (at 10–15 U/(kg/h). It would be sufficient to have variations like 500, 625, and 750 U/h to accommodate individualized needs. In regard to the administration method, either a combination of bolus doses and continuous infusion or bolus doses alone to maintain the anticoagulation effect in extracorporeal circulation can be selected. In the combined method, LMWH is administered at the bolus dose of 15–20 U/kg at the start of extracorporeal circulation, followed by continuous administration at 300–500 U/h (6–10 U/(kg/h). In the bolus dose alone method, the dose calculated by multiplying 7–13 U/kg by the scheduled extracorporeal circulation time required for hemodialysis is administered at the start of extracorporeal circulation, and no continuous administration is used at all before completion of the extracorporeal circulation.

For monitoring of the anticoagulant activity, the whole-blood Xa coagulation time would be desirable; however, it takes time to obtain the results of this test; therefore, it cannot be used for immediate dose adjustment during hemodialysis. In practice, the state of the in-circuit residual blood clot at the end of extracorporeal circulation is used as an index for dose adjustment at the next treatment. The bleeding-promoting action is mild; therefore, LMWH can be used for patients at a relatively high risk of bleeding complications.

7.2.3.3 Nafamostat Mesilate: NM

1. Mechanism of Action

Nafamostat mesilate is a synthetic serine protease inhibitor with a molecular weight of 539 Da (Fig. 7.9) and suppresses the actions of the enzymes (serine proteases) in the coagulation cascade. In addition to its antithrombin activity, nafamostat mesilate has anti-Xa activity, anti-XII activity, and anti-VII activity, thereby inhibiting the progression of coagulation. It also has an inhibitory effect on platelet aggregation. Since the half-life in extracorporeal circulation is short (about 8 min), nafamostat mesilate has a lesser influence on the blood coagulability in the body and is suitable for patients with moderate to

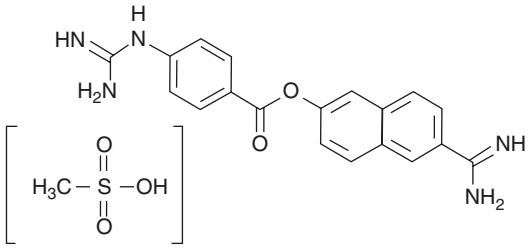

Fig. 7.9 Chemical structure of nafamostat mesilate

severe bleeding complications. In Japan, it is often used for patients receiving continuous renal replacement therapy (CRRT), who often suffer from many bleeding complications or a severe bleeding tendency. Care must be taken against the occurrence of allergic reactions or anaphylactic shock, which might occur when it is reused in patients after a while. When using the polyacrylonitrile membrane surface with a strong negative charge (AN69), note that a large amount of nafamostat mesilate can get adsorbed on to the membrane and increase the needed dose to prevent blood coagulation.

2. Usage

In the case of NM, no initial bolus dose is given; instead priming of the extracorporeal circulation circuit and dialyzer is performed using saline solution containing 20 mg/500 ml of NM to avoid reduction of the effective concentration by adsorption onto the dialysis membrane material at the start of hemodialysis treatment. Subsequently, the drug is usually administered by continuous infusion at the rate of about 20–40 mg/h (0.1–1.0 mg/(kg/h).

Since its half-life in the blood is as short as 5–8 min, the anticoagulant effect is predominant in the extracorporeal circuit. Therefore, blood coagulation is likely to occur in the venous chamber downstream of the dialyzer. To avoid this, split administration of NM can be performed into the venous chamber in addition to the usual injection line placed upstream of the dialyzer.

For drug efficacy monitoring, ACT is used in the same way as for UFH, but when kaolin is used as the coagulation activator of ACT measurement, the ACT cannot be accurately measured, because NM is adsorbed onto kaolin. Therefore, celite should be selected as the coagulation activator in the ACT measurement.

Since NM is a positively charged substance, it is strongly adsorbed onto negatively charged membranes such as the AN69 membrane, which leads to a decrease in the effective blood concentration. Therefore, close attention needs to be paid to the dose and the priming method when using negatively charged membranes for dialysis. We should also be especially careful during the first few times of NM use against the potential risk of NM allergy, which may cause anaphylactic shock immediately after the start of dialysis.

7.2.3.4 Argatroban

1. Mechanism of Action

Argatroban is a synthetic direct thrombin inhibitor with a molecular weight of 527 Da (as argatroban hydrate) (Di Nisio et al. 2005) (Fig. 7.10). Argatroban was approved in 1990 for use as an anticoagulant in patients with chronic peripheral arterial disease, including Buerger's disease and arteriosclerosis obliterans in Japan. It was additionally approved in 1996 for use in patients with acute cerebral thrombosis and for extracorporeal circulation (hemodialysis) in patients with reduced levels of antithrombin III. Use for inhibition of thrombosis in patients with HIT was approved in 2008, and use for prevention of coagulation during extracorporeal circulation (hemodialysis) in

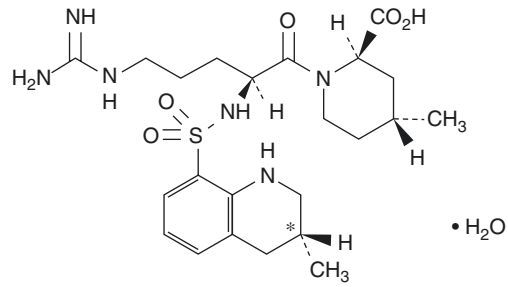

Fig. 7.10 Chemical structure of argatroban

patients with HIT and prevention of coagulation during percutaneous coronary intervention in patients with HIT were also approved in 2011.

Since argatroban selectively and directly binds with thrombin and exerts antithrombin activity, unlike UFH and LMWH, it can exert its anticoagulant effect in the absence of antithrombin III and thereby be useful for patients with antithrombin III deficiency. It is also useful in the management of patients with HIT (Dhillon 2009). Argatroban is metabolized in the liver and has a half-life of about 50 min. Blood coagulability can be monitored by measuring the partial thromboplastin time (PTT).

2. Usage

Argatroban is administered at the dose of about 10 mg (0.2 mg/kg) for the blood circuit at the start of the extracorporeal circulation (initial bolus dose) and by continuous infusion at about 5–40 mg/h (0.1–1.0 mg/(kg/h) into the extracorporeal circulation. APTT is used for monitoring the drug efficacy, and the dose of the drug is adjusted to prolong the APTT to 60 s or more.

Since ATIII is not involved in the anticoagulant effect of argatroban, this drug can be used for patients with AT III deficiency. Its half-life, however, is as long as 30–40 min and its hemorrhagic actions cannot be changed in the patients; it should be used with caution in patients with a severe bleeding tendency with a high risk of bleeding.

7.2.4 Selection of the Appropriate Anticoagulant and Adjustment of Its Dose

It is important to select the appropriate anticoagulant for each individual patient to prevent the occurrence of hemorrhagic complications during hemodialysis therapy. Also, the dose of the anticoagulant should be appropriately adjusted depending on the patient's condition and the material of the dialyzer. Blood coagulability monitoring by measuring indices like the ACT, APTT, or PT is also useful to check the required dose of the anticoagulant. Furthermore, the dose of anticoagulant for the next treatment can also be checked by examining the dialyzer membrane after treatment for residual blood clots or by measuring the degree of prolongation of the bleeding time from the needle insertion sites after needle removal.

If residual blood clots are observed in many fibers of the dialysis membrane, or coagulation occurs in the circuit or the chamber, or dialysis cannot be continued due to clot formation, the amount of anticoagulant injection can increased in the next treatment. The membrane material may affect the coagulation activity during hemodialysis therapy, and if this is suspected to be interfering with the therapy, a change of the membrane material can be considered. A checklist of the residual blood clots in the dialyzer can be used to adjust the dose of the anticoagulant.

If internal bleeding of causes that cannot be recalled by the patient himself/herself occurs frequently before dialysis or if prolonged bleeding from needle insertion sites after needle removal at the end of dialysis is frequently observed, a decrease of the dose can be considered. Careful examination for trauma or retinal hemorrhage is essential at the start of the treatment. And if these are present, the anticoagulant should be changed from heparin to NM. In addition, use of a local anticoagulation method using heparin and protamine sulfate or sodium citrate and calcium can be considered. In this method, the anticoagulant exerts effect only on the blood in the blood circuit and not that in the body because of neutralization by the protamine sulfate or calcium.

Since extracorporeal circulation itself is highly invasive, careful use of anticoagulant during hemodialysis is essential. It is important to select the appropriate anticoagulant and its dose, taking into consideration the characteristics of the anticoagulant and the patient's condition.

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8 The Concept of Hemodialysis Adequacy and Kinetics

Hideki Kawanishi

8.1 Introduction

The main purpose of hemodialysis (HD) is the removal of solute and excessive fluid from the body. Factors to consider during HD prescription are the dialysis time and frequency. Although the conventional dialysis time is 12 h (4 h, three times/week), a higher dialysis time may be necessary for patients with end-stage renal disease. For adequate dialysis, the time and frequency must be devised.

8.2 Dialysis Prescriptions for Solute Removal

The main purpose of dialysis is the removal of excessive solute including urea, phosphate, and uric acid, which originate from food intake, and creatinine and β2-microgluburin (β2M), which originate from the organism's metabolism. β2M is more difficult to migrate into the blood than others. In order to remove individual solutes by dialysis, the dialysis prescription needs to be adapted accordingly. However, the HD prescriptions are difficult to change for each target solute. The dialysis prescription that is the greatest common divisor is currently set.

8.3 Solute Clearance

Factors to consider for solute removal are blood flow rate, dialysate flow rate, and the performance of the dialyzer itself (hemodialyzer mass transfer-area coefficients; KoA). The substance removal efficiency (clearance) from plasma per a certain time (minute) is relied on the lowest value of blood flow rate, dialysate flow rate, and KoA. For example, the clearance of urea nitrogen at a blood flow rate of 200 mL/min, a dialysate flow rate of 500 mL/min, and dialyzer KoA of 700 mL/min, which is a standard dialysis condition, is dependent on the lowest value of blood flow rate and does not exceed a clearance of 180 mL/min. On the other hand, the clearance of β2M (11.8 kD) is relied on the lowest value of a KoA (50 mL/min). Therefore, a high blood flow rate is required to efficiently clear small molecules such as urea nitrogen, and a dialyzer with good performance must be selected for the removal of β2M having middle molecules. Hence, a high blood flow rate and a dialyzer with good performance are required to increase the removal efficiency (clearance) of all substances over a certain period of time.

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8.4 Solute Removal per Single Dialysis Session; Kt/*V*

Solute removal per dialysis session is expressed as Kt/*V* (Gotch and Sargent 1985). Kt/*V* is defined as the dialyzer clearance of small solute (*K*) multiplied by the duration of the dialysis treatment (*t*) divided by the volume of distribution of small solute in the body (*V*). Urea Kt/*V* is most popularly and conveniently measured using mathematical modeling. There are two methods to increase the Kt/*V*: (Gotch and Sargent 1985) increase of the *K* (clearance) and extension of the dialysis time (*t*). Although *K* can be increased easily by increasing the blood flow rate, there is a limit as described above, in which case the dialysis should be prolonged. The Japanese society for dialysis therapy (JSDT) guideline recommends small solute removal as shown in Table 8.1 (Watanabe et al. 2015). The basis for this recommendation is that the death rate is significantly higher when the Kt/*V* is lower than 1.2. Conversely, when the Kt/*V* reaches 1.6, the mortality rate significantly decreases according to a JSDT survey. In women and patients with low weight, the body fluid volume (*V*) is small, so Kt/*V* tends to increase with the same removal efficiency (Kt). Therefore, there is a possibility of underestimating the mortality rate, and in women or patients with low body weight, a slightly higher Kt/*V* than men is recommended.

8.4.1 Removal of β2M (Middle Molecules)

Since β2M has a larger molecular weight of 11.8 kD, permeability of the dialyzer is low, and in long-term dialysis cases, it accumulates and causes dialysis-related amyloidosis (Gejyo et al. 1985).

The JSDT guideline recommends β2M removal as shown in Table 8.2 (Watanabe et al. 2015). In the JSDT survey, the predialysis serum β2M concentration at the maximum interval (Monday and Tuesday) was significantly higher than 25–30 mg/L, above which the death rate was significantly high. Therefore, a predialysis maximum serum β2M concentration is required to achieve <30 mg/L.

Table 8.1 JSDT guideline for small solute

1. Dialysis dose is expressed by the single-pool Kt/*V* for urea (spKt/V)
2. Measurement of the dialysis dose is done at least once a month
3. Recommended delivered dialysis dose by spKt/*V* is the following:
(a) The minimal adequate dose is 1.2
(b) The target dose is 1.4 or higher
4. The recommended minimal dialysis time is 4 h or longer

[a]These recommendations are for patients with maintenance HD three times per week for less than 6 h

Table 8.2 JSDT guideline for β2M

1. Predialysis serum β2M level at the maximum intervals is a factor related to prognosis
2. The dialysis conditions are recommended to achieve the maximum predialysis serum β2M concentration of <30 mg/L
3. The dialysis conditions are preferred to achieve the maximum predialysis serum β2M concentration of 25 mg/L
4. Decreasing the concentrations of substances with greater than β2M can improve the prognosis of patients

The serum β2M concentration increases with inflammation and initial treatment to suppress the inflammatory state, and for further biological purification of the dialysis, fluid is important. As mentioned earlier, the factor that mostly affects the clearance of high-molecular-weight solutes such as β2M is the performance of the dialyzer, and the selection of a super high-flux membrane dialyzer and convective therapies is necessary. Additionally, since β2M has a low migration speed from the tissue into the blood, it is difficult to remove a sufficient amount if the dialysis time is short; therefore, dialysis should be performed for the maximum possible time.

Appendix 1: Kinetics Modeling of Dialysis: Reference for JSDT Guideline (Watanabe et al. 2015)

Indices of dialysis dose, solute removal, and the sampling methods of blood are mentioned below.

A. Indices

Kt/Vurea

Kt/Vurea is an index of the degree to which urea is removed in one dialysis session (i.e., dialysis dose). Although various definitive equations of Kt/Vurea have been proposed as described below, no absolute equation has been selected. It is important to use one of these appropriate equations consistently for each patient.

Gotch and Sargent's Equation (Kt/Vurea) (Gotch and Sargent 1985)

This model assumes the one-compartment model with no effect of fluid removal and urea production.

$$\mathrm{Kt\,V} = \ln\left(\mathrm{BUN_{Pre}} / \mathrm{BUN_{post}}\right) \tag{8.1}$$

where $\mathrm{BUN_{pre}}$ and $\mathrm{BUN_{post}}$ are the predialysis and post-dialysis BUN concentrations, respectively.

Daugirdas' Equation (Daugirdas 1989)

Single-pool Kt Vurea (spKt *V*)

Daugirdas proposed several definitive equations of Kt/Vurea. The following model assumes the one-compartment model with consideration of the effect of fluid removal and urea production,

$$spKt/V = -\ln\left(R - 0.008t\right) + \left(4 - 3.5R\right) \times \frac{\Delta V}{BW_{post}} \tag{8.2}$$

where R is the ratio of the post-dialysis BUN to the predialysis BUN concentration (= $\mathrm{BUN_{post}}/\mathrm{BUN_{pre}}$), t is the dialysis duration (h), ΔV is the fluid removal per-HD session (L), and BW post is the post-dialysis BW of the patient (kg).

Equilibrated Kt/Vurea (eKt/*V*) (Daugirdas 1993)

This equation is based on the so-called regional blood flow model.

$$\mathrm{eKt}/V = \mathrm{spKt}/V - 0.6\frac{\mathrm{spKt\,/\,V}}{t} + 0.03 \tag{8.3}$$

Reduction Rate (RR)

Definition: RR is an index of the solute clearance and is calculated using the predialysis and post-dialysis blood solute concentrations (C_{pre} and C_{post}, respectively) as follows.

$$\mathrm{RR} = 1 - \frac{C_{\mathrm{post}}}{C_{\mathrm{pre}}} \tag{8.4}$$

Usually, the obtained value is multiplied by 100 to be expressed in percentage.

For solutes of large molecular weight, the RR should be corrected by considering the effect of blood condensation caused by fluid removal (Mineshima 2010)

$$\mathrm{RR} = 1 - \frac{V_{\mathrm{Ppre}}C_{\mathrm{post}}}{V_{\mathrm{Ppre}}C_{\mathrm{pre}}} = 1 - \frac{V_{\mathrm{B\,post}}\left(1 - H_{\mathrm{post}}\right)C_{\mathrm{post}}}{V_{\mathrm{B\,pre}}\left(1 - H_{\mathrm{pre}}\right)C_{\mathrm{pre}}} = 1 - \frac{H_{\mathrm{pre}}\left(1 - H_{\mathrm{post}}\right)C_{\mathrm{post}}}{H_{\mathrm{post}}\left(1 - H_{\mathrm{pre}}\right)C_{\mathrm{pre}}} \tag{8.5}$$

where H_{pre} and H_{post} are the predialysis and post-dialysis hematocrit values.

Solute Removal (*M*)

It is estimated from the amount of solute in the dialysate discharged from the dialyzer, which is entirely or partially stored. *M* is considered to be an absolute index of cleared solute but does not include the amount of solute trapped by the membrane. *M* basically depends on the predialysis solute level (C_{pre}). The higher the C_{pre}, the higher the *M* when the dialysis prescription (therapeutic conditions) is fixed.

Clear Space (CS) and CS Rate (CSR)

Definition: CS indicates the normalized amount of removed solute and is given as follows;

$$\mathrm{CS} = M\,/\,C_{\mathrm{pre}} \tag{8.6}$$

The effect of C_{pre} is eliminated. CS is given in the unit of volume (space), depending on the distribution space of the solute of interest in patients (V), and corresponds to the distribution of space for solute removed in one dialysis session. CSR, expressed as CS/*V*, is used to compare the CS values among patients.

Sampling Methods

Predialysis and post-dialysis blood sampling

To determine predialysis concentration, the patient's blood should be sampled at the time of puncture of dialysis access before being connected to the blood circuit, in order to avoid the effects of dilution.

To determine post-dialysis concentration, the patient's blood should be sampled by the slow-flow method to minimize the effects of access recirculation and urea rebound. Specifically, the dialysate flow is stopped immediately after the dialysis session (practical end of dialysis), and the blood flow rate is reduced to 50–100 mL/min. After 1–2 min, the patient's blood is sampled from the port close to the patient on the A-side line.

Clearance (CL) of Dialyzer

CL is an index of the solute removal for dialyzers and is defined as follows:

$$\mathrm{CL} = \frac{Q_{\mathrm{Bi}} C_{\mathrm{Bi}} - Q_{\mathrm{Bo}} C_{\mathrm{Bo}}}{C_{\mathrm{Bi}}} \qquad (8.7)$$

where Q is the flow rate, C is the concentration of solute, and the subscripts B, i, and o indicate the blood, inlet, and outlet, respectively.

For solutes of small molecular weight, such as urea and creatinine, the flow rate of whole blood is substituted into Q_{Bi} in Eq. (8.7). For solutes of medium molecular weight, such as β2M, the flow rate of plasma is substituted into Q_{Bi}. The plasma concentrations obtained from clinical observations are substituted into C_{Bi} and C_{Bo}. For solutes of large molecular weight, such as α1-microglobulin and albumin, CL-based evaluation is difficult because of their large decrease with time.

- CL should be evaluated 60 min after the start of the dialysis session. If CL is expected to vary by more than 20% over 240 min, measurement of CL at 240 min after the start of dialysis treatment is recommended.
- Dialysate outlet (C_{Do}), blood outlet (C_{Bo}), and inlet (C_{Bi}) should be sampled in this order with great care so as not to affect the flow of dialysate or blood.
- Flow rates of blood (QB) and dialysate (QD) should be measured beforehand. The use of the actual blood flow rate is recommended to evaluate QB during dialysis.

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Complications of Hemodialysis

9

Joon Ho Song

9.1 Dialysis Reaction

Dialysis reaction is caused by the exposure of patient's blood to the components of extracorporeal circuit including dialysis membrane, tubes, and other contaminants used in the manufacturing processes or disinfection process. The frequency of dialysis reaction is a decreasing trend since the introduction of biocompatible dialyzers and many improvements of manufacturing and disinfection processes. However, when occurs, it may be severe enough to cause the patient death (Jaber and Pereira 1997). Dialysis reaction is divided into two types: anaphylactic/anaphylactoid type and nonspecific type.

9.1.1 Anaphylactic/Anaphylactoid Type (Life-Threatening Type)

9.1.1.1 Clinical Manifestations

The symptoms typically develop within the first 5 min of dialysis initiation. It can sometimes be delayed by up to 20–30 min. The common symptoms are difficulty in breathing and/or burning or tingling sense at the fistula area or whole body. Wheezing, angioedema, nausea, vomiting, abdominal cramp, diarrhea, hypotension, and hypertension can be seen. Respiratory failure, cardiac arrest, and death may result in extremely severe case.

9.1.1.2 Etiology and Pathogenic Mechanism

The first reaction syndrome: *ethylene oxide*: Ethylene oxide (ETO) has been widely used as a sterilant in the manufacturing process of dialyzer. Retained ETO in the potting compound of the hollow fiber causes previously called "first dialyzer use syndrome." Two-thirds of the patients have specific IgE antibody to ETO conjugated to human plasma albumin (HSA) (Dolovich et al. 1984).

Once ETO reaction is suspected, dialyzers should be replaced with gamma-, steam-, or electron-beam-sterilized dialyzers (Purello D'Ambrosio et al. 1997). The incidence decreased due to the increased efficiency of ETO removal and use of the materials less adsorbing ETO in the manufacturing process.

Bradykinin-mediated response: AN69-associated reactions: AN69 is a copolymer of polyacrylonitrile (PAN) and sodium methallyl sulfonate. Dialysis reaction can develop when AN69 dialyzer and ACE inhibitors are used simultaneously. This reaction has been considered to be mediated by bradykinin system

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activation (Verresen et al. 1990). Negatively charged AN69 membrane surface activates bradykinin system. ACE inhibitors prolong the biological action of the activated bradykinins. As a result, prostaglandins and histamine are increased abnormally and result in vasodilation and increased vascular permeability. It is unclear whether other PAN-based copolymers or non-PAN-based copolymers induce this kind of bradykinin-mediated response.

Reuse syndrome, *disinfectants*: Disinfectants for dialyzer reprocess can cause dialyzer reaction, so called the dialyzer reuse syndrome. Formaldehyde, glutaraldehyde, peracetic acid, and hydrogen peroxide are the common causes. Radioallergosorbent test (RAST)-positive patients to formaldehyde appear to develop a serious reaction (Bousquet and Michel 1991).

Bioincompatible dialyzers: Unsubstituted cellulose membrane or cuprophan can cause the activation of complement system by the contact of their free hydroxyl group to blood. Usually complement activation by itself causes mild nonspecific reaction and is sometimes related with dialysis-related neutropenia or hypoxia (see Sects. 9.1.2, 9.4.4 and 9.4.5). However, it can amplify the other dialyzer reactions such as ETO hypersensitivity through the supply of complements and histamine and causes severe reaction (del Balzo et al. 1989). Bioincompatible dialyzers are rarely used these days. Current substituted cellulose dialyzer or new synthetic dialyzers, in which free hydroxyl group is covered or substituted by other groups, have little biological reaction. In acute renal failure, complement activation by dialyzer can be the cause of the delay of the recovery of renal function (Schulman et al. 1991).

Dialysate contamination: Bacteria or endotoxin contamination in the dialysis solution and a water purification system can cause anaphylactic-/anaphylactoid-type responses. Bicarbonate dialysate is vulnerable to bacterial contamination than acetate dialysis. High-flux dialyzer has also increased vulnerability to endotoxin or bacterial contamination by the leak.

Drug-induced reaction: There have been reports that iron dextran (Chertow et al. 2006), heparin (Blossom et al. 2008), and deferoxamine (Felsenfeld 1990) can lead to anaphylactic-type reactions.

9.1.1.3 Management and Prevention

When anaphylactic reaction appears life threatening, blood lines should be immediately locked, and hemodialysis should be stopped. Extracorporeal blood should be discarded without returning to the patient's body. Depending on the symptoms, antihistamines, epinephrine, and/or steroids should be administered. Cardiopulmonary resuscitation and respiratory support should be provided within a reasonable time if needed.

Meticulous rinsing to remove antigenic substances such as ETO is needed before use. Once ETO reaction is suspected, dialyzers should be replaced with gamma-, steam-, or electron-beam-sterilized dialyzers.

If patients show weak reaction despite of change to non ETO dialyzer, administration of antihistamines before dialysis may be helpful. Dialyzer reuse can be another possible option. The AN69 and PAN-based dialyzers should be avoided in patients using ACE inhibitors.

9.1.2 Nonspecific Type (Mild Type)

9.1.2.1 Clinical Manifestations

The common symptoms are chest pain or back pain. It usually occurs within 20–40 min. It can be delayed up to an hour after the initiation of dialysis (Daugirdas and Ing 1988). Since symptoms are less severe, dialysis usually can be maintained. Mild nonspecific-type dialysis reactions should be diagnosed after the exclusion of all other diseases which can induce chest pain.

9.1.2.2 Etiology and Pathogenic Mechanism

The main mechanism of mild-type reaction is the activation of complement system by bioincompatibility of dialyzers (del Balzo et al. 1989). The incidence is lower with reused dialyzer than with new dialyzer. It is thought to be protein coating effect and removal of causative material by repeated use and cleaning that increases biocom-

patibility of reused dialyzers. Since bioincompatible dialyzers are now widely used, the frequency of nonspecific-type dialysis reactions is in a gradually declining trend.

9.1.2.3 Management and Prevention

Symptomatic treatments include oxygen supply, analgesics, and sometimes antihistamines. Since the symptoms are usually alleviated after an hour of dialysis, dialysis can be continued. It is very important to rule out other serious diseases that can cause chest pain, such as myocardial ischemia. If dialysis reaction is repeated, replacement of dialyzer with a higher biocompatible dialyzer or incorporation of the patient into dialyzer reuse program may be good options.

9.2 Intradialytic Hypotension

Intradialytic hypotension is common and a challenging complication of hemodialysis patients. Significant intradialytic hypotensive episodes requiring a series of treatment interventions occurs up to 10–30% of all dialysis. These patients have difficulty in maintaining adequate dry weight and sufficient dialysis dose due to frequent cessation of hemodialysis. Patients often lose the desire to maintain the quality of life. In acute renal failure, intradialytic hypotension may cause further renal insults and delay the recovery of renal function.

9.2.1 Clinical Manifestations

Some patients do not show noticeable symptom until the blood pressure is decreased to dangerous level. Thus blood pressure should be carefully monitored for all patients during dialysis session. Common symptom includes dizziness, nausea, vomiting, or muscle cramps. Sometimes it causes arrhythmias, convulsions, unconsciousness, and ischemic damage in cardiovascular or cerebrovascular system. It is one of the common causes of AV fistula failure. Unpredicted intradialytic hypotension may be a sign of serious illness, such as pericardial effusion or cardiac tamponade.

9.2.2 Etiology and Pathogenic Mechanism

In normal healthy patients, water can be removed up to 20% of plasma at the appropriate ultrafiltration (UF) rate since the physiological compensation occurs to reward hypovolemia. If water removal is too excessive or too quick, e.g., UF rate > 0.35 mL/min/kg, hypotension can occur (Ronco et al. 1988).

The compensation mechanisms include the increase of vascular resistance by the activation of sympathetic nervous system, the increase of heart rate and cardiac contractility, and the maintenance of central blood volume by systemic blood flow redistribution (Fig. 9.1).

There are a number of factors that interfere with these compensation mechanisms. Patient factors include loss of baroreflex and impaired autonomic nervous system in elderly and/or diabetic patients, the intensive use of antihypertensive drugs, structural abnormalities in the heart, arrhythmia, sepsis, bleeding, anemia, venous pooling during dialysis, elevation of core temperature, and meals during dialysis. Factors-related dialysis processes include use of low sodium or low calcium dialysates, use of acetate dialysis or bioincompatible dialyzers (K/DOQI 2005).

9.2.2.1 Humoral Factors

Excessive interdialytic weight gain causes the necessity of excessive UF rate and amount during dialysis. Similarly, excessive accumulation of uremic molecule also causes acute excessive osmolality change. Excessive water removal and acute decrease of osmolality are the common causes of intradialytic hypotension. Elderly or long-term diabetic patients frequently manifest the impaired autonomic function, which can cause intradialytic hypotension by impairing cardiac compensation. Hypoalbuminemia also causes intradialytic hypotension by the impairment in vascular refilling. Low sodium or low calcium dialysates can be a cause of hypotension.

9.2.2.2 Vascular Factors

Intradialytic hypotension occurs when compensations fail such as sympathetic reflex or blood flow redistribution from peripheral to central

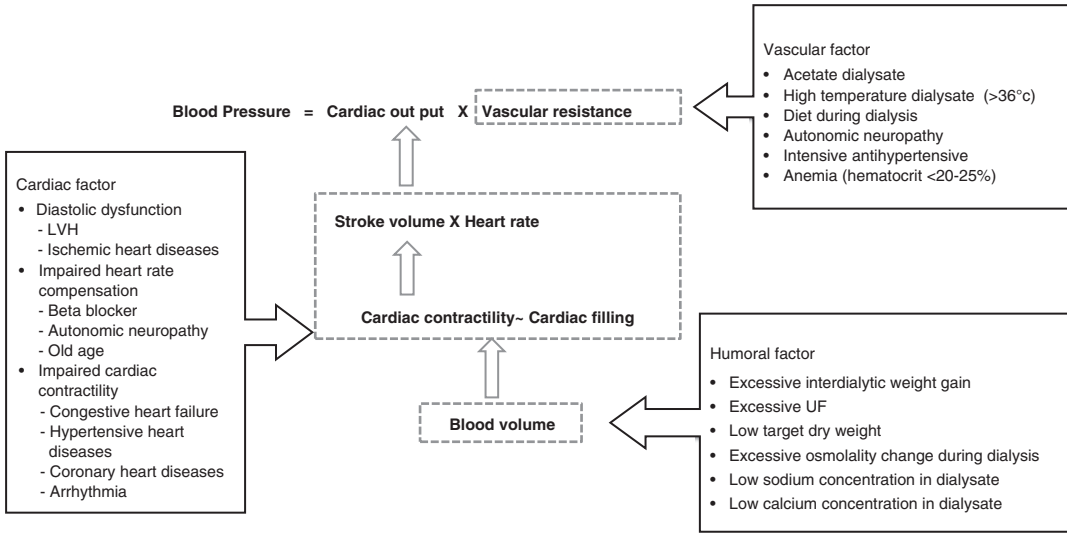

Fig. 9.1 The step of physiological compensation for hypotension and the related pathologic conditions in each step

vasculatures. Diabetic or uremic autonomic neuropathy, especially in the elderly, causes sympathetic failure in which the responsive secretion of norepinephrine is inadequate. Food intake during hemodialysis increases the splanchnic blood flow and reduces the amount of blood in the core vasculatures. Antihypertensive agents taken before dialysis are a common cause of intradialytic hypotension. Severe anemia (hematocrit <20–25%) tends to cause hypotension by hypoxia and consequent vasodilation. High temperature dialysate over 36 ° C causes peripheral vasodilation to reduce core temperature, which results in the decrease of core blood volume and consequently hypotension. In the past, intradialytic hypotension was frequent with use of acetate dialysate through the adenosine-mediated vasodilation and use of bioincompatible dialyzers through the complement activation.

9.2.2.3 Cardiac Factors

Conditions impairing the reflex response of cardiac output and heart rate result in intradialytic hypotension. It is difficult to compensate hypovolemia due to reduced cardiac filling in the patients with diastolic dysfunction such as left ventricular dysfunction or ischemic heart disease. Cardiac contractility is reduced in the patients with congestive heart failure, ischemic heart diseases, hypertensive heart diseases, and arrhythmia. The use of beta-blocker, uremic or diabetic autonomic neuropathy, and the elderly also frequently show the impairment of the reflex increase of heart rate.

Table 9.1 Bedside management of intradialytic hypotension

1. Trendelenburg position
2. Nasal oxygen supply
3. Discontinuation of ultrafiltration
4. Blood flow reduction
5. Saline (or mannitol) administration
6. Cessation of hemodialysis with cautious returning of blood to patient's body when necessary

9.2.3 Management

Immediate interventions should be performed for restoration of circulatory blood volume and ensuring vital organ perfusion. These include taking Trendelenburg positions, supplying oxygen, immediate cessation of UF and minimization of blood flow, and rapid recovery of circulation with saline or mannitol infusion (Table 9.1). If needed, hemodialysis has to be discontinued. However, it should be remembered that frequent interruption of hemodialysis session may cause chronically insufficient delivered dose

of dialysis and chronic blood loss. The returning of blood to the patient's body should be carefully done in consideration of the risk of air embolism or hemolysis.

9.2.4 Preventive Measures for Controlling Humoral Factors

9.2.4.1 General Measures

Reevaluation of Dry Weight: It is necessary to evaluate whether dry weight is set excessively low. Trial and error method by well-trained nephrologists is generally accepted. Blood volume marker such as ANP, BNP, or cGMP, bioimpedance analysis, and the measurement of inferior vena cava by ultrasound or echocardiograph have been reported helpful.

Restriction of Interdialytic Weight Gain: UF amount should not exceed 3 kg per session. If weight gain is more than this, education for water and diet uptake should be intensified targeting weight gain not exceeding 1 kg per day and/or not exceeding 2 kg for interdialytic period. To prevent excessive weight gain, salt restriction should be emphasized rather than water itself (Agarwal and Weir 2010).

Increasing Dialysis Duration and Frequency: If the restriction of interdialytic weight gain is impossible, it can be considered to extend the duration of dialysis session or to increase the frequency of dialysis to minimize UF per session.

9.2.4.2 Therapeutic Dialysis

Vascular refilling is an important physiological process to avoid hypovolemia during dialysis. Hypotension occurs if this process is inadequate. To achieve adequate vascular refilling, the rapidity of the osmolality change and that of water removal, i.e., UF rate, is most important. Recent dialysis machines can manipulate these two factors by adjusting dialysate sodium concentration and automatic control of ultrafiltration rate.

Sequential Dialysis (Isolated UF + Isovolemic Hemodialysis): Only ultrafiltration is performed for the initial 1 h without removing uremic molecules to keep the osmolality change minimally and to keep vascular volume. After then, hemodialysis is performed for the rest of the session to remove uremic molecules with minimal ultrafiltration. Usually 50% of target UF is achieved for the initial isolated UF time, and the rest is removed for the remaining 3 h of hemodialysis (Fig. 9.2).

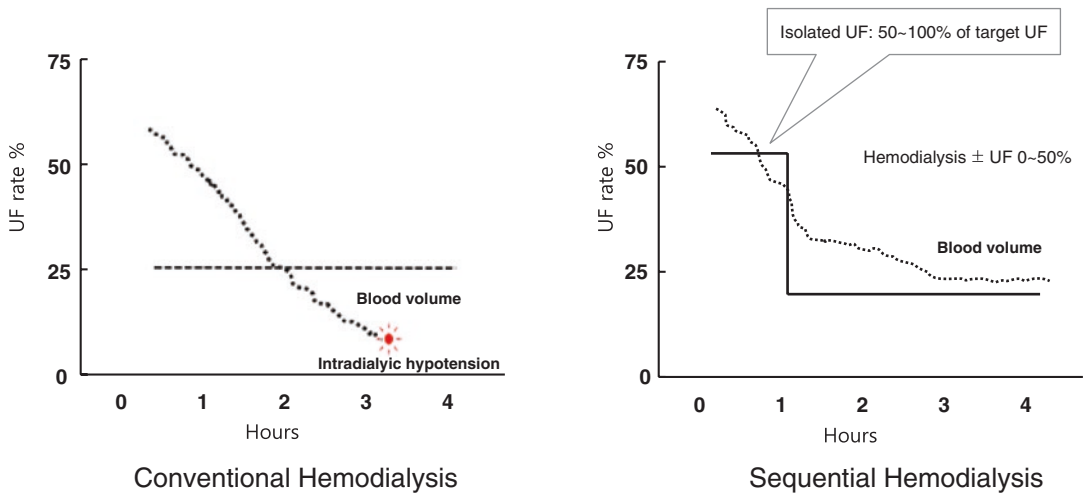

Fig. 9.2 Sequential hemodialysis (HD). Rapid decrease of osmolality may interfere the vascular refilling and results in hypotension in conventional HD. In sequential HD, most of target water removal is achieved during initial isolated UF period with minimal osmolality change. Uremic molecules are removed during latter hemodialysis period

Sodium Modeling: It is a method to maintain plasma osmolality, and thus to prevent hypotension by keeping dialysate sodium concentration higher than conventional HD (Zhou et al. 2006). Constant high sodium dialysis higher than 138 mmol/L frequently causes thirst and interdialytic weight gain. Sodium modeling dialysis is introduced to avoid these side effects. In sodium modeling dialysis, dialysate sodium concentration is initially high and decreased to normal or lower level linearly (linear sodium profiling) or stepwise (stepwise sodium profiling) to avoid patients' hypernatremia after finish of dialysis (Fig. 9.3). In general, it has been regarded to be effective and easy method, but thirst, excessive interdialytic weight gain, and hypertension are still limitation (Song et al. 2002, 2005). Recently, UF profiling is used in combination with sodium profiling (so-called combined sodium and ultrafiltration profiling) to maximize water removal and minimize hypovolemia (Fig. 9.4). Combination with cool temperature dialysis also is a convenient and effective option (K/DOQI 2005; van Der Sande et al. 2000).

Ultrafiltration Profiling: If vascular refilling rate does not match UF rate, blood volume will drop too early during the dialysis session. UF profiling is a method manipulating UF rate during the session to give the time for vascular refilling and to avoid intradialytic hypotension (Fig. 9.5). Reducing the UF rate sequentially or stepwise and keeping zero at the end of session is done to avoid the vascular refilling failure that usually occurs in the latter part of dialysis. Another method is the periodical stopping of UF, which gives enough time for vascular refilling.

Online Blood Volume Monitor and Automated Biofeedback-Controlled Dialysis: Online blood volume (BV) monitor can monitor real-time BV change. It is possible by measuring the hematocrit using optic or ultrasonic devices. Some recent dialysis machines are equipped with these

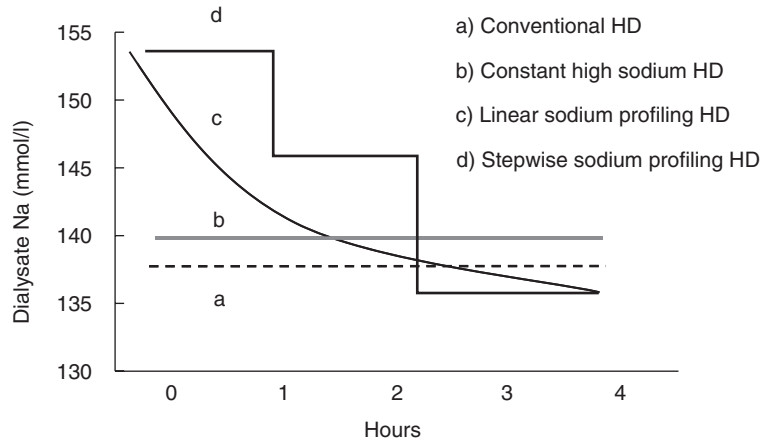

Fig. 9.3 Sodium modeling. In constant high sodium dialysis, dialysate sodium level is maintained higher than usual level, 138 mmol/L. In linear and stepwise sodium profiling, dialysate sodium concentration begins with high level and ends with normal or lower level

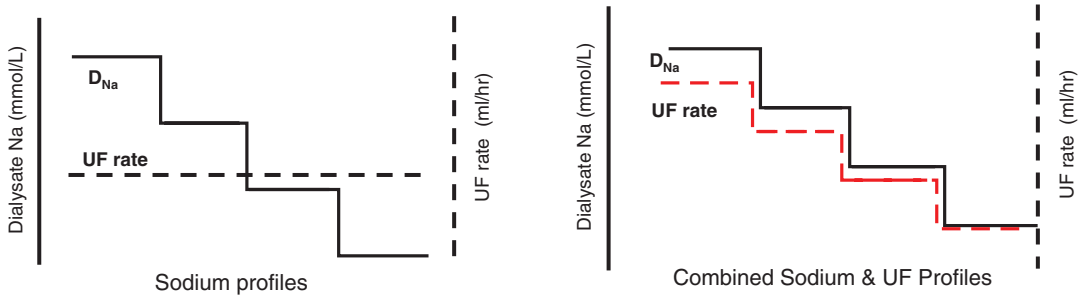

Fig. 9.4 Combined sodium and ultrafiltration profiling. UF rate is profiled in parallel with sodium concertation to maximize water removal and minimize hypovolemia

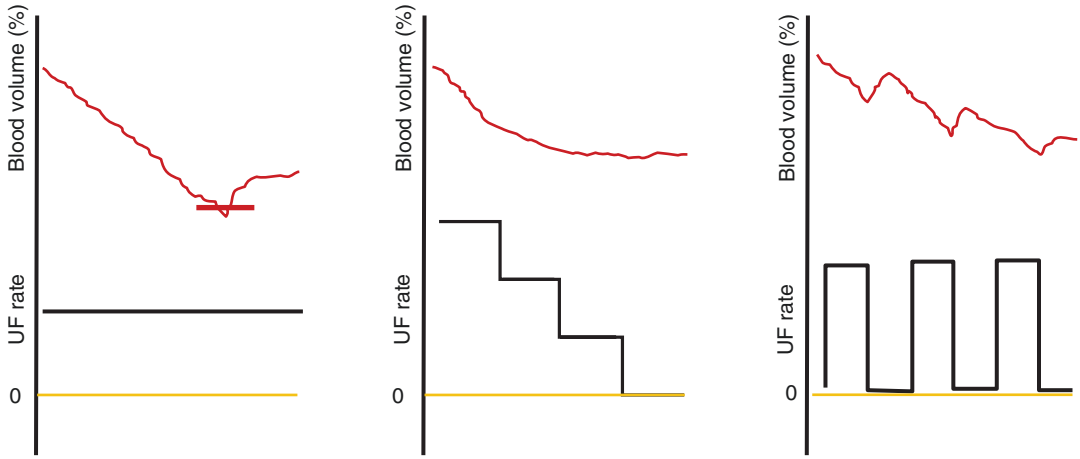

Fig. 9.5 Ultrafiltration profiling. Typical constant UF may cause transient significant hypotension in the patient with impaired plasma refilling ability (**a**). Stepwise lowering UF can avoid vascular refilling failure that usually occurs in the latter part of dialysis (**b**). Periodical stopping of UF can give the periodic chance for vascular refilling

devices, for example, Hemocontrol® (Fig. 9.6) or BVM® (Basile et al. 2001; Leypoldt and Lindsay 1999). Automated biofeedback-controlled dialysis system is a proprietary technology using "fuzzy logic" system (Mancini et al. 2007). These machines can automatically adjust dialysate conductivity, i.e., practically sodium concentration, and UF tracking on-line BV change (Deziel et al. 2007; Colì et al. 2011). This system appears to improve patients' tolerability to dialysis, but data is inconsistent and still insufficient. Further work is needed before it can be routinely recommended for intradialytic hypotension-prone patients.

9.2.5 Preventive Measures for Controlling Vascular Factors

9.2.5.1 Predialysis Antihypertensive Medication

Antihypertensive agents taken before dialysis are a common cause of intradialytic hypotension. Careful evaluation of the association of the timing and dosing of antihypertensive drugs and inter-, pre-, and postdialytic blood pressure is required in intradialytic hypotension-prone patients. If the association is suspected, it should be considered to skip or reduce the dose of predialytic antihypertensive drugs. It also can be helpful to move the prescription time of antihypertensive drug to evening.

9.2.5.2 Refraining from Food Intake During Dialysis

The food intake during dialysis increases the splanchnic blood flow. Consequently, the reduced blood flow in the core vasculatures may result in hypovolemia. Food intake should be refrained before and during the dialysis session in intradialytic hypotension-prone patients.

9.2.5.3 Bicarbonate Dialysate

Acetate dialysate was a culprit causing frequently dialysis reaction and intradialytic hypotension. Although it is now rarely used, acetate may be present in a small quantity, approximately 3 mmol/L, in some bicarbonate-based dialysates. There have been some reports that acetate, even in small quantities, may cause intradialytic hypotension (Bolasco et al. 2011; Agarwal 2012).

9.2.5.4 Cool Temperature Hemodialysis

When circulating blood volume is reduced, superficial vasculatures are constricted to redistribute blood flow to the core blood flow to compensate central hypovolemia by the sympathetic nervous system activation. During this process, core body

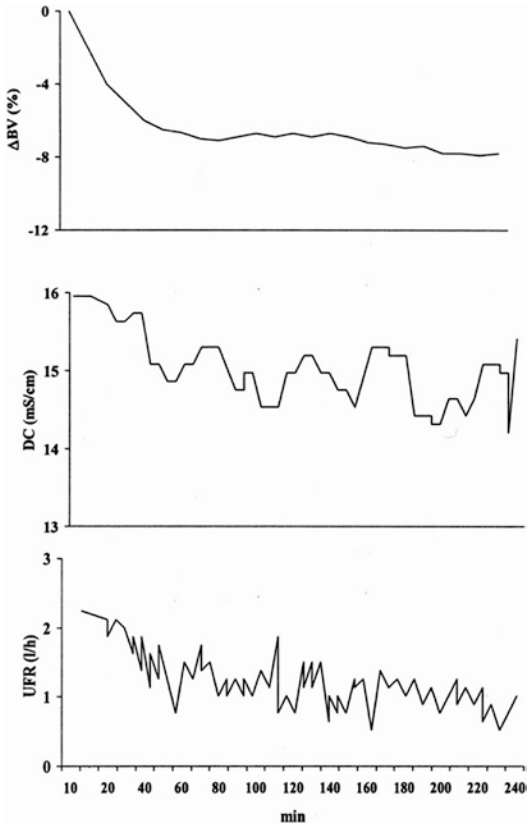

Fig. 9.6 Hemocontrol® continuous intradialytic recording of the blood volume obtained during a biofeedback system (*upper panel*). Middle and lower panels represent the intradialytic profiles of UF rate (UFR) and dialysate conductivity (DC), respectively, leading to the blood volume changes (ΔBV) shown in the upper panel (Basile et al. 2001) (need permission from Basile C, Giordano R, Vernaglione L, Montanaro A, De Maio P, De Padova F. Efficacy and safety of haemodialysis treatment with the hemocontrol biofeedback system: a prospective medium-term study. Nephrol Dial Transplant 2001;16(2):328–34)

temperature is elevated. In hypotension-prone patients, conventional dialysate temperature of 36–37 °C may elevate the core temperature too high to cause paradoxical superficial vasodilatation and hypotension (Fig. 9.7). Cool temperature dialysis with dialysate temperature of 34–36 °C is helpful to avoid intradialytic hypotension in these patients. A recent study suggested cool temperature hemodialysis also ameliorates subclinical myocardial ischemia (Selby et al. 2006). Recent biofeedback technology makes it possible to maintain patient's body temperature constantly (isothermic hemodialysis) and to profile the temperature as needed (dialysate temperature profile). Some authors reported that it is most effective when sodium modeling is combined with cool temperature dialysis (K/DOQI 2005; van Der Sande et al. 2000).

9.2.5.5 Drug Therapy

Midodrine: Patients with advanced stage of diabetes, long-term uremia, and/or old age do not respond to other methods due to severe autonomic nervous system dysfunction. In these intractable patients, alpha-1 adrenergic agonist, midodrine, can be helpful at a dose of 10 mg orally 30 min before dialysis session. Midodrine is effectively cleared, and its half-life is reduced to 1.4 h by hemodialysis. Since it has specificity for alpha-1 receptor, cardiac or central nervous system effect is minimal. Common side effects are nausea, heartburn, piloerection, scalp itching or tingling, urinary urgency, headache, nervousness, and sleep disturbance. Long-term use has been associated with supine systolic hypertension in less than 10% of patients, which warrants cessation of therapy (Jankovic et al. 1993). The combination of cool dialysate and midodrine may be helpful to decrease intradialytic hypotension.

Sertraline: A selective serotonin reuptake inhibitor, sertraline, was originally used for idiopathic orthostatic hypotension and neurocardiogenic syncope. Administration of 50–100 mg a day for 4–6 weeks has been reported to improve autonomic function neurocardiogenic syncope. It has been reported that 4–6 weeks of therapy improves the hemodynamic parameters in patients with intradialytic hypotension (Dheenan et al. 1998; Yalcin et al. 2002, 2003). It can be considered for the patient showing clue of paradoxical sympathetic withdrawal, i.e., sudden decrease in blood pressure with bradycardia.

L-*carnitine*: Carnitine deficiency is associated with several metabolic defects, defined as dialysis-related carnitine disorders, including intradialytic hypotension (Bellinghieri et al. 2003). L-carnitine therapy at 20 mg/kg into the dialysis venous port with each session reduces frequency of intradialytic hypotension and muscle cramps (Ahmad

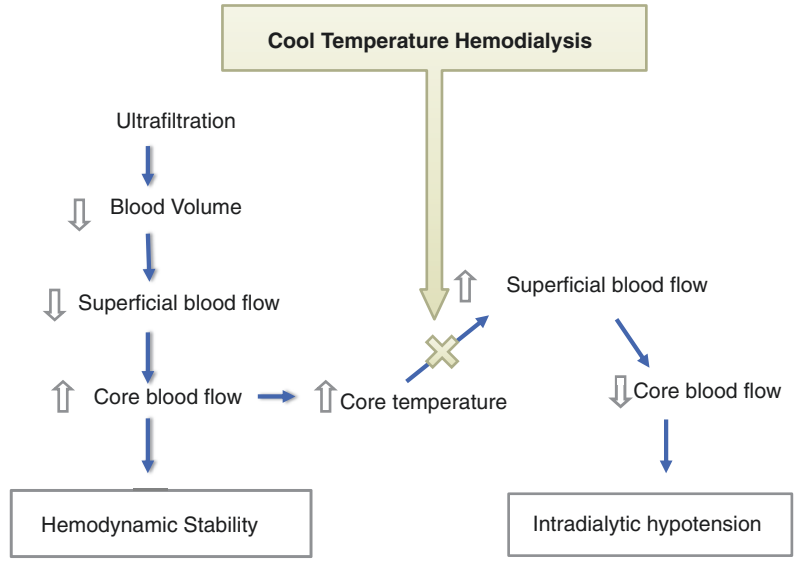

Fig. 9.7 Reduced blood volume by UF induces the decrease of superficial blood flow and redistribution of blood to body core, which is necessary to maintain hemodynamic stability. Elevated core temperature may paradoxically cause superficial vasodilatation and hypotension in hypotension-prone patients. Cool temperature dialysis can stop the latter response

et al. 1990; Riley et al. 1997). It is also effective in improving the quality of life in some patients. Mechanism of beneficial effect is not clear, but it could be due to improvement in vascular smooth muscle and cardiac muscle function.

Caffeine: Caffeine is an adenosine receptor antagonist. It may be helpful when the cause of intradialytic hypotension is increase of adenosine, an endogenous vasodilator, which is released due to anemia or organ ischemia.

Vasopressin: There is a report that the infusion of vasopressin infusion (0.3 mU/kg/min) reduces frequency of intradialytic hypotension and potentiates the removal of fluid although the subject number is too small to be conclusive (Santoro 2007).

9.2.6 Preventive Measures for Controlling Cardiac Factors

9.2.6.1 Identification and Treatment of the Underlying Cardiac Diseases

It is important to check the presence of underlying heart diseases, such as congestive heart failure, arrhythmias, or ischemic heart disease. When it is found, appropriate treatment is mandatory. In particular, it is necessary to check for pericardial diseases.

9.2.6.2 Correction of Anemia

According to K/DOQI guidelines, hemoglobin level should be maintained to 11–2 g/dL. It is an important and effective way to decrease vasodilation due to hypoxia. It also improves cardiovascular and myocardial function, and thus prevents hypotension.

9.2.6.3 Use of High Calcium and Low Magnesium Dialysate

High calcium dialysate (dialysate calcium concentration of 1.5 mmol/L) showed improvement of cardiac contractility and vasoconstriction in the patients with left ventricular ejection fraction of 40% or less or with NYHC III–IV heart failure as compared to low calcium dialysate (1.25 mmol/L) (Gabutti et al. 2009). Low magnesium dialysate (0.25 mmol/L) also may be helpful to improve heart function. The use of these dialysate can be considered for the patient with cardiac dysfunction. It should be made known that hypercalcemia may decrease bone turnover in some patients with the use of dialysate calcium of 1.5 mmol/L or more.

9.2.7 Stratified Approach to Prevent Intradialytic Hypotension

Recently, EBPG guideline has summarized the stratified approach to prevent hemodynamic instability and intradialytic hypotension as in Table 9.2, which can be easily practiced in general dialysis centers (Kooman et al. 2007).

Table 9.2 Stratified approach to prevent intradialytic hypotension from EBPG guideline on hemodynamic instability

First-line approach
• Dietary counselling (sodium restriction)
• Refraining from food intake during dialysis
• Clinical reassessment of dry weight
• Use of bicarbonate as dialysis buffer
• Use of a dialysate temperature of 36.5 °C
• Check dosing and timing of antihypertensive agents
Second-line approach
• Try objective methods to assess dry weight
• Perform cardiac evaluation
• Gradual reduction of dialysate temperature from 36.5 °C downward (lowest 35 °C) or isothermic treatment (possible alternative: convective treatments)
• Consider individualized blood volume controlled feedback
• Prolong dialysis time and/or increase dialysis frequency
• Prescribe a dialysate calcium concentration of 1.5 mmol/L
Third-line approach (only if other treatment options have failed)
• Consider midodrine
• Consider L-carnitine supplementation
• Consider peritoneal dialysis

9.2.8 Resistant Intradialytic Hypotension

K/DOQI Comments for Resistant Intradialytic Hypotension: K/DOQI guideline advised the use of combinations of modalities for resistant cases of intradialytic hypotension as below (K/DOQI 2005):

1. Combination of midodrine and dialysate temperature profiling or cold temperature hemodialysis
2. Combination of dialysate temperature profiling or cold temperature hemodialysis and high calcium dialysate
3. Combination of dialysate temperature modeling or cold temperature hemodialysis and sodium modeling

Convective Renal Replacement Therapy: Convective renal replacement therapy such as hemodiafiltration and hemofiltration may reduce the incidence of intradialytic hypotension in patients receiving hemodialysis in long term (Agarwal 2012). A recent randomized trial with 70 hemodialysis patients showed that the frequency of intradialytic hypotension fell from 9.8 to 8% in hemofiltration and from 10.6 to 5.2% in hemodiafiltration. The odd ratio for risk reduction in symptomatic intradialytic hypotension for hemofiltration was 0.69 and for hemodiafiltration was 0.6 (Locatelli et al. 2010). The benefits are thought to be due to improved plasma refill and neurohormonal response to loss of intravascular volume (van Der Sande et al. 2000).

Extended Daily Dialysis or Nocturnal Hemodialysis: These modalities of dialysis therapy have definitely the advantage of slow ultrafiltration rate. However, there is limited data about the benefit of extended daily dialysis or nocturnal hemodialysis. Furthermore, clinical studies are needed to prove the cost-effectiveness of these modalities in the treatment of intradialytic hypotension.

9.3 Other Common Complications

Besides intradialytic hypotension, frequent complications of hemodialysis include postdialysis fatigue syndrome (up to 33%), muscle spasms (5–20%), nausea and vomiting (5–15%), headache (5%), chest pain (2–5%), back pain (2–5%), pruritus (5%), and pyrogenic reaction (1%) in order of frequency. In addition, up to half of dialysis patients still show the uncontrolled hypertension (dialysis-refractory or intradialytic hypertension).

9.3.1 Postdialysis Fatigue Syndrome

Nonspecific fatigue and malaise appear in about 33% of dialysis patients (Abuelo et al. 1993). Possible causes include reduced cardiac output, peripheral vascular diseases, depressed mood, poor conditioning, postdialytic hypoglycemia, hypokalemia, mild uremic encephalopathy, neuropathy, and uremic myopathy.

It tends to be more frequent with non-glucose or acetate dialysate and to be reduced with glucose-containing or bicarbonate dialysate. Complement activation or cytokine production by bioincompatibility of the dialyzer has also been thought to be related, but the exchange of cuprophan with polysulfone dialyzer failed to show symptom improvement in double-blind studies (Group BCDS 1991; Sklar et al. 1998). Carnitine deficiency also causes malaise. Supplementing of L-carnitine has shown improvement of well-being sensation (Lindsay et al. 2006).

9.3.2 Muscle Cramps

9.3.2.1 Clinical Manifestations

Muscle cramps occur at a frequency of about 5–20%. It usually appears within the first month of starting hemodialysis treatment in the elderly, anxious patients, and non-diabetic patients. Symptom appears typically in the legs and/or hands and arms. It usually manifests in the latter half of hemodialysis session, in which skeletal muscle ischemia occurs after water is removed maximally by UF. It may disappear spontaneously within 10 min but sometime last several hours after dialysis. It is one of the common causes of the premature discontinuation of hemodialysis.

9.3.2.2 Etiology and Pathogenic Mechanism

Tissue hypoperfusion by plasma hypovolemia and rapid decrease of osmolality is thought to be the two main pathogenic factors (Canzanello and Burkart 1992). Predisposing clinical conditions include hypotension, excessive interdialytic weight gain, excessively low dry weight, excessive water removal during dialysis, and low dialysate sodium concentration. Electrolyte imbalance such as hypomagnesemia or hypocalcemia, uremic myopathy, peripheral neuropathy, peripheral vascular diseases, and sometimes alcohol or drugs such as clofibrate or nicotinic acid may also predispose to muscle cramps.

9.3.2.3 Management and Prevention

Education should be intensified to avoid excessive interdialytic weight gain. The daily weight gain should not exceed 1 kg. Salt restriction should be more focused than water restriction itself. It has been reported that enalapril, at the dose of 5 mg orally twice a week, may reduce weight gain by suppressing the angiotensin II-mediated thirst (Oldenburg et al. 1988). In patients who show no apparent signs of volume overload, it can be considered to elevate dry weight by 0.5 kg. Bicarbonate dialysate reduces the frequency of muscle cramps comparing to acetate dialysate. Sodium modeling is reported helpful by avoiding acute decrease of osmolality.

Infusion of hypertonic solutions including 15–20 mL of 23.5% hypertonic saline, 50–100 mL of 25% mannitol, or 25–50 mL of 50% dextrose water can be administered to relieve the cramp (Canzanello et al. 1991). Since high sodium solution may induce sodium load, thirst, and interdialytic weight gain, glucose solution may be a better choice except for diabetic patients. Oral quinine sulfate at the dose of 325 mg at the initiation of dialysis or oxazepam 5–10 mg 2 h before dialysis has been reported to reduce the frequency of muscle cramp (Kaji et al. 1976). Stretch exercise targeting at the affected muscles may be effective during dialysis (Sherman et al. 2015). L-carnitine, vitamin E (400 IU), prazosin, nifedipine, phenytoin, carbamazepine, amitriptyline, and gabapentin have been reported to be effective in some reports.

9.3.3 Restless Leg Syndrome

9.3.3.1 Clinical Manifestations

Restless leg syndrome is typically characterized by paresthesia, drawing and crawling sensation of legs and claves. Patients experience

insomnia because of a sense of discomfort and suffer from anxiety and depression. Diabetic or uremic neuropathy, anxiety, and progressive vascular disorders should be excluded. It can be differentiated from other types of peripheral neuropathy that it occurs while resting or in lying positions, such as during dialysis session, and is temporarily subsided by the movement of legs. Some patients also complain of pain near the same site. In general, restless leg syndrome tends to persist lifelong once it appears. It usually disappears after kidney transplantation. Restless leg syndrome of predialysis patients is improved within a few weeks of the initiation of dialysis therapy.

9.3.3.2 Etiology and Pathogenic Mechanism

Electromyography and nerve conduction test usually do not show any remarkable findings. The exact cause is unknown but believed to be associated with uremic toxins since it has been reported that severe restless leg syndrome is relieved by the initiation of dialysis therapy or kidney transplantation (Winkelmann et al. 2002).

9.3.3.3 Management and Prevention

Dialysis adequacy should also be checked. When intractable, benzodiazepines, opiates, and carbamazepine can be administered. Clonazepam acts long and can cause sleeping tendency during the day. Shorter half-life benzodiazepines such as temazepam may be better and tolerable. Opiates may be effective but can lead to abuse and tolerance. Carbamazepine or levodopa has been used successfully but tolerance occurs quickly too. Therefore, some authors prefer the alternative use of these pharmacologically unrelated drugs with 1 or 2 week's interval to avoid tolerance.

Recently, gabapentin at dose of 200–300 mg after dialysis has been reported effective to improve restless leg syndrome (Thorp et al. 2001). Dopamine receptor antagonists, pramipexole (Montplaisir et al. 1999) and ropinirole (Pellecchia et al. 2004), have showed effectiveness. For the patients not responding to the pharmacological treatments, TENS (transcutaneous electric nerve stimulation) can be an option although sufficient data are not yet reported.

9.3.4 Nausea and Vomiting

9.3.4.1 Clinical Manifestations

Nausea and vomiting are typical uremic symptoms and improved after the initiation of dialysis therapy. However, they continue or newly occur in about 10% of patients even with dialysis. Nausea and vomiting are usually nonspecific manifestations of various pathophysiological processes.

9.3.4.2 Etiology and Pathogenic Mechanism

Usually they appear in association with intradialytic hypotension and may also be the combined manifestation of dialysis disequilibrium syndrome or dialysis reactions. Excessive accumulation of uremic toxins or the electrolyte imbalance may cause nausea and vomiting. If they appear unrelated to dialysis session, adequacy of dialysis or electrolytes level such as calcium should be checked. If there is no reasonable reason, gastroenterological evaluation should be considered.

9.3.4.3 Management and Prevention

It is important to avoid intradialytic hypotension. The possibility of dialysis reaction should be evaluated. If symptoms persist, metoclopramide at the dose of 5–10 mg can be used orally or by injection before dialysis.

9.3.5 Headache

9.3.5.1 Clinical Manifestations

Headache is a common complication with a frequency of up to 60–70% (Antoniazzi et al. 2003). It usually is pulsatile pain in both temporal areas 3–7 h after dialysis and usually worsens in the supine position. Sometimes it is accompanied by nausea and vomiting but not by visual distur-

bances. When headache is severe and atypical especially during dialysis with the use of anticoagulation, other serous neurologic causes should be evaluated.

9.3.5.2 Etiology and Pathogenic Mechanism

It may be associated with intradialytic hypotension. Also it can be a weak manifestation of dialysis disequilibrium syndrome. Predisposing factors include new dialyzer and shorter dialysis time. In heavy coffee drinkers, caffeine withdrawal by dialysis can be a possible cause. Glucose-containing dialysate reduces the frequency of headache.

9.3.5.3 Management and Prevention

Oral acetaminophen can be given to the patients with severe headache. Maneuvers to prevent intradialytic hypotension (see Sect. 9.2) and dialysis disequilibrium syndrome (see Sect. 9.4.1) are helpful. The use of bicarbonate and/or glucose-containing dialysates can be considered. If caffeine withdrawal symptoms are suspected, drinking coffee can be beneficial.

9.3.6 Chest and Back Pain

Mild chest pain can occur in approximately 1–4% of dialysis session, often accompanied by back pain. It usually is associated with intradialytic hypotension or dialyzer reaction. Interventions for intradialytic hypotension are needed including supplying nasal oxygen, cessation of UF, and reduction of blood flow rates. The latter is associated with complement activation, and it may be helpful to change to biocompatible dialyzer.

It is very important to exclude the cardiac diseases such as myocardial ischemia or angina that occurs frequently during the dialysis session. If these diseases are suspected, sublingual nitroglycerine should be given, and ECG and cardiac enzyme tests should be done. Sometime it can be a symptom of rare but serious problems such as hemolysis, pericarditis, or air embolism.

9.3.7 Pruritus

9.3.7.1 Clinical Manifestations

Pruritus is a common and annoying problem in dialysis patients. It is usually persistent, deteriorated by dialysis, and worsened in the summer. Sometimes pruritus appears only during dialysis.

9.3.7.2 Etiology and Pathogenic Mechanism

Pruritus is multifactorial in origin. Dry skin (xerosis), hypercalcemia, hyperphosphatemia, hyperparathyroidism, and inadequate dialysis dose can be the cause. Acetate dialysate and unsubstituted dialyzer such as cuprophan cause pruritus more frequently. Sometimes it can be the allergic response to ETO and formaldehyde. Antiseptic solutions, rubber glove, nickel in the puncture needle, or epoxy glue used at the tube-needle joint can cause eczematous reaction. Heparin may also cause allergic reaction.

9.3.7.3 Management and Prevention

Plasma calcium, phosphorus, and parathyroid hormone levels should be checked. If plasma calcium and phosphorus level is high, dietary education and intensive use of phosphorus binder should be reemphasized. Hyperparathyroidism should be treated aggressively.

The adequacy of dialysis prescription should also be well monitored. If uremic pruritus is suspected, dialysis dose should be increased. High-efficiency dialysis can be a useful option for uremic pruritus although further larger study is required.

For dialysis-associated pruritus, change to substituted or synthetic dialyzers and bicarbonate dialysate can reduce the frequency. Dialyzer reuse program may also be helpful. If ETO or formaldehyde reaction is suspected, dialyzers can be replaced with gamma-, steam-, or electron-beam-sterilized dialyzers.

Moisturizing ointments or lotions are helpful for the patients with mild itching. Diphenhydramine 25 mg orally or by injection or cyproheptadine 4 mg orally can be given for

symptomatic patients. Ultraviolet therapy, especially UVB, is also helpful. Gabapentin 100–300 mg or oral activated charcoal (6 g/day) can be considered. Mast cell stabilizer ketotifen, oral naltrexone, topical capsaicin cream, and erythropoietin have been included to therapeutic options. Ondansetron has failed to demonstrate concrete effectiveness in randomized trials (Murphy et al. 2003; Ashmore et al. 2000).

9.3.8 Pyrogenic Reaction

Pyrogenic reaction is caused by endotoxin or bacterial contamination that induces the release of cytokines such as IL-1, IL-6, or TNF. The patients complain of fever and chills. Sometimes it is accompanied by muscle pain and hemodynamic instability in the later part of dialysis. It is very important to rule out septicemia before pyrogenic reaction is diagnosed.

In general, symptoms are well controlled with antipyretics and empirical broad-spectrum antibiotics. Blood culture should be obtained before the use of antibiotic. When hemodynamic instability presents, UF should be stopped, and the discontinuation of the session should be considered. Hospitalization should be considered in severe cases.

The possibility of bacterial contamination always should be suspected. Careful examination of the dialysis access and equipment is warranted. When high-flux dialysis is used, sterile pyrogen-free dialysis water should be used (Henderson 1993). Bicarbonate-containing solutions are highly susceptible to bacterial contamination (Jaber and Pereira 1997).

9.3.9 Dialysis-Refractory or Intradialytic Hypertension

9.3.9.1 Clinical Manifestations

Up to the half of dialysis patients still show hypertension in spite of adequate hemodialysis (dialysis-refractory hypertension) (Cheigh et al. 1992). Eight to 30% of patients show the paradoxical rise of blood pressure after the initiation of dialysis (intradialytic hypertension) (Chen et al. 2006). Uncontrolled blood pressure during and after dialysis is the strongest predicting factor of cardiovascular morbidity and mortality (Inrig et al. 2007); these patients need careful monitoring and efforts to control blood pressure.

9.3.9.2 Etiology and Pathogenic Mechanism

According to a recent study by the ANP measurement, many patients clinically showing dialysis-unresponsive hypertension are still volume overloaded and not at a “true” dry weight (Fishbane et al. 1996). Erythropoietin improves cardiac function and the quality of life, but it also induces hypertension in some patients. It increases blood viscosity and endothelin-1 secretion, decreases endothelium-derived relaxing factor (EDRF) activation, and finally raises blood pressure. It also increases the cytoplasmic calcium level, and thus increasing myocardial contractility and vascular smooth muscle tone (Vaziri 2001). Elimination of compensatory vasodilator effect of hypoxia by correcting anemia also contributes to hypertension.

Removal of fluid and potassium by dialysis provokes a compensatory activation of renin-angiotensin system and sympathetic nervous system (Fellner 1993; Ligtenberg et al. 1999). This usually contributes to intradialytic hypertension in young patients with residual renal function. Removal of antihypertensive drugs by dialysis induces the increase of blood pressure. Maximal increase of hematocrit by fluid removal near the end of dialysis also contributes to intradialytic hypertension. Therefore, the patient receiving a number of antihypertensive drugs, with hematocrit more than 33% and requiring large UF due to excessive interdialytic weight gain, are highly susceptible for intradialytic hypertension.

9.3.9.3 Management and Prevention

Reduction of dry weight by 0.5 kg with close observation of response is justified unless signs of volume contraction present. Subcutaneous injection of erythropoietin has been reported to be associated with better blood pressure control than intravenous route (Navarro et al. 1995).

For intradialytic hypertension, preventive administration of angiotensin receptor blockers or calcium channel blockers, which are minimally or non-dialyzable, can be considered.

9.4 Rare Complications

Hemodialysis also can cause uncommon but clinically significant complications, which include dialysis disequilibrium syndrome, seizure, dialysis-related neutropenia, complement activation and hypoxia, thrombocytopenia, and bleeding.

9.4.1 Dialysis Disequilibrium Syndrome

9.4.1.1 Clinical Manifestations

Dialysis disequilibrium syndrome (DDS) is a neurological complication due to a sudden osmolality change by the removal of large amount of uremic molecules. It typically occurs when acute renal failure or chronic renal failure patients with very severe azotemia receive the first dialysis. Risk factors for DDS are young age, severe azotemia, delayed initiation of dialysis therapy, malignant hypertension, and preexisting neurological disorders such as stroke or trauma (Arieff 1994).

Symptoms of DDS range from mild manifestations such as nausea, vomiting, restlessness, and headache to serious manifestations such as seizures, delirium, convulsions, coma, and death. It appears during the dialysis session but rarely can be delayed up to 24 h after dialysis. If recovered spontaneously, it usually takes several days. Brain CT or MRI usually shows nonspecific edema. There is no specific finding in other examinations including EEG. Thus diagnosis can be done clinically after the exclusion of other diseases. If coma is due to DDS, it usually improves within 24 h. Otherwise, other serious neurological disorders should be ruled out.

9.4.1.2 Etiology and Pathogenic Mechanism

DDS is a manifestation of cerebral edema. When removal of osmotic solutes occurs too fast and large, the imbalance of osmotic pressures between plasma and brain results in the movement of the water from plasma to brain tissue leading to cerebral edema (reverse urea effect) (Himmrlfarb et al. 2008). Rapid correction of acidosis can lead to the retention of carbon dioxide in the body, which moves into the cerebrospinal fluid (CSF) and causes temporary paradoxical acidosis (paradoxical CSF acidosis). This also is thought to contribute to the development of DDS.

9.4.1.3 Management and Prevention

Mainstay of prevention is the starting low efficiency dialysis with target reduction of BUN not more than 30–40% in the patients who initiate the first dialysis therapy with very high BUN level (>150–200 mg/dL). It is helpful to start the first day dialysis with blood flow rate of 50 mL/min for 2 h and then increase duration by 30 min and blood flow rate by 50 mL/min for 3–4 days. Dialyzer with small surface size (0.9–1.2 m^2), concurrent dialysate flow (in which dialysate and blood flow in the same direction), blood flow rate less than 200 mL/min, and high sodium dialysate are also valuable methods to prevent DDS.

When dialysis is initiated in the patients with decreased consciousness, neurologic problems, or very high risk for DDS, mannitol can be given intravenously at the dose of 12.5 g hourly. For people with high risk of epilepsy, phenytoin can be given before dialysis at the dose of 1 g in the first day and then 300 mg for the next 3 days. However, preventive use of mannitol and anticonvulsants is not recommended for general low-risk patients. For the patient showing chronic forms of DDS such as headaches, muscle cramps, or nausea, it is helpful to reduce blood flow rate and to use hypertonic dialysis solutions such as high sodium (Na > 140 mmol/L) or high glucose (>200 mg/dL). Current trend of early initiation of dialysis and introduction of UF volumetric control technique or sodium and UF profiles have reduced the serious forms of DDS. On the other hand, high-flux dialysis with large surface dialyzer increases the frequency of DDS.

Dialysis should be stopped when serious neurological symptoms such as seizure or coma occur. Anticonvulsants should be given for seizure. If necessary, intravenous mannitol and/or hyperventilation therapy to reduce intracranial pressure should be considered with careful monitoring in the intensive care unit. It is very important to differentiate other serious neurologic diseases such as subdural hematoma, stroke, hypertensive encephalopathy, toxic encephalopathy, meningitis, uremia, anoxia, primary seizures, or metabolic disorders.

9.4.2 Seizure

9.4.2.1 Clinical Manifestations

Seizure is rare in chronic dialysis patients but occurs infrequently in patients receiving acute or emergency dialysis (Swartz 1993). Hemodialysis-associated seizure is typically generalized and is easily controlled. If it is focal or treatment-resistant, it is necessary to rule out other causes such as cerebral hemorrhage.

9.4.2.2 Etiology

Causes include DDS, uremic encephalopathy, aluminum intoxication, hypertensive encephalopathy, hypoglycemia, and alcohol withdrawal. Hypernatremia, hypocalcemia, or some epileptogenic drugs such as theophylline, meperidine, or ß-lactamases may be the cause of seizure. Intradialytic hypotension and consequent brain anoxia may cause seizure. Erythropoietin can be a possible cause of seizure in the patient with preexisting hypertension but rare in normotensive patients.

9.4.2.3 Management

If serious attack occurs, dialysis should be stopped and respiratory patency should be maintained. Diazepam, clonazepam, or phenytoin can be given intravenously. If hypoglycemia is suspected, 50% glucose solution can be administered. If seizure is atypical or focal neurological sign is seen, further evaluation is warranted.

9.4.3 Arrhythmia

9.4.3.1 Clinical Manifestations

Arrhythmia is common in hemodialysis patient. More than 80% of the arrhythmia is atrial arrhythmia. Ventricular arrhythmia needs more special attention since it can progress to serious ventricular tachycardia. Arrhythmia should be cautiously evaluated in the patient receiving digitalis.

9.4.3.2 Etiology and Pathogenic Mechanism

Many clinical conditions predisposing persistent or recurrent arrhythmias include left ventricular hypertrophy, congestive heart failure, ischemic or hypertensive heart disease, and uremic pericarditis (Rutsky and Rostand 1989; Derfler et al. 1959). Asymptomatic myocardial ischemia during dialysis is the common cause of arrhythmia and requires attention. Since dialysis patients are unstable in volume, electrolyte, and acid-base states, digitalis or antiarrhythmic agents can trigger the arrhythmias more frequently.

9.4.3.3 Management and Prevention

Hypercalcemia, alkalosis, or hypokalemia may predispose the digitalis-induced arrhythmias (Kant 1994). In the patient receiving digitalis, serum digitalis levels should be monitored on a regular basis, and serum potassium level should be kept above 3.5 mEq/L. Therefore, no or low potassium dialysate is usually not recommended in these patients. High glucose dialysate or bicarbonate dialysate may induce the shift of potassium into the cell and thus causes hypokalemia. Glucose and bicarbonate concentrations in the dialysate should be kept at minimal level as permitted by clinical situation. High calcium dialysate improves cardiac contractility but sometimes causes ectopic cardiac beats.

Long-term treatment of hypertension and congestive heart failure and the effort to prevent myocardial ischemia are helpful to prevent the arrhythmias. It is also important to maintain the adequate hemoglobin level. Since excessive volume reduction during the dialysis increases the

risk of arrhythmia by decreasing the coronary artery blood, the efforts to reduce UF rate, for example, the control of the interdialytic weight gain, are important.

9.4.4 Dialysis-Related Complement Activation and Neutropenia

9.4.4.1 Clinical Manifestations

Bioincompatible dialyzers such as unsubstituted cellulose membrane or cuprophan can activate complement system. The complement activation results in mild nonspecific dialysis reactions with symptoms including hypotension, nausea, vomiting, chest pain, and back pain. It sometimes induces dialysis-related neutropenia. The number of circulating white blood cells including neutrophils decreases temporarily by 50–80% with the initiation of dialysis and returns to normal or higher level within 30–60 min of dialysis (Kaplow and Goffinet 1968). Dialysis-related neutropenia has been regarded as a marker of poor dialyzer biocompatibility. Complement activation has also been known to contribute in some part to dialysis-related hypoxia (see Sect. 9.4.5).

9.4.4.2 Etiology and Pathogenic Mechanism

As described above, free hydroxyl group of unsubstituted cellulose membrane or cuprophan activates the complement system. Activated complement fragments sequestrate the systemic neutrophils into the pulmonary vasculatures (migration and sequestration) (Dodd et al. 1983). This so-called pulmonary leukosequestration is the cause of dialysis-related leukopenia and hypoxia.

Complement activation can amplify the other serious dialyzer reactions such as ETO hypersensitivity (del Balzo et al. 1989). In acute renal failure, complement activation by dialyzer can be the cause of the delay of the recovery of renal function. Activated white blood cells and neutrophils by complement activation are migrated and sequestrated in the renal glomerulus and delay the recovery of renal function (Schulman et al. 1991).

9.4.4.3 Management and Prevention

Complications due to complement activation are currently uncommon and subtle in most cases. Synthetic membrane such as polysulfone, polycarbonate, or PMMA rarely causes complement activation and its related complications. PAN (polyacrylonitrile) activates the complement system in somewhat degree. However, the net effect is minimal since it also adsorbs the complement fragments.

9.4.5 Dialysis-Related Hypoxia

9.4.5.1 Clinical Manifestations

Dialysis-related hypoxia is frequently seen in up to 90% of patients but usually is negligible in most healthy patients. The oxygen concentration (PaO_2) is transiently reduced by 5–30 mmHg between 30 and 60 min and returned to 60–120 min (Patterson et al. 1981). In the patients with existing heart or lung disease, it can cause serious problems.

9.4.5.2 Etiology and Pathogenic Mechanism

Hypoventilation and the impairment of diffusion are the causes of the dialysis-related hypoxia. Dialysate CO_2 in acetate dialysate after the equilibrium with room air is less than 1 mmHg. Dialysis with acetate dialysate results in low patient's $PaCO_2$ and causes hypoventilation and hypoxia (Munger et al. 2000). This does not occur with bicarbonate dialysate since it contains high CO_2 concentration. However, when bicarbonate concentration is too high (>35 mEq/L), it can cause metabolic alkalosis and consequently results in hypoventilation and hypoxia (Himmrlfarb et al. 2008).

As described elsewhere, bioincompatible dialyzers can cause the sequestration of neutrophil within the lung and neutrophil pulmonary embolism resulting in hypoxia by the way of diffusion impairment (see Sect. 9.4.4).

9.4.5.3 Management and Prevention

It is usually sufficient to supply oxygen nasal cavity. Acetate dialysate is currently rarely used. In highly risky patients, biocompatible dialyzer and bicarbonate dialysate at the concentration of less than 35 mEq/L should be used. Maintaining hematocrit at optimal level is helpful. There is a report that cold dialysate may reduce hypoxic episode (Hegbrant et al. 1997).

9.4.6 Thrombocytopenia

Transient thrombocytopenia during the hemodialysis can occur as a dialyzer reaction. The number of the platelets decreases to less than 100,000/mm^3 with reaching a nadir within 1 h of the initiation of dialysis (Hakim and Schafer 1985). Use of the biocompatible dialyzers reduces the occurrence of the thrombocytopenia.

Drugs such as deferoxamine, vancomycin, or quinine may induce thrombocytopenia. Heparin can induce mild (type I) or serious (type II) type of thrombocytopenia (heparin-induced thrombocytopenia, HIT). HIT is caused by heparins extracted from bovine lung rather than those from bovine intestinal mucosa. Type I HIT is mild, and the platelet count rarely drops below than 100,000/mm^3. It usually resolves spontaneously, and heparin can be continued. Type II HIT is severe and associated with IgG antibody against heparin complex (Kelton et al. 1988). It is characterized by the clotting and thromboses with bleeding propensity simultaneously (Pham et al. 1995). The treatments are complete withdrawal of all heparin products and change to heparinoids such as direct thrombin inhibitors argatroban, bivalirudin, lepirudin, or indirect Xa-inhibitor danaparoid (Vanholder et al. 1997; Wittkowsky and Kondo 2000). Low molecular heparin is also contraindicated.

9.4.7 Bleeding

Uremic patients has bleeding tendency due to platelet dysfunction, abnormal interaction between platelet and vessel wall, abnormal blood rheology by anemia, abnormal platelet aggregation function, and abnormal production of nitrogen monoxide. The use of heparin during dialysis aggravates the bleeding tendency, which is actually the most common cause of bleeding in the dialysis patient.

It is important to maintain adequate dialysis dose to improve platelet function. Maintaining the hematocrit to 30% or more also improves the rheological interaction of the platelet-vessel wall. Before surgery or invasive procedure, antiplatelet agents should be stopped a week before, and hematocrit should be maintained at 30% or more. For the patients with high risk or active bleeding, heparin-free dialysis with saline washing every 15–30 min, local heparin anticoagulation, or heparin modeling should be considered. Use of low molecular weight heparin, citric acid, or prostacyclin can also be considered. Conjugated estrogen or DDAVP (1-deamino-8-D-arginine vasopressin) improves platelet function in short term. Conjugated estrogen can be administered intravenously at the dose of 0.6 mg/kg/day for 5 consecutive days. DDAVP can be administered at the dose 0.3ug/kg subcutaneously or intravenously for 15–30 min. In some case, conjugated estrogen and DDAVP can be used in combination. Cryoprecipitate is also useful (Liangos and Jaber 2010).

9.5 Technical Complication

9.5.1 Hemolysis

9.5.1.1 Clinical Manifestations

Hemolysis during dialysis is a medical emergency. It manifests as chest tightness, difficulty in breathing, and back pain firstly. Characteristic signs include deepening of skin pigmentation, port-wine color change of blood in circuit line, and pink discoloration of the centrifuged plasma from the patient's blood. It is also accompanied by acute decrease of hematocrit. If hemolysis is massive, hyperkalemia becomes the main problem. It causes muscle weakness, ECG abnormalities, and cardiac arrest.

9.5.1.2 Etiology and Pathogenic Mechanism

Acute hemolysis occurs due to the mechanical problems that cause the destruction of erythrocytes including twisting or kinking of blood lines or narrowing or obstruction of catheter or needle. Clinically insignificant hemolysis is always possible when blood flow rate is too fast and the needle size is relatively too small.

Accidental use of high-temperature dialysate, especially higher than 51 °C, or excessively hypotonic dialysate can cause hemolysis. Contamination of a dialysate with chloramine or nitrates of water supply and copper in pipes causes oxidative damage to red blood cells resulting in methemoglobinemia and hemolysis. Disinfectant formaldehyde transforms the epitope of erythrocytes to form the anti-N antibody cold agglutinin.

9.5.1.3 Management and Prevention

When suspected, blood line should be locked and blood pump stopped immediately. Blood in the lines should not be returned to the patient's body since it has a large amount of potassium. Hyperkalemia, arrhythmia, and a drop of hematocrit should be carefully monitored and prepared for the treatment. It should be kept in mind that serious problems may manifest later by delayed hemolysis. Hospitalization should be recommended in case. Dialysis circuit, air trapping pump, and roller pumps should be carefully examined, and dialysate sample should be obtained to investigate the cause.

9.5.2 Air Embolism

9.5.2.1 Clinical Manifestations

Air embolism is potentially fatal unless detected immediately. Air infusion more than 1 mL/kg is always life threatening. Symptoms depend on the posture of the patient since air tends to float. In a sitting position, air moves to the cerebral vasculature causing the loss of consciousness, convulsions, and death. In a supine position, it enters to the right ventricle and then passes into the lungs causing shortness of breath, cough, or chest tightness. When air passes through the pulmonary capillaries to the left heart and cerebral vasculature, serious cardiac and neurologic symptoms appear. When patient is in Trendelenburg position, air is trapped in the vasculature of lower extremities showing patchy cyanosis. Air bubble in the blood lines and/or peculiar churning heart sound on auscultation is the additional clue.

9.5.2.2 Etiology and Pathogenic Mechanism

The common site of air entry is the prepump arterial tubing segment, where it is vulnerable to air inflow due to very high negative pressure. Arterial needling, accidental opening of central venous catheter, and careless handling of intravenous solution bottles can also be the portals of air entry. When blood flow is excessively high, even a small leak may result in the entry of large volume of air.

9.5.2.3 Management and Prevention

When air embolism is suspected, dialysis should be immediately finished with clamping the venous blood lines and stopping blood pump. Patients should be immediately placed in "*a recumbent position on the left side with the chest and head tilted downward*" to prevent the air from moving to the left heart and cerebral vasculature. Depending on air volume, aspiration of air from the heart can be done by percutaneous needle or cardiac catheterization. Hyperbaric oxygenation is helpful if available (Baskin and Wozniak 1975). If necessary, cardiorespiratory support should be done including supply of 100% oxygen by mask or endobronchial tube.

9.5.3 Temperature Malfunction

Current dialysis machines have the internal thermostat controlling the dialysate temperature within 33–39 ° C. If the thermostat is failed, serious problems can occur from too hot or too cold dialysate.

When dialysate temperature exceeds 51 °C, hemolysis and life-threatening hyperkalemia

will always appear (Blagg 1989). Dialysis must be immediately stopped, and blood in the line should be discarded. Dialysis with a cool temperature dialysate of 35 °C may be needed to cool down the patient's blood and to treat subsequent hyperkalemia. Sometimes transfusion is required. When dialysate temperature is between 47 and 51 °C, hemolysis may appear up to 48 h later (Berkes et al. 1975). Patients should be monitored for the possibility of delayed manifestation. Cool dialysates cause cold sensation and shivering. It causes hypothermia in unconscious patients. Usually, accidental use of cool dialysates is not as dangerous as overheated dialysates. Sometimes it is beneficial in hemodynamically unstable patients or used for hypothermic therapy for the patients with hypoxic brain damage.

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Hemodiafiltration

10

M.P.C. Grooteman, M.J. Nubé, and P.J. Blankestijn

10.1 Introduction

In this chapter we discuss hemodiafiltration (HDF) as treatment option for patients with end-stage kidney disease. The concept was introduced decades ago, but only when technological developments made it possible to produce substitution fluid online and when this process was allowed by regulatory authorities that the modality received wider attention. We discuss the theoretical background, the clinical evidence, practical issues on how to perform HDF in clinical practice, potential mechanisms of the possible beneficial effects on clinical outcome, possible downsides, and finally some perspectives and conclusions.

10.2 Theoretical Background: Solute Transport, Water Treatment, and Equipment

10.2.1 Introduction

10.2.1.1 Short History

The fate of patients with end-stage kidney disease (ESKD) has changed dramatically since Kolff in 1946 performed the first hemodialysis (HD) as a temporary support for acute renal failure (Kolff 1946). Only after the creation in the 1960s of an arteriovenous (AV) connection, consisting of two permanent teflon-silastic tubes in an artery and a vein (Quinton et al. 1961), which were attached to each other shortly before the start of HD, and the discovery of hirudin to prevent clotting in the ECC that HD became available as a long-term life-saving treatment. In the following years, HD was performed with simple membranes, manufactured from cellulosic and modified cellulosic materials, which allowed the removal of small uremic compounds by diffusion. Since these (low-flux) dialyzers were relatively impermeable for larger uremic toxins and induced several bio-incompatible reactions in humans (Grooteman and Nube 1998), later on, high-permeable (high-flux) synthetic or modified cellulosic biocompatible materials were developed, which were capable of removing larger substances with less side effects. Yet, none of the large randomized controlled trials (RCT), comparing high-flux HD with low-flux HD, reported major differences in the all-cause and cardiovascular (CVD) mortality risks (Asci et al. 2013; Eknoyan et al. 2002; Locatelli et al. 2009). Hence, improvement of the uremic milieu, by adding a moderate degree of convective transport, generally less than 10 L/session, did not result in a clinical demonstrable long-term improvement.

To retain the diffusive capacity of low-flux HD and to improve the convective component of high-flux HD, a simple hemodiafiltration

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(HDF) system was developed many years ago (Henderson et al. 1975). Only after the introduction of HDF machines and water treatment systems which allow the online production (ol-HDF) of sterile and pyrogen-free substitution fluid, much larger convection volumes became accessible for everyday clinical practice (Canaud and Ledebo 2016).

10.2.2 Solute Transport

10.2.2.1 Diffusion

In low-flux HD small (up to 500 Dalton [D]) non-protein-bound molecules are removed by diffusion. Diffusion is dependent on the concentration gradient between blood and dialysis fluid of a certain particle (partly determined by blood flow rate (Qb) and dialysate flow rate (Qd), dialyzer characteristics, and molecular weight (MW)), as depicted in Fig. 10.1. When MW increases, the amount of diffusive transport and the sieving coefficient (SC) decline progressively due to the lower particle motility and the restricted pore size of the dialyzer membrane. To overcome this limitation of uremic purification, dialysis systems were developed with a convective component.

10.2.2.2 Convection

While urea removal was the leading concept since the 1970s (Gotch et al. 1976), later on, HD-associated morbidity and mortality were assigned to larger molecules, such as beta-2-microgobulin (β2M, MW 11.8 kilo Dalton [kD]) (Bardin et al. 1987). In an attempt to increase the amount of convective transport and to improve the sieving of larger particles, synthetic high-flux membranes were developed, which permitted the passage of molecules up to 40–50 kD ($SC_{\beta 2M}$ 0.8–0.9). To prevent unwanted fluid loss, HD machines with ultrafiltration (UF)-control devices were designed, which compensate the excess UF by backfiltration.

When convection is applied, water-soluble molecules are transported by solvent drag. The magnitude and the nature of convective transport are determined by the amount of water movement across the dialyzer per unit of time (UF rate) and the permeability of the membrane (Fig. 10.1). In standard low-flux HD, only the inter-dialytic weight gain, resulting from the intake of non-excreted drinks, is removed by UF (2.5–3.5 kg or L). During HDF, extra plasma water is ultrafiltrated during the treatment. In order to compensate for excess fluid loss, a substitution fluid is infused into the patient. This fluid can be infused either before the dialyzer (pre-dilution), after the dialyzer (post-dilution), both before and after the dialyzer (mixed-dilution), or within the dialyzer (mid-dilution) (see Fig. 10.2).

In pre-dilution HDF, the blood entering the dialyzer is diluted by substitution fluid. This

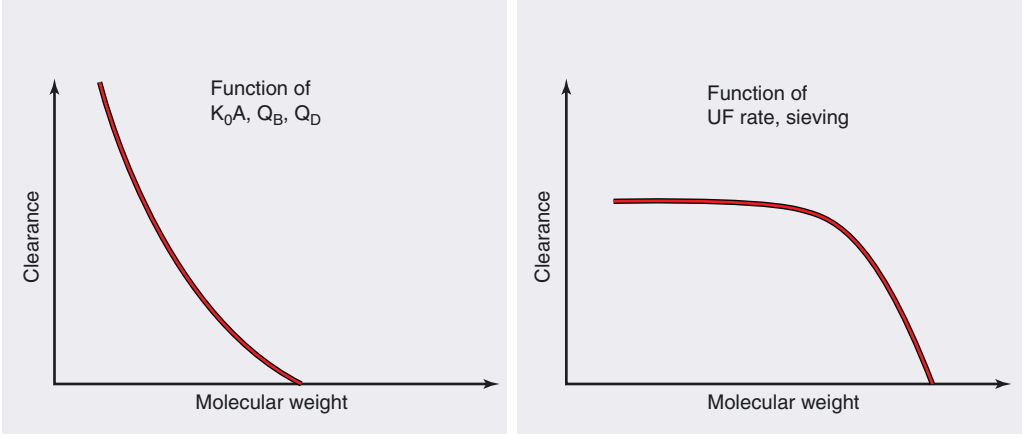

Fig. 10.1 characteristics of diffusion (*left*) and convection (*right*). Diffusion is a function of KoA (mass transfer area coefficient) of the dialyzer, Qb (blood flow), and Qd (dialysate flow); whereas convection is a function of UF rate (ultrafiltration and sieving of the dialyzer membrane)

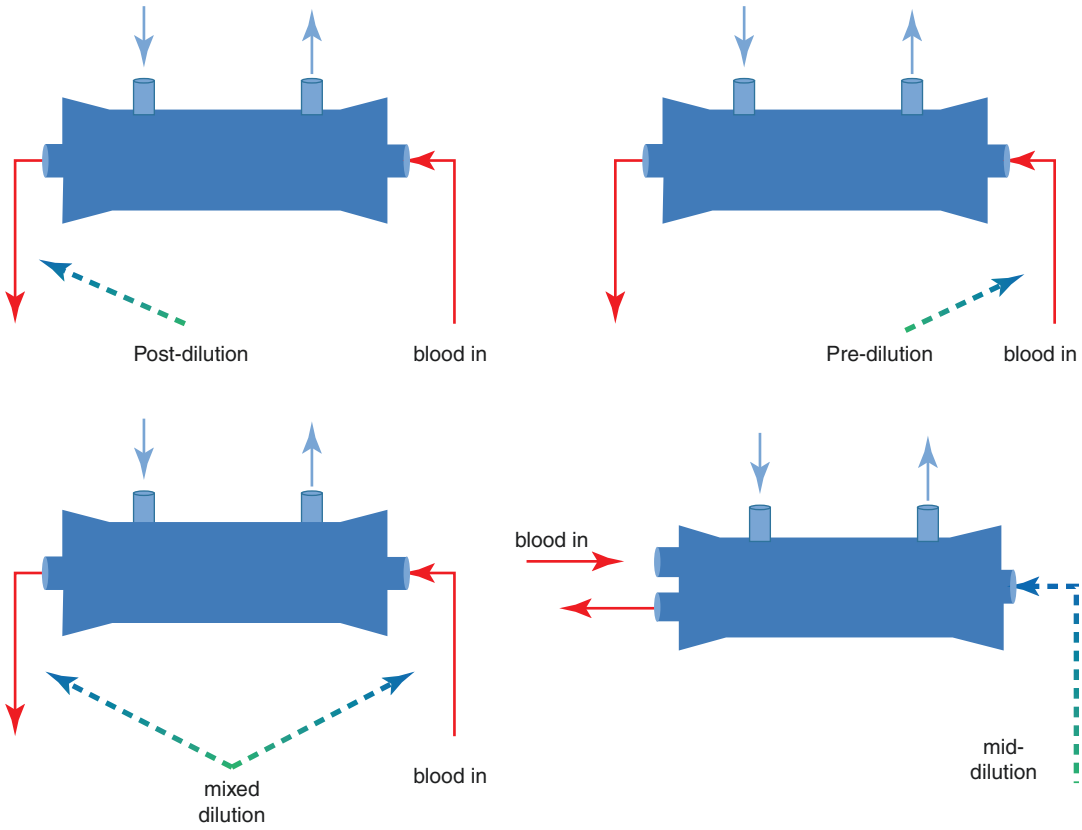

Fig. 10.2 Schematic illustration of post-dilution (*left top*), pre-dilution (*right top*), mixed- dilution (*left below*), and mid-dilution (*right below*) hemodiafiltration

results in a lower concentration of dissolved uremic toxins and a lower concentration gradient across the dialyzer membrane. Hence, diffusive clearance is less effective as compared to HD. Furthermore, the UF fluid consists of both substitution fluid and plasma water, reducing solute transfer.

In post-dilution HDF, UF results in a proportional increase in removal of middle molecular weight (MMW) toxins, as the substitution fluid is infused after the dialyzer. At the same time, hemoconcentration occurs inside the dialyzer, resulting in increased blood viscosity, restricting the amount of convection up to about 5–7 L/h. As the plasma solutes are not diluted before or within the dialyzer, diffusion is as effective as in HD, and the UF removed contains only plasma water.

With mixed-dilution HDF, the substitution fluid is infused with a variable rate both before and after the dialyzer, in an attempt to overcome the hemoconcentration occurring in post-dilution HDF, while retaining the superior clearance of pre-dilution. For mid-dilution HDF, special filters are used.

Online post-dilution HDF is the most widespread infusion mode and probably the most efficient in the removal of MMW substances. Data on clinical outcomes are available almost exclusively for post-dilution HDF.

10.2.3 Hemodiafiltration Equipment

10.2.3.1 Online-Hemofiltration Systems

In the early days of HDF treatment, substitution fluid was administered in bags, and fluid balance was obtained by weighing devices. In the 1980s, the first complete system for continuous online preparation of pyrogen-free substitution

fluid was launched (Canaud et al. 1985; Shaldon et al. 1982). Later on various modifications, improvements, and supplementary options were introduced (Canaud and Ledebo 2016).

Each modern ol-HDF (hereinafter just HDF) system has its own merits and (dis)advantages, which cannot be discussed in detail in this chapter. Differences include their cleaning and disinfection principles, consisting of chemical, thermal, and/or citro-thermal measures to eliminate contamination and avoid biofilm formation. Furthermore, the various HDF systems offer different blood tubing sets and occasionally a cassette system. Additional therapeutic and monitoring options include citrate administration, thermal balance measurement, and the monitoring of blood volume and temperature. All HDF systems have their own risk management system, additional to safety features required by international standards. In this regard the monitoring and warning of filtration fraction, inlet and outlet pressures, and their adjustable alarm limits should be mentioned. While each machine has its own display of settings and prescribed parameters, several manufacturers offer the choice between manual and automatic handling. Connection to a hospital information system is provided by some but not by all manufacturers of HDF equipment. Likewise, the possibility to perform different modalities of HDF with one machine, such as pre-, post-, mid-, or mixed-dilution HDF is provided by some but not by all systems (Fig. 10.2). Finally, each HDF system has its own costs assessment for machines, disposables, and microbiological monitoring. For further reading see Sternby et al. 2016.

10.2.3.2 Dialyzers for Hemodiafiltration

Theoretical Considerations

A prerequisite to perform HDF efficiently and safe is the selection of an adequate dialyzer. Criteria for selection include the material of the membrane, its biocompatibility profile, its hydraulic permeability (UF coefficient [KUF] generally expressed in mL/h/mmHg/m^2), the magnitude of the membrane surface area, its cutoff point for molecular size, and its physical strength to resist the intra-dialyzer transmembrane forces (Ronco et al. 2016). In addition, the material and structure of the membrane should be resistant to chemical and physical sterilizing agents. High adsorptive properties may contribute to the solute removal capacity of some membranes (Sombolos et al. 1997).

In HDF, dialyzer membrane wall thickness should be small enough (<45 μm) to permit diffusion but also strong enough to resist the high transmembrane pressure (TMP) needed for large convection volumes and to prevent rupturing of the membrane and leakage of blood. The hydraulic permeability of the dialyzer membrane should be sufficient (KUF >30 mL/h/mmHg/m^2) to allow the passage of uremic toxins up to 40–50 kD but simultaneously minimize albumin (66.4 kD) loss ($SC_{albumin}$ <0.001). As indicated in the KUF formula, the surface area of the membrane is an important determinant of UF rate. Various technical options have been applied to optimize the distribution of blood and dialysis flow in the central parts of the dialyzer and in peripheral areas, to obtain the most favorable exchange of uremic toxins (Vienken and Ronco 2001). Finally, a beneficial biocompatibility profile and an optimal endotoxin retaining capacity are fundamental aspects of the filter.

Dialyzers for HDF in Clinical Practice

Only a few studies provided information from clinical practice. In the multicenter Convective Transport Study (CONTRAST), dialyzers were used with a membrane surface area between 1.7 and 2.2 m^2, KUF between 56 and 85 mL/h/mmHg/m^2, capillary lumen diameters between 185 and 215 μm, and capillary lengths between 225 and 280 mm (Chapdelaine et al. 2014). Regardless of these differences, achievement of a high convection volume was above all dependent of treatment time and blood flow, while the type of membrane and its surface area was not determining. Nonetheless, in a comparative crossover study with four different membranes, the highest convection volumes were achieved by a dialyzer with the largest surface area (2.2 m^2), a high KUF (85 mL/h/mmHg/m^2), and capillaries with a wide

lumen (215 μm) and a short length (200 mm) (Albalate et al. 2011). Since high convection volumes (>29 L/5 h) could also be obtained with a special designed 1.4 m^2 dialyzer, these investigators raised the question whether a smaller membrane surface area than usual would induce fewer bio-incompatible side effects and less fouling and clotting (Maduell et al. 2014, 2015).

With respect to bio-incompatibility, even less studies have been performed. From a sub-study in patients from CONTRAST, it appeared that alterations in platelet activation, as measured by CD62p expression and platelet numbers, was more pronounced during HDF than during HD, most probably due to a higher TMP and increased hemoconcentration (Gritters-van den Oever et al. 2009). Electron microscopic evaluation revealed that the surface area of platelets was considerably reduced (Schoorl et al. 2011). In CONTRAST and in the Turkish HDF study (THDFS), the dose of heparin and low-molecular-weight heparin (LMWH) was 10%, respectively, 25% higher in HDF patients as compared to those who were treated by HD (de Roij van Zuijdewijn et al. 2014; Ok et al. 2013). Since high-volume (HV) HDF is associated with a significantly better clinical outcome than both standard HDF and HD, it appears that these potential harmful side effects are counterbalanced by dominant beneficial effects, such as a better intradialytic hemodynamic stability and/or a superior clearance of MMW uremic toxins (see next paragraph).

10.2.3.3 Water Treatment Systems

General Considerations

During standard HD, 500 mL/h of dialysis fluid flows through the water compartment of the dialyzer, which is separated from the blood compartment by the membrane of the dialyzer only. Depending on the concentration of the contaminant, the characteristics of the membrane, and the mode of HD, water-soluble contaminants may cross the membrane from the dialysis fluid into the blood. In Table 10.1, a number of low-molecular-weight substances are shown which are commonly found in drinking water and are toxic to HD patients. The recommendations for dialysis water are around tenfold lower than allowed for drinking water. Water treatment systems to produce water for dialysis, including HDF, consist of nonspecific purification steps, such as softeners and carbon filtration, which are centered around a reverse osmosis (RO). To achieve high-quality dialysis fluid, both prevention of bacterial entry to the system and controlling of bacterial growth within the system, especially slime-producing pseudomonas species, are important. To prevent biofilm formation, the material of the distribution systems must allow disinfection with hot water or water containing ozone.

Considering the entry of viable bacteria or their products, current HDF machines use a validated two-stage process. The first stage generates ultrapure (UP) dialysis fluid, and the second step reduces endotoxin levels further by a factor

Table 10.1 Standards for drinking water and dialysis water

Contaminant	WHO recommendations for drinking water (mg/L) (World Health Organization 2011)	ISO 13959:2014 standards dialysis water (mg/L) (International Organization for Standardization 2014a)
Aluminum	0.1	0.01
Arsenic	0.01	0.005
Barium	0.7	0.1
Cadmium	0.003	0.001
Calcium	200	2.0
Total chlorine	5	0.1
Chromium	0.05	0.014
Copper	2	0.1
Fluoride	1.5	0.2
Lead	0.01	0.005
Magnesium	50	4.0
Mercury	0.006	0.0002
Nitrate	50	2.0
Potassium	—	8.0
Selenium	0.04	0.09
Silver	0.05	0.005
Sodium	200	70.0
Sulfate	—	100.0
Zinc	5	0.1

Adapted from World Health Organization (2011), International Organization for Standardization (2014a), and Ward and Tattersall (2016)

Table 10.2 Maximum allowable levels of microbiological contaminants in dialysis fluids

	Endotoxin EU/mL	Bacteria CFU/mL
Standard dialysis fluid	<0.5	<100
Ultrapure dialysis fluid	<0.03	<0.1
Sterile, pyrogen-free infusion fluid	<0.03	<0.000001

EU endotoxin units, *CFU* colony forming units. Based on International Organization for Standardization (2014b)

100. Since it is not possible to verify the required purity, the validated process is automatically controlled and monitored by the dialysis machine. With respect to bacterial-derived products in the dialysis water, both diffusion and convection to the bloodstream of the patients may play a role: diffusion in low-flux and high-flux HD and convection by backfiltration in high-flux HD. Since bacteria and most bacterial-derived products, such as endotoxins and DNA fragments, which vary widely in size and composition, are too large for diffusion but not for convective transport, bacteriological safety requirements for high-flux HD (ultrapure [UP] dialysis fluid) are more stringent than for low-flux HD (standard dialysis fluid) (see Table 10.2).

Dialysis and Substitution Fluid for Hemodiafiltration

Similar to HD, HDF patients are exposed to 120–240 L of dialysis fluid during treatment. Purified RO water enters the machine and is mixed with bicarbonate and acid concentrate. In HDF, however, a considerable amount of plasma water is extracted from the patients on top of the UF requirements. To maintain volume balance, a similar amount of fluid is dispensed directly into the bloodstream of the patients. This substitution is produced online from dialysis fluid. While the fresh RO water passes upstream through an ultrafilter to ensure microbial purity and enters the ECC, the redirected substitution fluid passes through a downstream final filtration system to remove residual pyrogens and endotoxins before administering to the patients. This substitution fluid must not only be free of chemical contaminants, as in HD, but also highly pure, that is sterile and pyrogen-free (Table 10.2). The intravenous administration of large amounts of substitution fluid necessitates levels of microbiological quality far below detection limits.

10.2.4 Purity of HDF in Clinical Practice

Only little data are available on the water quality of HDF in clinical practice. Pyrogenic reactions were not reported in 4.284 HDF sessions over a 6-year period (Pizzarelli et al. 1998). In a crossover study in 27 patients, C-reactive protein (CRP) and tumor necrosis factor α (TNFα) did not differ between patients who were treated with HDF and low-flux HD (Vaslaki et al. 2005). From another study it appeared that the levels of the pro-inflammatory cytokines interleukin-6 (IL-6) and TNFα were lower during HDF than during HD (Panichi et al. 2006). Since in this study the two arms differed not only in the type of treatment (low-flux HD versus [low-volume] HDF) but also in the bacteriological quality of the dialysis fluid, the exact reason for these differences is not completely clear. Yet, the nature of these findings was confirmed in a large study on 11.258 HDF sessions in 97 CONTRAST patients (Penne et al. 2009a). From this study it appeared that the UP dialysis fluid was compliant with bacteriological and endotoxin reference levels in 99.3% and 98.8% of the samples, respectively. Clinical reactions did not occur. Moreover, from another report from the CONTRAST group in 405 patients, who were followed for 3 years on average, it appeared that both CRP and IL-6 levels were significantly lower in HDF patients as compared to individuals who were treated with low-flux HD (den Hoedt et al. 2014a). Finally, from a recent meta-analysis based on the individual participant data of four recent major randomized controlled trials (RCT), comparing HDF with HD, it appeared that hospital admissions because of infections were not different between HDF and HD patients (Peters et al. 2016).

From these studies it can be concluded first that HDF, when properly performed, does not result in an increased incidence of pyrogenic reactions. Second, these data also show that UP water can be obtained over a prolonged period

of time. Third, HDF does not aggravate the micro-inflammatory state which is commonly observed in patients with ESKD. Actually the risk of infection and markers of inflammation seem to be lower in patient on HDF than in patients who were treated with HD.

10.3 Clinical Evidence on Hemodiafiltration

10.3.1 Introduction

Clinical research on HDF has been focused both on indirect or surrogate parameters, including relevant biomarkers and the functioning of vital organs, and hard endpoints, such as mortality. The assessment of its benefits and disadvantages, however, is complicated since in many of these investigations, different HDF techniques were used (e.g., off-line HDF, pre- and post-dilution online HDF, acetate-free biofiltration, hemofiltration [HF]). Moreover, most comparative studies differed markedly in size, follow-up period, design, and methodology (e.g., observational versus RCT). As nearly all evidence on clinical endpoints is obtained from studies comparing online post-dilution HDF with other dialysis techniques, in the following section we will predominantly, but not exclusively, discuss this type of HDF.

10.3.2 Hemodiafiltration and Survival

10.3.2.1 Observational Studies

Several large observational studies on convective techniques have been published in the last decades. Apart from one Italian study (Locatelli et al. 1999), all investigations showed a reduction in the mortality risk of patients treated with HDF (Canaud et al. 2006a; Jirka et al. 2006; Mercadal et al. 2015; Panichi et al. 2008; Siriopol et al. 2015; Vilar et al. 2009). However, since the decision to treat patients with HDF in observational studies is generally based on clinical grounds and not on selection by chance, residual confounding can never be ruled out, even though extensive corrections are made to minimize selection bias.

10.3.2.2 Randomized Controlled Trials

Recently, three large RCTs, comparing mortality in HDF with HD, have been published. While in CONTRAST and the Turkish HDF study (THDFS) a modest, nonsignificant effect of treatment with HDF on all-cause mortality was shown (hazard rate [HR] 0.95 (95% CI 0.75–1.20) and HR 0.79 (95% CI 0.55–1.14), respectively) (Ok et al. 2013; Grooteman et al. 2012), in the Spanish ESHOL study a markedly reduced mortality risk was observed [HR 0.70 (95% CI 0.53–0.92)] (Maduell et al. 2013). Whereas the achieved convection volume was 20.7 L/session in CONTRAST and 19.6 L/session in THDFS, in ESHOL this figure was 22.9–23.9 L/session. Post hoc analysis of all three studies showed a significantly lower mortality in the group of patients treated with the highest convection volumes, even after extensive adjustments.

10.3.2.3 Meta-analyses

In recent years, several meta-analyses on the effects of convective therapies have been published, which, though, produced conflicting results (Mostovaya et al. 2014a; Nistor et al. 2014; Susantitaphong et al. 2013; Wang et al. 2014). At closer look, these meta-analyses differed considerably in the selection of the studies in the convective treatment arm [off-line HDF, online HDF, acetate-free biofiltration (AFB), hemofiltration (HF), and high-flux HD]. Since the magnitude of the convection volume is currently considered a key parameter for the efficacy of HDF, comparison of various low-dose convective techniques among themselves, nowadays, does not seem to be very helpful (see Table 10.3).

To avoid doubtful conclusions from meta-analyses on *aggregated patient data* from individual studies, which include low-dose convective therapies—such as high-flux HD—as well, the *individual participant data (IPD)* from CONTRAST, THDFS, ESHOL, and the French HDF study (Morena et al. 2017). French HDF study were combined. After collecting the mortality data for patients who were censored alive in the individual studies—352 out of a total of 355 censored patients were traced—the IPD base encompassed 2793 patients (Peters et al. 2016; Davenport et al. 2015). From this IDP meta-analysis, which includes only RCTs with a

Table 10.3 Overview of meta-analyses on convective therapies

First author and year of publication	Convective therapy	Comparator	No of RCTs[a]	No of patients[a]	Effect on all-cause mortality	Effect on cardiovascular mortality
					HR (95% CI)	HR (95% CI)
Rabindranath (2005)	HF, HDF, AFB	lfHD, hf HD	4	326 (–)	1.68 (0.23–12.13)	–
Susantitaphong (2013)	HF, HDF, AFB, hfHD	lfHD	21 (3)[b]	4766 (3207)	0.88 (0.76–1.02)	0.84 (0.71–0.98)
Mostovaya (2014a)	HDF	lfHD, hf HD	6[c] (3)	2885 (2402)	0.84 (0.73–0.96)	0.73 (0.57–0.92)
Nistor (2014)	HF, HDF, AFB	lfHD, hf HD	11 (6)	3396 (2889)	0.87 (0.70–1.07)[d]	0.75 (0.58–0.97)
Wang (2014)	HF, HDF, AFB	lfHD, hf HD	10 (4)	2998 (2487)	0.83 (0.65–1.05)	0.85 (0.66–1.10)
Peters (2016)	HDF	lfHD, hf HD	4	2793	0.86 (0.75–0.99)	0.77 (0.61–0.97)

RCT randomized controlled trial, *HR* hazard ratio, *CI* confidence interval, *HF* hemofiltration, *HDF* hemodiafiltration, *AFB* acetate-free biofiltration, *HD* hemodialysis, *hfHD* high-flux HD, *lfHD* low-flux HD

[a]Number of trials (respectively, patients) used for meta-analysis effect on all-cause mortality or (between brackets) cardiovascular mortality

[b]For the Susantitaphong meta-analysis: number of convective study arms

[c]Adapted in part from Grooteman et al. (2016a)

[d]If studies with low convection volumes (<12 L/treatment) are excluded from this meta-analysis, the HR for mortality is 0.82 (95%CI 0.72–0.93) (Grooteman et al. 2014)

mean convection volume around 19 L/session, now it appeared that the risk of all-cause and cardiovascular (CVD) mortality was significantly reduced in the HDF group (HR 0.86 [95% CI 0.75-0.99]), HR 0.77 (95% CI 0.61–0.97) respectively. Post hoc analysis in tertiles of the achieved convection volume (<19, 19–23, >23 L body surface area [BSA] adjusted) suggested a minimum necessary volume of 23 L/1.73 m^2 BSA/session, which was recently confirmed in a large observational study (Canaud et al. 2015). In an Editorial to the meta-analysis, it was speculated that effects on the hemodynamic stability during treatment could be the main mechanism of the beneficial effect (Daugirdas 2016).

10.4 How to Achieve High-Volume Hemodiafiltration?

10.4.1 Introduction

Actually, "convection volume" is the key parameter in HDF prescription, as it determines the magnitude of the convective transport and has been related to the reduced mortality in clinical trials (Peters et al. 2016; Tattersall and Ward 2013). From the IPD meta-analysis of four European RCTs on post-dilution HDF, it appeared that a convection volume >23 L/1.73 m^2 BSA/session is necessary to reduce mortality (adjusted HR 0.78 [0.62–0.98]), as compared to patients treated with HD (Peters et al. 2016). Obviously, in this respect dose targeting bias might play a role (Daugirdas 2013): ESKD patient characteristics which have been associated with an improved survival [such as the presence of an AV fistula (Slinin et al. 2010)] may enhance the chance of achieving a high convection volume. Yet, in the three recently published RCTs, comparing HDF with HD, the association between a high convection volume and survival remained after extensive correction for confounders. In clinical practice, a substitution volume of >21 L/session, which corresponds to >23 L of convection when UF volume is included, could be achieved in 81.5% of the sessions in 3315 patients (Marcelli et al. 2015).

10.4.2 Determinants of the Convection Volume in Post-dilution Hemodiafiltration

In CONTRAST, *treatment-related* factors (including treatment time, blood flow rate, and filtration fraction [FF]) were far more impor-

tant in determining the convection volume than *patient-related* factors (such as comorbidity, vascular access, albumin, hematocrit, age, and body size) (Chapdelaine et al. 2014; Penne et al. 2009b). The convection volume is defined by three treatment parameters: treatment time, blood flow rate, and filtration fraction. A sufficient treatment time and high blood flow rate result in a high processed blood volume:

$$\text{processed blood volume}(L) = \text{treatment time}(h) \times \text{blood flow rate}(L/h)$$

10.4.2.1 Treatment Time

Treatment time is highly practice dependent. Worldwide, treatment times during standard HD differ from 4 h 16 min in the Australia/New Zealand area to 3 h 34 min in the United States (Tentori et al. 2012). Even within countries, treatment time differs widely: in some centers participating in CONTRAST, treatment time was 4 h for all patients, whereas in other centers, It varied between 2.5 and 4 h (Chapdelaine et al. 2014). 'From a Dutch feasibility study which aimed to optimize the convection volume as much as possible, it appeared that none of the patients was willing to increase their treatment time (de Roij van Zuijdewijn et al. 2016). Hence, to achieve a high convection volume, it seems wise to start immediately with sessions of at least 4 h in incident HDF patients.

10.4.2.2 Blood Flow Rate

Blood flow rate prescription varies markedly as well between countries: from 200 mL/min in Japan, via about 300 mL/min in Europe and Australia/New Zealand, to 400 mL/min in the United States (Asano et al. 2013). Also within countries, large differences exist (Chapdelaine et al. 2014; Ponce et al. 2015). Hence, again, practice patterns seem to play a significant role. As can be seen from Table 10.4, for HV-HDF a blood flow of 350 mL/min (and preferably higher) is necessary. In order to achieve high blood flow rates, a few aspects should be taken into account:

Needle Size

A high blood flow (350 mL/min or more) can only be achieved with a larger bore needle: 14 or 15 G. With needles of 16 and 17 G, only <20% and <5% of patients, respectively, showed blood flow rates of >350 mL/min (Gauly et al. 2011). When changing to a 1 G larger needle (i.e., needle size 1 G), blood flow rates could be increased by about 20%, which was accompanied by lower venous and arterial pressures (Mehta et al. 2002).

Vascular Access

An adequate vascular access is required in order to achieve high blood flow rates in the ECC. Unfortunately, data on the relation between access flow rate, blood flow rate, and convection volume are not available. In some (Marcelli et al. 2015) but not all (Chapdelaine et al. 2014) studies, the presence of an AV fistula in particular was associated with a high convection volume. Data from CONTRAST, however, indicate that the achievement of HV-HDF was independent of the type of vascular access (Chapdelaine et al. 2014). Hence, a central venous catheter is not a contraindication for high-volume HDF.

10.4.2.3 Filtration Fraction

Besides treatment time and blood flow rate, the convection volume is defined by FF as well (Rabindranath et al. 2005). FF is the third treatment-related—and hence modifiable—determinant of the convection volume. In mathematical terms, FF is the ratio between the total UF volume and the plasma flow rate ($FF_{pw} = (Q_{conv}/Q_{pw})*100$, where FF_{pw} = plasma water filtration fraction, Q_{conv} = convection flow rate, and Q_{pw} = plasma water flow rate). The plasma water flow rate depends on the blood flow rate (Q_b, in mL/min or L/h), hematocrit (Ht), and total protein concentration in the plasma (TP, in g/dL) and can be calculated by the formula: $Q_{pw} = Q_b*(1-Ht)*(1-0.0107*TP)$. At the bedside, however, it is much more convenient to consider the blood flow rate instead of the plasma water flow rate, as it is readily apparent from the prescription and the dialysis machine.

$$FF_b = \left(Q_{conv} / Q_b\right) \times 100$$

Table 10.4 Convection volumes at different treatment times, blood flow rates, and filtration fraction

Filtration fraction 20%						
	Blood flow rate (ml/min)	**200**	**250**	**300**	**350**	**400**
	Treatment time					
	3 hrs	7.2	9	10.8	12.6	*14.4*
	3.5 hrs	8.4	10.5	12.6	14.7	16.8
	4 hrs	9.6	12	14.4	16.8	19.2
	4.5 hrs	10.8	13.5	16.2	18.9	21.6
	5 hrs	12	15	18	21	24

Filtration fraction 25%						
	Blood flow rate (ml/min)	**200**	**250**	**300**	**350**	**400**
	Treatment time					
	3 hrs	9	11.3	13.5	15.8	18
	3.5 hrs	10.5	13.1	15.8	18.4	21
	4 hrs	12	15	18	21	24
	4.5 hrs	13.5	16.9	20.3	23.6	27
	5 hrs	15	18.8	22.5	26.3	30

Filtration fraction 30%						
	Blood flow rate (ml/min)	**200**	**250**	**300**	**350**	**400**
	Treatment time					
	3 hrs	10.8	13.5	16.2	18.9	21.6
	3.5 hrs	12.6	15.8	18.9	22.1	25.2
	4 hrs	14.4	18	21.6	25.2	28.8
	4.5 hrs	16.2	20.3	24.3	28.4	32.4
	5 hrs	18	22.5	27	31.5	36

Filtration fraction 33%						
	Blood flow rate (ml/min)	**200**	**250**	**300**	**350**	**400**
	Treatment time					
	3 hrs	12	25	18	21	24
	3.5 hrs	14	17.5	21	24.5	28
	4 hrs	16	20	24	28	32
	4.5 hrs	18	22.5	27	31.5	36
	5 hrs	20	25	30	35	40

Convection volume >23 L/treatment is marked in green and convection volume 20–22.9 L in gray. From this table, it is evident that in order to achieve adequate convection volumes, a treatment time of ≥4 h is mandatory, as is a blood flow rate of ≥350 mL/min. Furthermore, filtration fraction should be ≥25% and preferably 30%

During post-dilution HDF, generally a FF of 25–30% can be easily obtained (Marcelli et al. 2015). When targeting a certain FF, several factors have to be taken into account.

Filtration Fraction as a Preset Target Parameter

On most HDF monitors, it is not possible to set FF as a separate target parameter (unlike blood flow rate, UF volume, and treatment time). Therefore, the following surrogate parameters must be prescribed, which, however, differ per machine: substitution ratio [(Q_b/Q_{subs})*100], substitution flow rate, or target substitution volume. Regrettably, however, these parameters are only based on the substitution volume, without taking net UF into account. When net UF increases, the difference between substitution ratio and FF raises, as illustrated in Table 10.5.

Filtration Fraction and Blood Flow (Set and Actual)

In clinical practice, the *actual* or effective blood flow rate may be lower than the *set* blood flow rate. As FF is calculated from the *set* blood flow rate, the *actual* FF may be higher than targeted. In HDF patients with an AV fistula, the difference is generally less than 5% but may amount to 10% in patients with catheters (Canaud et al. 2002) and small needles (Mehta et al. 2002; Kimata et al. 2013).

Table 10.5 The difference between filtration fraction and substitution ratio with different net ultrafiltration rates, at different blood flow rates

Blood flow rate	Net ultrafiltration rate (L/h)	Filtration fraction (%)	Substitution ratio (%)
350 mL/min	0	30	30
	0.25	30	29
	0.5	30	28
	0.75	30	26
	1	30	25
400 mL/min	0	30	30
	0.25	30	29
	0.5	30	28
	0.75	30	27
	1	30	26

Table 10.6 Variation of plasma water filtration fraction at given filtration fractions (based on blood flow) and hematocrit at dialyzer inlet

Filtration fraction of blood flow (%)	Hct at dialyzer inlet	Corresponding FFpw (%)	Estimated Hct at dialyzer outlet
25	0.25	36	0.33
	0.30	39	0.40
	0.35	42	0.47
30	0.25	43	0.36
	0.30	46	0.43
	0.35	50	0.50

For simplicity, hematocrit values do not take the influence of time into account, and total plasma protein remains stable at 7 g/dL. Dialyzer outlet is before infusion port of substitution fluid. FFpw is plasma water filtration fraction. Hct is hematocrit. Reprinted from Grooteman et al. (2016b)

Filtration Fraction and Hemoconcentration

Finally, when performing post-dilution HDF, blood viscosity may increase considerably when a high FF is applied. Depending on the magnitude of FF and resulting hemoconcentration, both Ht and plasma protein levels rise proportionally. At a FF of 30% and Ht of 0.35, the estimated Ht at the dialyzer outlet is as high as 0.50 (Table 10.6).

Filtration Fraction and Automated Machine Settings

On several dialysis machines, automated settings are available to optimize the convection volume. When targeting a high convection volume manually, TMP and/or filter entrance pressures will rise and alarms may occur (Teatini et al. 2011). With these automated settings, however, treatment becomes less complicated and less operator dependent (Panichi et al. 2012). Yet, despite automatic pressure control, surveillance, and FF adjustments, it should be kept in mind that the most important determinants of convection volume, i.e., treatment time and blood flow rate, still have to be prescribed and set manually.

Anticoagulation

As mentioned before, in comparison with HD, both platelet activation and coagulation activity are increased during HDF. Its cause is multifacto-

rial and results most probably from a combination of hemoconcentration and shear stress and possibly also from removal of anticoagulant medication by convective transport from the blood to the dialysate compartment within the dialyzer [MW of LMWH <10 kD].

Only a few studies have addressed the question whether coagulation activity differs between HD and HDF. From a comparative analysis between high-flux HD and pre-dilution HDF, it appeared that coagulation activity at identical anti-Xa levels was considerably higher during HDF (Klingel et al. 2004). When the dose of the LMWH enoxaparin was kept constant and anti-Xa activity was compared between post-dilution HDF, low-flux HD, and high-flux HD, anticoagulant activity was significantly lower during HDF than during the two HD modalities (Sombolos et al. 2009). In clinical practice, the dose of the prescribed anticoagulant, either unfractionated heparin (UFH) or LMWH, was 10–20% higher in patients treated with HDF than in HD patients (de Roij van Zuijdewijn et al. 2014; Ok et al. 2013). Injection of LMWH in the outlet blood line seems most effective (Dhondt et al. 2015).

10.4.2.4 Summary of Basic Requirements

High-volume HDF can be achieved in the majority of patients. At the center level, this requires:

- Presence of modern dialysis machines, water treatment, and delivery system
- A dialyzer with features minimizing pressure, high UF coefficient, and adequate surface area
- Technical staff able to deliver HDF matching quality reference standards
- Dialysis staff adequately trained on and aware of specific features of HDF, also including the fact that a certain minimum dose is necessary to obtain full benefit

And at the patient level:

- Vascular access able to deliver a blood flow 350–400 mL/min in the ECC, using a large bore needle (14 or 15 G). In order to limit the risk of (frequent) machine alarms, it seems advisable that a fistula or graft should have a flow of at least 600 mL/min.
- Dialysis over a central venous catheter or graft is not a contraindication to perform HV-HDF.
- Adequate treatment time (at least 4 h).
- Optimization of filtration fraction (toward 30% or more).
- Increase dose of anticoagulation if necessary.

10.5 Mechanisms of Beneficial Effects

10.5.1 Introduction

As outlined in the preceding paragraphs, online HDF is associated with a significantly reduced risk on all-cause and cardiovascular disease (CVD) mortality, if compared with HD. From an IPD meta-analysis of four recent RCTs, comparing post-dilution HDF with HD, it appeared that all-cause mortality was reduced by 14% and CVD by 23% (Peters et al. 2016). These results were lately confirmed in a survey of the French Rein Registry (Mercadal et al. 2015). The lowest mortality risks were found in patients who were treated with the highest convection volumes (>23 L/1.73 m^2 BSA/session) (Peters et al. 2016).

10.5.2 Cause-Specific Benefits of Hemodiafiltration

To answer the question *why* all-cause and CVD mortality are reduced by HDF, we must first ascertain that other causes of death, such as fatal infections and malignancies, the most common noncardiac fatalities (de Jager et al. 2009), sudden deaths, and withdrawal from treatment (den Hoedt et al. 2013), are equally distributed between the HD and HDF groups. If so, the question arises whether the reduction in CVD mortality is mainly due to a decrease in heart diseases only or also to a decline in fatal vascular events, such as stroke and ruptured aneu-

rysms. If not, it is useful to know whether all potential causes of cardiac death are reduced, including heart failure, ischemic heart disease, and arrhythmias, or just one specific diagnosis, such as sudden cardiac death.

With respect to the first question, recent findings from the IPD analysis indicate that treatment with HDF is neither associated with beneficial effects on fatal infections nor with a lower incidence of fatal malignancies, withdrawal from treatment, or sudden death. With respect to the second question, observations from the IPD analysis also show that the beneficial effect of HDF is restricted to *cardiac* causes only: splitting up fatal CVD in cardiac and noncardiac sources did not show any beneficial effect on stroke or peripheral vascular disease (Fig. 10.3). Finally, subdivision of *cardiac* fatalities in congestion, arrhythmias, and myocardial infarction did not suggest that one particular type of heart disease is prevented by treatment with HDF.

Yet, since the absolute number of fatalities in the latter subgroups was rather small, caution is warranted. Moreover, although overall not significant, stratification in thirds of the convection volume showed a distinct trend for sudden death: the larger the convection volume, the lower the mortality risk. Hence, it cannot completely be ruled out that unusual large convection volumes lower the incidence of sudden death.

10.5.3 Why Is Especially Cardiac Mortality Reduced By HDF?

10.5.3.1 Removal of Uremic Toxins

As mentioned in the preceding paragraphs, HDF is capable of removing retained small and MMW substances, which accumulate in patients with ESKD who are treated with HD.

Uremic solutes are generally subdivided in three major classes: (1) small water-soluble compounds (WSCs <500 D), (2) MMW substances (0.5–40 kD), and (3) protein-bound toxins (PBTs) (Neirynck et al. 2013a). While WSCs, such as urea and creatinine, are mainly removed by diffusion, convection is the driving force for the removal of larger MMW solutes, which cross the dialysis membrane by solute drag effectuated by the TMP gradient. While WSCs can be removed with any membrane, MMW can only be eliminated through high-flux dialyzers. PBTs are difficult to remove, since only the free fraction, consisting mostly of low MW substances, can cross the dialysis membrane. For this purpose, again, any membrane is appropriate (Glorieux and Krieter 2016).

Small Water-Soluble Compounds (WSC <500 D)

Urea, a small solute (60 D) that accumulates in chronic kidney disease (CKD), is most frequently used as a measure for dialysis adequacy

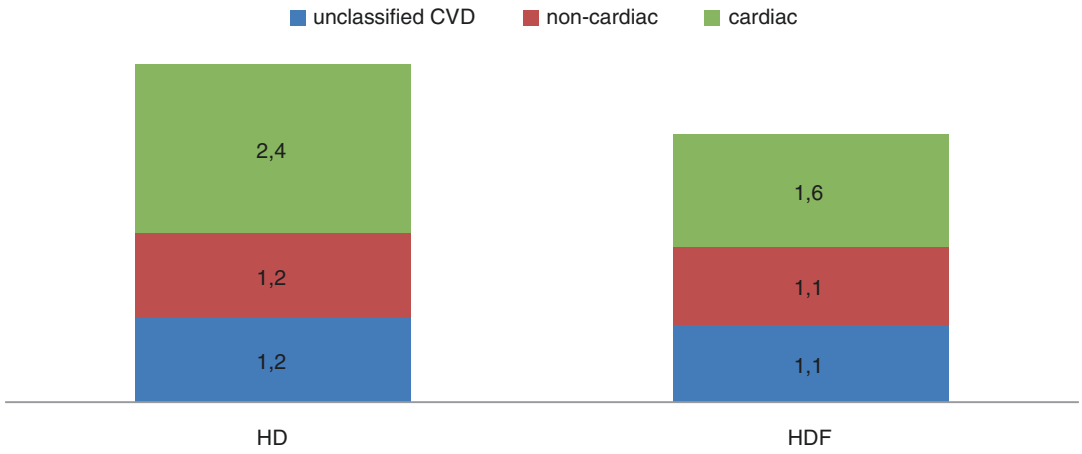

Fig. 10.3 Annualized CVD mortality per 100 patient-years in the HD and online HDF groups. The numbers in boxes represent fatal CVD events/100 patient-years. The difference in fatal cardiac events between HD and HDF is significant (p=0.01). Reprinted from Nube et al. (2017)

by the formula Kt/V_{urea}. Although Kt/V_{urea} is increased by HDF (Nube 2016), previously it was found that an increase in urea clearance did not improve survival (Eknoyan et al. 2002). With respect to creatinine (113 D), which is most frequently used for the estimation of kidney function by measuring creatinine clearance, similar findings have been found. Elevated phosphorus (95 D) levels are associated with vascular calcifications and CVD death (Palmer et al. 2011). Although phosphorus itself is a small molecule, it behaves more or less like a middle molecule due to the surrounding water mantle. While both phosphorus levels and the prescription of oral binders were lower in HDF as compared to low-flux HD (Grooteman et al. 2012; Penne et al. 2010), in two recent RCTs (Ok et al. 2013; Maduell et al. 2013), blood levels did not differ between high-flux HD and HDF. It should be realized, however, that an elevated phosphate value is just one component of the multifaceted CKD-mineral bone disease (MBD), which includes also derangements in calcium, vitamin D status and resistance, levels of parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Since in these patients phosphate is also dependent on residual kidney function (RKF) and the use of CKD-MBD-specific medication, including phosphate binders, vitamin D analogues, and calcimimetics, the dialysis mode is just one aspect in the complex interplay between these components. Currently, it is questionable whether the lowering of serum phosphorus itself is associated with an improved clinical outcome in patients with ESKD (Cannata-Andia and Naves-Diaz 2009).

Middle Molecules (500 D–40 kD)

The group of MMW substances that accumulates in ESKD consists mainly of small peptides, many of which have been implied in inflammation, endothelial damage, smooth muscle cell proliferation, oxidative stress, and interference in the coagulation cascade (Filiopoulos et al. 2008; Molino et al. 2006). As most of these processes may contribute to CVD, its removal—by convection—may improve clinical outcome. Although their elimination is considerably enhanced by application of HDF (Maduell et al. 2002), especially in patients with only marginal RKF, neither the lowering of β2M (MW 11.8 kD) (Neirynck et al. 2013b), the pro-inflammatory cytokines IL-6 (MW 21 kD), and TNFα (MW 25.6 kD) (Leurs et al. 2013) nor the complement factor D (MW 24 kD)(Tsuchida and Minakuchi 2011) has been convincingly shown to underlie the beneficial clinical effects of convective therapies.

Considering CKD-MBD, high PTH (MW 9.4 kD) levels have been associated with various manifestations of CVD (Kovesdy et al. 2008). Reduction by medication, however, did not improve clinical outcome (Chertow et al. 2012). In studies comparing high-flux HD with HDF, differences were not observed (Ok et al. 2013; Maduell et al. 2013). By contrast, promising results have been obtained for FGF23 (MW 32 kD), which is the earliest detectable biochemical alteration in CKD-MBD (Isakova et al. 2011). Levels of this phosphatonin are 100–1000-fold higher in ESKD than in healthy individuals. Removal of FGF23 was markedly higher during HDF than during high-flux HD (Patrier et al. 2013). As FGF23 has been related to left ventricular hypertrophy (LVH) and CVD events (Scialla and Wolf 2014), especially congestive heart failure in patients with CKD stages 2–4 (Seiler et al. 2014), reduction by HDF may lower CVD mortality in ESKD.

Protein-Bound Compounds (PBCs >500 D)

Multiple toxic effects have been attributed to retained PBCs, which are largely intestinally generated. Retention of PBCs may contribute to inflammatory processes, oxidative stress, endothelial dysfunction, cardiac cell proliferation, and mesenchymal transition, which all may have an adverse influence on the cardiovascular system (Mallipattu et al. 2012). P-cresol is generated by intestinal bacteria and conjugated to *p*-cresylsulfate and *p*-cresylglucuronide. *p*-cresol derivatives (pCS, MW 188 D), indoxylsulfate (IS, MW 212 D), and indoleacetic acid (IAA, MW 175 D) are shown to contribute to the uremic syndrome (Barreto et al. 2009; Liabeuf et al. 2010). In addition, in CKD increased levels have been described of a variety of hippurates, includ-

ing glucuronide conjugates of hydroxyhippuric acid (HA, MW 179 D), which originates especially from polyphenolic compounds in the diet, such as fruit, tea, and coffee. Increased HA levels appear especially toxic for renal tubular and glomerular functions (Satoh et al. 2003).

Advanced glycation end products (AGEs), such as *N*-carboxymethyl-lysine and pentosidine, are a complete other category of PBCs, as these compounds have a heterogeneous MW (<10 kD) and originate partly from AGE-rich food products. AGEs have a profibrotic action, contribute to the release of pro-inflammatory cytokines, and promote oxidative stress (Forbes et al. 2003).

The PBCs pCS, IS, and IAA are difficult to eliminate because of the large distribution volume, their high binding coefficient, and the fact that only the free fraction can be removed by diffusion. Whereas high-flux HD did not augment the reduction of the unbound fraction as obtained by low-flux HD, addition of convective transport by post-dilution HDF yielded conflicting results (Krieter et al. 2010; Meert et al. 2009). Considering AGEs, HDF resulted in considerably enhanced reduction ratios, most likely due to the fact that the MW of several of these peptides is substantially greater than that of other PBCs (Lin et al. 2003). Whether these maneuvers contribute to the improved clinical outcome of HDF, however, is uncertain.

10.5.3.2 Hemodynamic Factors

Intradialytic Hemodynamic (In)Stability

The most important acute complication of dialysis is intradialytical hypotension (IDH), which has been defined as a decline in systolic blood pressure (BP) >20 mmHg, or a decline of mean arterial pressure by 10 mmHg, associated with clinical events and need for nursing interventions. Other definitions have been used as well. Depending on the definition used and the population investigated, the reported incidence varies roughly between 10 and 30%. Notably, IDH has been related to end-organ ischemia and mortality (van der Sande et al. 2001). Recent sophisticated studies demonstrated that IDH is associated with hypoperfusion of vital organs, including the gut, brain, and heart (Burton et al. 2009; Eldehni et al. 2015; Vanholder and Glorieux 2015). As a result, not only translocation of bacterial products from the intestinal cavity to the blood may occur but also brain and cardiac dysfunctioning. In fact, the dialysis procedure itself may worsen the prevalent microcirculatory dysfunction of many organs which is a common feature in these patients (Thang et al. 2011).

Treatment with cool dialysate reduced IDH, mitigated HD-induced brain injury (Eldehni et al. 2015), and improved CVD survival (Hsu et al. 2012). In two large RCTs, blood pressure stability during HDF was superior to HD (Maduell et al. 2013; Locatelli et al. 2010) but not in a third (Ok et al. 2013). When cool dialysate was used both in HDF and HD, hemodynamic changes, as measured by BP, blood volume, cardiac output, and microcirculation, did not differ (Cornelis et al. 2014). Likewise, solute movements between the intra- and extracellular compartments during HDF and cool dialysate HD were similar (Kumar et al. 2013). Hence, it appears that intradialytic hemodynamic stability is better preserved during HDF than during standard HD, but analogous to cool dialysate HD. Unfortunately, none of the recent RCTs, comparing HDF with HD, reported the temperature of the dialysis fluid.

Interestingly, from a recent echocardiographic study, it appeared that neither the variations in BP nor UF rate was related to the HD-induced changes in the perfusion of the heart (Assa et al. 2012). Hence, non-hemodynamic factors may contribute substantially to the HD-induced perfusion defects in vital organs.

Long-Term Hemodynamics

Apart from repetitive and recurring intradialytical hemodynamical changes, the chronic hypertensive BP burden in ESKD, with an estimated prevalence of 85% in chronic HD patients (Agarwal et al. 2014), may also affect the structure and function of vital organs in the long term. By meta-analysis, however, convective treatment did not influence pre-dialysis systolic BP, diastolic BP, MAP, or the number of prescribed antihypertensive drugs (Nistor et al. 2014; Susantitaphong et al. 2013).

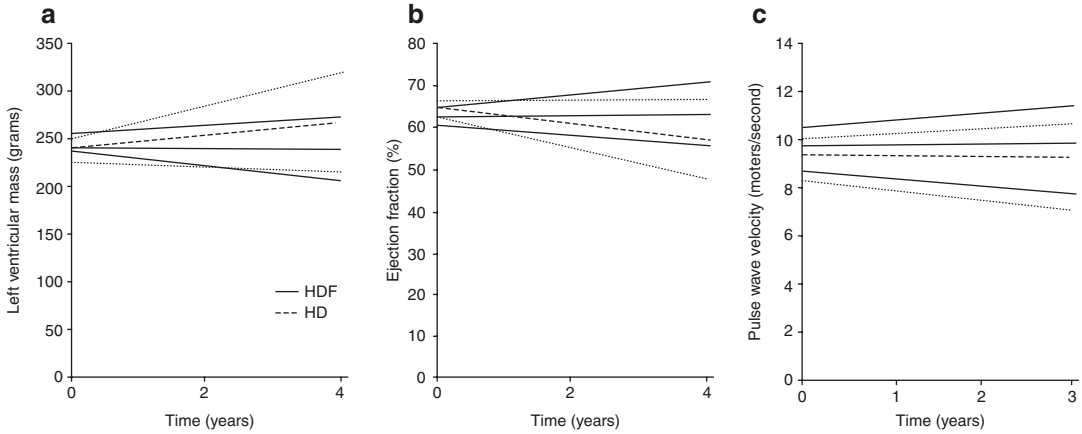

Fig. 10.4 Linear mean changes over time (with 95% confidence limits) of (**a**) left ventricular mass (LVM), (**b**) ejection fraction (EF), and (**c**) pulse wave velocity stratified by dialysis modality. Reprinted from Mostovaya et al. (2014b)

In the IPD analysis from four RCTs, comparing HDF with HD (Peters et al. 2016), the reduction in the all-cause and CVD mortality risk in HDF patients was independent from predialysis blood pressure values. More or less in agreement with a small RCT (n=21) (Ohtake et al. 2012), echocardiographic analysis of a large subset of the CONTRAST cohort (n=342) revealed that left ventricular mass (LVM) and ejection fraction (Fig. 10.4) tended to worsen over time in the HD group but remained stable in HDF patients. The difference between HD and HDF was borderline significant at 1 year (p=0.06) (Mostovaya et al. 2014b). Pulse wave velocity did not differ in this study. Independent of treatment allocation, however, MAP decreased over time, mainly due to a reduction in peripheral resistance (Mostovaya et al. n.d.). With respect to arterial function and stiffening, both improvement and lack of benefit were reported in small (n=<50) studies comparing HDF with HD (Bellien et al. 2014; Georgianos et al. 2014).

10.5.3.3 Removal of Uremic Toxins and Hemodynamic Factors

Yet, although the abovementioned findings are appealing and may help to explain the lower *cardiac* mortality risk in this patient group, it is far from clear whether the beneficial effects of HDF are caused by the addition of adequate amounts of convective transport and/or by a superior hemodynamic profile. Most likely, avoidance of harmful IDH during successive dialysis sessions, in concert with a superior long-term improvement of the uremic environment, may mitigate or even prevent the cardiovascular system from the rapid deterioration as observed during standard HD. Obviously, this view should be confirmed in future studies.

10.5.3.4 Other Mechanisms

Although both a better hemodynamic profile and an improvement of the uremic environment may contribute to the beneficial effects of HDF on clinical outcome, the exact mechanisms are still unclear. Actually, attenuation of inflammation (den Hoedt et al. 2014a; Panichi et al. 2008; Filiopoulos et al. 2008; Akoglu et al. 2013) and oxidative stress (Calo et al. 2007) and improvements in CKD-MBD (Penne et al. 2010), nutritional state (Grooteman et al. 2012; Maduell et al. 2013), anemia control (Macdougall 2001), and disorders of acid-base status (Morel et al. 2012) have also been related to treatment with HDF. Although an improvement in selected parameters, such as a reduction in the blood levels of FGF23 (Patrier et al. 2013), may indeed contribute to the favorable effects of HDF, so far, however, definite proof is lacking that HDF exerts its beneficial effects via one or a combination of these items.

10.6 Potential Drawbacks, Costs, and Medication

Having discussed the merits and the implications of HDF in the preceding paragraphs, it seems appropriate to address the question whether there are any negative aspects, challenges, or barriers in performing HDF in everyday clinical practice. To the best of our knowledge, however, there are no studies specifically designed and executed to address that question. Yet, the presently available evidence allows us to give some comments on this matter. We will discuss this subject briefly from a medical/practical point and in a few words from a financial/economic perspective as well. As outlined before, online post-dilution HDF will be our particular point of interest, as this dialysis modality is the currently the most frequently used convective technique.

10.6.1 Medical and Practical Issues

10.6.1.1 Hazards of Infusing Online Prepared Substitution Fluid

In HDF, large amounts of online prepared fluids are directly infused into the patients. So, the level and stability over time of the microbiological and chemical quality is of utmost relevance as was discussed earlier in this chapter. Summarizing the available evidence, there is strong evidence that online HDF can be performed in a microbiological safe way. The data also show that adequate quality of dialysis water can be produced over a prolonged period of time and that online post-dilution HDF does not induce or worsen the micro-inflammatory state that is commonly observed in ESKD patients (den Hoedt et al. 2014a). If anything, the contrary.

10.6.1.2 Unintended Convective Loss of Albumin and Vitamins

HDF is a nonselective process. Due to the large pore size of the membranes and the high convection volumes, online filtration techniques might lead to unintended losses of essential nutritional substances, such as amino acids, albumin, trace elements, and water-soluble vitamins (Fournier et al. 2015). While there is not much data on this subject, albumin seems best studied. Its loss has been quantified in various studies and ranges between 0.5 and 3.0 g/session. In CONTRAST, blood albumin levels decreased over time, which, however, was comparable between the HD and HDF groups (den Hoedt et al. 2014b). Since albumin was not measured in the dialysate of HDF patients, actually it is unknown whether losses occurred from the blood to the dialysis fluid. Relying on the blood levels, which were similar in HDF and low-flux HD patients after 3 years of follow-up, though, it appears unlikely that albumin loss in HDF patients was beyond limits.

Considering vitamins, there is no evidence that supplements in ESKD patients should be adjusted to the treatment modality used. During dialysis, vitamins are either cleared by diffusion (vit C, MW 176 D) or hardly removed at all due to the high protein binding (vit B12, MW 1346 D) or to a large volume of distribution (vit B9, MW 169 D).

10.6.1.3 Hemodiafiltration and Drug Prescription

Drug clearance by dialysis is determined by patient factors, such as an altered pharmacokinetic in renal failure; characteristics of the drug, including its MW, protein binding, and volume of distribution; and the distinct features of the dialysis procedure itself, such as treatment with low-flux HD or HDF.

Due to the small MW of sulfonamides and most penicillin's (MW <500 D), the addition of convective transport is unlikely to increase their clearance. As opposed to these drugs, HDF may substantially increase the elimination of larger medicines (MW >500 D), such as the antibiotic piperacillin (Oh et al. 2009) and the aminoglycosides.

With respect to erythropoietin-stimulating agent (ESA) resistance, conflicting data have been obtained. Whereas a decrease in ESA resistance was observed in THDFS (Ok et al. 2013), no effect was noted in CONTRAST and in ESHOL (Maduell et al. 2013; van der Weerd et al. 2014).

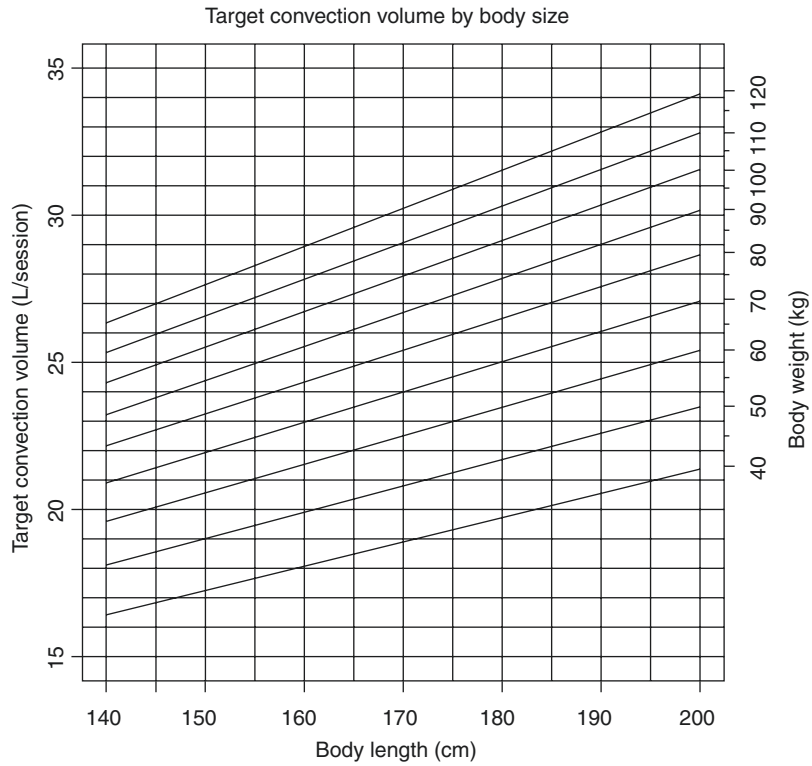

Fig. 10.5 Convection volume per session needed for an individual patient to have at least a BSA adjusted convection volume of 23 L or above, based on measurements of height and weight of the patient. The formula used was convection volume needed = (23 * individual BSA)/1.73. Here BSA is $(m^2) = 0.0235 \times \text{height}\ (cm)^{0.42246} \times \text{weight}\ (kg)^{0.51456}$. Reprinted from Peters et al. (2016)

Coumarins are highly protein-bound and therefore not easily removed by HDF. Unfractionated heparin (UFH, MW 12–15 kD) removal may increase during convective treatment but possibly less than anticipated because of their negative charge (most dialyzer membranes are also negatively charged). Yet, in THDFS, the UFH dose was approximately 25% higher in the HDF group, as compared to the high-flux HD group. As the MW of LMWH is between 4 and 6 kD, these drugs will also be removed by convection. In CONTRAST the LMWH dose was about 10% higher in HDF patients than in individuals treated with low-flux HD. How to adjust drug dosing in HDF is discussed in more detail elsewhere (Zandvliet et al. 2016).

10.6.1.4 Uncertainties About the Required Amount of Convection

Available data suggest that a certain minimum convection volume is necessary to obtain the clinical benefits of HDF. As discussed earlier, overall, there was no survival benefit in THDFS and in CONTRAST (Ok et al. 2013; Grooteman et al. 2012). Post hoc analysis, however, indicated that mortality was significantly reduced in the groups with the highest convection volumes (Ok et al. 2013; Grooteman et al. 2012). Similar results were obtained from the aforementioned IPD meta-analysis (Peters et al. 2016). As it seems more rational to adjust the target convection volume to body size instead of a "one size fits all" approach, a convenient schematic graph, based on body height and weight, was developed by the IPD investigators (Fig. 10.5) (Peters et al. 2016; Davenport et al. 2016).

Notably, this figure, which is no more than a starting point to achieve a certain convection volume, is based on treatment with post-dilution HDF. While In Europe HDF is mostly applied in the post-dilution mode, in Japan the pre-dilution mode is almost exclusively applied. Therefore, in that region, the accompanying scheme is not valid. Whereas pre-dilution HDF may have the advantage that it is more easily achievable, post-dilution HDF is considered to be somewhat more effective in removing uremic retention com-

pounds. To the best of our knowledge, there are no large-scale comparisons of these modes. Hence, it may be wise for doctors and staff to perform HDF in the mode they are most familiar with.

10.6.2 Financial and Economical Perspectives

Apart from potential medical and practical objections, financial and economical arguments may also withhold doctors and institutions from starting a HDF program. According to a formal cost-effectiveness analysis, which was published in 2009 by CONTRAST researchers, HDF entails approximately 3% more expenses than standard low-flux HD. The extra costs were mainly caused by more frequent cultures of the dialysate and more pricey disposables (Mazairac et al. 2013). In recent years, however, the frequency of testing has decreased considerably and disposables became cheaper. Therefore, it is hardly surprising that more recent evaluations showed that the costs of HDF are comparable to high-flux HD or even lower (Lebourg et al. 2013; Takura et al. 2013).

In this respect it should be realized that it is conceptually incorrect to demand different and stricter quality levels for the water treatment system in HDF settings than in high-flux HD. Actually, HD with high-flux membranes, which is presently considered the preferred dialysis mode in guidelines, should be considered as "low-dose" HDF. As mentioned before, in this modality approximately 10 L/session of dialysate is infused into the patients by obligate backfiltration (Blankestijn 2013). The exact amount of backfiltration, however, is immeasurable, uncontrollable, and unpredictable.

10.7 Perspectives and Conclusions

Online HDF is generally considered to be safe, on the condition that it is performed and monitored according to the manufacturer's instructions and (inter)national guidelines on this subject. The key requirements are logical and not terribly difficult to implement. Indeed, starting up an HDF program may mean extra investments in machinery and in training of personnel. But after that, the costs of the maintenance phase appear more or less identical to a regular HD program using high-flux membranes. Online HDF is probably cost-effective. Analyses so far have not identified specific subgroups more likely to benefit than others. That suggests that it could be applied to large groups of patients. It is important to mention that all studies so far were done in the standard three-times-weekly schedule. There is virtually no data on the effects of HDF in more intensified schedules.

So what are the real barriers to spread out online HDF as the new standard of care? HDF is mostly accepted in Europe, whereas acceptance in Japan is clearly increasing, being the choice of therapy in, respectively, approximately 20 and 15%. Presently, in the United States, acceptance is virtually zero, but this may be changing in the (near) future. Within Europe there are enormous differences between regions, cities, and hospitals/centers. The main explanation seems to be that there is considerable variability in the acceptance of the idea that HDF is superior to standard HD. There are "believers" and "nonbelievers." One might argue that the suggestion of superiority with the apparent lack of side effects allows widespread acceptance. A factor that may be of relevance in this respect is that the mechanism(s) of a possible beneficial effect is (are) not completely clear, as we discussed earlier. It may help when future studies try to unravel the possible mechanism(s), because that will create an even stronger case in favor of HDF. These studies should also address quality of life. The overall impression is that HDF is associated with improved quality of life, at least certain aspects of it. However, this is difficult to quantify. Aspects of quality of life as study endpoint(s) are very important, because a clear difference in (certain aspects of) quality of life could already be enough reason to choose for it, also in the absence of an effect on so called "hard" clinical endpoints.

In the meantime one must realize that if the dialysis team chooses for the use of high-flux membranes (which is suggested by most guidelines) and allowing convective transport, one may

decide to invest some effort (and may be some funds) and choose not for the "low-dose" version but for a version for which there is a strong suggestion that it is beneficial for our patients, i.e., online HDF with a minimum convection volume of 23 L/1.73 m^2/session and more.

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Part III

Peritoneal Dialysis

Peritoneal Physiology and Peritoneal Membrane

11

Hiroyuki Terawaki

11.1 Gross Anatomy

The peritoneum is defined as the serosal membrane that covers the peritoneal cavity. The main role of the peritoneum is to fix and protect the intra-abdominal organs and to minimize the friction between intra-abdominal organs, including the abdominal wall, that is caused by intestinal peristalsis or respiratory movement. In the physiological state, the peritoneal cavity retains 50–100 mL of peritoneal fluid. Peritoneal fluid, which is constantly produced by the peritoneum, contains various lubricants including hyaluronan (Yung and Chan 2011). The peritoneal fluid circulates constantly at a rate of 30–35 mL/h. It is impossible to identify normal peritoneum by imaging procedures, because the thickness of the mesothelial layer, which covers the surface of the peritoneum, is about 10 μm, which is far thinner than the spatial resolution of CT and MRI (Hayashida 2016).

The peritoneum is grossly divided into two parts: the parietal peritoneum, which covers the diaphragm, abdominal wall, and pelvic wall, and the visceral peritoneum, which covers intra-abdominal organs (Fig. 11.1). The parietal and visceral peritonea are merged together and thus form one peritoneal sac. The right and left parietal peritonea meet each other dorsomedially and form the dorsal mesentery, and they transit to the visceral peritoneum, which covers the surfaces of organs. The visceral peritoneum at the part of the ex-foregut further transits to the ventral mesentery or ventral mesogastrium, which contains the round ligament and the common bile duct in its free edge. Because the liver grows very large within the ventral mesogastrium, the transit portion of the mesogastrium to the dorsal parietal peritoneum opens widely, and thus the rostrodorsal area of the liver is not covered by serosal membrane. This bare area of the liver, or the area nuda hepatis, occasionally functions as a corridor of inflammation to the pleural cavity in cases of infectious peritonitis.

From the viewpoint of the insertion of a peritoneal dialysis catheter (PDC) from the anterior abdominal wall, the area below the umbilicus should be encouraged, because the ventral mesogastrium is present in the area above the umbilicus. Usually the tip of a PDC is placed at the rectovesical/rectouterine pouch (of Douglas), which is the lowest area of the peritoneal cavity in the upright position (Fig. 11.2). On the other hand, in the supine position, the lowest area of the peritoneal cavity is posterior to the liver and spleen.

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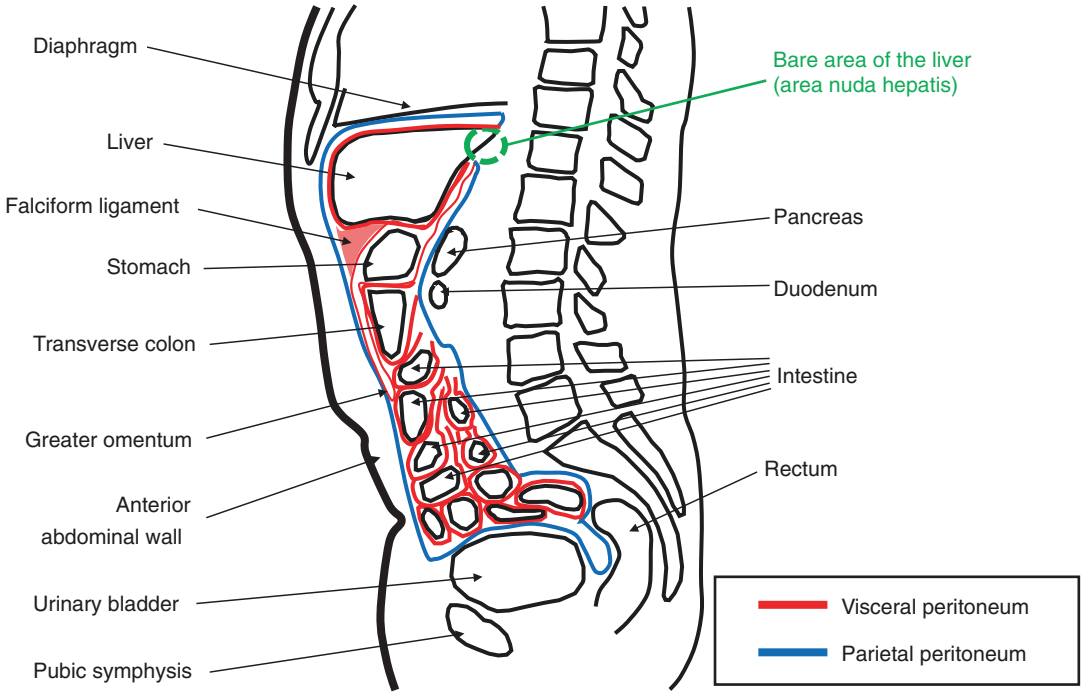

Fig. 11.1 A sagittal section through the abdomen. Visceral and parietal peritoneum is shown, respectively

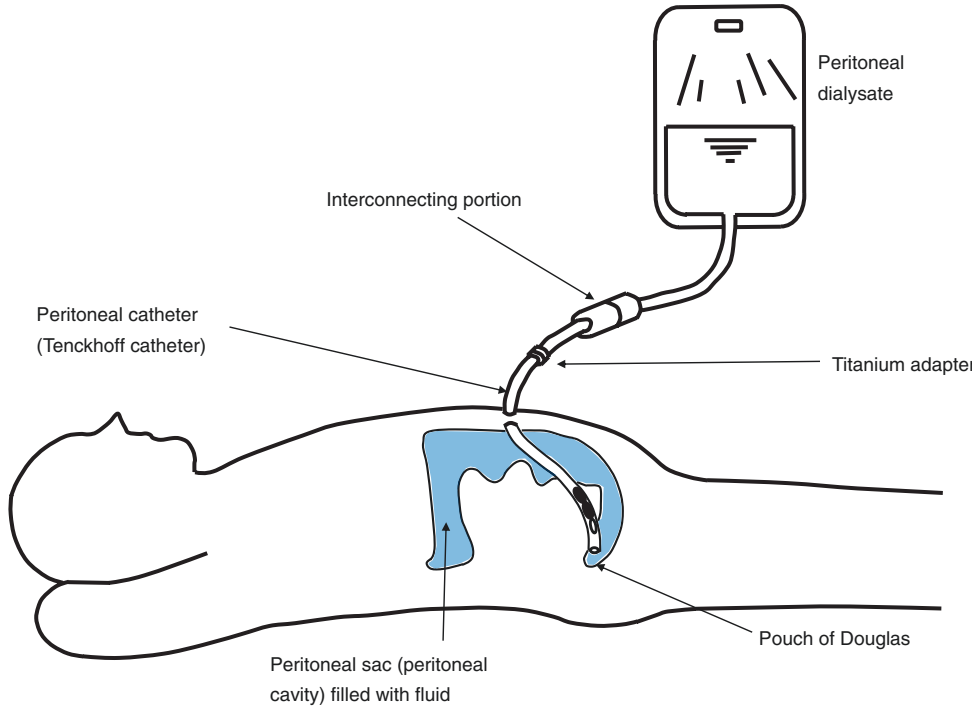

Fig. 11.2 A schematic representation of the peritoneal sac (cavity). A peritoneal catheter is in place

In the physiological condition, the visceral peritoneum and parietal peritoneum are in contact. When massive ascites occurs, or peritoneal dialysate is administered, the peritoneal sac functions as a "peritoneal cavity" (Fig. 11.3). The peritoneal cavity is entirely closed in the male, while it is connected to the outside through the oviduct and uterus at the free end of the oviduct in the female. Therefore, bloody effluent fluid is occasionally observed in female peritoneal dialysis patients during menstruation.

As mentioned above, what connects the parietal and visceral peritoneum is the mesentery, the structure formed by the double-ply serosal membrane. The mesentery, which connects the organs, is called a "ligament," and that which directly contacts with the stomach is called the "omentum." These mesenteries, or superimposed peritonea, allow blood vessels and nerves to pass through (Table 11.1).

Of these double-ply serosal membranes, the greater omentum is a distinctive structure. The greater omentum, which is called the "policeman in the abdomen" (Morison 1906), covers the frontal surface of the peritoneal cavity widely, finds an emergent situation at an early stage, and acts as a defense mechanism, as, for example, by covering a perforating intestine. The greater omentum has on its surface a large number of opalescent spotty microstructures named "milky spots." A precise description of the milky spots is provided later.

According to Collins, the surface area of the peritoneum (cm^2) is 177 × kg body weight (Esperanca and Collins 1966). Other reports, however, suggest that there is considerable individual variation in the surface area (Wegener 1877; Rubin et al. 1988). About 90% of the peritoneum consists of visceral peritoneum (one-third of this consists of mesenterium and omentum), and only 10% is parietal peritoneum (40% of this covers the diaphragm) (Esperanca and Collins 1966) (Fig. 11.2). Moreover, the submesothelial basement membrane is thicker in the parietal peritoneum than in the visceral peritoneum (Jaquet and Sugarbaker 1996). As a result of such conditions, 80% of intra-abdominal fluid is adsorbed from visceral peritoneum in the physiological state (Torres et al. 1978).

Irrespective of its lesser surface area ratio, however, the parietal peritoneum plays not a small part in solute transport during peritoneal dialysis treatment. Alon et al. reported a case of successful peritoneal dialysis treatment after almost total enterectomy (Alon et al. 1988). In addition, Fressner et al. reported the importance of the parietal peritoneum that covers the diaphragm in solute transport of peritoneal dialysis treatment (Fressner and Dedrick 1994).

11.2 Sensory Innervation of the Peritoneum

Sensory nerves are grossly divided into two categories: somatic afferent nerves and visceral afferent nerves. Somatic afferent nerves transmit sharp and focal sensations, whereas visceral afferent nerves transmit dull and abrupt sensations. Accordingly, somatic pain transmitted by somatic afferent nerves is epicritic, and visceral pain transmitted by visceral afferent nerves is protopathic. Sensory nerves that are distributed to the parietal peritoneum are somatic nerves, while those that are distributed to the visceral peritoneum are visceral nerves. Therefore, signs of peritoneal irritation, such as muscular guarding and Blumberg's sign, which is a typical finding of acute peritonitis, reflect peritoneal damage on the parietal side. From the viewpoint of innervation area, nerves that distribute to the parietal peritoneum are branches of lower intercostal nerves and subcostal nerves; therefore, referred pain that reflects their skin innervation area could be induced in cases of parietal peritoneal damage. Somatic sensory nerves distribute not only to the parietal peritoneum but also to a part of the mesentery (Uchida and Onda 1995); a pain that occurs with drainage of peritoneal solution from the peritoneal cavity is probably due to traction of the mesentery or parietal peritoneum caused by negative pressure around the tip of the peritoneal dialysis catheter.

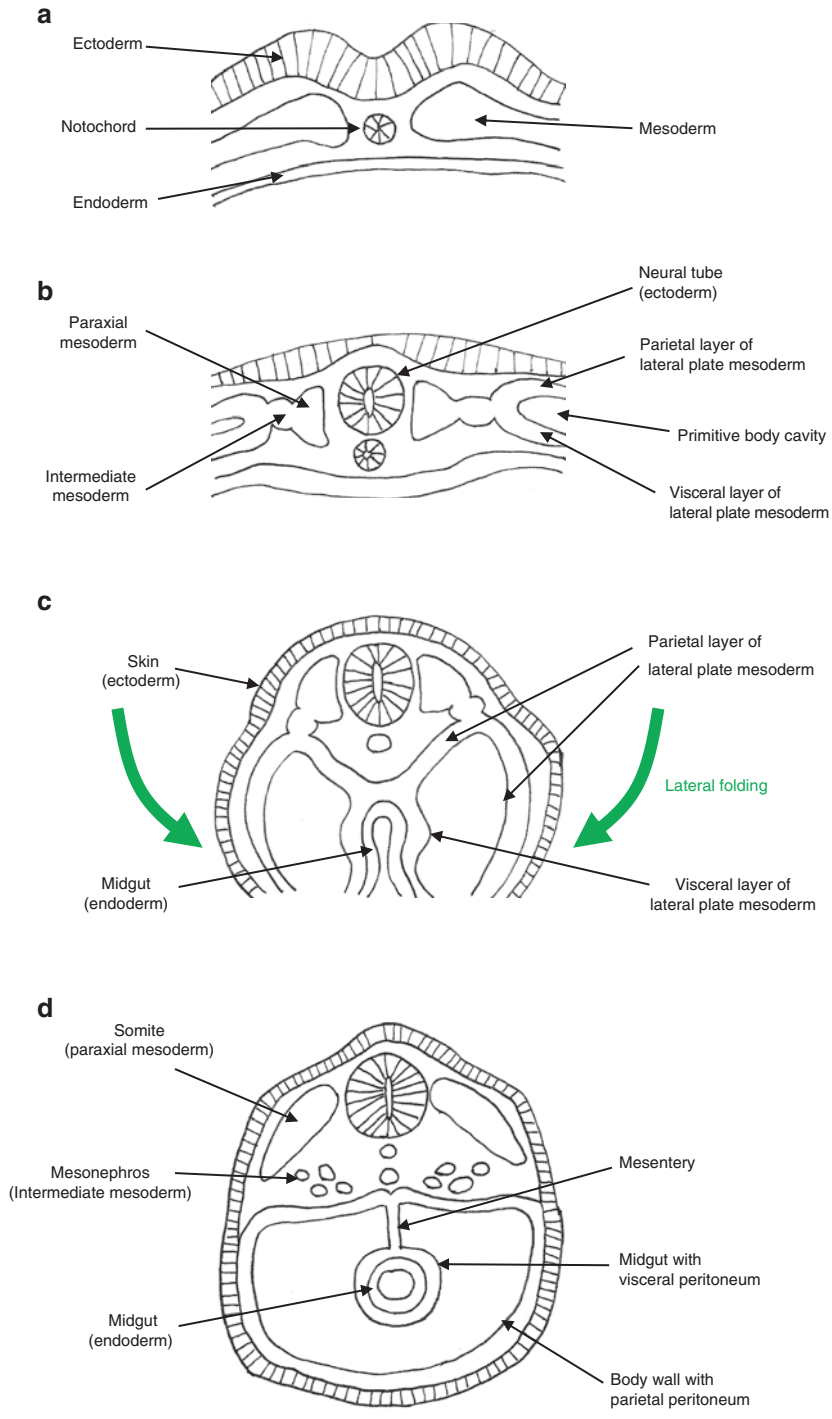

Fig. 11.3 A schematic representation of the development of embryo and peritoneal cavity between embryonic 3–4 weeks. **(a)** The early phase of embryonic third week. Intraembryonal mesoderm is divided into three parts: paraxial mesoderm, intermediate mesoderm, and lateral plate mesoderm. **(b)** The late phase of embryonic third week. The lateral mesoderm causes the intercellular cleft, which divides the lateral mesoderm into two layers, the parietal layer and the visceral layer. **(c)** The early phase of embryonic fourth week. Lateral folding makes the embryonic body cylindrical. **(d)** The and of embryonic fourth week. The formation of the peritoneal cavity as a closed space is completed by conglutination of the lateral body wall in the midline

Table 11.1 Superimposed peritoneum and intraperitoneal vasculature

Superimposed peritoneum	Intraperitoneal vasculature
Falciform ligament	Round ligament (remnant of the umbilical vein)
Gastrosplenic ligament	Short gastric artery/vein
Splenorenal ligament	Splenic artery/vein
Gastrocolic ligament	Right gastroepiploic artery/vein
Small intestinal mesentery	Superior mesenteric artery/vein
Transverse mesocolon	Middle colic artery/vein
Sigmoid mesocolon	Inferior mesenteric artery/vein
Hepatogastric ligament (lesser omentum)	Left gastric artery/vein
Hepatoduodenal ligament (lesser omentum)	Proper hepatic artery, portal vein, common bile duct
Greater omentum	Gastroepiploic artery/vein
Median umbilical fold	Remnant of the urachus
Medial umbilical fold	Remnant of the umbilical artery
Lateral umbilical fold	Inferior epigastric artery/vein

11.3 Distribution of Blood Vessels

The arteries that distribute to the peritoneum are branches of arteries that distribute to organs covered by the peritoneum. Namely, the parietal peritoneum is mainly fed by the inferior phrenic artery, lumbar artery, renal artery, and iliac artery, whereas the visceral peritoneum is mainly fed by the celiac artery, superior mesenteric artery, and inferior mesenteric artery.

In like manner, the veins that distribute to the peritoneum are radices of veins that distribute to organs covered by the peritoneum. Namely, the parietal peritoneum is mainly drained by the inferior phrenic vein, lumbar vein, renal vein, and iliac vein, whereas the visceral peritoneum is drained by the portal vein. A large amount of small molecular solutes that are administered intra-abdominally is absorbed via the portal vein and transported to the liver and therefore promptly metabolized, because 80% of intra-abdominal water is absorbed from visceral peritoneum under physiological conditions, as mentioned above.

11.4 Development of the Abdominal Cavity and Peritoneum

The peritoneal cavity is formed between the embryonic third and fourth weeks. Intraembryonal mesoderm is divided into three parts: paraxial mesoderm, intermediate mesoderm, and lateral plate mesoderm (Fig. 11.3a). Of these, the lateral mesoderm causes the intercellular cleft, which divides the lateral mesoderm into two layers, the parietal layer and the visceral layer (Fig. 11.3b). The space surrounded by the parietal and visceral layers is called the primitive body cavity. The cell population that covers the primitive body cavity differentiates into mesothelial cells. The "primitive" mesothelium appears as pseudostratified columnar epithelium in its early stage and then metamorphoses into simple squamous epithelium in accordance with the development process. Lateral folding in the embryonic fourth week makes the embryonic body cylindrical, and the formation of the peritoneal cavity as a closed space is completed by the end of the embryonic fourth week by conglutination of the lateral body wall in the midline (Fig. 11.3d).

11.5 Histological Structure

A schematic representation of the histological structure of the peritoneal membrane is shown in Fig. 11.4. The human peritoneum is composed of two primary layers: the mesothelium, which is composed of a monolayer of mesothelial cells, and the connective tissue layer under the mesothelium. The mesothelium and the connective tissue layer are separated by a thin sheet of fibers called the basement membrane.

The diameter of mesothelial cells is 22–125 μm. The surface of mesothelial cells is covered by microvilli (brush border) with a length of 3–12 μm (Wilkosz et al. 2005). Mesothelial cells synthesize and excrete various substances. Many kinds of substances that decrease friction, such as phosphatidylcholine, proteoglycan, and hyaluronan, are thought to be synthesized by mesothelial cells. Mesothelial

cells also synthesize and excrete various kinds of mediators, such as cytokines, growth factors, and prostaglandin, and accordingly take part in mediation of biological reactions (Topley et al. 1993). As such, mesothelial cells play quite an important role in the physiological function of the peritoneum.

As to the connective tissue layer, the interstitial matrix consists mainly of mucopolysaccharides such as hyaluronan. The peritoneal microvessels are located within this layer and play a major role in the transport of small molecular substances during peritoneal dialysis treatment.

The histological change of the peritoneum induced by continuous peritoneal dialysis treatment, so-called peritoneal damage, is one of the most interesting areas related to peritoneal dialysis for researchers. The reason for this is that peritoneal damage is supposed to precede the pathological change of encapsulating peritoneal sclerosis, which is one of the most life-threatening complications of peritoneal dialysis treatment.

11.6 Milky Spots

Milky spots are small, milky-white, punctate structures that lay mainly in omental fatty tissue. The mean number of milky spots in greater omentum is about 2/cm^2 (Shimotsuma et al. 1989). Milky spots are also distributed in the pancreatic capsule, the root of the mesentery, and the uterine fringe, but milky spots are not found in parietal peritoneum, including the diaphragmatic portion.

Milky spots are composed of aggregated microvessels, called an "omental glomerulus," surrounding many mesenchymal cells such as macrophages and lymphocytes (Fig. 11.5) (Shimotsuma et al. 1991). From the interstitium between milky spots and covering mesothelium, lymphatic ducts, which accompany the intercellular space (stomata) of the mesothelium, originate. Such a microstructure strongly suggests that the milky spot is an apparatus that plays a role in omental immune function.

11.7 Stomata on the Peritoneal Side of the Diaphragm

Although milky spots are not found in the diaphragmatic peritoneum, just like milky spots, the diaphragmatic peritoneum also has "stomata," empty areas between mesothelial cells in a sprinkled manner (Fig. 11.6). According to a previous study dealing with the human diaphragm, there are many stomata on both the muscular part and the central tendon, the mean diameter of stomata on the muscular part is 10 μm, and that on the

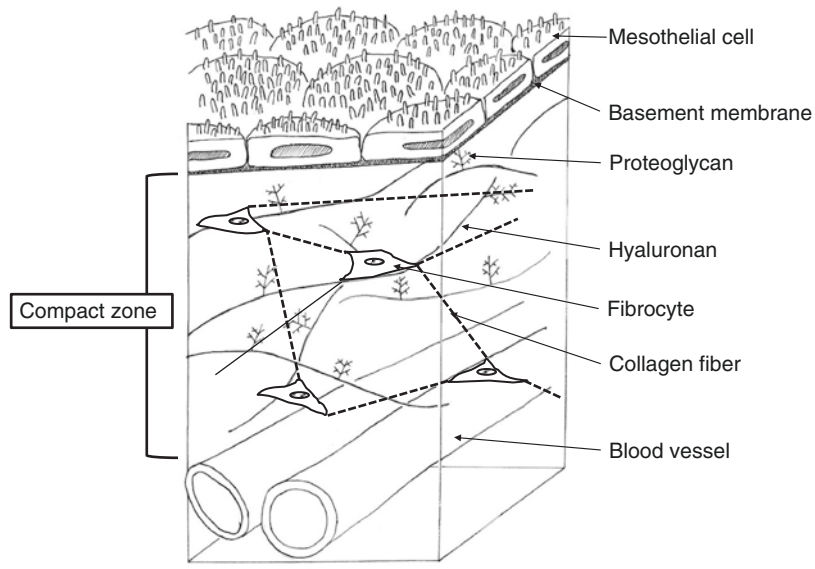

Fig. 11.4 A schematic presentation of the histological structure of peritoneal membrane

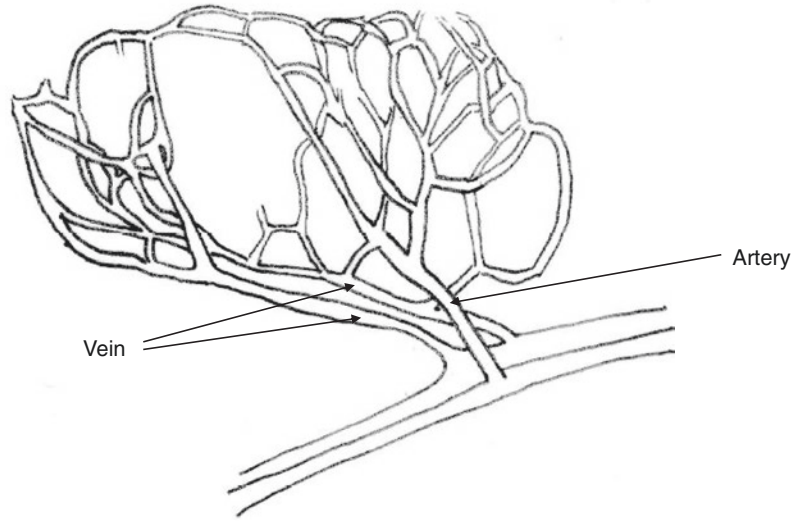

Fig. 11.5 A vessel structure of milky spot which consists one artery and two veins

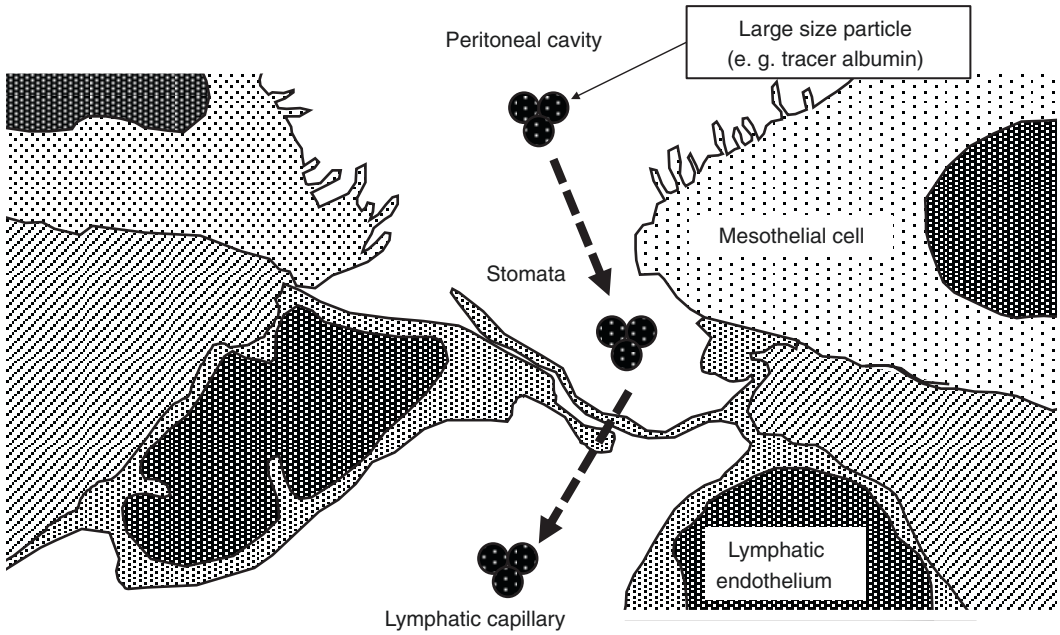

Fig. 11.6 Diagram showing a region around stomata on the peritoneal side of the diaphragm. A lymphatic capillary is situated beneath the mesothelium

central tendon is 8 μm (Chang and Shon-min 1991). At both milky spots and the diaphragm, the stomata act as a drainage pathway for large particles that cannot be absorbed by diffusion and free cells such as lymphocytes, leukocytes, and erythrocytes into the lymph duct.

Regarding such translymphatic absorption, the role of stomata on the peritoneal side of the diaphragm is quite important. Specifically, most translymphatic absorption (70–80%) passes through diaphragm stomata, whereas only 20–30% passes through other than diaphragm stomata, e.g., stomata on milky spots (Fig. 11.7). Substances absorbed via the diaphragm stomata mainly pass the paravertebral region and finally flow into the right venous angle (Fig. 11.8).

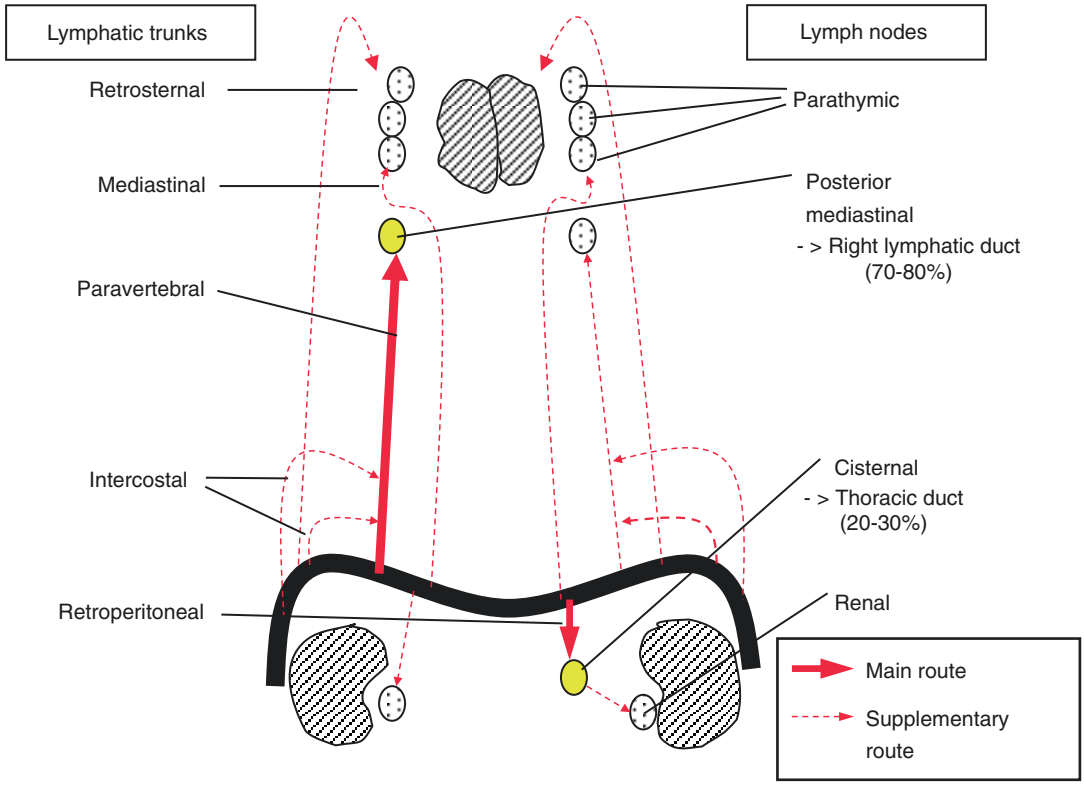

Fig. 11.7 A schematic representation of the lymphatic absorption. Lymphatic absorption from the peritoneal cavity is mainly directly into the subdiaphragmatic lymphatics. Absorbed fluids finally flows into right lymphatic duct (70–80%) or thoracic duct (20–30%)

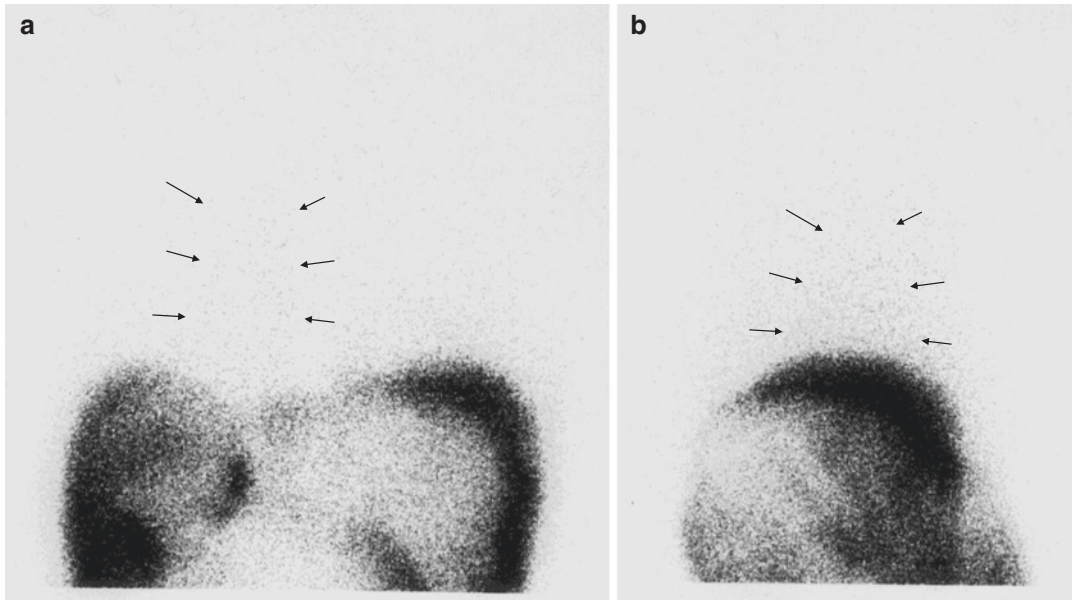

Fig. 11.8 Images from the gamma-camera taken 4 h after intraperitoneal administration of tracer (human serum albumin diethylenetriaminepentaacetic acid) with (**a**) supine and (**b**) lateral view. The tracer was taken up to the right paravertebral trunk legion

According to a study using tracer albumin in peritoneal dialysis patients, the rate of translymphatic absorption was 1.48 ± 1.32 mL/min (range, 0.30–4.66 mL/min), which might decrease with the decline of residual renal function (Terawaki et al. 2004). A previous animal study suggested that translymphatic absorption from the diaphragm stomata plays an important role in the systemic inflammatory response during peritonitis (Gürleyik et al. 1996).

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Types of PD

12

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Treatment of peritoneal dialysis (PD) contains the sequential peritoneal fluid exchange which is various lengths of time and amount of fluid. These various types and modalities of PD allow the therapy to be adaptable and adjustable to the lifestyle and medical needs of each patient. PD (1) can be performed either manually by a patient or automated fashion using a cycler (automated PD) and (2) can be performed continuous or intermittent regimen. In this chapter, various types of PD are described.

12.1 Types of Manual PD

Manual PD, which exchanges PD solution manually by patients, is usually prescribed as continuous ambulatory peritoneal dialysis (CAPD). CAPD, first described by Popovich et al. in 1976 (Moncrief et al. 1990; Popovich et al. 1978), is a manually performed continuous PD technique which instilled dialysis solution constantly in the abdomen. It provides continuous treatment and a steady physiologic state. CAPD is free from dialysis machine and requires relatively low cost. It has been brought out that CAPD is historically the most popular chronic PD modality.

The dialysis solution is typically exchanged four times over a 24-h period, with a range of three or five times, depending upon the patient requirements, each taking up 30–40 min. The PD solution remains in the peritoneal cavity for dwell time, 4–6 h during the day and 8–9 h overnight. The example of prescription of CAPD is three 5-h dwells during daytime (diurnal dwell) and a 9-h dwell during overnight (nocturnal dwell) (Fig. 12.1). The prescription of CAPD could be adjusted according to individual patient requirements. The standard filling volume is 2.0 L, but lower volume or higher volumes up to 2.5 L are also widely used depending on the patient size. Large volumes are usually prescribed for increasing solute clearance, but there are limitations since a large instilled volume increases intra-abdominal pressure and results in back pain, abdominal distension, hernias, abdominal dialysate leaks, shortness of breath, and so on. Glucose is the commonly used osmotic agent in CAPD dialysis solution. Typically, the majority of exchanges will use 1.5% and 2.5% (as glucose monohydrated, molecular weight 198) glucose-containing PD solution, with 4.25% glucose-containing PD solution being utilized when additional fluid removal is required. The true anhydrous glucose concentrations (molecular weight 180) in these PD solutions are 1.36%, 2.27%, and 3.86%, respectively. Other

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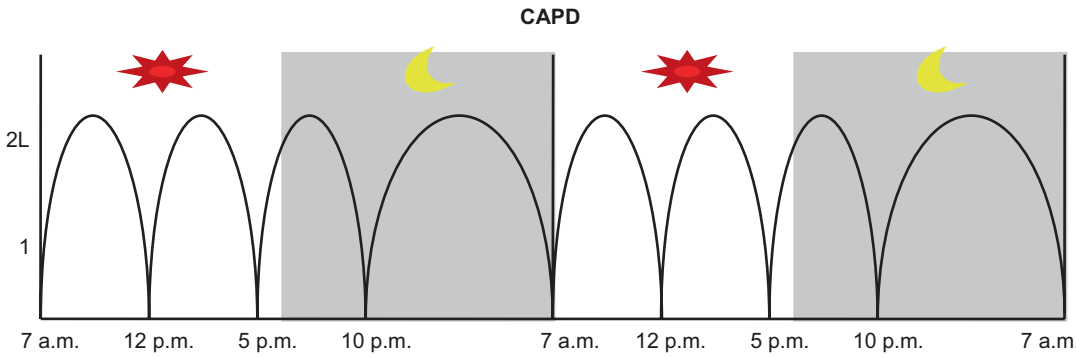

Fig. 12.1 Diagrammatic representation of continuous ambulatory peritoneal dialysis (CAPD)

non-glucose solution and amino acid-based solution are also available. Detailed prescriptions of PD are described in Chap. 4.

Choosing the PD modality takes into consideration both medically optimal adequacy and patient preferences. Patient preferences are considered for patient lifestyle, employment, family or caregiver support, residence circumstance, familiar with cycler technology, and so on. In the past, peritoneal transport status and its effect on fluid removal and solute clearance were considered to be crucial to choose PD modalities such as CAPD and the various types of automated PD (APD). However, recently patient preferences have been emphasized to decide PD modality.

Daytime ambulatory peritoneal dialysis (DAPD) is a modified method of CAPD in which patients carry out two to four exchanges during the daytime with dwell time of 3–4 h and an empty abdomen at night. DAPD is helpful of improving the quality of sleep and recovering peritoneal cells due to a dry abdomen overnight. However, this modality should be applied to patient with significant residual renal function who has high (or fast)-membrane transporters which reabsorb significant amounts of fluid with the long overnight dwell of CAPD.

12.2 Types of Automated PD

Automated peritoneal dialysis (APD) is referred to as all forms of PD that apply an automated device to perform in the instillation and drainage of the dialysis solution. Mechanized cyclers are used in continuous cyclic peritoneal dialysis (CCPD), nocturnal intermittent peritoneal dialysis (NIPD), tidal peritoneal dialysis (TPD), intermittent peritoneal dialysis (IPD), and continuous-flow peritoneal dialysis (CFPD). In addition, some patients on CAPD may perform one or more overnight exchanges with a night exchange machine. In the previous, APD has been recommended mainly for patient who had high (or fast) peritoneal transporters. However, these days, patient preferences have more emphasis on choosing PD modality, and improved technology of automatic machine, APD, using a cycler, has become very popular across the world over the past 10–15 years. The majority of PD patients especially in wealthier countries are treated with this method. Development of APD machine and newer APD schedules enable individualized treatment prescription and could enhance patient compliance to the prescribed regimens. Automation could handle some of the limitations of manual PD, including ultrafiltration failure, patient treatment fatigue, complications of increased intra-abdominal pressure, and failure to get treatment clearance goals.

The APD have some advantages compared with CAPD. APD had less number of on-off procedures needed each day, especially daytime. All preparation of apparatus and on-off procedures are usually performed in the private home. Therefore, patients feel more comfortable and less inconvenient with APD, which improves patient satisfaction and decreases patient fatigue. APD is a therapy of choice for active patients who would not be interrupted during their daily

routine. APD is the modality of choice in children and adolescents, because it allows free daytime without bag exchanges, thereby not interrupting the daytime academic or work schedule of their parents. In addition, APD is also an attractive treatment option for patients who require support to perform their dialysis (e.g., the dependent elderly, healthcare residents, patient with visual impairments, and children). APD is a practical modality option for patients with increased intra-abdominal pressure complications (back pain, dialysate leaks, hernias, hemorrhoids, and uterine prolapse) (Negoi and Nolph 2006). The disadvantages of APD relative to CAPD are the need for an automated machine, the higher cost, and the complexity to deal with a cycler. Some patients may not tolerate the dependence on a machine or the prolonged confinement to bed overnight. Patients could have sleep disturbances by the cycler alarms. Additionally, sodium sieving and the consequent low sodium in the ultrafiltrate may bring about hypernatremia, poor blood pressure control, and increased thirst (Shen et al. 1978).

APD with the development of automatic machine is ready to deliver a dose range beyond traditional dialysis and to provide individualized composition of PD solution to meet individual requirements by online preparation or teledialysis technique (Ronco et al. 2006).

12.2.1 Continuous Cyclic Peritoneal Dialysis (CCPD)

Continuous cyclic peritoneal dialysis (CCPD), also known as APD with a day dwell, is a continuous automated PD regimen. CCPD is a reversal type of CAPD where the shorter multiple exchanges are performed overnight, while the longer dwell are provided during the day. APD was introduced in the late 1970s with the purpose of attaining higher fluid and solute removal compared to CAPD (Diaz-Buxo et al. 1981). CCPD provides much flexible regimen and endures larger dwell volume due to decreased intraperitoneal pressure at a supine position. Figure 12.2 shows the diagrammatic

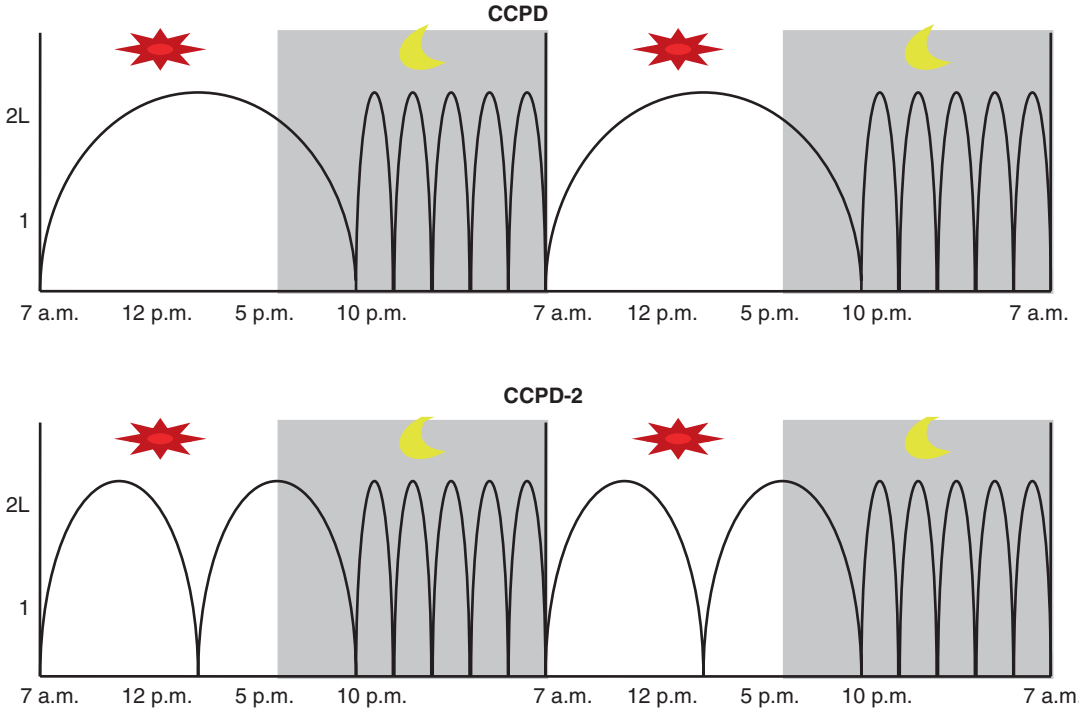

Fig. 12.2 Diagrammatic representation of continuous cyclic peritoneal dialysis (CCPD)

feature of CCPD regimen. Typically, overnight dialysis is performed for 8–12 h with each dwell volumes of 1.5–3.0 L and 3–5 automated cycles. The total volume of instilled dialysis solution is 8–12 L. After the last overnight cycle, the automated machine is programmed to deliver a last bag fill (with 1.5–2 L of dialysis solution) for day dwell with hypertonic dialysis solution or non-glucose osmotic agent like icodextrin. Additional daytime exchanges can be performed in addition to typical CCPD (e.g., 2 daytime exchanges (CCPD-2)). These daytime exchanges could be carried out manually or by the cycler. CCPD could be the regimen of choice in patient with high membrane transporter who has ultrafiltration failure, especially without residual kidney function. In addition, this regimen is suitable for the employed workers or school children who have difficulty to perform multiple daytime exchanges. For patients who need assistance to conduct dialysis, CCPD could be better than CAPD. To achieve target clearance, dwell volume, dwell time, and number of exchanges can be manipulated. Detailed prescription methods to meet dialysis adequacy are described in Chap. 4.

12.2.2 Nocturnal Intermittent Peritoneal Dialysis (NIPD)

Nocturnal intermittent peritoneal dialysis (NIPD), also known as dry-day APD, is an intermittent dialysis regimen performed every night using a cycler (Fig. 12.3) (Twardowski 1990). Typically, dialysis is performed for 8–12 h with each fill volume of 2–2.5 L for average-sized patient. The total volume of dialysis solution used overnight is 8–12 L. To avoid insufficient solute clearance associated with dry abdomen in the daytime, time for each dialysate drainage should be limited to approximately 15 min. Large volume (up to 20 L) and extended dialysis hours (high-dose NIPD) may be needed for anuric patients. NIPD regimen has empty the abdomen during daytime; it is advantageous for patients suffering from various complications due to elevated intra-abdominal pressure. APD with dry day enhances patient daytime activity and decreases glucose absorption, leading to a better appetite. NIPD, a PD method that uses short dwells, is suitable for patients who have high membrane transporter and who have type I ultrafiltration failure. Patient with residual renal function could be initially started on PD with NIPD regimen. However, the "dry-day" NIPD, as compared to continuous PD modality, decreases at least 10–15% of small-solute clearance and almost 50% of middle-solute clearance which is highly time dependent (Gahl and Jorres 2000; Brophy et al. 1999). NIPD have limitations when prescribed for patients with large body surface area and those with low or low-average membrane transporter with no or minimal residual renal function, as dialysis adequacy cannot be fulfilled (Gahl and Jorres 2000). The average cost is higher than CAPD.

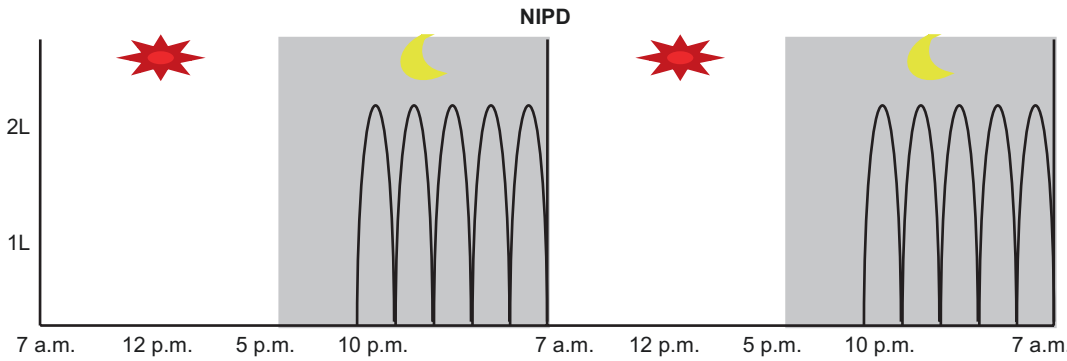

Fig. 12.3 Diagrammatic representation of nocturnal intermittent peritoneal dialysis (NIPD)

12.2.3 Intermittent Peritoneal Dialysis (IPD)

Intermittent peritoneal dialysis (IPD) is the first APD modality and a classical PD regimen wherein several short-dwell exchanges are performed intermittently in a hospital or dialysis center. It had been widely used and remained popular until the 1980s when more efficient newer forms of PD such as CAPD and APD were introduced. During classical IPD, the patient generally receives frequent, short-dwell exchanges over 8–10 h per session with a high-dose dialysis volume (20–40 L), three times weekly (Fig. 12.4). The dialysis procedure is carried out manually or with cyclers. IPD has been no longer prevalent modality due to long duration and poor solute clearances. However, IPD could be the suitable option for elderly and multimorbid dialysis patients who have failed hemodialysis (HD) (e.g., recurrent vascular access problems) or are unable to perform PD on their own and lacking social support at home (Fourtounas et al. 2009; Woywodt et al. 2008). IPD could also be an option for acute rescue PD as bridge therapy before long-term HD or PD and transient therapy for patients who have hernias or recently undergone abdominal surgery (Kleinpeter and Krane 2006; Shah et al. 2006). Lower dwell volume is recommended during postoperative periods. In addition, IPD regimen could be applied for those with congestive heart failure who have difficulty to achieve volume control on maximal medical treatment (Basile et al. 2009; Koch et al. 2012a). Long duration of dialysis needs longer nursing time, larger volume of dialysis fluid, and higher staffing costs. However, funding and insurance reimbursement may not fully cover the cost.

12.2.4 Tidal Peritoneal Dialysis (TPD)

Tidal peritoneal dialysis (TPD) is a modality combining intermittent and continuous-flow regimen (Fig. 12.5). The variant of APD was developed to

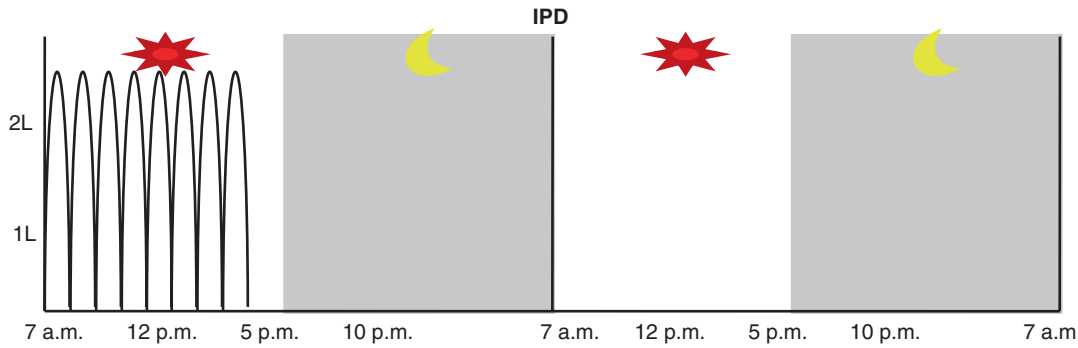

Fig. 12.4 Diagrammatic representation of intermittent peritoneal dialysis (IPD) prescription

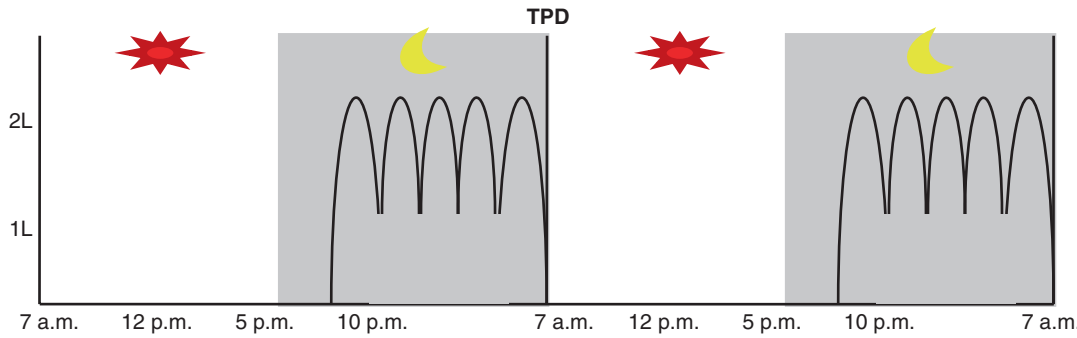

Fig. 12.5 Diagrammatic representation of tidal peritoneal dialysis (TPD) prescription

increase solute clearance by maintaining a reserve volume in the abdominal cavity throughout all the cycles. It was considered that this might enable diffusive clearance to be sustained throughout the dialysis period without interruption. The prime purpose of TPD was to improve small-solute clearance by minimizing the interruption of diffusive clearance during the drainage of dialysis solution. Typically, initial volume is filled as large as possible without discomfort. The volume is determined according to patient body size but is usually 2–3 L. After initial volume is instilled, only a portion of solution is drained, leaving the rest of the solution (reserve volume or residual volume) in the peritoneal cavity. Then, the peritoneal cavity is refilled by fresh dialysis solution (tidal volume, usually 50% of initial volume, 50% TPD). For example, if 2 L is initially filled, the next fill volume (tidal volume) is 1 L, the next drain volume is approximately 1 L. TPD may be done with or without a daytime dwell. The ultrafiltration volume must be closely calculated and refilled with each exchange to maintain reserve volume unchanged. If ultrafiltration volumes are underestimated, lower volumes will be drained. Therefore, the reserve volume will gradually increase, potentially resulting in increased intraperitoneal pressure and abdominal discomfort. To reduce overfill risks (Fernando and Finkelstein 2006), the peritoneal cavity can be completely drained before cycling initiation or every third or fourth cycle. On the other hand, if ultrafiltration volumes are overestimated, the residual volume might be decreased. Initially, TPD have been developed to improve dialysis efficiency. However, TPD with usual fluid volumes does not improve solute clearances compared with similar amounts of PD fluid delivered by conventional APD (Perez et al. 2000; Juergensen et al. 2000). Small-molecule (Juergensen et al. 2000; Aasarod et al. 1997) and middle-molecule (Vychytil et al. 1999) clearances, blood pressure regulation (Balaskas et al. 1993), and sodium sieving (Perez et al. 2000) in TPD have found little differences from other APD regimen. Today, the most common indications for TPD are relieving infusion or drain pain and avoiding low-drain cycler alarm, especially with poor catheter function (Blake et al. 2014). Most automated cyclers use hydraulic suction, rather than gravity, to drain the dialysate (Neri et al. 2001). That leads to painful suction on the parietal peritoneum or visceral organs. TPD minimizes the time period with completely empty abdomen, thereby minimizing infusion or drain pain (Juergensen et al. 1999). However, TPD needs higher dialysis volume to improve small-solute clearance, and this is very expensive.

12.2.5 Adapted APD

Adapted APD is a novel approach to the APD regimen to reach optimal PD prescription for improving solute and fluid removal (Fischbach et al. 2016). Reaching adequacy goals in PD for both clearance and ultrafiltration is challenging. Smaller fill volumes and shorter dwell times enhance the process of ultrafiltration (aquaporin exchange) and while large fill volumes and longer dwell times increase solute clearance (small pore exchange) (Fischbach et al. 2011). Adapted APD promotes ultrafiltration and solute clearance within one PD session. The adapted APD regimen consists of two different sequences of exchanges during one PD session (Fig. 12.6). The first sequence is short-dwell and small fill volume to facilitate ultrafiltration. The next sequence is longer dwell (longer diffusion time) with large fill volume (recruitment of wetted peritoneal membrane) to improve the removal of solute and uremic toxins. Dwell volume and dwell time are determined by the body surface area and the membrane transport characteristics of the patient, respectively (Fischbach et al. 1994; van Biesen et al. 2010). The short-dwell time in adapted APD may be established according to the membrane transporter status or directly evaluated from the crossing time point of the urea (D/P) and glucose (D/D0) curves on the peritoneal equilibrium test, also known as “optimal ultrafiltration dwell time” by accelerated peritoneal examination (APEX) test (Fischbach et al. 1996). The longer dwell time (90–240 min) may be prescribed as 3–4 times the APEX time (30–60 min). The large dwell volume is the highest fill volume endured in the supine position, not to

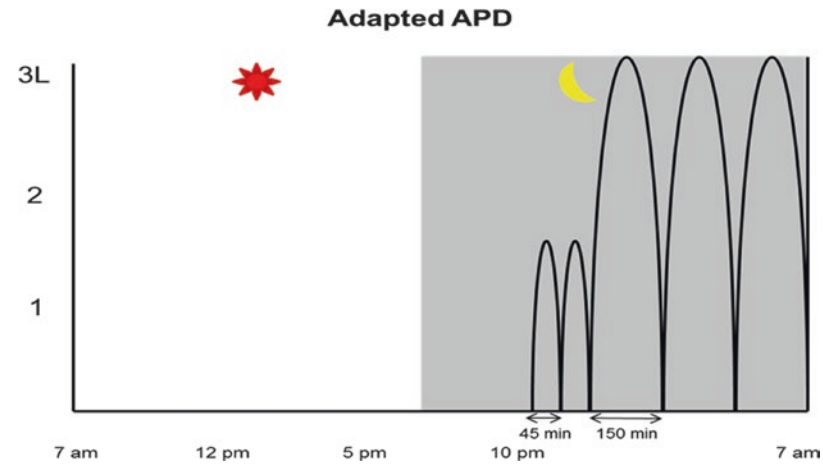

Fig. 12.6 Diagrammatic representation of adapted APD prescription

be over an intra-abdominal pressure of 18 cm H_2O (>14 cm H_2O is associated with increased risk of hernia and leakage) (Durand et al. 1994; Fischbach et al. 2014). Small fill volume is one-half of the large volume. Proper dwell volume not exceeding the upper limit of intra-abdominal pressure should be applied (Fischbach et al. 2014). Further studies on the mechanisms of enhanced clearances and the outcomes of adapted APD are needed.

12.2.6 Outcomes Between CAPD and APD

The choice of PD modality type is mostly based on peritoneal membrane type and patient preferences. Many investigators have compared these two submodalities—CAPD and APD.

Higher residual renal function is associated with improved solute and volume control and patient survival (Susantitaphong et al. 2012). APD, particularly in patients undergoing NIPD, has been described as an intermittent treatment more similar to HD. CAPD is regarded as more gradual, with performance at a near-constant rate over the 24-h period. Some reports showed that APD was associated with a faster decline in residual renal function (Hufnagel et al. 1999; Hamada et al. 2000; Hidaka and Nakao 2003). However, the majority of studies do not show a definite difference of residual renal function change by PD modality (Moist et al. 2000; Cnossen et al. 2011; Bro et al. 1999). In this considerations, whether APD brings about rapid decline in residual renal function is not convincing.

The number of connections and disconnections between PD catheter and the tubing system is regarded as an important factor of developing PD-associated peritonitis. Since APD required fewer connections and disconnections than CAPD, PD-associated peritonitis rates with APD were lower than with CAPD in the past. However, in connection systems of CAPD, not only APD has been improved dramatically. With the use of contemporary connection systems, there is no significant difference in the risk of PD-associated peritonitis between CAPD and APD (Nessim et al. 2009; Ruger et al. 2011). Further studies comparing the response, severity, and recurrence rates of peritonitis in CAPD versus APD are needed.

There are no significant differences in volume overload or blood pressure control between patients with CAPD and APD (Frankenfield et al. 1999; Van Biesen et al. 2011). Individualized and proper prescription of PD therapy can improve solute and water removal and achieve target clearance. There is no convincing evidence for a difference in the overall survival and technique survival between the two PD modalities (Mehrotra et al. 2009; Badve et al. 2008; Michels et al. 2009). In addition, there is no evidence that

patients on APD have a better health-related quality of life (Balasubramanian et al. 2011; Michels et al. 2011). Therefore, there is no persuasive evidence of a significant difference in any clinically relevant outcomes between patients on CAPD and APD (Mehrotra et al. 2009; Bieber et al. 2014). Individualized and differential application of the two PD modalities is likely to continue according to patient preferences, peritoneal membrane type, and lifestyle.

12.3 Hybrid Dialysis (Bimodal Dialysis)

The basic role of dialysis is to maintain the adequacy of solute clearance and ultrafiltration. When patients on PD cannot meet target clearances, especially with decreasing residual renal function, the higher dialysis dose is needed. If increasing the dose by PD alone is limited, combined prescription of PD and HD can be considered. HD and PD have different techniques and advantages. PD enables slow continuous ultrafiltration without rapid hemodynamic changes but less efficient solute removal. On the other hand, HD enables efficient solute removal but rapid ultrafiltration and hemodynamic changes. Historically, both modalities have been considered as mutually exclusive. However, on the basis of the unique characteristics of the two modalities, combination therapy of both modalities simultaneously may be a good option for individual patient. This combination therapy with PD and HD is referred as "hybrid dialysis," "bimodal dialysis," or "complementary dialysis" (McIntyre 2004; Kawanishi and Moriishi 2007). Combined regimen with PD and HD was first introduced in Japan in the 1990s by Watanabe and Kimura [abstract: Watanabe S, Kimura Y et al. Nihon Touseki Igakukai Zasshi. 1993;26(suppl 1):911]; it has been rapidly applied in Japan. In 2013, 20.4% of the patients on PD were receiving combined therapy with PD and HD (Masakane et al. 2015). Usual prescription is the addition of once weekly HD to established 5–6 days of PD prescription (CAPD or CCPD). Any combination of PD with HD schedule could be adjusted with clinical needs and psychosocial issues. Medical indications for hybrid dialysis are as follows: inadequate solute removal resulting in uremic symptoms; loss of residual renal function resulting in unsatisfied dialysis goal; insufficient ultrafiltration, chronic volume overload, and difficult-to-manage fluid balance; avoiding an increased dialysate volume for preventing pressure-related problems such as hernia and hydrothorax; peritoneal rest; and cardiovascular instability in HD patients (Kawanishi and Moriishi 2007; Agarwal et al. 2003). Psychosocial factors such as employment, work schedule, patient preferences, and patient or caregiver support also influence the choice of hybrid dialysis. In the previous studies, mostly based on retrospective analysis, hybrid regimen improved solute removal, increased serum albumin and hemoglobin, and improved patient quality of life (Agarwal et al. 2003; Suzuki et al. 2012). In other studies, patients with hybrid dialysis improved volume and blood pressure control with the same or decreased dose of antihypertensive drugs and reduced left ventricular mass index (McIntyre 2004; Tanaka et al. 2011). Other advantages of hybrid dialysis are permitting a "PD holiday" with peritoneal rest (with expectation of reducing glucose exposure and improving peritoneal function and glycemic control), achieving PD prolongation with a minimal change in lifestyle, and increasing flexibility of renal replacement therapy and seamless transition to single modality if access problem develops (Kawanishi and Moriishi 2007). However, the requirement for the formation of dual access is a potential drawback, exposing the patient to the possible complications of both. In addition, total solute clearance goals and methods for evaluating total clearance need to be standardized. Criteria for discontinuation of hybrid therapy (long-term PD therapy may increase the risk of encapsulating peritoneal sclerosis) are needed (Maruyama et al. 2014). Reimbursement issues may be a problem in the majority of cases. Further large, prospective studies are needed.

12.4 Incremental PD vs. Full-Dose PD

There are still controversies about when to start dialysis in advanced renal failure patients. The benefit of starting dialysis earlier before definitive uremic symptoms develop is that the patients can avoid the malnutrition associated with uremia and can have a healthy start. Clinicians either start with full dose of peritoneal fluid exchanges regardless of residual renal function or, alternatively, incrementally increase the dose of PD depending on the decline of residual renal function.

By starting PD with full-dose prescription, either in CAPD or CCPD, one might have lower risk of inadequate dialysis, by delivering sufficient dialysis dose, regardless of the amount of the residual renal function. However, beyond the issues of increased medical cost, full-dose PD prescription is associated with longer exposure of the peritoneal membrane to PD fluid resulting in increased risk of peritonitis and the peritoneal membrane degeneration. Besides, larger burden with PD fluid exchange procedure might interfere with work or daily routine, resulting in the sacrifice of the quality of life and eventually patient "burnout."

Alternatively, clinicians may start with lower dose of peritoneal dialysis—i.e., two or three bags a day for CAPD or fewer nighttime cycles in NIPD – and increase the dialysis component of solute clearance incrementally, depending on the decline of residual renal function. In this situation, clinicians need to measure the residual renal function more frequently at every three-to-six-month interval and increase the peritoneal solute clearance accordingly. To increase the peritoneal solute clearance, clinicians can choose to increase either the number of exchanges or dwell volume. Otherwise, they can choose to switch to high-dose NIPD or CCPD (Fig. 12.7). Incremental PD was associated with improved quality of life. One retrospective analysis suggested that it was associated with lower risk of peritonitis and improved preservation of residual renal function (Sans et al. 2016). However, it needs more frequent evaluation of the peritoneal and renal solute clearance in order to avoid inadequate dialysis.

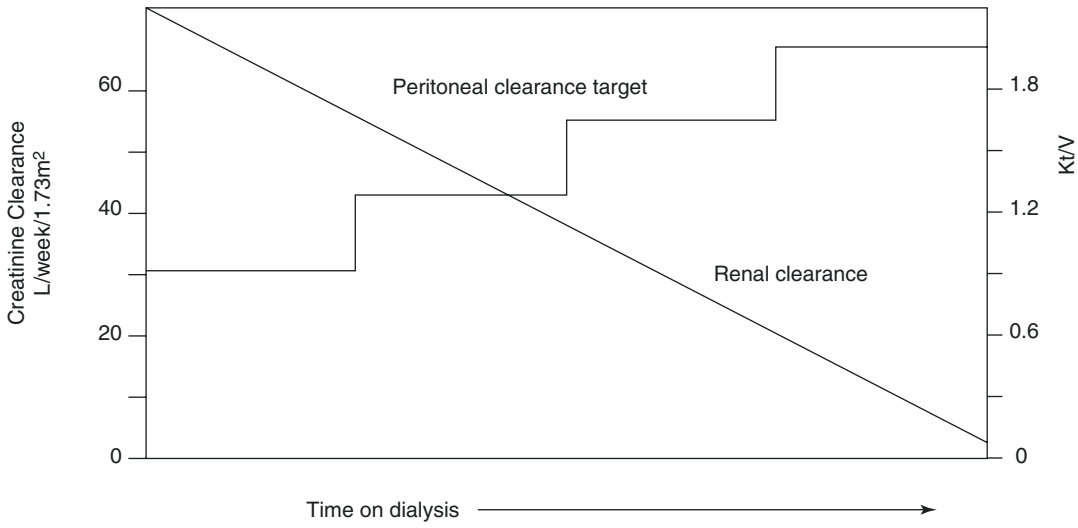

Fig. 12.7 Adaptation of PD prescription and target clearance to adjust to the decline of residual renal function

12.5 Urgent-Start PD (Unplanned Start on PD)

Some patients with advanced kidney disease who present late during the disease course are obliged to start urgent dialysis without preestablished permanent dialysis access. Such patients are, in most cases, initiated on in-center hemodialysis with central venous catheter, although many of them are candidates of PD. Starting dialysis with temporary central catheter is associated with increased risk of lethal complications such as bacteremia and central vein thrombosis. However, recently, the concept of urgent-start PD in late presenting patients has been introduced in the USA, Europe, and Asian countries.

Urgent-start PD can be defined as starting PD before the break-in period of two or more weeks. Traditionally, for a planned PD, break-in period of two or more weeks is needed for the healing of the catheter tunnel in order to prevent pericatheter or incisional leaks. However, for urgent start of PD, unplanned APD is initiated immediately or soon after PD catheter implantation in the hospital, with the prescription of low-volume, frequent dialysis exchange overnight using a cycler (Fig. 12.8). Initiating PD fluid exchange immediately after catheter placements renders the patients at a high risk of pericatheter or incisional leaks. Therefore, PD should be delivered using low exchange volumes and only in a recumbent position in order to minimize the intra-abdominal pressure and the risk of fluid leaks. In one center, the cycler delivered

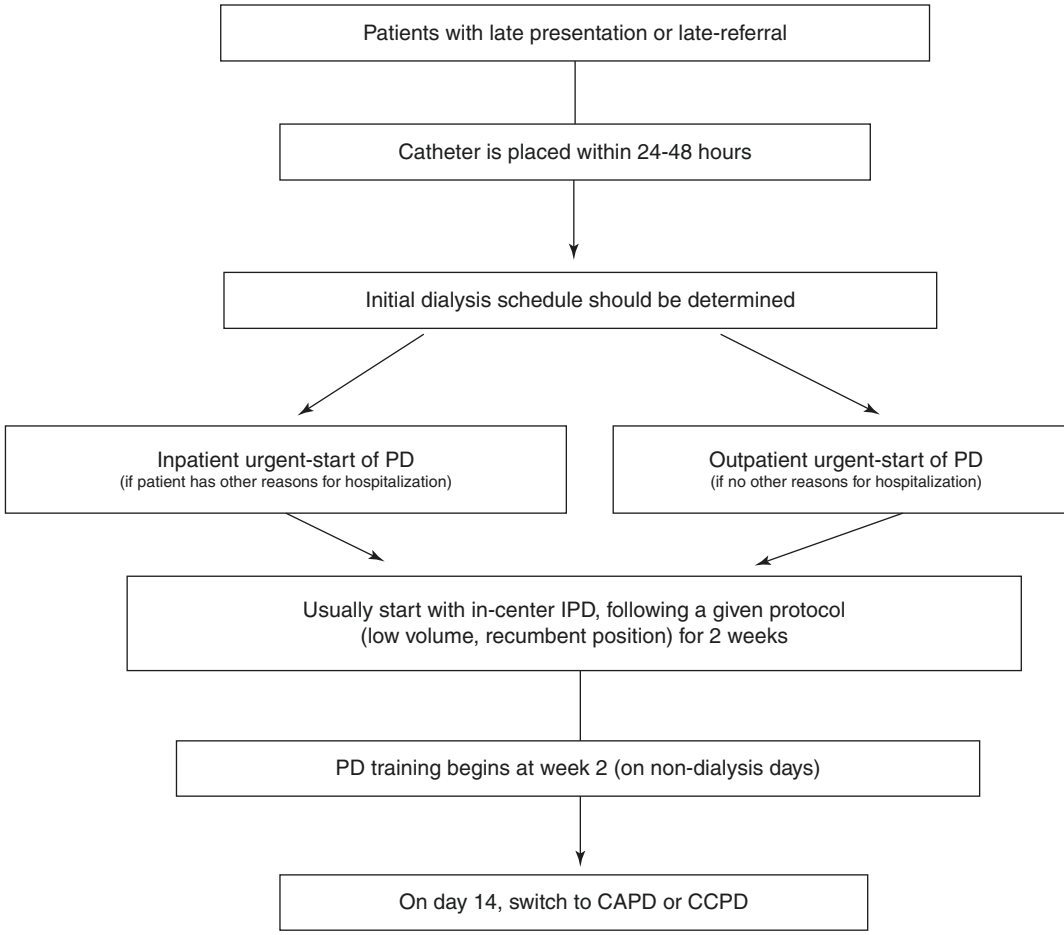

Fig. 12.8 Clinical process for urgent-start PD

14 cycles per session with a dwell time of 45 min to ensure adequate solute and fluid removal (Povlsen et al. 2015). On the second week of treatment, the patients begin to receive PD training on the non-dialysis days. After 8–14 days of treatment, the patients are converted to the standard CAPD or CCPD. For urgent-start PD, PD could be initiated either in hospital or in an outpatient setting. The hospital setting may be indicated for patients with more advanced uremia or concurrent medical issues. The outpatient setting may be used for the initiation of urgent, but not emergent, treatments.

One large-scale Chinese study (Liu et al. 2014), including 657 patients, showed that the length of break-in period between catheter implantation and start of PD was associated with catheter-related complications. The groups who started PD within 7 days after catheter placement exhibited higher incidence of mechanical complications (catheter leak, catheter dysfunction), as compared to those with break-in period >14 days. However, above issues were mostly treated with conservative treatment such as low-volume dialysis in a supine position. There was no difference in the need for surgical intervention between the two groups. The two groups did not differ in the mortality or technique failure, either.

Although published data are limited on the outcome of unplanned start on PD, mortality after starting unplanned PD is equal to or less than mortality after starting unplanned HD (Lobbedez et al. 2008; Koch et al. 2012b; Foote et al. 2012). Unplanned start on HD using temporary central venous catheter is associated with lethal complications such as catheter-related bacteremia or venous thrombosis, while unplanned start on PD is not.

Infrastructure needed for urgent-start PD is described in the Table 12.1.

12.6 Futuristic Modalities of Peritoneal Dialysis

12.6.1 Continuous-Flow Peritoneal Dialysis

The relationship between dialysate flow rate and urea clearance is described in Fig. 12.9. The initial part (Part A) of the curve denotes the dialysate flow rate of CAPD (×3 ~ 5 exchanges a day). Here, in this part of the curve, the urea clearance is limited by the dialysate flow rate. Higher urea clearance can be obtained by increasing the number of exchanges or the dwell volume in CAPD. The second part (Part B) of the curve describes the typical region of APD, where dialysate flows may vary significantly due to variations in the dwell time and the exchanges per day.

Table 12.1 Requirements for urgent-start PD program (Ghaffari et al. 2013)

Objective method for patient selection
Urgent PD catheter placement
Nursing support: training and staffing
Hospital administrative support:
Dialysis unit administrative support: space and material
Protocol-driven orders

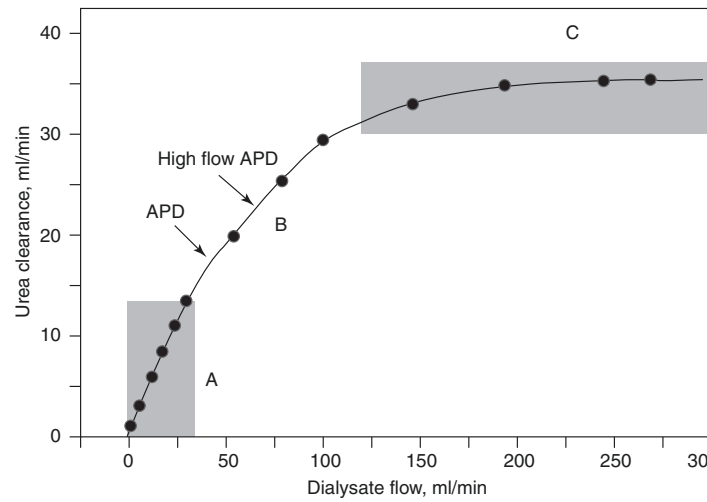

Fig. 12.9 The relationship between dialysate flow and urea clearance

The third part (Part C) of the curve is the region where the dialysate flow is maximized and plateau is reached in terms of urea clearance. Here, the urea clearance is limited by mass transfer area coefficient (MTAC) of the peritoneal membrane. This region has been explored only experimentally by continuous-flow peritoneal dialysis (CFPD).

CFPD is an experimental modality to maximize the small-solute clearance by maintaining a fixed intraperitoneal volume (2–3 L) with a constant inflow and outflow. The dialysate is infused at a very high speed (100–300 mL/min), and sophisticated control of the dialysate inflow and outflow should be available. CFPD necessitates two catheters or a double-lumen catheter in order to ensure continuous and uninterrupted dialysate flow. Therefore, there is no time wasted during the inflow or drainage of the dialysate. It also necessitates a technical support to generate or regenerate large volumes of sterile PD fluid. CFPD can ensure sufficient solute clearance, especially for large, anuric (with no urine production) patients or high transporters who do not acquire enough ultrafiltration volume during CAPD. CFPD is a highly efficient dialysis modality with the peritoneal clearance of 42 mL/min for urea using a dialysate flow rate of 200 mL/min and 2-L initial fill volume.

However, technical challenges remain in terms of catheter design, ultrafiltration control, and real-time measurement for intraperitoneal volume. Particularly, at high flow rates, the issues of recirculation and fluid channeling may restrict mixing. CFPD relies on a high dialysate flow and requires a large amount of dialysate fluid to achieve maximal efficiency. Therefore, CFPD using commercial PD fluid is very costly and accompanied by storage issues. Another approach to solve these issues could be extracorporeal regeneration of PD fluid from spent dialysate by either hemodialysis filter or adsorption through sorbent column. Protein-bound uremic toxins such as *p*-cresol, homocysteine, and asymmetric dimethylarginine (ADMA) are hardly removed by dialysis but may be amenable to sorbent removal. Middle molecules and low-molecular-weight proteins including β2-microglubulin, AGEs, leptin, and proinflammatory cytokines and chemokines are also uremic toxins that are poorly removed by conventional dialysis modalities. Sorbents have the potential for an effective removal of these uremic toxins. Sorbents can be applied to the CFPD system and assist the regeneration of PD fluid.

12.6.2 Wearable PD Devices

Continuous ambulatory PD typically requires three or four exchanges of PD fluid a day. The conventional peritoneal dialysis has several drawbacks, particularly in terms of time spent on PD fluid exchange, dietary and fluid restrictions, and transport and storage of large volumes of PD fluid, especially when traveling far away from home. Although automated PD using cycler allows daytime freedom, it also requires the patient to be connected to the machine overnight. These limitations have motivated a search for a brand new device of PD—wearable PD devices (Fig. 12.10). Such device not only would allow patients to receive continuous dialysis therapy while going on with their work or everyday activities, it could also enable better improved blood pressure control by providing continuous fluid and electrolyte exchange.

Currently, two types of wearable artificial devices are under development. Vicenza wearable artificial kidney (ViWAK) (Ronco and Fecondini 2007) employs continuous-flow PD (CFPD) mode using a dual lumen catheter. PD fluid is continuously recycled by passing through a series of sorbent. Urea in the spent dialysate is metabolized by urease into ammonia and carbon dioxide. Ammonia is then rapidly absorbed by zirconium phosphate in the absorbents. The ViWAK system does not have any specific system to correct electrolyte changes, nor does it have any ultrafiltration control. Therefore, ViWAK is designed to use two peritoneal dialysate exchanges a day in order to maintain electrolyte balance.

Automated wearable artificial kidney (AWAK) (Fig. 12.11) (Lee and Roberts 2008) is another wearable PD device. AWAK utilizes a single lumen catheter – therefore, as such dialysate flow is on and off. The AWAK system is designed to regenerate PD fluid continuously, thereby allowing the usage of a single conventional PD fluid for 1 month. It requires a reservoir for storing regenerated PD fluid. AWAK has another chamber that contains lactate, glucose, and electrolytes to refresh the regenerated fluid. Currently, the AWAK device is undergoing a clinical trial.

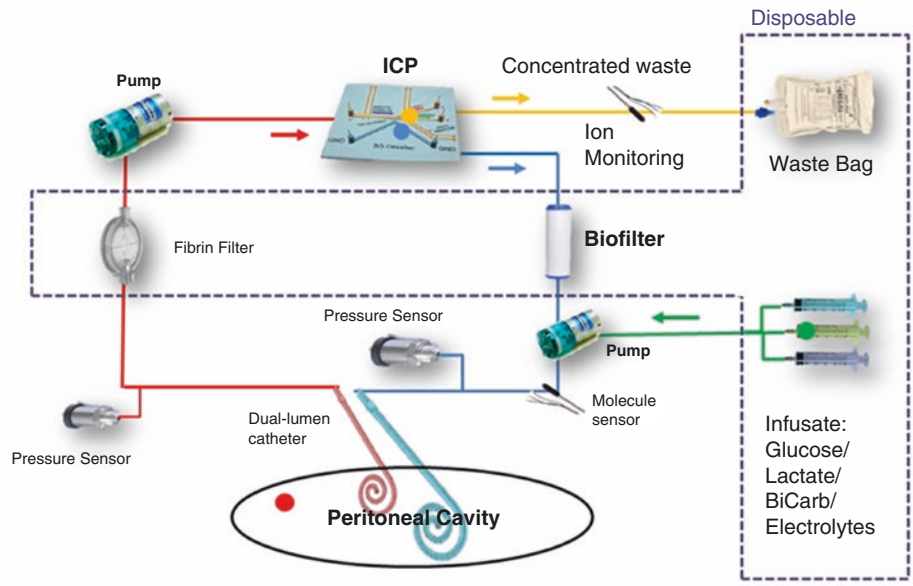

Fig. 12.10 Basic concepts of wearable artificial device for peritoneal dialysis

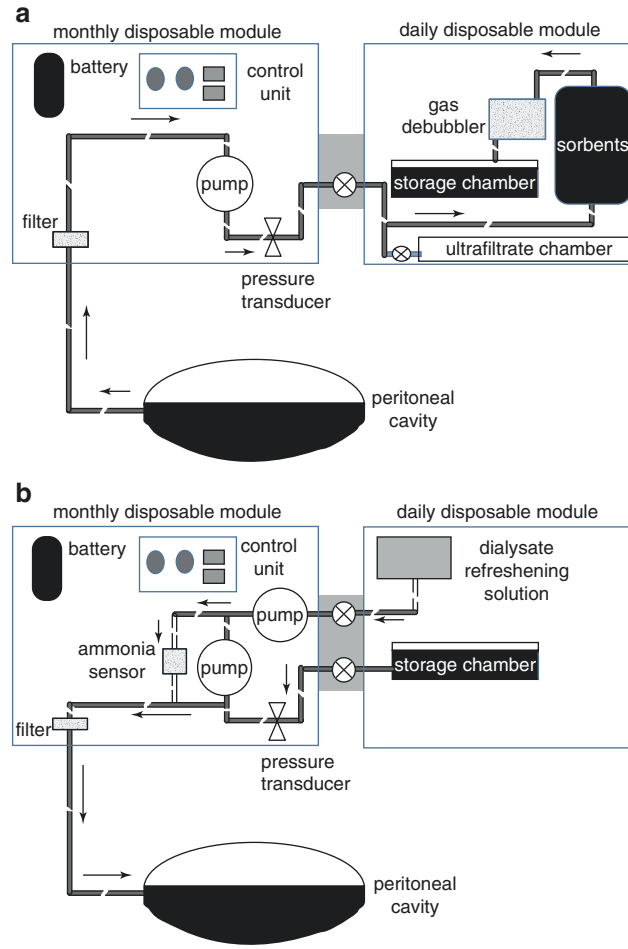

Fig. 12.11 Automated wearable artificial kidney (AWAK) (Davenport 2015)

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Peritoneal Access

13

Mizuya Fukasawa

13.1 Perioperative Care

Good surgical results require not only appropriate implementation of surgical procedures, but also adequate preoperative and postoperative care, which is applicable to every surgery. In particular, when peritoneal access (PA) surgery is required, sterile manipulation should be maintained because a catheter is an artificial device to a living body. The surgical procedure involved during PA is itself not the final goal, unlike other surgical operations, such as resection in common cancer therapy. After catheterization, it is necessary to attempt to use an implantation that allows long-term access.

13.1.1 Preoperative Preparation

Table 13.1 includes a checklist for use prior to PA surgery. Previously, a history of abdominal surgery was regarded as a contraindication to peritoneal dialysis (PD). Currently, difficulties in catheterization are encountered in limited cases, such as in cases of abdominal adhesions. In many cases of abdominal surgery, a catheter can be inserted; however, PA should be performed at a site other than at the site of a previous surgical wound in which abdominal organs may be present. Thus, PD catheters can be implanted by traditional laparotomy in most patients. In cases of widespread abdominal adhesions, laparoscopy is also useful for observing the abdominal cavity and dividing adhesions.

Table 13.1 Peritoneum dialysis catheter insertion technique, a preoperative confirmation matter and measures

Confirmation of the past of the abdominal surgery (standard laparotomy/laparoscopic surgery, decision of the insertion part)
Decision of exit site position (standard abdominal position/previous fort/lower fort/upper abdominal wall/other special exit)
Bacterial culture examination (nasal cavity and umbilicus): In the case of MRSA bacteria carrier, the removal with mupirocin is needed
Disposal of body hair (method, timing)
Take a bath to keep skin clean
Decrease in capacity in the abdominal cavity (stool processing with a laxative, the enema, empty bladder by letting self-urinate or urination by a catheter)
Prescription of infusion, the antibiotic
For patients with diabetes, normalization of blood glucose should be done

Various PD catheters are commercially available from many manufacturers (available products depend on each country). In Japan, a long catheter of 65 or 80 cm in total length is available and an exit site can be established without

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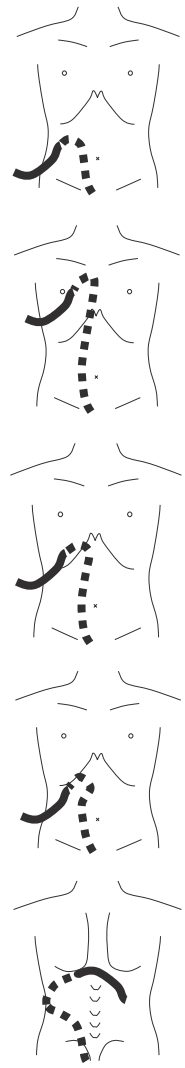
limitations (Fig. 13.1). Discussion with the patient should be conducted as needed.

Since this surgery involves the implantation of an artificial material, special considerations are necessary to prevent infection. In particular, confirmation of the patient being a carrier of methicillin-resistant Staphylococcus aureus (MRSA) is more likely to be associated with subsequent infection. Therefore, it may be effective that the nasal cavity and umbilicus are cultured for bacteria and subsequent bacterial elimination is conducted as needed. As per common surgical procedures, antibiotic agents should be administered just prior to surgery to increase the drug blood concentration level. Regarding preoperative body hair removal, it is desirable to refer to the Centers for Disease Control and Prevention (CDC) guidelines for the USA (Mangram et al. 1999). These guidelines indicate that hair shaving with a razor increases the occurrence of surgical site infection (SSI). In our hospital, as a general rule, hair shaving is not conducted or is conducted using a surgical clipper, as necessary. In addition, sebum and protein deposits that can not be disinfected with swabs done in the operating room on the day of surgery should be washed away with soap during bathing, or washed with soap with a disinfectant before surgery to reduce SSI risk.



a abdominal exit, traditional exit

Because the existing catheter had only a short thing, We couldn't but manufacture it in the abdomen.
Abdominal progress is flexural, and piston motion is easy to happen (risk upswing in exit part infection) In the obesity case, the discovery of the tunnel infectious disease may be late.
Distence to the abdominal cavity is short at the time of tunnel infection (risk upswing in influence to peritonitis).
A surgical procedure is relatively easy

b presternal exit, bathrib exit

An exit–site is not buried water at the time of bathing.
Subcutaneous fat is thin, and the fixation of the catheter is good.
Therefore, piston motion is hard to happen, and a risk of the tunnel infection is reduced.
Two catheters were necessary before, but now, there is a long catheter,
it is possible in one of them.
Because distance to the abdominal cavity is reduced at the time of tunnel infection.

c lower thoracic exit: LTE

Subcutaneous fat is thin, and the fixation of the catheter is good.
Therefore, piston motion is hard to happen, and
a risk of the tunnel infection is reduced. Two catheters were necessary before, but now, there is a long catheter, it is possible
Because distance to the abdominal cavity is reduced at the time of tunnel infection.

d upper abdominal exit: UAE

Two catheters were necessary before, but noe, there is a long catheter, it is possible in one of them.
Bacuse distence to the abdominal cavity is long, a risk of the influence in the abdominal cavity is reduced at the time of tunnel infection.

e shoulder blade exit: SBE

For dementia patient, Risk aversion such as cutting a catheter by oneself. subcuttaneous fat is thin, and the fixation of the catheter is good. Therefore, piston motion is hard to happen, and a risk of the tunnel infection is reduced.
Two catheters were necessaty before, but now, there is a long catheter,
it is possible in one of them. Because distance to the abdominal cavity is long, a risk of the influence in the abdominal cavity is reduced at the time of tunnel infection.

Fig. 13.1 Various catheter exit site (kidney and dialysis 66, access 2009 (in Japanese)—part modification)

For PD, the tip of the catheter is commonly inserted into the Douglas Pouch. Disposal of stool in the rectum and emptying of the bladder are therefore critical to secure a wide Douglas Pouch. These procedures are essential and complications with catheterization may arise when these procedures are not performed. Administration of cathartic drugs and preoperative enema are necessary for disposal of stool in the rectum. Preoperative urination is required for emptying of the bladder. Especially for elderly patients, higher amount of residual urine is present in most cases; therefore, urethral catheterization should be considered, as required.

13.1.2 Surgery: Standard Implantation by Laparotomy

An inconsequential discussion concerning whether surgery should be performed by a surgeon or nephrologist often takes place. As a minimum, the operator must be trained and have mastered surgical procedures. Additionally, if the situation of each country permits it, this surgery should be performed by a physician who manages PD, namely a "specialist of dialysis: 'Dialysist'." Therefore, whether the physician is a nephrologist or surgeon becomes irrelevant.

After having confirmed the method of the operative procedure and the exit site, the surgical procedure is initiated. To reduce pain, local anesthesia, lumbar anesthesia, or general anesthesia is considered, and the application varies depending on the system of each institution and the area of surgical wound. However, elevated intraoperative intra-abdominal pressure may lead to prolapsed intestinal tract from the wounded area and may cause damage to the abdominal organs during surgery. Therefore, this author often elects general anesthesia.

13.1.2.1 Access to the Posterior Sheath of the Rectus Muscle After Skin Incision

A catheter with a suitable tip length according to the body type should be selected. To prevent subsequent displacement of the catheter, it is desirable to choose a catheter with a thick-walled cuff to enhance self-recovery. Usually, the site of insertion is set at the breadth of 2–3 fingers inferior to the umbilicus. For incision into the abdomen, we believe that a transabdominal rectus incision should be considered rather than a median section or pararectal incision. First, as will be described later, it is necessary to lay a PD catheter as much as possible in order to insert it along the previous abdominal wall in the abdominal cavity. To achieve this, it is necessary to allow a long catheter to enter beneath the anterior sheath of the rectus abdominis muscle, which is an important factor in preventing dislocation of the catheter in the abdominal cavity. Details of this procedure are described below. Second, a transabdominal rectus incision should be used to prevent the spread of tunnel infection. There are abundant blood vessels in the rectus muscle, and their tissue affinity is also high, which results in the excessive formation of tight capsula fibrosa with many blood vessels around a catheter. This is effective in controlling infections because leukocytes respond to infection when a tunnel infection is spread towards the abdominal cavity beyond an external cuff.

The length of skin incision can be determined according to the operator's skill. Safe and sufficient implantation, rather than the size of the wound, is priority. The anterior sheath of the rectus abdominis muscle can be accessed by a sharp and blunt dissection of subcutaneous fat after skin incision. Dissection bluntly sideways, rather than an incision, is conducted with a delicate retractor. The surgery time can be shortened by having an image that the stiff site is incised using an electric knife, which prevents damage to the anterior sheath of the rectus abdominis muscle. As shown in Fig. 13.2, the subcutaneous fat processes the head side than caudalis longer in asymmetric. As will be discussed later, this is necessary to insert it to let a catheter comply with the anterior sheath of the rectus abdominis muscle. Then which enables confirmation of the anterior sheath of the rectus abdominis muscle of approximately 5–6 cm. Before a longitudinal incision of this anterior sheath can be made, a pair of traction sutures is placed sideways to

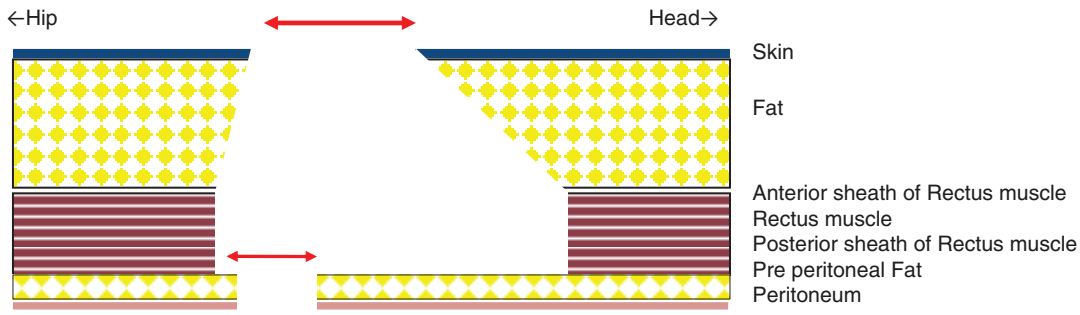


Fig. 13.2 Incision approach

make a slight pull to expose the area at a shallow depth, which will allow a surgeon to perform the surgery. Subsequently, a small incision is made at the anterior sheath using an electric knife. The muscle is isolated with a Pean forceps, and then an incision is made while paying attention not to damage the rectus muscle. During this procedure, an incision is also longer in the head side than it is in the caudal side. Furthermore, the incision is oriented asymmetrically. The rectus muscle can thereby be observed under direct visualization. The elderly, particularly elderly women, may have small rectus muscles, which vary with each individual. The rectus muscle, which runs longitudinally, needs no incision as a matter of course. The posterior sheath of the rectus muscle can be exposed, after having isolated it sideways by inserting a Pean forceps into the muscular layer of the rectus muscle. The muscle is easily separable sideways by opening a delicate retractor slowly under this condition. The blood vessels and fibers, which are obstructive for isolation, are incised as needed, while creating a coagulation with an electric knife. Concurrently, attention should be paid to the presence of the inferior epigastric artery that ascends. This artery is wide and can be used for coronary artery bypass. When it is damaged, the visual surgical field is worsened and the occurrence of postoperative hematoma increases a risk of infection. If you recognized the inferior epigastric artery in this phase, you should not hesitate about ligation and cutting. Because it may cause the trouble when this artery is damaged when you have to remove the catheter for any reasons.

13.1.2.2 From Access to the Posterior Sheath of the Rectus Muscle to Catheterization

Once the posterior sheath of the rectus muscle is observed, the cavity in which the operation is performed should be shallow in order to secure a good visual field and a pair of traction suture is put in a similar manner, as described above. In doing so, it is important to create a thin and wide cavity, while taking into account the location of the concealed muscles that are close to the intestinal tract. This traction suture is pulled to make a small incision at the posterior sheath of the rectus muscle. The incision is made caudally, as shown in Fig. 13.2, in order to place a catheter during insertion, as mentioned above. Prior to incision, the peritoneum is pressed sideways and elevated with a small forceps to confirm that it forms a tent-like structure. This procedure is conducted by taking account of intestinal adhesion located under the peritoneum. When there are adhesions of the abdominal contents, such as intestinal tracts, the peritoneum does not become like a tent, but instead forms a thick shape that is easy to find. The fibers of the tent-like posterior sheath are incised gradually in a stepwise manner using a round-edged knife because the risk of damage will be increased if there are adhesions of the abdominal contents while incising it using scissors.

In many cases during this procedure, the peritoneum may also be incised together with the sheath and a small hole may be created that may reach to the abdominal cavity. In patients with severe obesity, pre-peritoneal fat may be observed. In such a case, particularly in patients in whom abdominal adhesions are sus-

pected, it may be difficult to judge whether subcutaneous fat is pre-peritoneal or is in the peritoneal cavity, such as the mesenterium or omentum. A thin layer of peritoneum can be found after having slowly isolated the subcutaneous fat using a small forceps, which is pre-peritoneal fat. By incising its membrane, the abdominal cavity is exposed. It is likely to be peritoneal tissue when a wide blood vessel is observed. Even if peritoneal tissue is encountered, it is not difficult to manage unless vascular is damaged. In that case, insertion is performed from other sites.

After having approached the abdominal cavity, a traction suture is placed in four directions from the small hole, taking account of subsequent visual field (Fig. 13.3). In our hospital, non-absorbable threads are used for fixation using this thread. Handling of a needle is transmitted from the outside to the inside while paying attention not to damage abdominal organs. A space is created between the intestinal tracts by elevating these four threads, which facilitates the subsequent procedures. Then, a purse-string suture is placed, which is effective in preventing leakage after surgery (Fig. 13.3e). By doing this in a 6

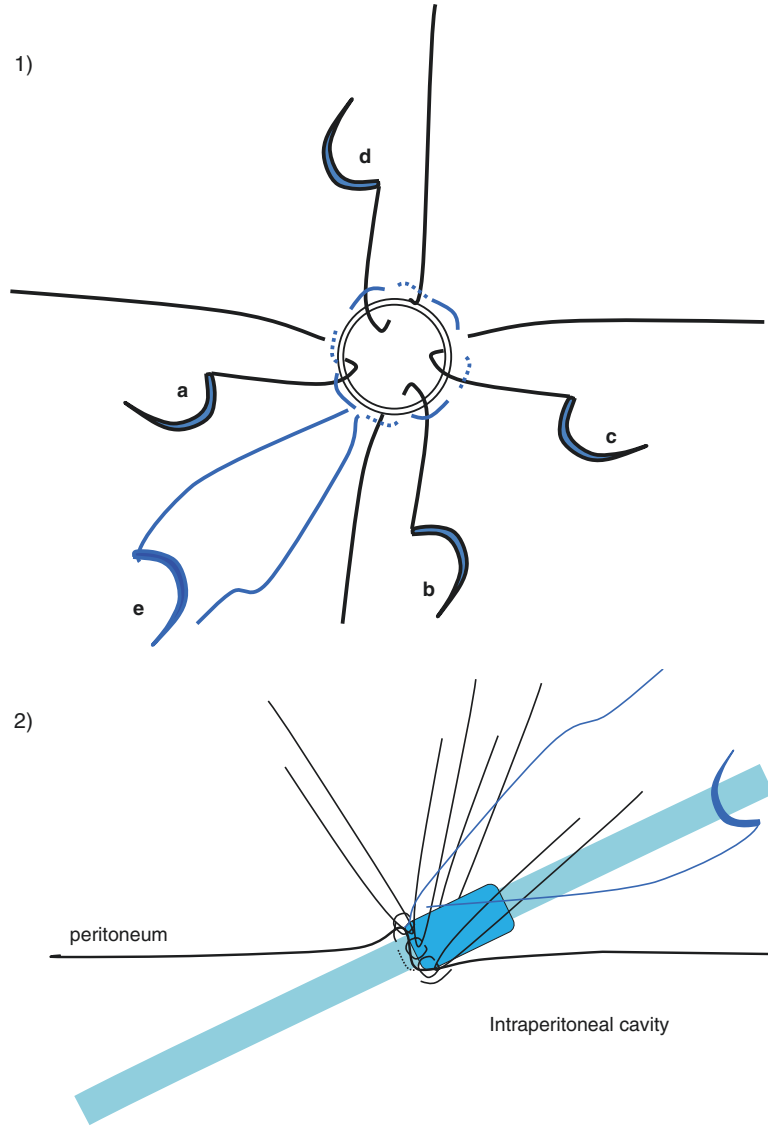
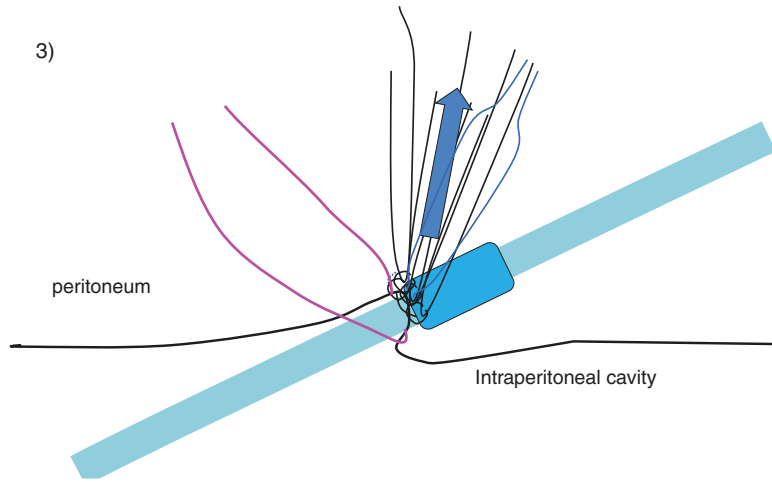


Fig. 13.3 Suture

Fig. 13.3 (continued)



o'clock direction, the catheter is not required to be elevated during subsequent reefing, which can prevent intraoperative displacement of the catheter. In our hospital, this purse-string suture is dualized as it may often be cut.

13.1.2.3 Standard Catheterization Using a Stylet

Recently, the non-stylet method (Kubota et al. 2008; Okamaoto et al. 2010) has been used. In this study, we describe a standard procedure first. Non-stylet method will be included in an additional note later.

A stylet, which is appropriate for each catheter, should be used. It is important to not use any inappropriate stylet because it may project from the catheter tip and may damage the abdominal organs during operation. After the lumen is lubricated with sterile glycerin, a stylet is inserted. The tip is slightly curved. First, the above-mentioned traction sutures from the four directions are elevated and then a catheter is inserted along the anterior abdominal wall from the small hole, which was opened at the abdominal cavity. In doing so, it is important to always confirm the direction in which the catheter tip is facing, using the handle of the stylet. Resistance occurs in the anterior surface of the bladder when it is inserted in the pelvic direction. Second, pull the stylet itself slightly and turn it 90 ° while elevating the catheter. When it advances to an appropriate position in the Douglas pouch, an operator can feel that the catheter is inserted in the appropriate site. At this point, do not push the catheter since it could easily damage the mesentery and the omentum.

In this position, pull up the stylet calmly while holding the catheter to prevent it from dropping off. At that time, the catheter is placed in an approximately good position unless it is floating. Placement in the Douglas pouch can be confirmed using the normal saline solution to be charged and discharged by injecting normal saline solution of 50–60 mL and turning the catheter tip downward, without strongly absorbing it. In doing so, drainage can be confirmed based on the principle of the siphon. If the drainage is confirmed as being similar to continuous water flow, a good position is indicated (Video 13.1). If dripping is noted, it indicates that the position is inappropriate; in such cases, insertion should be repeated until continuous water flow is confirmed. The confirmation by the radioscopy is not necessary if I can confirm this operation.

13.1.2.4 Fixation of the Catheter

After having inserted the catheter in an appropriate position in the Douglas pouch, catheter fixation is initiated. The catheter should be fixed using the above-mentioned thread as a traction suture. It is necessary to be careful of the white line of the catheter so that the twisting of a subcutaneous catheter does not result from previous procedure's operation.

The threads over the position at 3:00, 6:00, 9:00, and 12:00 are fixed to each internal cuff. In doing so, the threads have to be placed over the peripheral side of the Dacron cuff to place the cuff outside of the abdominal cavity during suturing (Fig. 13.3 (2)). This is important since, when cuff fibers advance into the abdominal cavity, ascites may leak outside the abdominal cavity through the spaces among the fibers due to capillary pressure. Second, the abdominal organs (e.g., the small intestine and the omentum) may adhere to cuff fibers. Third, bacteria adhere to cuff fibers at the onset of peritonitis just after surgery, which may result in refractory peritonitis. Finally, the purse-string suture is tightened at the abdominal cavity side of the internal cuff, which is considerably useful in preventing early leak. The presence of leak from the peritoneal part can be confirmed by injecting normal saline solution (100–200 mL).

When PD is not performed early, tissue repair occurs over time and a risk of leak is further reduced. However, when PD has to be initiated relatively early and with a substantial amount of solution, the additional procedure described below may reduce the risk of leak. Furthermore, the peritoneum sutured to the cuff forms a tent-like shape by elevating the sutured threads upward (Fig. 13.3 (3)). A silk thread is placed to surround the entire peritoneum and is sutured at the lower part of the inside cuff using one thread. In doing so, it is necessary to discontinue it when it is too tight since it causes occlusion of the lumen of the catheter.

13.1.2.5 From Implantation of the Catheter to Formation of the Exit Site

After the catheter is inserted into the abdominal cavity, it moves to the subcutaneous burial. The above-mentioned anterior sheath of the rectus abdominis muscle left of the head side is repaired at the upper part of the catheter, when possible (Fig. 13.4b). When a suture of the anterior sheath is conducted at the lower part of the catheter (Fig. 13.4a), the catheter advances into the abdominal cavity, but does not enter the Douglas pouch along the abdominal cavity. It is the most important factor for preventing subsequent displacement of the catheter to allow the catheter to advance the upper part of the intestinal tract along the anterior abdominal wall towards the Douglas pouch, as shown in Fig. 13.4b. In order to achieve this procedure with high precision, it is important to suture the anterior sheath at the upper part of the catheter.

Next, the external cuff is positioned. If the wound is large, the operation of the cuff can be conducted under direct visualization. However, skin incision is required at the external cuff when the wound is small. In such a case, a small incision is placed and then a sharp and blunt dissection of subcutaneous fat is performed until the anterior sheath of the rectus abdominis muscle is exposed. Using a Pean forceps or a tunneler, the external cuff is placed over the anterior sheath of the rectus abdominis muscle. Although it is not required to secure it with sutures, it is desirable to rigidly adhere it over the fascia. When an external cuff is present within the subcutaneous fat, its permanence may be poor and may cause subcutaneous flexure of the catheter.

The tunneler is used to induce the catheter to the planned exit site afterwards. You should keep 4–5 cm from external cuff and exit site. With the aforementioned procedures, it is preferable to prevent intraoperative displacement of the catheter by checking the direction of the linea alba and by maintaining the solution used during surgery.

After having washed each wound sufficiently with normal saline solution, the skin is sutured not to create a dead space, with a subcutaneous suture being used as much as possible. In our hospital, an intradermal suture with a monofilament absorptive suture material is performed in order to reduce a risk of subsequent cutaneous infection.

13.2 Postoperative Care

Treatment procedures (a wound was sterilized and coated with a gauze) deviating from wound healing were widespread until a while ago. Currently, preparation of the wet environment and maintenance of the condition without infection are thought to be critical for wound healing. For PD catheter, it is important to maintain the rest of the exit site. With that in mind, it is ratio-

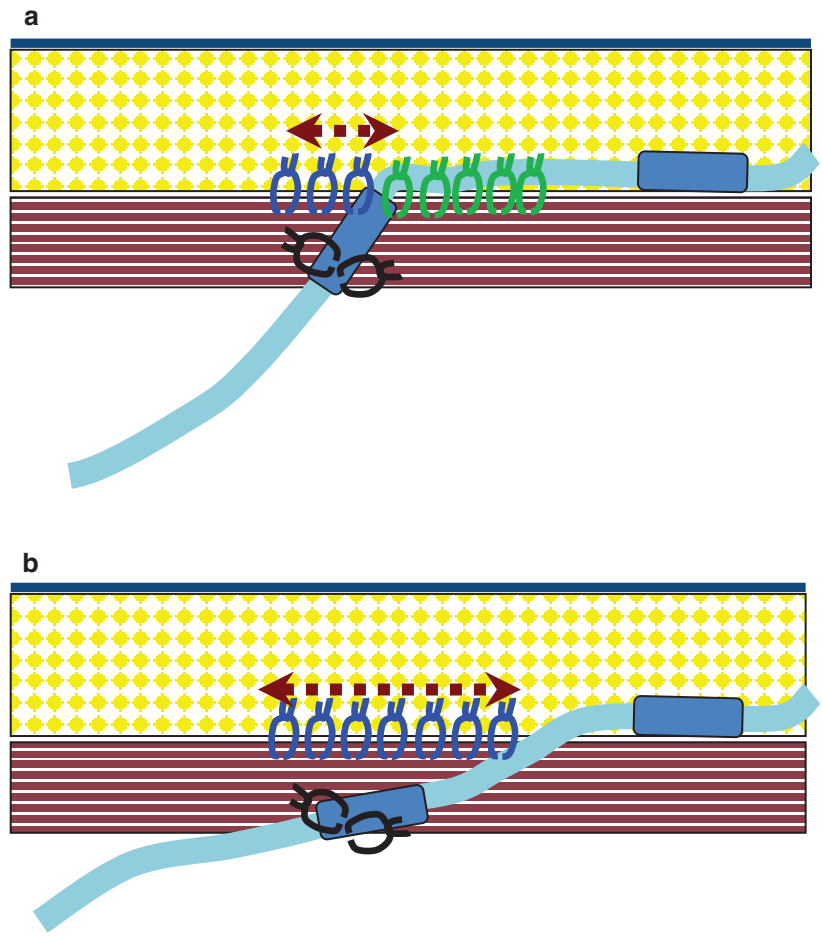


Fig. 13.4 Difference with the way of the catheter

nal to coat the wound with a dressing film in an operating room as a clean field to shut off the outside world. It is not reasonable for wound healing to coat the wound with gauze and perform disinfection regularly given cytotoxicity.

13.3 Other Procedures Associated with PA

13.3.1 Stepwise Initiation of PD using Moncrief and Popovich technique: SMAP

Moncrief et al. reported a method that a small incision was put during the introduction but no exit site was created during PD catheterization (Moncrief et al. 1993a, b, c). In Japan, the stepwise initiation of PD using Moncrief and Popovich technique (SMAP) introduced by Kubota et al. has been widely used (Kubota 2002). This surgical form provides many benefits such as reduced tunnel infection, adjustment of the initiation time of dialysis, shortened hospitalization, and prevention of early leak of dialysis fluid. We describe this effective surgical form for patients who want to undergo PD and have enough time before introduction.

This surgical form is the same as routine surgery since there is insertion of a catheter in the abdominal cavity and implantation of an external cuff before the anterior sheath of the rectus abdominis muscle. During traditional surgery, an exit site is created using a tunneler. However, in this surgical form, no exit site is created and the catheter is implanted subcutaneously.

First, heparin is injected into a catheter to prevent coagulation in the lumen after having

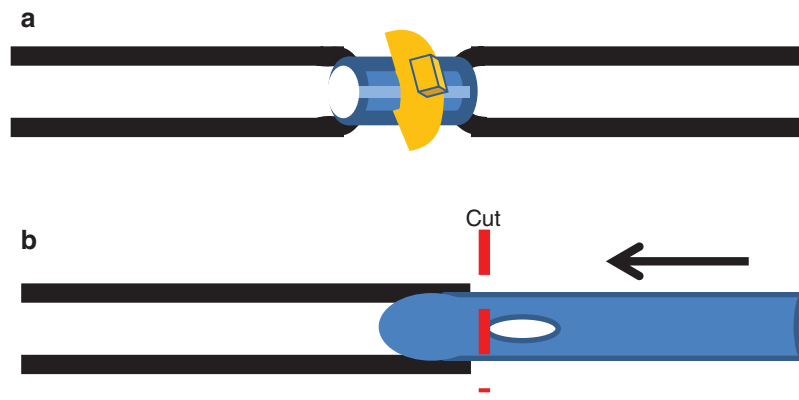


Fig. 13.5 PD catheter obstruction method

placed an external cuff (there is no conclusive evidence regarding how this procedure is effective). Second, the catheter is occluded in order to prevent subcutaneous outflow of ascites, which can be achieved by several methods.

One method of avoiding this outflow is to cut the portion of the edge of the PD catheter (approximately 1 cm) longitudinally. It is coated at the planned exit site of the catheter and tightened with a sterilized banding band (Fig. 13.5a). The catheter is implanted subcutaneously using a tunneler under this condition. At that time, the banding band should be placed at the future exit site.

On the introduction of PD, a small incision is put at the planned exit site under local anesthesia. After having held the banding band from here and isolated from the surrounding area, we removed the catheter from the body. When the banding band is cut, it is important to be attentive regarding potential damage to the PD catheter and to cut the band over the coated site. A titanium adapter is attached afterwards.

Alternatively, the PD catheter can be introduced subcutaneously using tunneler and finally heparin is enclosed. Sterilized Nelaton catheter 10Fr (no aperture) is inserted and the excessive part is cut off afterwards (Fig. 13.5b). In this method, the planned exit site cannot be marked though similarly it is grubbed under local anesthesia.

The advantages of the SMAP method are mentioned above. There are disadvantages of this method, such as fibrin formation and obstruction in the catheter when the exit site is created. In many cases, they are often removed easily by aspiration and pressurization infusion of normal saline solution.

13.3.2 Peritoneal Wall Anchor Technique: PWAT

It is a procedure that was developed in order to reduce displacement of the PD catheter in the abdominal cavity. In this procedure, the above-mentioned catheter is thoroughly inserted along the abdominal wall into the Douglas pouch. However, as the effectiveness is poor by peritoneal wall anchor technique (PWAT) (Fukasawa et al. 2003, 2004, 2006) alone; this method is always performed in addition to the above-mentioned procedures secondarily.

It is the same as standard surgical operation until catheterization. After having opened a small hole at the peritoneum, the site of PWAT is determined. It is set approximately 4–5 cm caudally since this location may damage the bladder. By inserting an endoscope (or cystoscopes) from the site, it is important to confirm the planned site of PWAT using a source of light from the intra-abdominal cavity. The inferior epigastric artery can be thereby confirmed and non-run site is marked not to damage it, and then a small incision is placed on the site to expose the rectus muscle. (Video 13.2) PWAT applicator is inserted to the abdominal cavity (Fig. 13.6a) to place it on the planned site along the anterior abdominal wall. (Video 13.3) A 20G PTCD needle is punctured on the site from the direction of the abdominal cavity

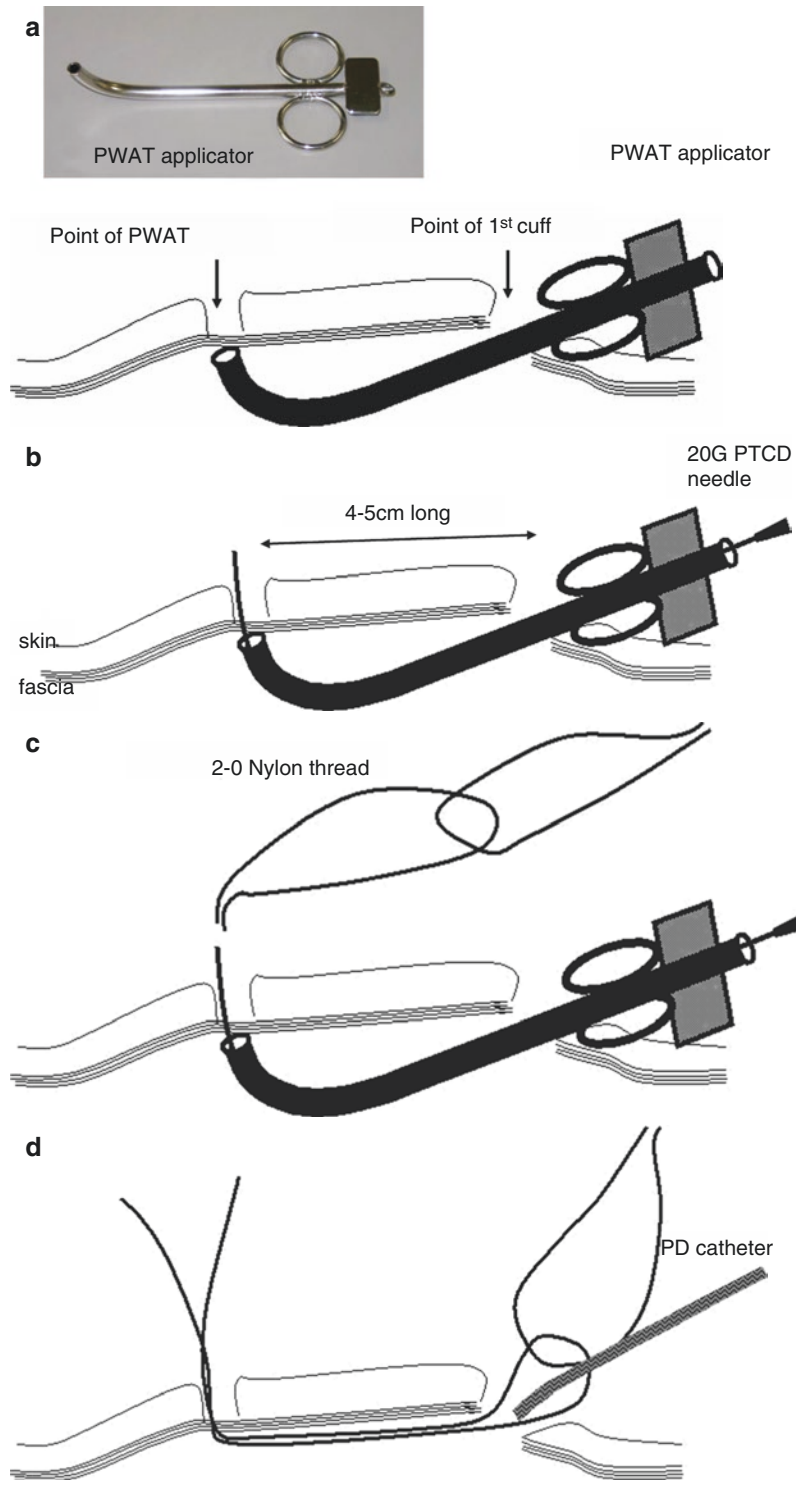
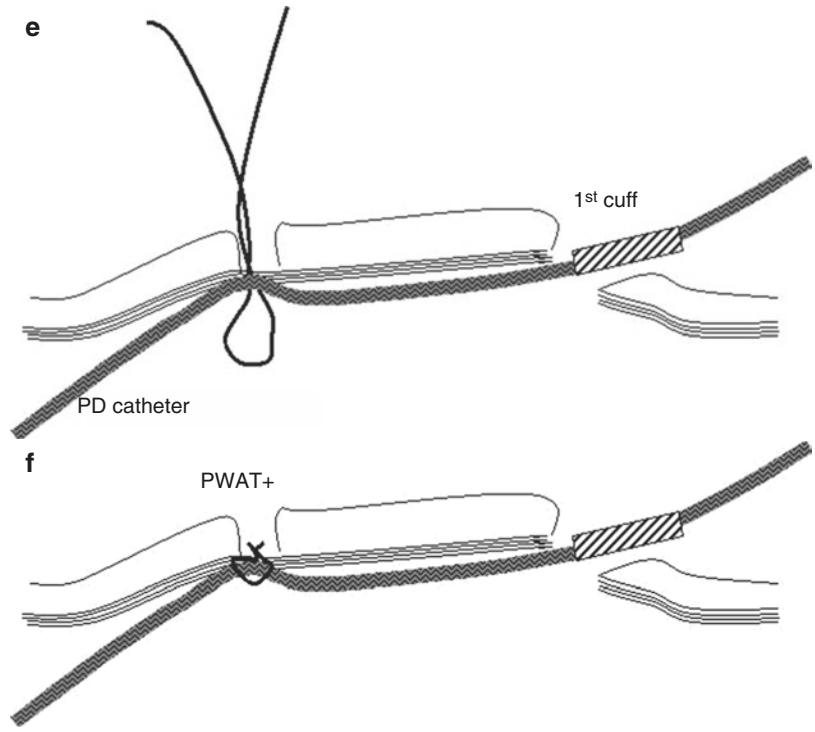


Fig. 13.6 Procedure of PWAT

Fig. 13.6 (continued)



to the anterior sheath of rectus muscle (Fig. 13.6b). (Video 13.4) After having pulled a stylet, one of two 2-0 nylon threads is inserted into the sheath (Fig. 13.6c). (Video 13.5) PWAT applicator is pulled up to derive introduced nylon thread outside the peritoneum. This thread has an important role in deriving the nylon suture through the abdominal cavity. (Video 13.6) After having inserted the PD catheter into the loop-formed nylon suture, it is then inserted into the Douglas pouch, as mentioned above (Fig. 13.6d, e) (Video 13.7). The PD catheter is thereby suspended on the anterior abdominal wall. As it falls into the abdominal cavity, even if it is sutured in a manner as described above, it is inserted by the same pinholing. After having greatly taken one stitch in the anterior sheath, it is sutured loosely. (Video 13.8) It is important to suture it loosely due to risk of the damaged catheter when it is tightened and the rectus muscle is constructed due to risk of ileus when the intestinal tracts are inserted between the catheter in the abdominal cavity (insertion site and PWAT site) and anterior peritoneal wall.

This procedure is expected to reduce the incidence of malposition of catheter by PWAT, which shortens the effective movable length in the abdominal cavity.

13.3.3 Non-Stylet Insertion Technique

Although PD catheterization using a stylet is common, the catheter with a straight tip can be inserted easily without a stylet. In Japan, the usefulness of this method has been reported (Kubota et al. 2008; Okamaoto et al. 2010) because a catheter of 65–80 cm that recently has been used commonly may become contamination at the distal portion of such a long stylet. In addition, the method using the conventional stylet may damage the abdominal organs because of the stylet that is projected from the catheter tip. Therefore, we consider that this non-stylet insertion technique is safer and that it should become standard during surgery.

Similar procedures are used until opening of a small hole on the abdominal cavity. Using a retractor and Pean forceps, elevation of the abdominal wall towards 6:00 is required for insertion. This procedure creates a space by isolating the intestinal tract from the abdominal wall. By inserting the catheter here, as is done while sliding the body surface, it can be inserted into the Douglas pouch, such as while sliding to the back of the bladder (Video 13.9). It is important to insert the catheter by considering that a catheter is put on the body surface via the small hole into the abdominal cavity, and not an image to insert a catheter in the deep place (Douglas pouch) in the abdominal cavity from the hole. In patients with severe obesity, a catheter tends to be inserted into the standing position, which results in difficulties in insertion. In such a case, it is better to try to insert a normal stylet technique.

It is possible to judge whether the catheter has been inserted in a good position by confirming whether injected normal saline solution can be discharged consecutively.

13.4 Final Comments

Implantation of a PD catheter is an important factor in judging whether subsequent PD is performed smoothly. An early leak of dialysis fluid and the early displacement of a catheter is caused by inefficient surgical skills. According to previous studies, approximately 8% of patients abandon continuation of PD due to abnormalities in solution changes.

For a medical worker, we have a duty to avoid it that not being able to continue PD for malposition though a patient hopes for continuation and shift to hemodialysis (HD). Treatment for displacement, which will be discussed later, may rarely be necessary if the insertion is performed carefully.

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Peritoneal Dialysis Prescription

14

Mi Jung Lee and Dong-Ryeol Ryu

Peritoneal dialysis (PD) has a variety of advantages over hemodialysis (HD), such as autonomy and flexibility. If an individual patient on PD has a deep understanding and sufficient experience of PD, PD prescription can be modified by his or her own will and purpose on a daily basis. However, many PD patients have trouble with adapting themselves to changing their residual renal function (RRF) and dialysis prescription because of their lack of insight for the importance of PD prescription and adherence to it. As a result, they often encounter various medical problems such as volume overload, electrolyte imbalance, or uremic syndrome, which could lead to fatal conditions. Therefore, we should educate and guide PD patients well on PD prescription and stick to it for themselves to avoid those difficulties and the way to solve their ordinary but potentially serious problems. In addition, we should do our best to improve quality of life as well as the survival rate and other medical outcomes by trying to guarantee autonomy and flexibility of PD patients.

The importance of personalization has been emphasized across the medicine in modern era. In particular, prescription of PD should be tailored to the medical condition and preference of patients. Compared with HD, PD patients more often participate in the decision process of treatment and perform dialysis by themselves. Therefore, comprehensive aspect regarding both objective indicators and subjective consideration of patients is mandatory for us to prescribe PD optimally. In this chapter, we will look at prime determinants for optimal PD, PD prescription at first, and strategies of prescription adjustment for optimal PD during maintenance of PD.

14.1 Factors for Determining PD Prescription

Providing optimal dialysis is the primary goal of treatment in patients undergoing PD, which is ultimately associated with clinical outcomes. For obtaining "optimal PD dose," we first need to identify what the important issues are for determining optimal PD dose and understand what's the meaning of minimum dialysis dose that should be performed.

"Adequate" and "optimal" dialysis has been differently defined (NKF-DOQI 1997). An "effective dose" is that which achieves its stated goal. That goal is some form of outcome measure(s) and could be determined by the patient, provider, payer, regulator, or a combination of these parties. At the lower extreme is the "minimal effective dose." In certain circumstances this may be interpreted as

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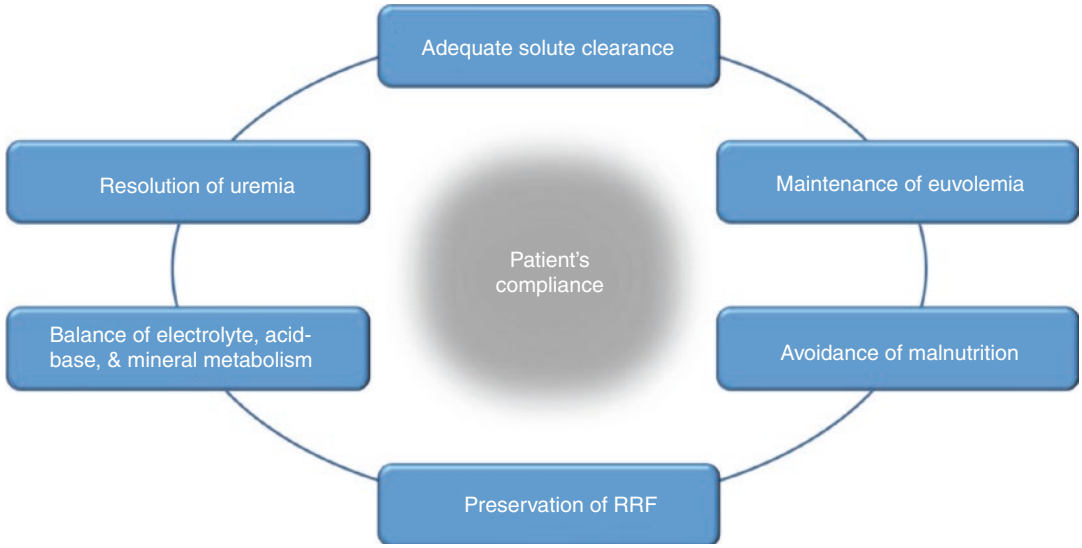


Fig. 14.1 The essential indicators for determining optimal dialysis. RRF, residual renal function

"adequate." At the other extreme is the "maximal effective dose," the dose above which there are no additional benefits. For HD and PD, the maximal effective dose is not known. Somewhere between these extremes is the "optimal dose," the dialysis dose above which the incremental clinical benefit does not justify the patient burden or financial costs. There are key indicators for determining whether delivered dialysis therapy to patients is optimal or not (Fig. 14.1).

14.1.1 Adequate Solute Clearance

In dialysis patients, solute clearance is determined by clearance derived from both dialysis therapy and RRF. When we examined solute clearance of dialysis patients, we have to consider total solute clearance, the sum of clearance delivered by dialysis and RRF. In the early period of dialysis, most patients are likely to have sufficient RRF, which lead to significant contribution to total solute clearance. As dialysis duration is prolonged, RRF tends to decline. Therefore, patients may require more solute clearance via dialysis, and prescribing greater dose of dialysis may be necessary over time. Previous clinical studies and guidelines indicated a minimum or "adequate" solute clearance target. If this solute clearance target is achieved, further adjustment of dialysis dose may depend on various essential indicators for optimal dialysis.

14.1.1.1 Solute Clearance Derived from PD

For the estimation of solute clearance by PD, there are two commonly used methods: the weekly Kt/Vurea and the creatinine clearance normalized to body surface area (Chatoth et al. 1999). Using the Kt/Vurea is preferred more to the creatinine clearance, since it has been widely mentioned in the various clinical practice guidelines, including the 2006 Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (Peritoneal Dialysis Adequacy Work Group 2006), the 2005 European Best Practices Guidelines (EBPG) (Dombros et al. 2005a), and the 2006 International Society for Peritoneal Dialysis (ISPD) guidelines/recommendations (Lo et al. 2006).

The Kt/Vurea is consisted of daily peritoneal urea clearance (Kt) and volume of distribution of urea (Vurea). The daily peritoneal urea clearance (Kt) is the value for the amount of 24-h drained dialysate multiplied by the ratio of the urea concentration in the drained dialysate to that in the plasma (dialysate/plasma urea, D/P urea).

Compared with partial collection of dialysate or kinetic modeling programs, a 24-h collection of dialysate has been known to be more accurate (Burkart et al. 1993).

$$\text{Peritoneal Kt} = \frac{\text{Dialysate Urea Concentration}\left(\text{mg/dL}\right)}{\text{Plasma Urea Concentration}\left(\text{mg/dL}\right)} \times \text{24-h PD Drain Volume}\left(\text{L}\right)$$

$$\text{Peritoneal Kt/V} = \frac{\text{Peritoneal Kt}\left(\text{L}\right)}{\text{Urea Volume of Distribution}\left(\text{L}\right)}$$

The volume of distribution of urea (Vurea) is approximately equal to body water and can be estimated by proposed equations. One should estimate V in adults by either the Watson or Hume equation in adults and by the Mellits-Cheek method in children (Table 14.1) (NKF-DOQI 1997; Peritoneal Dialysis Adequacy Work Group 2006).

Although actual body weight was recommended to use in 1997 K/DOQI guideline (NKF-DOQI 1997), the use of the patient's ideal or standard (rather than actual) weight should be considered in the calculation of V in the subsequent guideline (Peritoneal Dialysis Adequacy Work Group 2006). The reason for using the ideal body weight (IBW) is that actual body weight results in underestimation of Kt/Vurea in large patients or overestimation of Kt/Vurea in malnourished or small patients (Tzamaloukas et al. 1993; Tzamaloukas et al. 1998). Although various equations for calculating IBW have been suggested, the results derived from those equations are similar; thus any one of them may be used to estimate IBW (Pai and Paloucek 2000).

The Devine formula in adults is as follows:

$$\text{Male IBW} = 50\,\text{kg}\left(110\,\text{lb}\right) + 2.3\,\text{kg}\left(5.1\,\text{lb}\right) * \left(\text{height}\left(\text{cm}\right)/2.54 - 60\right)$$

$$\text{Female IBW} = 45.5\,\text{kg}\left(100\,\text{lb}\right) + 2.3\,\text{kg}\left(5.1\,\text{lb}\right) * \left(\text{height}\left(\text{cm}\right)/2.54 - 60\right)$$

14.1.1.2 Solute Clearance Derived from RRF

If PD is initiated, there are many patients having still significant RRF, a urine volume of >100 mL/day (Peritoneal Dialysis Adequacy Work Group 2006). At first, they can be started with low-dose PD, and then the peritoneal Kt/V could be increased incrementally so the combined value of weekly peritoneal Kt/V and renal Kt/V (or total Kt/V) does not fall below the target level (NKF-DOQI 1997). With the incremental initiation approach, frequent measurement of RRF will be necessary to assure that total delivered solute removal does not drop below targets (NKF-DOQI 1997). Similar to calculation of peritoneal Kt/Vurea,

Table 14.1 Equations for estimating the volume of distribution (V)

Watson method	
Men	V (L) = 2.447 + 0.3362*Wt (kg) + 0.1074*Ht (cm) - 0.09516*Age (y)
Women	V (L) = −2.097 + 0.2466*Wt (kg) + 0.1069*Ht (cm)
Hume method	
Men	V (L) = −14.012934 + 0.296785*Wt (kg) + 0.192786*Ht (cm)
Women	V (L) = −35.270121 + 0.183809*Wt (kg) + 0.344547*Ht (cm)
Mellits-Cheek method for children	
Boys	V (L) = −1.927 + 0.465*Wt (kg) + 0.045*Ht (cm), when Ht is ≤132.7 cm
	V (L) = −21.993 + 0.406*Wt (kg) + 0.209*Ht (cm), when Ht is >132.7 cm
Girls	V (L) = 0.076 + 0.507*Wt (kg) + 0.013*Ht (cm), when Ht is ≤110.8 cm
	V (L) = −10.313 + 0.252*Wt (kg) + 0.154*Ht (cm), when Ht is >110.8 cm

the 24-h urine collection is necessary for calculation of renal Kt/Vurea and is usually performed at the same day of 24-h dialysate collection.

$$\text{Renal Kt} = \frac{\text{Urine Urea Concentration}\left(\text{mg / dL}\right)}{\text{Plasma Urea Concentration}\left(\text{mg / dL}\right)} \times \text{24-h Urine Volume}\left(\text{L}\right)$$

$$\text{Renal Kt / V} = \frac{\text{Renal Kt}\left(\text{L}\right)}{\text{Urea Volume of Distribution}\left(\text{L}\right)}$$

Although 24-h urine collection may be cumbersome in the everyday clinical practice, it should not be ignored. If we want the patient not to perform more dialysis than he or she actually requires, 24-h urine needs to be collected regularly until RRF disappears and solute clearance from RRF should be added up to peritoneal solute clearance when calculating total solute clearance. Thus, in the perspective of individualized care medicine, we suggest that PD dose should be changed and personalized according to RRF, volume status, uremic symptoms, and other factors in a specific PD patient.

14.1.1.3 Target of Total Solute Clearance

Continuous Ambulatory PD (CAPD)

In CAPD patients, the 2006 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guideline (Peritoneal Dialysis Adequacy Work Group 2006), the 2005 EBPG (Dombros et al. 2005a), and the 2006 ISPD guidelines/recommendations (Lo et al. 2006) suggest a total weekly Kt/Vurea ≥1.7 as the minimum target of solute clearance. Previous randomized study clearly demonstrated that patients with Kt/Vurea <1.7 were significantly associated with higher erythropoiesis-stimulating agent use and more uremic symptoms than those with Kt/Vurea of 1.7–2.0 and >2.0 (Lo et al. 2003). Furthermore, targeting a Kt/Vurea higher than 1.7 did not show additional improvement in other randomized controlled study (Lo et al. 2003; Paniagua et al. 2002), securing a total weekly Kt/Vurea ≥1.7 as the minimum target in CAPD patients. Detailed review of evidences would be described in "Chapter 5: Kinetic Modeling and Adequacy in Peritoneal Dialysis."

Automated PD (APD)

In APD patients, the 2006 K/DOQI guideline recommended a total weekly Kt/Vurea ≥1.7 as the minimum target of solute clearance (Peritoneal Dialysis Adequacy Work Group 2006). However, this recommendation is actually based on the results of CAPD patients. Although some patients require midday exchange ("wet abdomen" in daytime), a number of APD patients performed only overnight exchange with "dry abdomen" in daytime and did not undergo dialysis during 24 h.

Example of Total Solute Clearance Calculation

A 66 kg male patient undergoes CAPD, and these are the results of 24-h peritoneal dialysate and urine collection to calculate total weekly Kt/Vurea. The steps for calculating total Kt/Vurea is as follows (Fig. 14.2):

24-h drained PD effluent	
Drained volume	7.0 L
Dialysate urea nitrogen concentration	48 mg/dL
Plasma urea nitrogen concentration	50 mg/dL
24-h urine	
Urine volume	0.6 L
Urine urea nitrogen concentration	230 mg/dL
Plasma urea nitrogen concentration	50 mg/dL

In this example, weekly peritoneal Kt/Vurea of 1.2 may be suboptimal, if this patient is anuric. However, because RRF provides renal Kt/Vurea of 0.5 in this patient, minimal target of solute

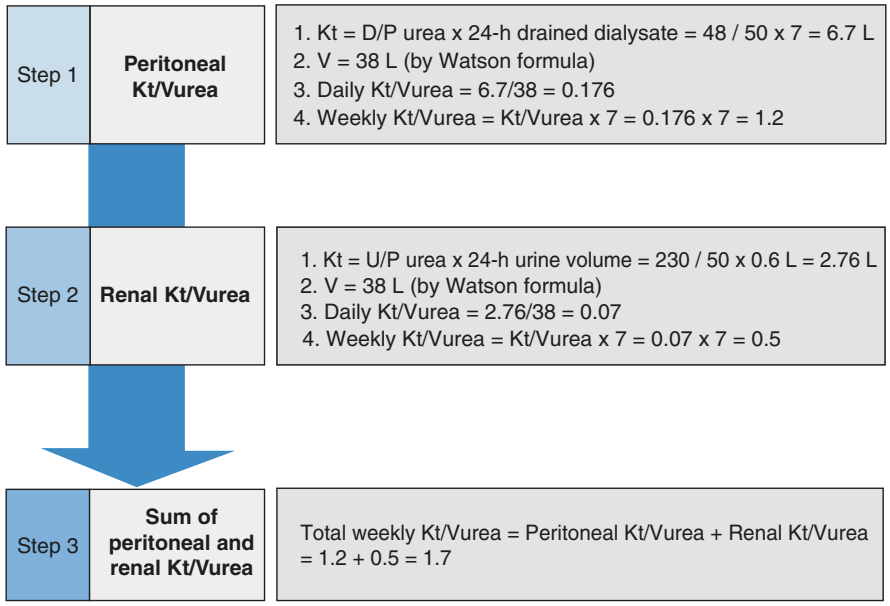
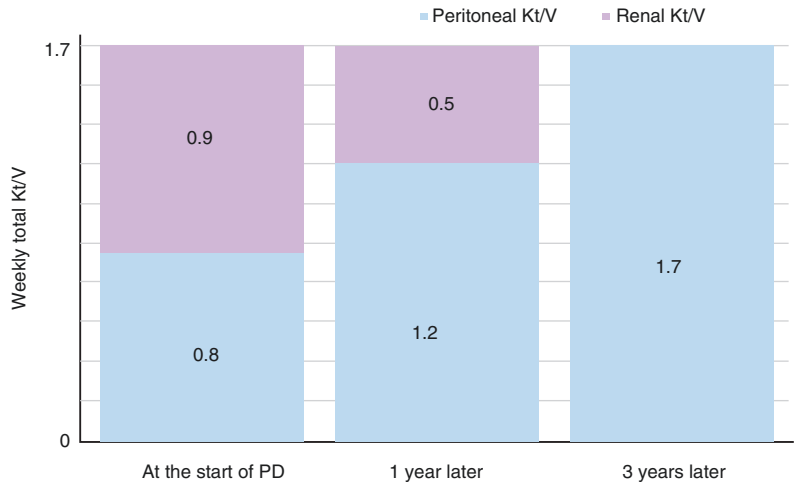


Fig. 14.2 Calculation of total weekly Kt/Vurea

clearance is considered to be achieved. Again, total weekly Kt/V is peritoneal Kt/V plus renal Kt/V; we should adjust the PD prescription as RRF declines for achieving target minimum Kt/V of 1.7 (Fig. 14.3).

14.1.2 Maintenance of Euvolemia

Volume overload is significantly implicated with adverse cardiovascular disease including congestive heart failure, left ventricular hypertrophy, and hypertension; therefore, it is important to monitor ultrafiltration volume, dry weight, sodium intake, and other clinical assessments of volume status (Peritoneal Dialysis Adequacy Work Group 2006). In addition, several studies have indicated that volume overload is closely implicated with mortality in PD patients, irrespective of symptom and signs of volume overload (Blake 1997). Although there was no published evidence, the EBPG committee suggested an arbitrary target ultrafiltration goal of 1.0 L/day to increase the awareness of the maintenance of a euvolemic state (Dombros et al. 2005a). Afterward, the work group for the clinical practice guidelines on PD adequacy of Canadian Society of Nephrology suggested the more detailed guidelines on the management of hypervolemia. They suggested that a low net daily peritoneal ultrafiltration volume (<750 mL in anuric patients or <250 mL in patients with RRF) would be an indication for careful evaluation of volume status (looking for evidence of volume overload) and of dietary fluid and food intake (looking for evidence of insufficient intake or malnutrition) (Blake et al. 2011). In contrast, some experts did not suggest a minimum target of ultrafiltration volume, because aggressive ultrafiltration may facilitate RRF decline. In accordance with the 2006 NKF-K/DOQI guidelines (Peritoneal Dialysis Adequacy Work Group 2006), we propose that optimal amount of ultrafiltration should be tailored by individual volume status and blood pressure levels rather by arbitrary goal. In addition, we need to monitor the nutritional status such as the amount of food and water intake in patients without any sign of volume overload in spite of an ultrafiltration volume of <1.0 L/day.



Year	Age	Sex	V (L)	BUN (mg/dL)	Urine volume (L)	Urine UN (mg/dL)	Weekly renal Kt/V	Drained volume (L)	Dailysate UN (mg/dL)	Weekly peritoneal Kt/V	Weekly total Kt/V
At the start of PD	50	Male	38.1	50	1	230	0.8	5	48	0.9	1.7
1 year later	51	Male	38.0	50	0.6	230	0.5	7	48	1.2	1.7
3 year later	53	Male	37.8	50	0	0	0	9.5	48	1.7	1.7

Fig. 14.3 Contribution of renal solute clearance to achieve a total weekly Kt/V = 1.7 in patients with decreasing RRF. In this imaginary patient, if we assume the values of BUN, urine and dialysate urea nitrogen are not changed during the 3-year follow-up period, weekly renal Kt/V decreases according to the reduction in urine volume; solute clearance should be replenished by the increment of the dose of PD for achieving Kt/V of 1.7, and PD effluent volume should be increased from 5 L/day at the start of PD to 9.5 L/day at 3 years later. As a result, the patient who could achieve target Kt/V with 2 PD exchanges should increase the number of PD exchanges up to 4 times a day at 3 years later. Volume (V) of urea distribution is calculated by Watson formula. UN, urea nitrogen

14.1.3 Avoidance of Malnutrition

Nutrition is an important predictor of clinical outcomes in dialysis patients whether on HD or on PD. A large number of factors have been identified as the causes of malnutrition in dialysis patients, which include anorexia, uremia derived from insufficient dialysis, advanced age, chronic inflammation, metabolic acidosis, impaired anabolism, gastrointestinal or medical comorbidities, and socioeconomic problems (Blake et al. 2011). Notably, in PD, protein loss to dialysate may happen, resulting in increased risk of malnutrition. Estimated amount of protein and amino acid loss is reported to be up to 15 g and 2–4 g per day, respectively (Bergstrom et al. 1993). Therefore, assessment of nutritional status should be performed as a routine practice in PD patients. The EBPG recommended to use subjective global assessment (SGA), protein intake derived from the protein equivalent of nitrogen appearance (PNA) or dietary recall, and an assessment of protein nutrition in PD patients every 6 months (Dombros et al. 2005b). Multidisciplinary team including physician, nurse, dietician, social worker, and family members is necessary for comprehensive assessment and effective management of malnutrition. If malnutrition of the patients is likely to be associated with underdialysis, the adherence of the patients to the PD prescription and the delivered dose of PD

should be reevaluated at the time and adjusted to a sufficient level.

14.1.4 Resolution of Uremia

Routine evaluation for uremia in PD patients is required for determining optimal dialysis. Patients may be asked if they have intractable anorexia, vomiting, or itching for the assessment of uremic symptoms. In addition to uremic symptoms, pericardial effusion, confusion suggestive of uremic encephalopathy, and gum or mucosal bleeding are also indications to deliver more dialysis dose even the minimum target Kt/Vurea of 1.7 is achieved.

14.1.5 Balance of Electrolyte, Acid-Base, and Mineral Metabolism

Prevention of hyperkalemia is crucial in dialysis patients. Because PD solution does not contain potassium and potassium is constantly removed by diffusion, hyperkalemia is less likely to occur in PD patients who maintain adequate dialysis. Therefore, PD patients with severe hyperkalemia should be evaluated whether they had drugs causing hyperkalemia including renin-angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, nutritional supplements, and herbal remedies or whether they skip PD exchanges. Metabolic acidosis has been regarded to induce harmful complications such as malnutrition, inflammation, and mineral bone disease (Kraut and Kurtz 2005). However, only 25% of CAPD patients achieve normal serum bicarbonate value by using a lactate solution (Feriani 1996). Although there is no consensus regarding the optimal serum bicarbonate levels in PD patients, individualizing PD solution using different buffers may be helpful to correct metabolic acidosis (Feriani et al. 1997; Feriani et al. 2004). To date, there is growing attention to mineral metabolism and patient outcome in PD patients (Noordzij et al. 2006). Standard solution containing 3.5 mEq/L calcium may be associated with hypercalcemia especially in patients with high-dose calcium-based phosphate binders. Even though optimal calcium concentrations of PD solution remain unclear, adjusting dialysis solution and phosphate binders is necessary in patients with hypo-/hypercalcemia.

14.1.6 Preservation of RRF

RRF is independently associated with clinical outcomes in dialysis patients. It is recognized that PD preserves RRF better than HD at the initiation of dialysis. RRF promotes urea or creatinine clearance, helping to achieve target Kt/Vurea. If a patient has a creatinine clearance of 1 mL/min and weekly creatinine clearance reaches 10 L/week, it is a very considerable value which we should do our best to preserve. RRF also increases fluid excretion, leading to mitigation of adverse effect derived from chronic volume overload (Bragg-Gresham et al. 2007). Furthermore, greater clearance of middle molecule such as β2-microglobulin and indoxyl sulfate (Bammens et al. 2003), better phosphate and anemia control (Penne et al. 2011), and increased dietary protein and calorie intake representing better nutritional status (Wang et al. 2001) were significantly associated with RRF. To preserve RRF, all PD patients are indicated to take renin-angiotensin receptor blockers, even they are not hypertensive. Two randomized controlled study demonstrated that angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACE inhibitor) preserved RRF in PD patients (Li et al. 2003; Suzuki et al. 2004). In addition, although blood pressure requires strict control, excessive ultrafiltration should be avoided due to harmful effect of volume depletion (Table 14.2).

14.1.7 Patient's Adherence to the Dialysis Prescription

Since PD is a home-based therapy, it usually requires a daily performance of dialysis and clinical assessment of patient's condition by a patient and/or a caregiver. Therefore, adherence to therapy is a critical issue in PD. However, according

Table 14.2 Clinical advantages of RRF preservation and treatment strategies

Clinical advantages of RRF preservation
Acceleration of achieving euvolemia via renal clearance of solute and fluid
Better blood pressure control
Stabilization of left ventricular hypertrophy
Greater clearance of middle molecule including β2-microglobulin
Better phosphate control
Better anemia control
Improvement of nutritional status
Improvement of quality of life
Strategies to preserve RRF
Strict blood pressure control
Use of renin-angiotensin receptor blockers, irrespective of hypertension
Avoidance of nephrotoxic drugs
Avoidance of excessive ultrafiltration, resulting in volume depletion

to a systematic review investigating nonadherence in PD patients, rates of missing PD exchanges or sessions were reported to be 2.5–53%, and shortening of cycles was reported in 4–15% of patients (Griva et al. 2014). Moreover, over half of the studies (13 of 20 studies, 65%) indicated the rates of nonadherence to PD regimen to be higher than 20%. Previous studies have demonstrated that non-compliance to dialysis therapy increased the risk of mortality and hospitalization in PD patients (Bernardini et al. 2000; Bernardini and Piraino 1998). In this regard, clinician should pay attention to patient's adherence and adjust dialysis regimen.

14.2 Prescribing PD at the Start of Dialysis

Each of the patients starts PD for a wide variety of reasons. PD prescription should be tailored in consideration of these reasons and circumstances. However, in real world, it is impossible to fulfill all of the aforementioned indicators for optimal dialysis at the first prescription of PD. For practical application, we categorized patients into three groups according to the chronicity of kidney disease and planned start of dialysis, (1) acute PD in patients with acute kidney injury (AKI), (2) urgent start of PD in newly diagnosed chronic kidney disease (CKD) patients, and (3) planned start of PD in known CKD patients, and suggest empirical prescription of the first PD. Nevertheless, we should keep in mind that these empirical prescriptions may not be appropriate for all patients and prescription can be changed for individual goal of optimal dialysis.

14.2.1 Acute PD in Patients with AKI

In the management of AKI, there are few data comparing the effect on mortality between PD and extracorporeal blood purification therapies, such as intermittent HD and continuous renal replacement therapy. Recent systematic review showed that the mortality rate of acute PD is at least comparable with continuous or intermittent HDs (Chionh et al. 2013). Although the application of PD to AKI patients has been overlooked particularly in the developed countries, PD should be considered as a relevant option having several advantages in the management of AKI. First, due to continuous nature of modality, PD can be utilized in hemodynamically compromised patients. Continuous and slow removal of solutes and fluid permit large amounts of fluid removal without hemodynamic instability. PD enables gradual removal of uremic toxin and slow correction of acid-base and electrolyte imbalance. High-volume PD can attain at least 2 L of ultrafiltration during 24 h and stable value of serum urea, creatinine, bicarbonate, and potassium concentrations within 3–4 days in AKI patients (Gabriel et al. 2007; Ponce et al. 2012a). Technically, insertion of PD catheter can be easily performed even in the bedside and there is no need for temporary vascular access and the use of anticoagulants. Therefore, patients with bleeding diathesis or contraindicated to systemic anticoagulation, including trauma, operation, and internal bleeding might have benefit from PD. Furthermore, PD is widely accessible, which has less constraint such as dialysis machinery, water or power supply.

Table 14.3 Relative indication and contraindications for PD in AKI patients

Indications
Hemodynamically compromised patients
Patients with bleeding diathesis
Patients who have contraindications to systemic anticoagulation
Patients who do not have available vascular access
Patients with clinically significant hypothermia and hyperthermia
Refractory congestive heart failure
Contraindications
Recent abdominal and/or cardiothoracic surgery
Abdominal wall or peritoneal infection
Diaphragmatic peritoneal-pleural connections
Severe respiratory insufficiency
Life-threatening hyperkalemia
Life-threatening volume overload
Severe hypercatabolism or malnutrition
Pregnancy

14.2.1.1 Patients Selection

There are few absolute indication and contraindication for PD in AKI, if patients require renal replacement therapy and there were no other modalities except PD. Patients should be carefully selected by considering the following relative indications and contraindications (Table 14.3).

Although solutes and fluid are removed slowly in PD, PD can be an effective modality for the management of hyperkalemia and volume overload by adjusting dwell volume, time, number of exchanges, or dialysate tonicity (Cullis et al. 2014).

14.2.1.2 Peritoneal Access

For acute PD, the flexible Tenckhoff catheter is preferred to the rigid catheter. Rigid catheter is easily inserted at the bedside under local anesthesia, but several disadvantages such as high risk of infection, bowel perforation, and catheter dysfunction exist (Wong and Geary 1988; Chadha et al. 2000). Since the rigid acute PD catheter does not have cuff, it is associated with greater risk of bacterial migration and peritonitis and should be removed within 72 h (Wong and Geary 1988). For mechanical reasons, movement of patients is restricted and the risk of bowel perforation and catheter dysfunction increased unless colon evacuation persists well (Ash 2004). In contrast, the flexible Tenckhoff catheter is usually inserted in the operating room by a surgeon. However, recently, many nephrologists have inserted the Tenckhoff catheter at the bedside using fluoroscopy or peritoneoscope. This cuffed permanent catheter has several benefits over the rigid catheters (Wong and Geary 1988; Chadha et al. 2000). The risk of peritonitis and bowel perforation is lower and patients feel more comfortable. This catheter also assures a good immediate catheter function and high dialysate flow rate.

14.2.1.3 Techniques

Similar to chronic PD, there are various techniques in acute PD according to the use of cycler and patterns of inflow and outflow (Chionh et al. 2009). Manual PD requires a lot of nursing effort, whereas the use of cyclers can decrease nursing labor. A cycler also makes the number of interruptions or breaks to be reduced, because setting of dialysate is usually preceded at the start of session. Patterns of inflow and outflow are determined by demand of fluid and solute removal.

Acute Intermittent PD (AIPD)

This technique is widely applied to AKI patients, which consists of frequent exchanges with short dwell time, an inflow volume of 1–3 L, and a dialysate flow rate of 2–6 L per hour (Ponce et al. 2012a; Cullis et al. 2014; Chionh et al. 2009; Passadakis and Oreopoulos 2003). Each session, which lasts 12–24 h, is intermittently (2–3 sessions a week) occurred. Because of its intermittent nature, AIPD may provide inadequate fluid and solute clearance. This technique can be performed manually or using an automated cycler.

Chronic Equilibrated PD (CEPD)

CEPD is similar to chronic ambulatory peritoneal dialysis (CAPD), which has 4 exchanges a day with inflow volumes of 2 L and dwell times of 4–6 h (Steiner 1989). In accordance with CAPD, this technique provides stable fluid and solute clearance, but adequacy may be insufficient. However, due to long dwell times, middle molecule clearance may be higher than other

techniques with short dwells. Not only manual exchange but an automated cycler can be utilized in this technique.

Tidal PD (TPD)

The key features of TPD are "tidal" drain and fill volume. Initial inflow volume (2–3 L) infused to the peritoneal cavity; then, a constant tidal volume is drained (tidal drain volume, usually 10–50%, 0.3–1.5 L) and replaced with fresh dialysate (tidal fill volume). The peritoneal cavity always contains the reserved volume across the whole session (Agrawal and Nolph 2000). Since TPD requires rapid and multiple exchanges with large volume dialysate, it needs automated cycler often and relatively higher costs. Theoretically, TPD improves solute clearance that reserved dialysate and continues to increase solute and water removal during inflow and outflow time. But increased solute clearance has not consistently confirmed in chronic dialysis patients. In AKI patients, one randomized crossover study showed that urea clearance of TPD was significantly higher than that of CEPD with 2 L of tidal fill volume (Chitalia et al. 2002). Another advantage of TPD is the relief of drainage problems including inflow/outflow pain and slow drainage, because PD catheter does not irritate the peritoneal membrane directly (Dombros et al. 2005c). When prescribing TPD, tidal volume, flow rate, and expected ultrafiltration should be considered.

High-Volume PD (HVPD)

HVPD employs very frequent exchanges with a large volume of dialysate, and this is usually delivered by an automated cycler. HVPD involves 18–22 exchanges (30–60 min of dwell time) with 2 L of dialysate, resulting in a total of 36–44 L of total dialysate volume per day (Gabriel et al. 2007; Ponce et al. 2012a). HVPD can provide the greatest small solute and fluid clearance than any other acute PD techniques, and one study showed that urea clearance of HVPD with 36–44 L of dialysate per day was comparable to that of daily HD (Gabriel et al. 2007). However, it needs very large volume of dialysate; consequently, it is highly expensive. Moreover, due to rapid exchanges and reduced contact time between dialysate and peritoneum, middle and larger molecule clearance may be reduced compared to technique with slower exchanges (Cullis et al. 2014; Chionh et al. 2010).

Continuous Flow PD (CFPD)

CFPD involves continuous and simultaneous inflow and outflow of dialysate via two accesses, respectively. This technique allows increased dialysate flow rates close to 300 mL/min, leading to achieve high peritoneal urea clearance in the range of 30–60 mL/min (Ronco and Amerling 2006). Because originally described CFPD needs two separate accesses and has a risk of recirculation in the peritoneal cavity, newly designed catheters are now available to alleviate these limitations (Ronco et al. 2006). Furthermore, measuring ultrafiltration volume in real-time is difficult in CFPD. Although segmental bioimpedance analysis was suggested to determine intraperitoneal volume and ultrafiltration, it has not been widely used in routine clinical practice because of the necessity of additional equipment (Zhu et al. 2003).

14.2.1.4 Prescription

In AKI, there is no definite target of optimal PD dose. Although urea kinetic modeling is not validated for AKI, target dose may be derived from the CKD setting (Chionh et al. 2010). There are few studies comparing the effect of dialysis dose on clinical outcomes between PD and other renal replacement therapies. Only one randomized controlled study compared continuous PD with HD in AKI patients with acute tubular necrosis. There was no significant difference in mortality between PD group with an achieved weekly Kt/Vurea of 3.5 and HD group (Gabriel et al. 2008). Recently, a systematic review extrapolated a target dose of a weekly Kt/Vurea of 2.1 from the studies of extracorporeal therapy (Chionh et al. 2013). Based on these results, the guideline by the International Society for Peritoneal Dialysis (ISPD) recommended a weekly Kt/Vurea of 3.5 as the optimal dose of PD in AKI (Cullis et al. 2014). In environment with poor resource, a weekly Kt/Vurea of 2.1 would be the minimum optimal dose. We suggested the actual prescription in each well- and poor-resourced environment (Figs. 14.4 and 14.5). However, evidence

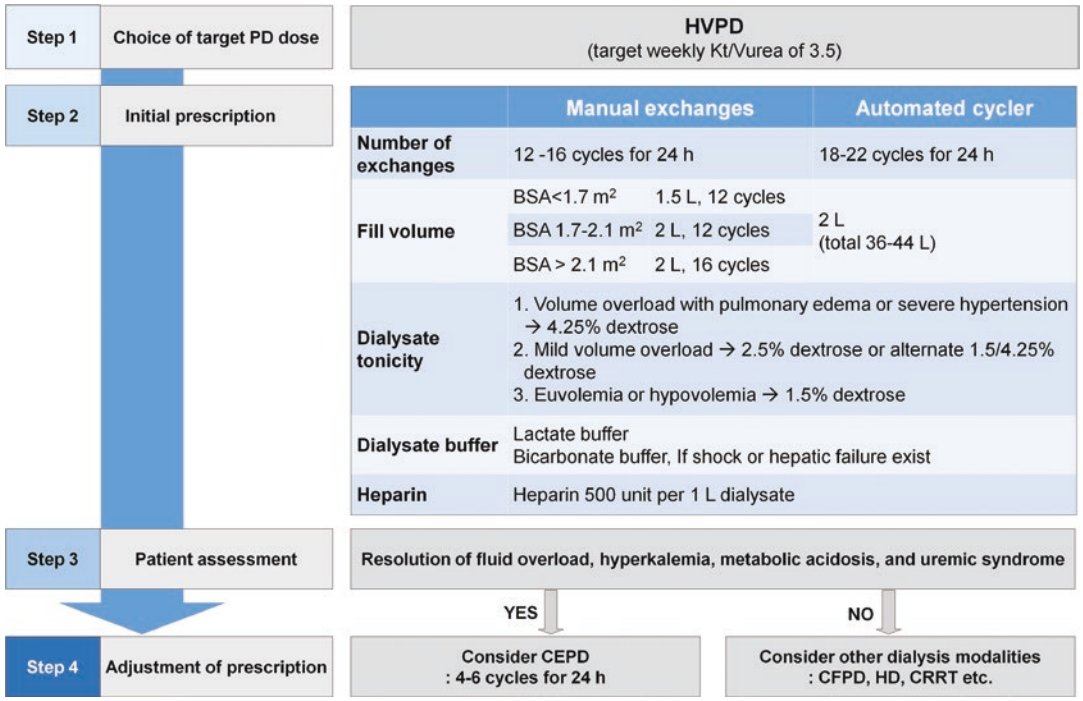


Fig. 14.4 Stepwise approaches to prescribe HVPD in AKI patients under well-resourced environment (Cullis et al. 2014). HVPD, high-volume PD; CEPD, chronic equilibrated PD; CFPD, continuous flow PD; CRRT, continuous renal replacement therapy (Adopted and modified for this publication)

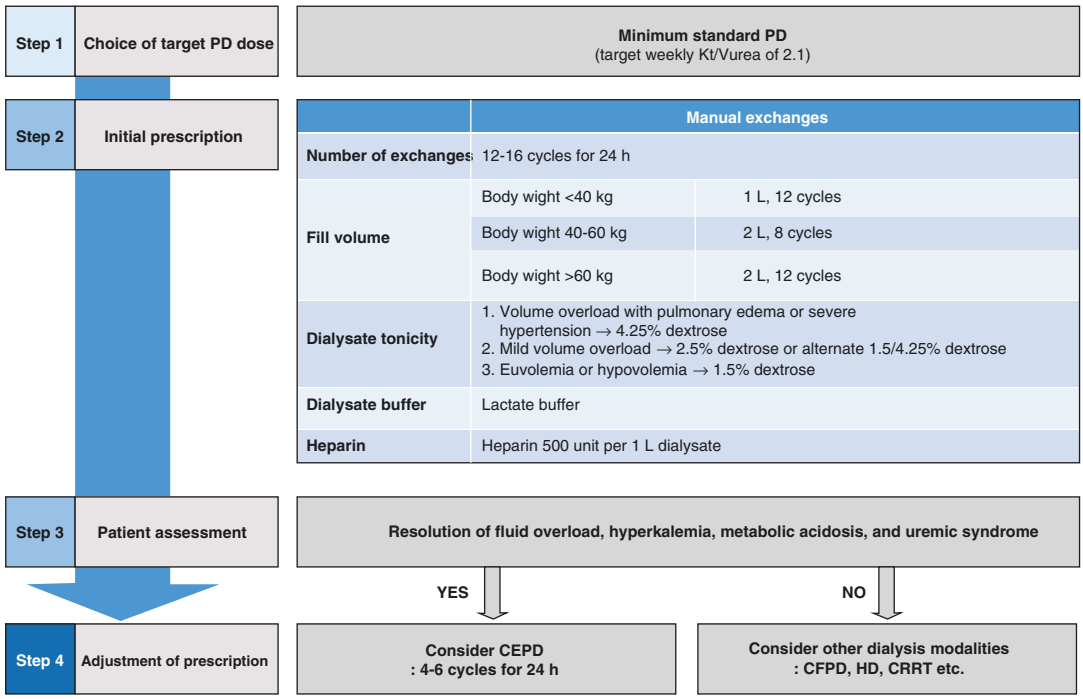


Fig. 14.5 Stepwise approaches to prescribe the minimum standard PD in AKI patients under poor-resourced environment (Cullis et al. 2014). CEPD, chronic equilibrated PD; CFPD, continuous flow PD; CRRT, continuous renal replacement therapy (Adopted and modified for this publication)

for the optimal dose of PD in AKI is still lacking; patients with hypercatabolism and complex illness may require higher dialysis dose.

Number of Exchanges

During the early period of PD, frequent exchanges with short dwell time such as HVPD may be reasonable to correct volume overload, electrolyte imbalance, and/or metabolic complications. After resolution of aforementioned acute problems, the number of exchanges can be reduced to 4–6 exchanges per day (CEPD).

Fill Volume

Fill volume is determined by body surface area, presence of pulmonary disease, hernias, and peritoneal leakage. Patients with body surface area (BSA) of 1.7–2.1 m^2 usually can tolerate 2 L of fill volume. Patients with smaller or greater BSA may be necessary for adjustment of fill volume, from 1.5 to 3 L. Patients with pulmonary disease, especially chronic obstructive lung disease and abdominal or inguinal hernia, may require smaller fill volume to relieve mechanical discomfort. Occasionally, fill volume may be escalated gradually to prevent peritoneal leakage.

Dialysate Tonicity

Choice of dialysate tonicity is largely affected by volume status. According to patient's volume status, 1.5, 2.5, and 4.25% of dextrose concentrations may be utilized. Mild volume overload patients can be usually treated with 2.5% dextrose solution or alternate 1.5/4.25% dextrose solution. If a patient is treated with 4.25% dextrose solution due to severe hypervolemia, one should be cautious for hyperglycemia and/or hypernatremia. Dialysate tonicity should be adjusted based on individual volume status and ultrafiltration requirement.

Dialysis Buffer

Lactate is the most commonly used buffer in PD solution, which is converted to bicarbonate by pyruvate dehydrogenase in the liver and muscles. In case of poor perfusion status including shock or hepatic failure, conversion of lactate to bicarbonate is impaired, resulting in development or aggravation of metabolic acidosis (Bai et al. 2010; Ponce et al. 2012b; Kooienga and Teitelbaum 2009). Therefore, bicarbonate-buffered solution is recommended in patients with shock or hepatic failure (Cullis et al. 2014).

14.2.1.5 Adjustment of Prescription

Due to unpredictable clinical course of AKI, patient evaluation and prescription adjustment should be performed on a daily basis. In particular, avoiding hypervolemia has been received a greater attention in critically ill patients (National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, et al. 2006). Therefore, it is important to monitor patient's volume status and adjust dialysis prescription according to ultrafiltration requirements. If a patient still remained hypervolemic, ultrafiltration can be augmented by increasing the number of exchanges, dialysate tonicity, and/or fill volume.

14.2.2 Urgent Start of PD in CKD Patients

14.2.2.1 Patient Selection

Urgent start of PD is likely to be performed in newly diagnosed end-stage renal disease patients. It is critical to place and secure a PD catheter at the urgent initiation of PD. Therefore, urgent start of PD is indicated to patients who are not indicated to emergent dialysis but cannot delay dialysis initiation more than 2 weeks after PD catheter placement. If a patient is anticipated to require emergent dialysis therapy within 24–48 h, this patient may not be suitable for PD therapy; if a patient is expected to postpone the PD start in 2 weeks, this patient can be treated with planned PD protocol (Fig. 14.6).

In real-world practice, urgent start of PD is not often performed. Insufficiency of experienced and trained clinician or nursing staff may be the reason for limited use of urgent PD. Moreover, many clinicians feel some burden to use peritoneal catheter within 2 weeks after catheter placement due to risk of peritoneal leakage or catheter dysfunction. However, previous studies

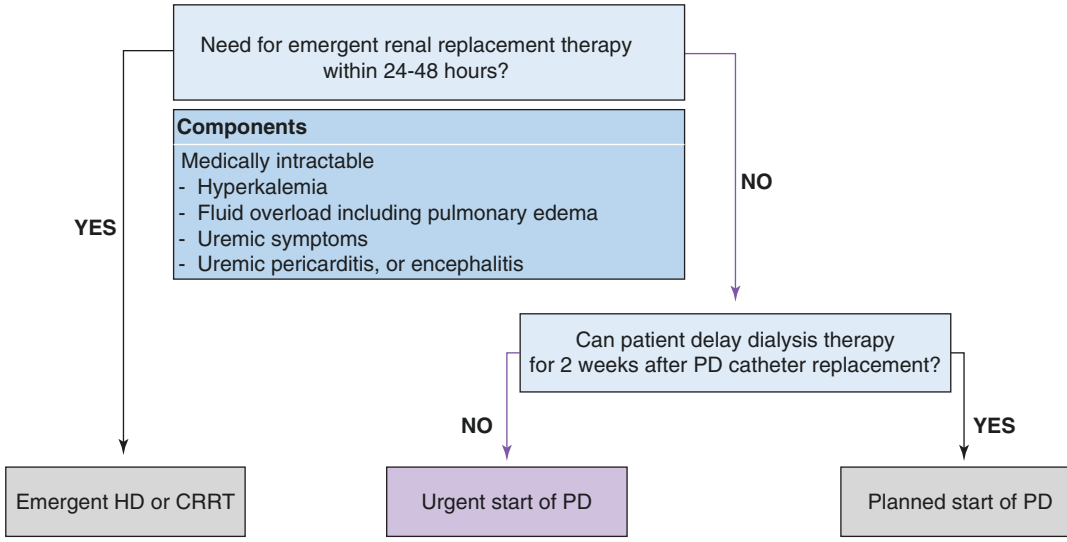


Fig. 14.6 Patient selection for urgent start of PD. CRRT, continuous renal replacement therapy

Table 14.4 Proposed initial prescription of urgent start of PD (Ghaffari 2012) (Adopted and modified for this publication)

Parameters	Values		
Number of exchanges	4–6 cycles for 24 h		
Fill volume		eGFR >7 mL/min/1.73 m^2	eGFR ≤ 7 mL/min/1.73 m^2
	BSA ≤ 1.7m^2	750 mL, 4 cycles	1000 mL, 6 cycles
	BSA > 1.7m^2	1000 mL, 5 cycles	1250 mL, 6 cycles
Dialysate tonicity	1. Volume overload with pulmonary edema or severe hypertension—4.25% dextrose		
	2. Mild volume overload—2.5% dextrose or alternate 1.5/4.25% dextrose		
	3. Euvolemia or hypovolemia—1.5% dextrose		

indicated that using peritoneal catheter before 2 weeks could be feasible (Povlsen and Ivarsen 2006; Jo et al. 2007; Yang et al. 2011). In terms of clinical outcomes, there was no significant difference in risk of infection, hospitalization, or short-term mortality between urgent start and planned start of PD (Povlsen and Ivarsen 2006; Jo et al. 2007; Yang et al. 2011; Ghaffari 2012; Ivarsen and Povlsen 2014). Therefore, urgent PD may be a reasonable dialysis option, especially in patients who select PD as a long-term dialysis modality, avoiding temporary HD catheter insertion.

14.2.2.2 Peritoneal Access

Doubled cuff Tenckhoff catheter should be utilized for maintaining further dialysis and minimizing risk of infection. After peritoneal catheter insertion, catheter function should be tested using 500 mL of 1.5% dextrose dialysate. If the effluent is mixed with blood, administration of heparin via PD solution is necessary to avoid catheter obstruction (Ghaffari 2012).

14.2.2.3 Initial Prescription

In urgent start of dialysis, prescribing the first PD is based on various assumptions including urea/creatinine clearance, peritoneal transport type, and RRF. Furthermore, there are few studies to establish consensus regarding urgent PD (Povlsen and Ivarsen 2006; Ghaffari 2012; Povlsen and Ivarsen 2008; Povlsen 2009). One center in the United States suggested the dialysis prescription for urgent-start PD using CAPD (Table 14.4).

Table 14.5 Proposed initial prescription of urgent start of PD using TPD (Povlsen and Ivarsen 2006; Povlsen and Ivarsen 2008; Povlsen 2009) TPD, tidal PD (Adopted and modified for this publication)

Parameters	Values	
Number of exchanges	12 cycles for 12 h, TPD using automated cycler	
	Body weight < 60 kg	Body weight ≥ 60 kg
Initial fill volume	1200 mL	1500 mL
Tidal volume	500–750 mL	500–750 mL
Total volume	10 L	14 L

Another center in Denmark suggested the initial prescription in the setting of TPD (Povlsen and Ivarsen 2006; Povlsen and Ivarsen 2008; Povlsen 2009) (Table 14.5). Treatment involves 12-h overnight TPD during initial 1–2 weeks. After then, treatment is converted to 8-h APD program, with or without wet day.

Number of exchanges and fill volume were determined by body surface area, RRF, and various clinical parameters such as symptom or complication associated with uremia, electrolyte imbalance, or metabolic acidosis. Compared with other dialysis modalities and planned start of PD, key feature of urgent-start PD is the early use of PD catheter. Therefore, fill volume should be smaller, such as 750–1500 mL, for preventing pericatheter leakage or incomplete wound healing. Furthermore, dialysis can be performed on alternate day; dry abdomen can allow to facilitate wound healing. In this regard, prevention of catheter dysfunction and incomplete wound healing is crucial for maintaining dialysis. Clinical efforts to reduce intra-abdominal pressure are necessary.

14.2.3 Planned PD in CKD Patients

At the initiation of planned dialysis, most patients tend to have RRF. In this regard, no matter which dialysis modality they choose, CAPD or APD, they are likely to achieve solute clearance and ultrafiltration targets for adequate dialysis. Therefore, patients can choose dialysis modality initially based on their lifestyle or preference. Although APD can be chosen at the very moment of starting PD, every patient on APD should understand CAPD technique and be trained well for the exchange technique of CAPD because one needs to use CAPD when APD cycler is not available.

14.2.3.1 Factors to Be Considered at the First Start of PD

When we prescribe PD in the patients starting PD, we have to focus on an individualized prescription considering the key underlying parameters, including solute clearance, peritoneal transport type, RRF, patient size, and patient's preference.

Solute Clearance

In patients receiving CAPD or APD, clinical guidelines/recommendations suggest a total weekly Kt/Vurea ≥1.7 as the minimum target of solute clearance (Peritoneal Dialysis Adequacy Work Group 2006; Dombros et al. 2005a; Lo et al. 2006).

Peritoneal Membrane Transport Type

Theoretically, PD prescription must be individualized according to peritoneal membrane transport type. However, at the start of dialysis, peritoneal membrane transport is not known. If the patients have some RRF at the start of dialysis, it may not be important to identify membrane transport type for deciding the number of exchanges and dwell time, because RRF can provide additional solute clearance and ultrafiltration. A peritoneal equilibration test (PET) is used to delineate membrane transport type at approximately 4 weeks after initiation of PD and regularly thereafter (Twardowski 1989). Although a traditional PET used a 2.5% dextrose solution, a PET using a 4.25% dextrose solution is more widely performed now.

Renal Function

In patients with enough RRF, a full dose of dialysis is not mandatory. However, as RRF decreased, dialysis prescription should be modified to fulfill adequate dialysis.

Body Size

BSA should be considered in the initial PD, because targets of solute clearance such as Kt/Vurea or creatinine clearance are normalized to body size. An absolute Kt/Vurea of 1.7 has a

different meaning between small and large person. Therefore, fill volume should be reduced in patients with small BSA, whereas it should be increased in patients with large BSA.

Lifestyle and Patient's Preference

Patients who want to work during the day or are not able to do exchanges by themselves have advantage on APD. In comparison, patients who had suffered from insomnia or sleep apnea are likely to choose CAPD without nocturnal exchanges.

14.2.3.2 Peritoneal Access

PD catheter should be inserted timely and not be used, if possible, for 2 weeks before starting PD. Catheter function can be tested using low volume of dialysate. If the color of effluent is blood tinged after 500 mL of 1.5% dextrose dialysate infusion, exchanges should be repeated with addition of heparin to dialysate.

14.2.3.3 Initial Prescription

Principle of Stepwise Approaches to Initial Prescription

Step 1. Choose the PD type between CAPD and APD based on patient's preference.

Step 2. Consider the standard prescription of each PD type.

Step 3. Tailor the prescription according to individual clinical status.

The number of exchanges, fill volume, and dialysate tonicity can be modified according to volume status, RRF, body size, and uremic symptoms.

Step 4. Assess the patient regularly for further adjustment of prescription.

Essential indicators (Fig. 14.1) determining optimal dialysis including solute clearance, volume status, nutrition, uremia, electrolyte and acid-base balance, mineral metabolism, RRF, and patient's adherence to therapy should be monitored in 1 week after beginning of PD.

Continuous Ambulatory PD (CAPD)

Generally, CAPD includes three exchanges during the day, followed by an overnight dwell (four exchanges per day). Patients or caregivers perform manual exchanges. Patients with BSA of 1.7–2.1 m^2 tend to tolerate 2 L of fill volume. According to body size, fill volume can be modified from 1.5 to 2.5 L. Because RRF is usually preserved in most patients at planned start of dialysis, 1.5% dextrose solution can be utilized as standard prescription. According to volume status and RRF, dialysate tonicity and the number of exchanges should be modified (i.e., increase dialysate tonicity and number of exchanges in case of hypervolemia), and icodextrin may be added to gain adequate ultrafiltration (Fig. 14.7).

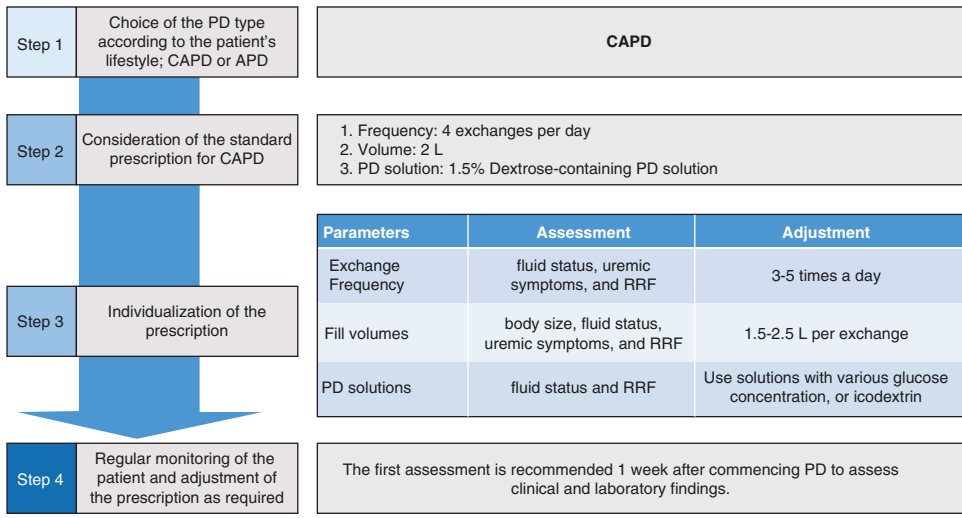


Fig. 14.7 Stepwise approaches to the initial CAPD prescription

Automated PD (APD)

APD involves multiple overnight exchanges using a cycler. Continuous cycler PD (CCPD), nightly intermittent PD (NIPD), and tidal PD (TPD) are subsets of APD. Detailed characteristics of each technique were described in "Chapter 2: Types of Peritoneal Dialysis."

CCPD is the most commonly used technique which has a long daytime dwell (also known as "last bag fill") and multiple overnight exchanges. According to an individual, technique can be modified including overnight exchanges without daytime dwell ("dry day") and additional midday exchange ("MDE") (Teitelbaum and Burkart 2003). We suggest standard CCPD prescription, consisting of four exchanges for using 2 L-PD solution with 1.5% dextrose (Fig. 14.8). Similar to CAPD, fill volume may be adjusted from 1.5 to 2.5 L according to body size and dialysate tonicity, and the number of exchanges can be modified according to ultrafiltration requirement in the CCPD setting. When prescribing APD, clinicians pay attention to inflow, outflow, and dwell time. Inflow time is the duration for infusing dialysate into the peritoneal cavity. About 10–15 min usually is required to complete infusion. Outflow time is the duration for draining dialysate out of the peritoneal cavity. Outflow time is affected by gravity; usual outflow time is about 20–30 min. Maintaining both inflow and outflow a minimum is important to ensure adequate dwell time. Dwell time is the time which instilled dialysate volume remains in the peritoneal cavity or the time between the end of inflow and the start of drainage. During the dwell time, contact of dialysate on peritoneal membrane has occurred; small solute and fluid moved according to the gradient. When gradient disappears after a certain amount of dwell time, solute and fluid movement is stopped. Therefore, if the number of exchanges increases, dwell time may be shortened, leading to increase in solute clearance.

If one patient has significantly lower RRF or is anuric, adequate solute clearance and ultrafiltration cannot be achieved by "dry day abdomen." Midday exchange using dextrose solution or long dwell of icodextrin can be utilized in this patient. Among patients requiring midday exchange, icodextrin solution is preferred in rapid transporters,

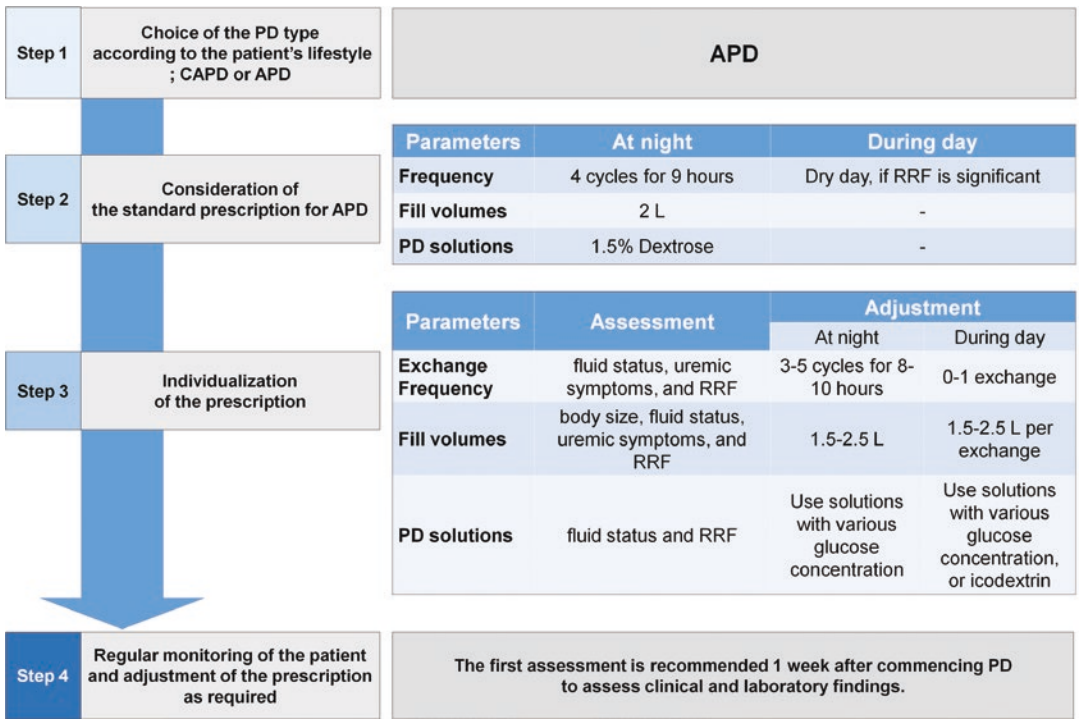


Fig. 14.8 Stepwise approaches to the initial APD prescription

because long dwell of dextrose solution induces absorption of fluid into the body.

14.3 Prescription Adjustment During Maintenance of PD

14.3.1 Monitoring of Therapy for Adjustment of PD Prescription

Because initial prescription of PD depends on assumptions and clinical experience regarding solute clearance, peritoneal transport type, and volume status, actual solute clearance and characteristics of peritoneal membrane should be determined within 4–8 weeks after dialysis initiation and monitored serially. Although the optimal interval of measuring these values remains unclear, the K/DOQI guideline suggested that total solute clearance (peritoneal and renal) should be measured within the first month after initiation of PD and at least once every 4 months (Peritoneal Dialysis Adequacy Work Group 2006). In patients with significant RRF (> 100 mL/day), 24-h urine collection is recommended every 4 months. Moreover, for clarifying the characteristic of peritoneal membrane, peritoneal equilibration test (PET) should be performed within 4–8 weeks after starting PD and then at least annually or when clinically indicated (Table 14.6) (Peritoneal Dialysis Adequacy Work Group 2006).

Table 14.6 Indications for repeated PET during follow-up

Unexplained decrease in ultrafiltration
Decreased peritoneal solute clearance
Intractable hypervolemia and hypertension, despite increasing hypertonic solution
Aggravation of uremic symptoms and sign

Besides the amount of solute clearance and the characterization of peritoneal transport type, various clinical and laboratory indicators representing optimal dialysis such as fluid balance, nutritional status, or RRF should also be evaluated during routine visit (Fig. 14.9).

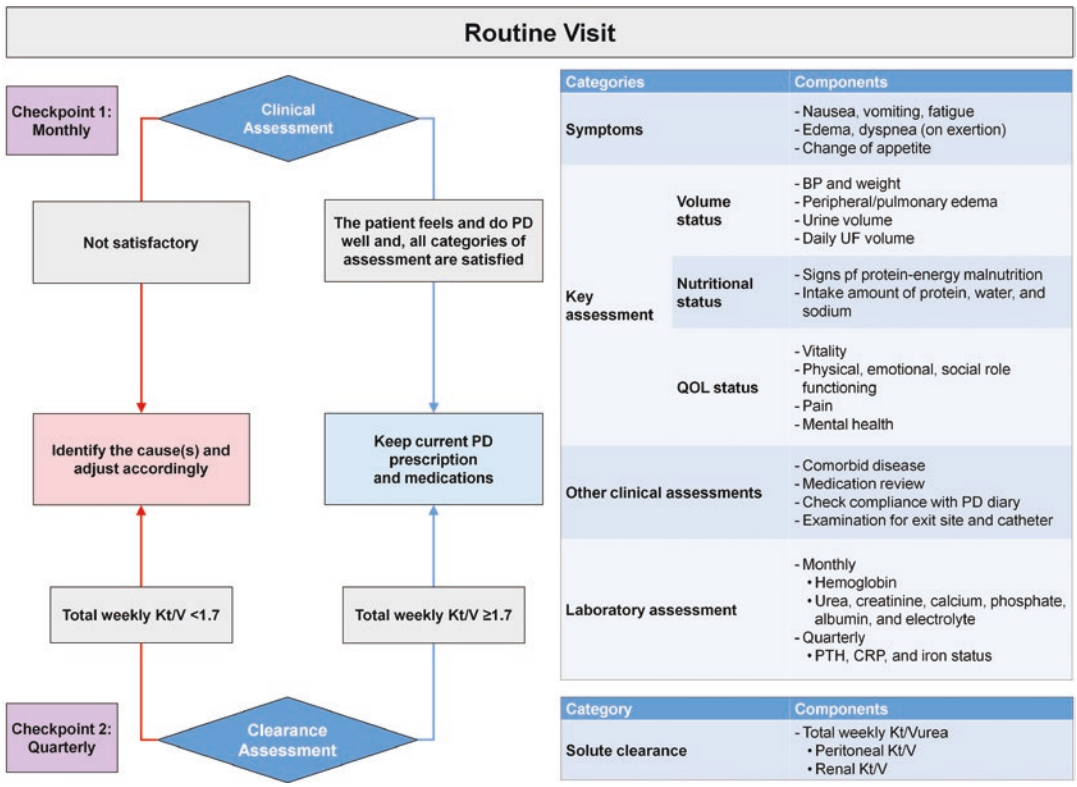


Fig. 14.9 Clinical assessment of patients during maintenance of PD

14.3.2 Prescription Adjustment in Patients with Insufficient Solute Clearance

Because total solute clearance of PD consists of clearance derived from PD and RRF, patients who do not achieve minimum target of solute clearance should be evaluated in respect of both dialysis therapy and RRF. Particularly, as RRF declines over time, renal clearance decreases, resulting in inadequate total solute clearance.

If RRF decreases, many patients may not achieve the minimum target of solute clearance. In these patients, dialysis dose should be elevated. Since peritoneal Kt/Vurea is determined by peritoneal Kt, which is a product of D/P urea and 24-h drained dialysate volume, urea concentrations in the dialysate and drained volume should be increased to enhance peritoneal Kt/Vurea. Therefore, increasing fill volume may be a simple solution. Furthermore, increasing exchanges and total session length and midday exchange would facilitate movement of solute, leading to greater urea concentrations in drained dialysate (Table 14.7).

A patient on PD often needs to increase the dialysis dose due to various symptoms and signs related to inadequate dialysis as well as the Kt/V value below the target. We may simply choose the way to increase the number of exchanges per day or to increase the fill volume per exchange. Practically, we prefer increasing larger volumes per exchange to increasing the number of exchange in order to encourage compliance. Many patients and physicians are reluctant to use large fill volumes because of patients' discomfort. However, we don't need to be worried about it and try it on the basis of a simple evidence in which 75% of participants in a study did not even identify the changes of fill volume from 2 to 3 L (Sarkar et al. 1999).

14.3.3 Prescription Adjustment in Patients with Volume Overload

PD prescription traditionally had been focused on small solute removal. However, since the milestone studies suggested that the higher small solute clearance did not always guarantee the better survival rate (Lo et al. 2003; Paniagua et al. 2002), achieving adequate ultrafiltration to maintain euvolemia is considered another important goal to improve the outcomes of PD patients. Although PD is a continuous therapy allowing for a steady solute clearance and ultrafiltration, quite a number of PD patients still have a problem of volume overload.

Volume status is primarily the sum of intake and output of fluid, and several factors can modify this association. When a patient is diagnosed as "volume overloaded," one can be evaluated by the causes, the amount of intake and output, and aggravating factors. Although PD patients are less limited in dietary sodium or water intake, low-salt diet remains to be necessary. In addition to dietary intake, absorption of fluid from the peritoneal cavity may also lead to input excess. If daytime dwell is too long or an inappropriate osmotic agent is used, fluid and electrolytes may be absorbed, so that the drain volume is actually

Table 14.7 Stepwise approaches to meet the target Kt/V in PD patients with suboptimal solute clearance

	Patient selection	CAPD	APD	Monitoring
Strategy 1	Patients with larger body size	• Increase fill volume per exchange	• Increase fill volume per exchange	Pressure symptoms, especially at night
Strategy 2	Patients with high peritoneal transport type	• Increase the number of exchanges	• Increase duration on cycler therapy or night time exchange number	Compliance and quality of life
			• Add a daytime exchange	
Strategy 3		• Consider APD	• Consider HD	

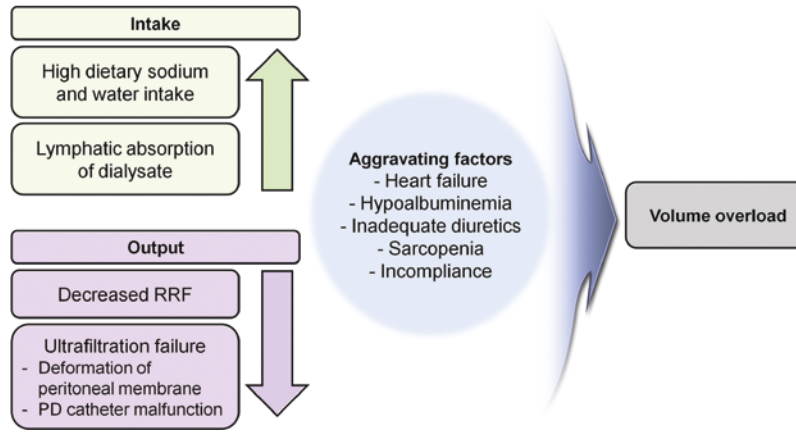


Fig. 14.10 Various causes of volume overload in PD patients

less than the instilled volume. Loss of RRF and inadequate ultrafiltration are output-dependent factors. Inadequate ultrafiltration may be attributed to peritoneal membrane failure or catheter problem. Ultrafiltration may be reduced, when peritoneal membrane does not respond to osmotic stimuli or even rapidly respond (rapid transporter). If patients have catheter problems and the preceding drain is not complete, a large residual dialysate remained in the peritoneal cavity. The new instilled dialysate is diluted, decreasing osmotic or oncotic transmembrane pressure, resulting in lack of ultrafiltration. Several factors including heart failure whether newly developed or acute exacerbated, hypoalbuminemia or decreased oncotic pressure, inadequate use of diuretics, loss of lean body mass (sarcopenia), and patient's nonadherence may aggravate volume overload (Fig. 14.10).

Volume status is often decided by clinical judgment. In contrast to HD, "dry weight" or "euvolemia" often needs to be decided by PD patients by themselves. Therefore, a clinician educates patients to ascertain their volume status appropriately. Recently, bioelectrical impedance study or left atrial diameter measured by echocardiography is applied to evaluate the volume status. However, the use of these methods is limited in clinical practice due to costs and reimbursement problems in some countries. Careful history taking and physical examination can give us valuable information regarding volume status (Table 14.8).

The ultrafiltration target should be individualized for maintenance of euvolemia. Preservation of RRF, low-salt diet, high-dose diuretics, and enhancing compliance are helpful to reduce volume overload. Increasing fill volume and dialysate tonicity is simply applicable. For facilitating water movement, maintaining osmotic gradient is critical.

Table 14.8 Evaluation of volume status in PD patients

	Parameters
History taking	Dietary sodium and water intake
	Urine volume
	Any changes in drain or ultrafiltration volume
	Any changes in inflow/outflow/dwell time
	Aggravation of comorbid disease (cardiovascular disease, liver cirrhosis, multiple myeloma, etc.)
	Use of nephrotoxic drug (NSAIDS, aminoglycoside, herbal remedies, etc.)
	Loss of appetite, dietary intake, or lean body mass
	Patient's compliance (transportation records of dialysate, treatment data of cycler if, APD)
Physical examination	Body weight
	Blood pressure
	Peripheral edema
	Visualization of abdomen and PD catheter (hernia, leakage, etc.)
Studies	Peritoneal equilibration test
	Total solute clearance (peritoneal and renal)
	Radiographic studies (X-ray, CT, MRI, etc.)
	Echocardiography
	Bioelectrical impedance analysis

Therefore, the use of glucose polymer (icodextrin)-based dialysate can be utilized in long dwell. Icodextrin is a mixture of oligo-polysaccharides of variable chain lengths. Icodextrin has been recognized to induce greater ultrafiltration due to sustained osmotic gradient. Average molecular weight of icodextrin is 16,200 DA, which leads to be less absorbed and is not metabolized locally during a dwell. By using icodextrin, glucose exposure to peritoneal membrane in dextrose-based dialysate can be reduced and may have protective effect of peritoneal membrane. In addition, icodextrin use showed an advantage in glycemic control (Li et al. 2013). Therefore, icodextrin is considered an option for providing ultrafiltration (Table 14.9 and Fig. 14.11).

14.3.4 Prescription Adjustment in Patients with Malnutrition

Theoretically, amino acid PD solution may improve nutritional status by replacing the protein loss and providing additional calorie (Jones

Table 14.9 Stepwise approaches in PD patients with volume overload

	CAPD	APD	Non-PD-related approaches
Strategy 1	• Check patient diary and PET result for the evaluation of UF		• Protect RRF
			• Increase the dose of furosemide
	• Check mechanical problems, including catheter malfunction, hernia, and leaks		• Restriction of salt intake
			• Enhancement of patient compliance
			• Improve glycemic control
Strategy 2	• Increase fill volume	• Increase fill volume	
	• Increase glucose concentration	• Increase glucose concentration	
	• Consider icodextrin for long night dwell	• Consider icodextrin for long daytime dwell	
		• Consider 2 short daytime glucose dwells	
Strategy 3	• Consider APD	• Switch to HD in high transport type	
	• Switch to HD in high transport type		

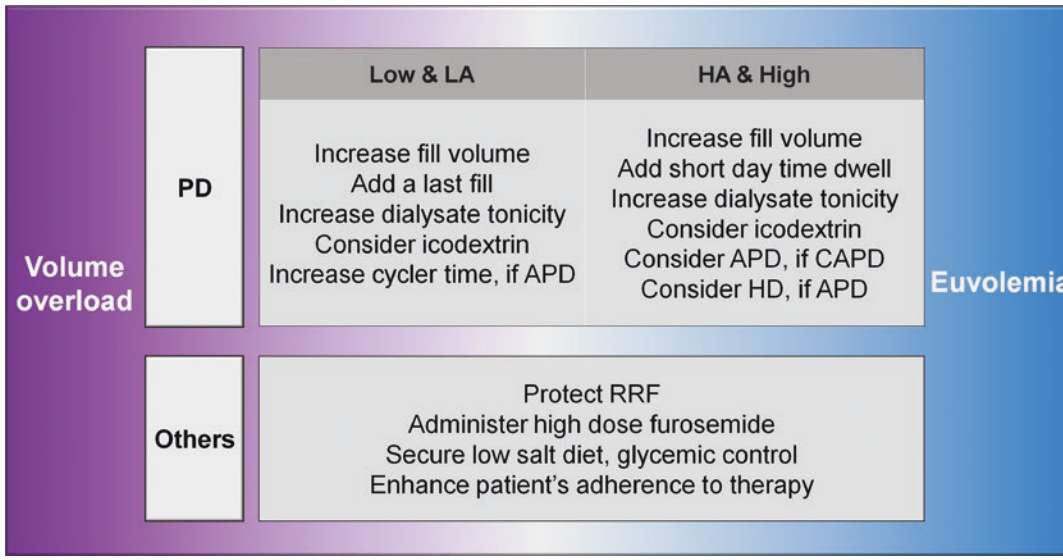


Fig. 14.11 Strategies according to peritoneal membrane characteristics in PD patients with volume overload

et al. 1998). However, not all amino acid solution showed a nutritional benefit, and only 1.1% solution of a combination of essential amino acids and some nonessential amino acids is currently available. Although this solution showed a nutritional benefit (Ohkawa et al. 2004), it has adverse effect including metabolic acidosis and increased urea concentrations, due to its low pH of 6.7. Metabolic acidosis can be induced from hydrogen ion contained in cationic amino acids (such as lysine) (Tjiong et al. 2005). Therefore, K/DOQI guideline recommended that amino acid solution should be indicated in only malnourished or diabetic patients and/or those with recurrent peritonitis (National Kidney Foundation 2000). Furthermore, no more than one exchange per day of amino acid solution should be prescribed in patients with sufficient concurrent caloric intake. In all cases, blood urea and bicarbonate concentrations should closely be monitored.

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Kinetic Modeling and Adequacy in PD

15

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15.1 Urea Kinetic Modeling in Peritoneal Dialysis

Dialysis dose in peritoneal dialysis (PD) is measured by Kt/*V* urea or creatinine clearance (CrCl). In hemodialysis, it is not easy to add residual renal function (RRF) for the calculation of total Kt/*V* urea because Kt/*V* urea is expressed as a value per single dialysis session. To overcome this issue, "standard Kt/*V*" has recently been introduced (Leypoldt 2004; Daugirdas et al. 2010). It includes RRF and dialysis clearance and is expressed as weekly Kt/*V* as in PD. This equation enables us to compare dialysis adequacy between different dialysis modalities. However, it is a very complicated equation to calculate and thus is not widely used in clinical practice. Nowadays, it is generally performed for research purposes. In PD, RRF can be easily calculated and be added to peritoneal Kt/*V* urea, making weekly Kt/*V* urea. RRF is particularly important in PD because patients on PD can maintain urine output longer than those on hemodialysis. It is well known that RRF is an independent predictor of mortality in both PD and hemodialysis patients. In addition, patients on PD have better patient survival than those on hemodialysis up to 2 years after dialysis initiation. This is presumably attributed to more preserved RRF by PD. Therefore, RRF should be incorporated to Kt/*V* when it comes to PD adequacy.

15.1.1 Measurement of Kt/*V* Urea

As aforementioned, Kt/*V* should encompass both peritoneal and renal clearance in PD. A schematic calculation is illustrated in Fig. 15.1. It is a dimensionless index determined by measuring fractional urea clearance. To calculate this, all drained dialysates should be collected over a 24-h period. Urea concentration is measured from the effluent and patient's plasma. Kt represents urea clearance, which is calculated by total drained volume × (urea concentration in dialysate effluent/blood urea nitrogen level). For renal clearance, 24-h urine collection is also required. Similar to peritoneal Kt/*V*, urea concentration in the urine is divided by blood urea nitrogen level, and this value is then multiplied by urine volume, giving renal Kt. A total Kt is a sum of peritoneal Kt and renal Kt. This is then normalized to volume of distribution of urea (*V*). *V* represents total body water and urea has a

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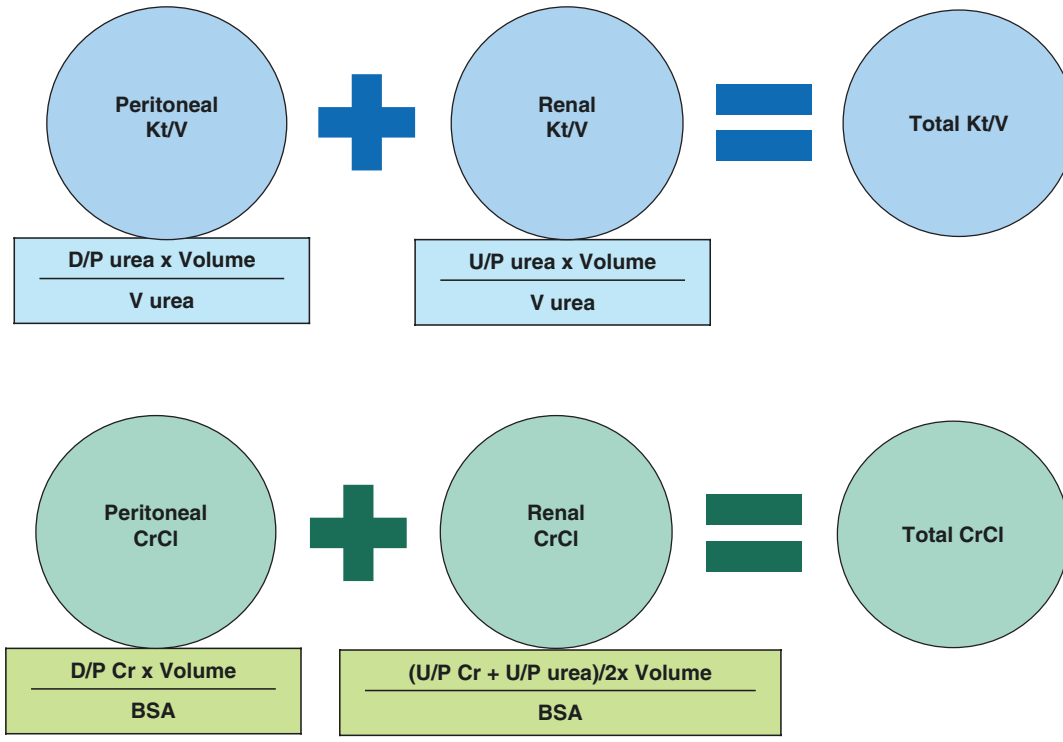

Fig. 15.1 A schematic concept of Kt/*V* urea and creatinine clearance. *D* dialysate, *P* plasma, *V urea* volume of distribution of urea, *CrCl* creatinine clearance, *Cr* creatinine, *BSA* body surface area

volume of distribution equal to total body water. Various formulas have been established to estimate volume of distribution of urea using age, sex, height, and weight of the patient. Among these, the Watson or Hume-Weyers formula is most commonly used in clinical practice. Total Kt is then divided by *V*, giving a daily Kt/*V*. Weekly K/*V* is calculated as daily Kt/*V* multiplied by 7 (days). A summary of the equation is presented in Table 15.1.

Because CAPD is a continuous therapy, blood urea nitrogen concentration is relatively constant throughout the day, thus sampling timing is not a major concern. However, in intermittent PD such as CCPD and NIPD, plasma urea concentration differs between daytime and nighttime. The general rule regarding sampling time in patients treated with these modalities is to take blood sample in the middle of the non-cycling daytime period when urea concentration represents the average value of blood urea for a day. This is usually between 1:00 and 5:00 p.m.

15.1.2 Measurement of Creatinine Clearance (CrCl)

Molecular weight of creatinine is slightly higher than urea (113 D vs. 60 D). Although urea and creatinine are well dialyzed by diffusion, creatinine equilibration is relatively lower than urea equilibration (Fig. 15.2). Therefore, monitoring both Kt/*V* urea and CrCl is recommended in clinical practice. CrCl is calculated in the same manner as in the measurement of Kt/*V*. For peritoneal CrCl, creatinine concentration is measured in the effluent from the 24-h collection of dialysates and in the plasma. For renal CrCl, creatinine concentration is also measured in the 24-h collection of urine. However, it is well known that renal CrCl overestimates true GFR because creatinine is exceedingly secreted by the proximal tubules in advanced stages of CKD. Therefore, renal CrCl is generally expressed as an average of the urinary urea clearance and creatinine clearance. Total CrCl is calculated as a sum of peritoneal CrCl and

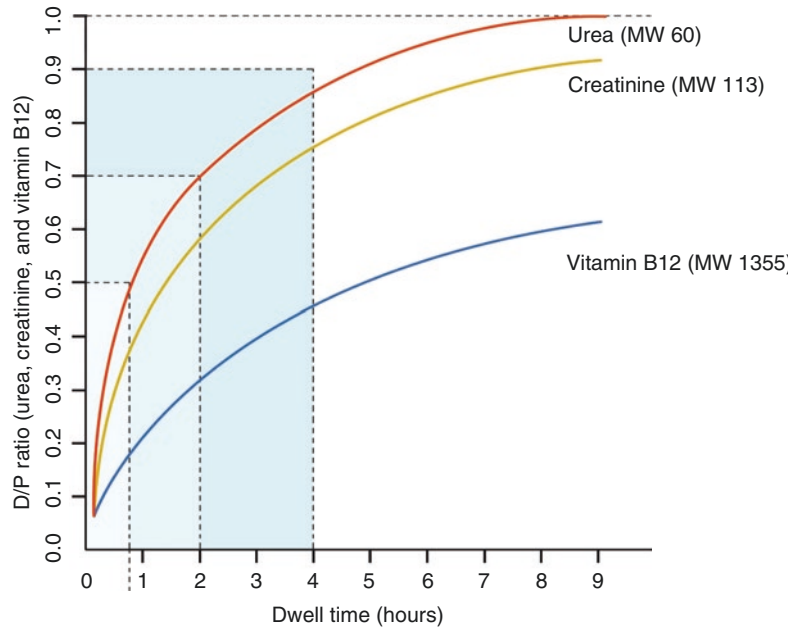

Fig. 15.2 Urea and creatinine equilibration. Urea diffuses rapidly into PD solution compared with creatinine. Rate of entry of a larger molecule, vitamin B12, is slower than urea and creatinine. D/P ratio indicates dialysate concentration of urea, creatinine, and vitamin B12 divided by plasma urea concentration of each molecule

renal CrCl and is then normalized for 1.73 m^2 body surface area (BSA). BSA can be estimated using the DuBois formula, which is most commonly used worldwide. These are summarized in Table 15.1.

15.1.3 Clinical Examples of Measurement of Kt/*V* Urea and CrCl

PD adequacy can numerically be determined by Kt/*V* urea and CrCl. Therefore, physicians should be familiar with these formulas. Examples of how the formulas are calculated and how we put these into clinical practice are presented as follows:

1. A 60-year-old female started PD due to hypertensive nephrosclerosis. She underwent three exchanges of a 1.5% 2 L glucose PD solution. A daily net peritoneal ultrafiltration and urine volume were 1 L per day and 500 mL per day, respectively. She was 165 cm tall and weighed 62 kg. Laboratory findings were as follows:

Dialysate (24-h collection): Urea, 55 mg/dL; creatinine, 6 mg/dL

Table 15.1 Formulas for Kt/*V* urea and CrCl

Kt/*V* urea
Peritoneal Kt = Total drained volume (*L*) × (24-h dialysate effluent urea concentration/blood urea nitrogen level)
Renal Kt = Total urine volume (*L*) × (24-h urinary urea concentration/blood urea nitrogen level)
Total Kt = peritoneal Kt + renal Kt
Watson formula for estimating *V*
V (*L*, in males) = 2.447–0.09516 × (age, years) + 0.1704 × (height, cm) + 0.03362 × (weight, kg)
V (*L*, in females) = −2.097 + 0.1069 × (height, cm) + 0.2466 × (weight, kg)
Daily Kt/*V* = (peritoneal Kt + renal Kt)/*V*
Weekly Kt/*V* = 7 × daily Kt/*V*
CrCl
Peritoneal CrCl = Total drained volume (*L*) × (24-h dialysate effluent creatinine concentration/serum creatinine concentration)
Renal CrCl = Total urine volume (*L*) × ([24-h urine creatinine concentration/serum creatinine concentration] + [24-h urine urea concentration/blood urea nitrogen level])/2
Daily CrCl = (peritoneal CrCl + renal CrCl)/1.73 m^2 BSA
The DuBois formula for calculation of BSA
BSA (m^2) = 0.007184 × (weight, kg)$^{0.425}$ × (height, cm)$^{0.725}$
Weekly CrCl = 7 × daily CrCl (*L*/week)

Plasma: BUN, 75 mg/dL; creatinine, 8 mg/dL
Urine (24-h collection): Urea, 600 mg/dL; creatinine, 48 mg/dL
What is a total weekly Kt/*V* urea and CrCl?

15.1.3.1 Kt/*V* Urea

Step 1 Calculate peritoneal Kt/*V*.

Daily peritoneal Kt = total ultrafiltration × (dialysate urea nitrogen/serum BUN) = 7 (L) × (55/75) = 6.4 L per day.
Weekly peritoneal Kt = 7 (days) × 6.4 L/day = 44.8 L.
By the Watson formula, *V* = 30.8 L.
Weekly peritoneal Kt/*V* = 44.8/30.8 = 1.45.

Step 2 Calculate renal Kt/*V*.

Daily renal Kt = urine volume × (urinary urea nitrogen/serum BUN) = 0.5 (L) × (600/60) = 5.0 L per day.
Weekly renal Kt = 7 (days) × 5.0 L/day = 35 L.
Weekly renal Kt/*V* = 35/30.8 = 1.14.

Step 3 Calculate weekly Kt/*V*.

Weekly Kt/*V* = peritoneal Kt/*V* + renal Kt/*V* = 1.45 + 1.14 = 2.59.

15.1.3.2 CrCl

Step 1 Calculate peritoneal CrCl.

Daily peritoneal CrCl = total ultrafiltration × (dialysate creatinine/serum creatinine) = 7 (L) × (6/8) = 5.25 L per day.
Weekly peritoneal CrCl = 7 (days) × 5.25 L/day = 36.75 L.
By the DuBois formula,
BSA = 1.68.
BSA corrected to 1.73 m^2 = 1.73/1.68 = 0.97.
Weekly peritoneal CrCl normalized to 1.73 m^2 BSA = 36.75/0.97 = 37.9 L.

Step 2 Calculate renal CrCl.

Daily renal CrCl = urine volume × ([urinary urea nitrogen/serum BUN] + [urinary creatinine/serum creatinine])/2 = 0.5 (L) × (600/60 + 48/8)/2 = 4.0 L per day.
Weekly renal CrCl = 7 (days) × 4.0 L/day = 28 L.
Weekly renal CrCl normalized to 1.73 m^2 BSA = 28/0.97 = 28.9 L.

Step 3 Calculate weekly CrCl.

Weekly CrCl = peritoneal CrCl + renal CrCl = 37.9 + 28.9 = 66.8 L/week

2. She had been well maintained on CAPD without symptoms and signs of uremia until 1.5 years after commencing dialysis. At 2 years, urine volume was decreased to 100 mL per day, and she was not quite well and could not eat much. Her body weight decreased to 60 kg. Laboratory findings revealed dialysate urea of 72 mg/dL, serum BUN of 80 mg/dL, and urinary BUN of 350 mg/dL. Assuming the same net peritoneal ultrafiltration, calculate Kt/*V* and what should physicians do?

Using the same steps above, weekly total Kt/*V* is calculated as a sum of peritoneal and renal Kt/*V*: peritoneal Kt/*V* = 44.1/30.3 = 1.46; renal Kt/*V* = 3.08/30.3 = 0.1. Thus, weekly Kt/*V* is 1.56.

In this case, the patient does not meet the optimal target value of Kt/*V* as recommended by the current guidelines (see Sect. 15.2). Her symptoms and signs are most likely to be caused by inadequate dialysis. This is attributed to a significantly decreased RRF. She needs to do one more exchange of PD solution, four exchanges in total.

3. A 55-year-old male patient had been treated with APD for 3 years. Using a cycler, he underwent 8.0 L during nighttime only, and the abdomen was dried during daytime. He became anuric 6 months ago. At that time, Kt/*V* urea and CrCl were 1.8 and 48 L/week per 1.73 m^2. This time, laboratory tests showed dialysate urea of 55 mg/dL, serum BUN of 65 mg/dL, dialysate creatinine of 4.8 mg/dL, and serum creatinine of 7 mg/dL. Total mean drained volume was 9.0 L. He weighed 68 kg and was 172 cm tall. How would you like to adjust dialysis prescription?

Following the steps above, peritoneal Kt/*V* urea = 1.61 and peritoneal CrCl = 41.5 L/week per 1.73 m^2. We have several options to increase Kt/*V* urea and CrCl to the target levels. These can be (1) adding daytime dwell, (2) increasing dwell volume during nighttime, or (3) increasing frequency of exchanges on a cycler. Strengths and problems of each strategy are discussed below in Sect. 15.3.2.

15.2 Therapeutic Targets of Kt/*V* Urea and CrCl

Many studies have been conducted to find the optimal target values of small solute clearance by using Kt/*V* urea and CrCl. In1996, the Canada-USA (CANUSA) PD study group reported the results of the prospective cohort study of 680 patients commencing continuous PD in 14 centers in two countries (1996). They found a 5% increase in the relative risk of death in proportion to a decrease of 0.1 unit of Kt/*V* urea, suggesting the importance of small solute clearance. Two-year survival rates were 78 and 81% in patients with Kt/*V* urea of 2.1 and 2.3, whereas it was only 66% in patients with Kt/*V* urea of 1.5. Similarly, patients with CrCl of 80 L/week per 1.73 m^2 had a higher 2-year survival rate than patients with CrCl of 40 L/week per 1.73 m^2 (81% vs. 65%). In line with this finding, many observational studies consistently found a decreased risk of mortality as Kt/*V* urea or peritoneal CrCl increased. Encouraged by the results of the observational studies, two randomized controlled trials had been consecutively published in 2002 and 2003 (Table 15.2). Both studies aimed to evaluate whether higher target of small solute clearance could improve patient survival. The ADEMEX (Adequacy of PD in Mexico) study first addressed this issue in 965 patients from 24 centers in 14 Mexican cities (Paniagua et al. 2002). The participants were randomized into two arms, and a modified PD regimen to achieve a peritoneal CrCl of 60 L/week per 1.73 m^2 was prescribed to the intervention group. Fifty-nine percent of the intervention group achieved this target value by either an increase in exchange volume or the addition of a nighttime exchange or both. Contrary to the findings of the previous observational studies, this study failed to show a better survival rate in patients with an increased peritoneal clearance than in control group. In the following year, another randomized controlled trial produced similar results. A total of 320 patients were recruited from six centers in Hong Kong and were randomized into three groups with total Kt/*V* targets of <1.7, 1.7–2.0, and >2.0 (Lo et al. 2003). The 2-year survival rates did not differ among the three groups (87.3% in patients with Kt/*V* of >2.0, 86.1% in patients with Kt/*V* of 1.7–2.0, and 81.5% in patients with Kt/*V* < 1.7). In addition, there were no significant differences in technique survival, nutritional score, and hospitalization rate. However, erythropoietin was more used in patients with the lowest Kt/*V* group, and more patients in that group dropped out from the study due to inadequate dialysis and inadequate ultrafiltration. Although survival rates were not statistically significant, *p*-value was 0.054

Table 15.2 Main findings of the ADEMEX and Hong Kong study

	ADEMEX		Hong Kong		
	Control	Intervention	Group A	Group B	Group C
No. of patients	484	481	104	104	112
Target clearance	pCrCl <60 L/week per 1.73 m^2	pCrCl >60 L/week per 1.73 m^2	Kt/V 1.5 to 1.7	Kt/V 1.7 to 2.0	Kt/V >2.0
2-year patient survival	68.3%	69.3%	87.3%	86.1%	81.5%
	$P=0.9842$		$P=0.9924$		
Other findings	– No difference in hospitalization rates		– No differences in hospitalization rates and nutritional parameters – More EPO requirement in group A – More patients who withdrew from the study in group A		

pCrCl peritoneal creatinine clearance

Table 15.3 Target values of small solute clearance

	European (2005)	CARI (2005)	KDOQI (2006)	ISPD (2006)	UK (2010)	Canadian (2011)
Kt/*V* urea (per week)	> 1.7	≥ 1.6	> 1.7	> 1.7	≥ 1.7	> 1.7
CrCl (L/week per 1.73 m^2)	> 45 L/week/1.73 m^2 for APD patients with slow transport	> 60 L/week in H and HA transporters >50 L/week in LA and L transporters	NA	> 45 L/week/1.73 m^2 for APD patients with slow transport	≥ 50 L/week/1.73 m^2	NA
Evidence level[a]	(A) for Kt/*V* (C) for CrCl	(II)	(B)	(A) for Kt/*V* (C) for CrCl	1A	(C)

RRF RRF, *APD* automated PD, *H* high, *HA* high average, *LA* low average, *L* low
[a]Grades A to D, I to III, or 1A to 2D: evidence grade high to low, for example, "A" means the high quality of evidence.

between patient with Kt/*V* of <1.7 and patients with Kt/*V* of 1.7–2.0, suggesting a poorer outcome in patients with lowest Kt/*V*.

Consequently, many guidelines proposed by the National Kidney Foundation (Peritoneal Dialysis Adequacy Work 2006), the International Society of PD (Lo et al. 2006), the UK Renal Association (http://www.renal.org/guidelines/modules/peritoneal-dialysis-in-ckd#sthash.Re0T4XBR.dpbs), the European Best Practice Working Group (Dombros et al. 2005), the Canadian Society of Nephrology (Blake et al. 2011), and the Australian Society of Nephrology (Johnson et al. 2005) adopted the findings of these two randomized controlled trials and agreed on the minimum target for Kt/*V* urea of at least 1.7 per week (Table 15.3). Some groups suggest a minimum target for CrCl depending on dialysis modality or transport types. In fact, there has been concern about inadequate dialysis with respect to CrCl in patients with a slow transport-type peritoneal membrane. In general, patients on APD use short and frequent exchanges, thus the target value of CrCl may not be achieved particularly in patients with a slow transport status. It takes only several hours for urea to equilibrate between plasma and peritoneal fluid (Fig. 15.2). D/P urea ratio typically is 0.7 at 2 h and 0.9 at 4 h after the dwell, where D and P represent dialysate and plasma, respectively. Creatinine equilibration is relatively lower than urea equilibration. Therefore, in slow transporters, creatinine may not be adequately removed particularly when short and frequent exchanges are used. This phenomenon becomes more evident once RRF is lost. In this regard, some guidelines additionally suggest targets of CrCl and recommend a regular monitoring. Nevertheless, compared to relatively strong evidence for Kt/*V* target supported by the two previous randomized controlled trials, CrCl targets for slow transporters have weak evidence. To date, there is no randomized controlled trial to support the minimum targets of CrCl in patients on APD or in patients with a slow transport-type peritoneal membrane. For this reason, it is acceptable to use the same targets as for CAPD in these patients.

15.2.1 Frequency of Measurement

Many guidelines suggest measurement of Kt/*V* urea and CrCl within the first month of dialysis initiation. These are typically done together with peritoneal equilibration test. As seen in Sect. 15.1, total Kt/*V* and CrCl are a sum of peritoneal and renal clearance. Thus, dialysis adequacy assessed by small solute clearance significantly relies on RRF during the initial period of PD. Because RRF gradually declines over time, it should be regularly monitored. It is generally recommended that a 24-h urine collection for urine volume and solute clearance measurement should be performed at a minimum of every 1–2 months for patients who have a significant residual urine volume. These can be monitored at longer intervals,

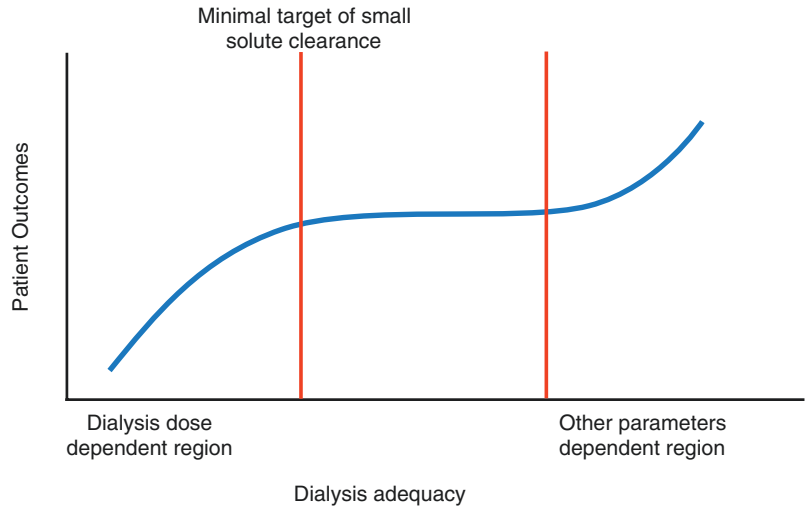

Fig. 15.3 Relationship between dialysis adequacy and survival. Once the minimum target of small solute clearance is achieved, survival rate does not increase. Beyond this point, other factors can play an important role in improving patient outcomes (see Sect. 15.4)

for example, every 4–6 months if RRF is lost and patients do well without any significant deterioration in physical health. For patients without RRF, peritoneal Kt/*V* should be targeted to at least >1.7 by increasing frequency of exchanges or dialysis solution volume.

15.2.2 Kt/*V* Urea vs. CrCl

There is lack of evidence as to which parameter is superior in predicting adverse outcome. An early observation showed more experience and fewer methodological problems with Kt/*V* (Twardowski 1998). In addition, Kt/*V* urea is exclusively used for measurement of hemodialysis adequacy. In this regard, many physicians are more familiar with Kt/*V* urea than CrCl, and the former is more commonly used in clinical practice. As aforementioned, renal creatinine clearance overestimates true clearance and generally exceeds urea clearance. In contrast, creatinine slowly diffuses into the peritoneum due to higher molecular weight than urea; peritoneal CrCl is lower than urea clearance (Fig. 15.2). Therefore, CrCl should be interpreted with caution depending on PD modality and membrane types. Nevertheless, these two measures are small solute clearance and do not reflect middle molecule clearance. Given a variety of uremic toxins beyond small solute and disappointing results of the ADEMEX and the Hong Kong study, the targets for small solute clearance proposed by many guidelines should be understood as the minimum level to accomplish dialysis adequacy (Fig. 15.3).

15.3 Factors Affecting Peritoneal Clearance

There are number of factors that determine peritoneal small solute clearance. As presented in Table 15.4, these can be classified into inherent and modifiable factors. Factors such as RRF, body size, and peritoneal membrane characteristics are inherent in individual patient, thus not easily modifiable. In contrast, we can adjust dwell volume, frequency of PD solution exchange, and use of high glucose concentration PD solution depending on patient's inherent factors. Strategies for increasing small solute clearance are summarized in Fig. 15.4.

15.3.1 Inherent Factors

15.3.1.1 RRF

As noted above, total Kt/*V* urea and CrCl are largely dependent on RRF, while urine volume is maintained. It can contribute approximately up to 50% of total clearance during the initial period of dialysis. Accordingly, physicians should be alert

on decline of RRF and consider increasing peritoneal clearance targeted to Kt/*V* of at least >1.7 when patients become anuric (Fig. 15.4 and Fig. 15.5). The importance of RRF has recently been highlighted in many aspects. It has been well demonstrated that RRF is more important than small solute clearance in determining clinical outcomes in dialysis patients. Therefore, much effort should be made to preserve RRF. This is discussed in detail in Sect. 15.5.

Table 15.4 Factors affecting peritoneal clearance

Inherent	Modifiable
RRF Body size Peritoneal membrane transport type	Dwell volume Dwell duration and exchange frequency The use of high glucose concentration PD solutions

15.3.1.2 Body Size

Body size can also affect total clearance because Kt and CrCl are normalized to volume of distribution of urea, which is equal to total body water, and BSA, respectively. Theoretically, patients with extremely large body size may not adequately maintain PD in terms of small solute clearance. If a patient undergoes four exchanges of 2.0 L PD solutions per day to meet the target of Kt/*V* of >1.7 and net ultrafiltration is 1.0 L, then *V* = D/P urea ratio × (7 days × 9.0 L)/1.7. Assuming a D/P urea ratio of 0.9, then *V* is 40.6 L, which approximately fits to a man with a standard body size, 170 cm in height, and 70 kg in weight. Thus, obese patients have extremely high *V*, it is difficult to achieve a Kt/*V* urea target of >1.7 when typical peritoneal dialysis prescription is given. Conversely, Kt/*V* can be interpreted

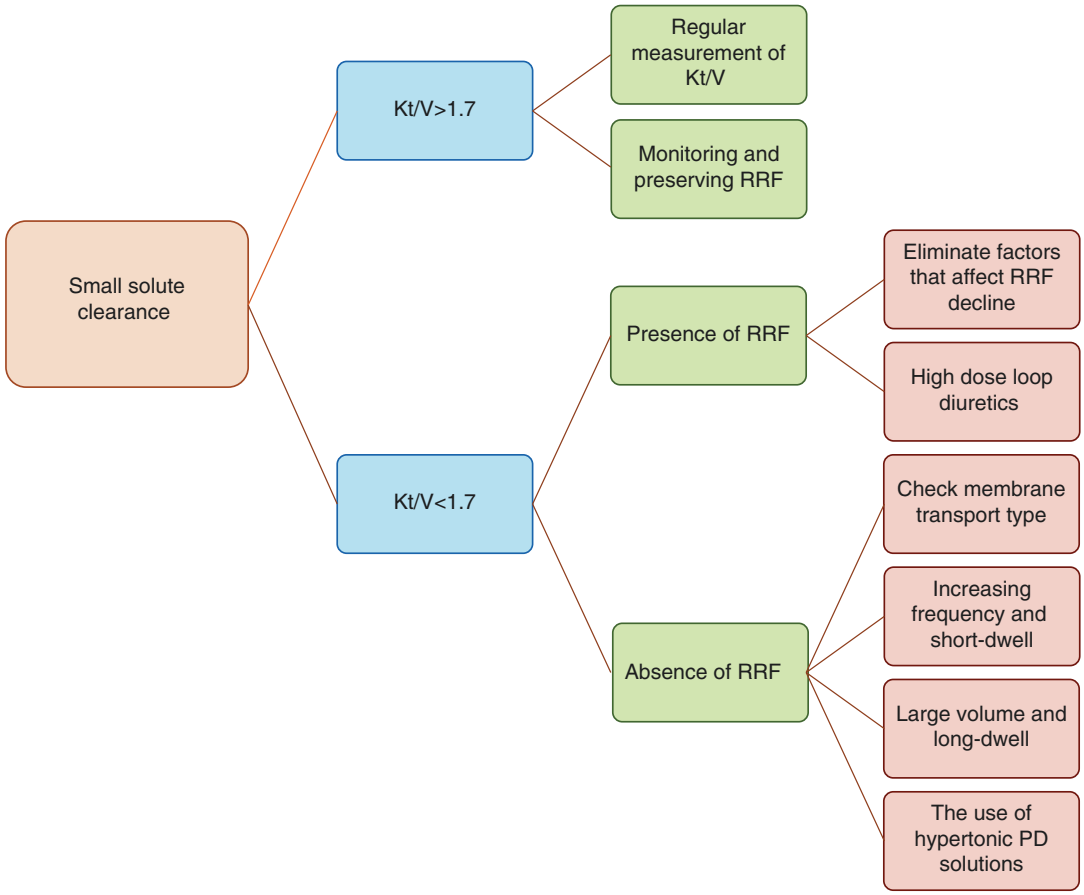

Fig. 15.4 Strategies for improving small solute clearance

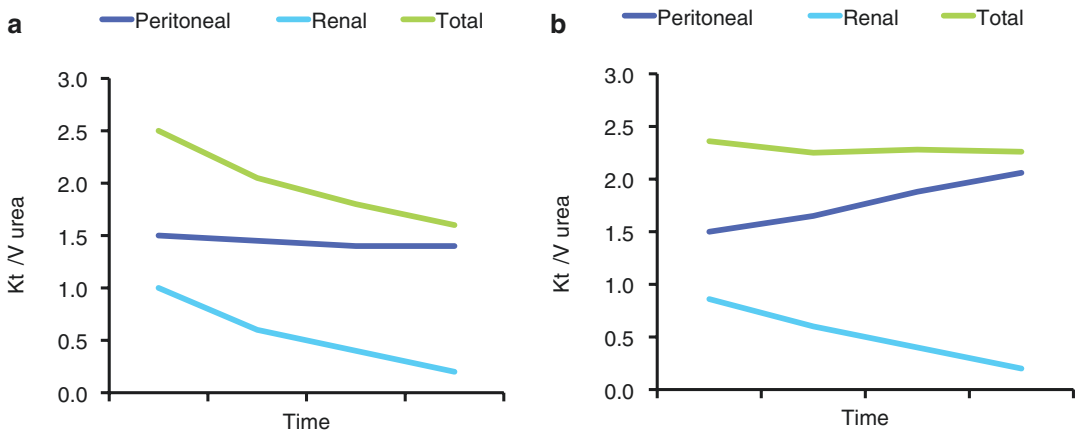

Fig. 15.5 Relationship between total Kt/*V*, peritoneal clearance, and residual renal function over time. (**a**) Total clearance decreases without increasing peritoneal clearance as residual renal function declines. (**b**) Total clearance remains unchanged if peritoneal clearance increases corresponding to a decrease in residual renal function

with caution in patients with very low *V*. Because these patients are more likely malnourished and deprived of muscle, it is not fair to say they do well on dialysis even though Kt/*V* is >1.7.

15.3.1.3 Peritoneal Membrane Characteristics

Peritoneal membrane transport types can be determined by peritoneal equilibration test. It is important to define membrane transport status in dialysis prescription. As seen in Fig. 15.2, equilibration of creatinine or larger molecules is slower and lower than that of urea. This can raise a problem regarding dialysis adequacy in patients on APD. These patients use a cycler and typically do 4–5 exchanges during 8–10 h. This inevitably requires short and frequent exchanges, resulting in lack of enough time for larger molecules to equilibrate. Urea clearance is acceptable because urea rapidly equilibrates within several hours. However, larger molecules than urea are not adequately removed due to the slower diffusion. This becomes more pronounced in slow transporters (previously known as low transport). These patients exhibit much slower equilibration of solutes than fast transporters. For this reason, dialysis prescription can be tailored depending on transport types. In general, high-volume exchanges and long-duration dwells are recommended in slow transporters, whereas short-duration dwell is more effective in fast transporters.

15.3.2 Modifiable Factors

These factors are related to dialysis prescription. When the target of Kt/*V* or CrCl is not achieved, we can adjust dialysis prescription by increasing dwell volume, increasing exchange frequency, and using hypertonic PD solutions. This adjustment is largely dependent on inherent factors, particularly such as transport types.

15.3.2.1 Dwell Volume

As explained above, increasing the dwell volumes is commonly used to achieve the target of Kt/*V* > 1.7, particularly in slow transporters. This strategy is also more effective in patients with large body size than in those with small body size. By doing this, peritoneal clearance can be increased because total drained volume is increased, while urea and creatinine equilibration are slightly decreased, giving a small dip in D/P urea or creatinine. As a result, total Kt calculated as total drained volume multiplied by D/P urea is increased. In patients with small body size, clearance is unlikely to increase by increasing dwell volume because of the greater decrease in equilibration. It is generally known that, assuming four

exchanges given, increasing volume from 2.0 to 2.5 L can induce an approximately 20% increase in peritoneal clearance. However, patients may feel uncomfortable with larger instilled volume and may complain of back pain, abdominal discomfort, or shortness of breath. In addition, inguinal, ventral, or diaphragm hernia can develop due to an increase in intra-abdominal pressure. This complication can cause peritoneal fluid leak into soft tissue, thus leading to localized edema.

15.3.2.2 Adjusting Dwell Duration and Frequency of Exchanges

In typical patients on CAPD with average peritoneal transport types, increasing frequency from four to five exchanges per day accompanied by shortened dwell time does not hamper urea equilibration, which remains at 85–90% as long as patients ensure adequate dwell time of at least 4 h. In slow transporters, increasing clearance can be achieved by increasing dwell duration because creatinine equilibration still rises 4 h after the initiation of the dwell. On the other hand, in fast transporters, osmotic gradient is dissipated soon after the dwell, thus increasing frequency of daily exchanges can be an option to increase peritoneal clearance in these patients. However, one more exchange can be burdensome and limit daily activities in patients who have active lifestyle. They do not want to be tied up with PD exchange procedure. In this regard, increasing dwell volume is more effective and preferred to enhance clearance.

In patients on APD, this strategy of adjusting dwell time and frequency of exchanges can be also applied in clinical practice. These patients use a cycler during nighttime, thus problems of increasing frequency of exchanges can be resolved by the aid of the machine, which is particularly helpful in fast transporters. However, as aforementioned, shortened dwell time caused by frequent exchanges may result in insufficient solute clearance. Loss of RRF can worsen this problem. Moreover, middle molecule clearance is time dependent. Therefore, in this case, many patients require one or more exchanges of daytime dwell to increase clearance. Another way to increase clearance is to increase dwell volume as in CAPD. APD patients are unlikely to complain of abdominal discomfort because intra-abdominal pressure is not increased in supine position. How to prescribe dialysis in APD is described in detail in Chap. 4.

15.3.2.3 The Use of High Concentration Glucose Solution

Because ultrafiltration is mainly derived from osmotic gradient, the use of high concentration glucose solution can increase ultrafiltration volume by inducing higher osmotic gradient. Accordingly, peritoneal clearance can increase as total drained volume is a determinant of Kt. However, there is much concern about glucose toxicity to the peritoneal membrane damage. In addition, glucose can be absorbed via peritoneal capillary beds, leading to systemic harmful effects such as hyperglycemia, hypertriglyceridemia, weight gain, inflammation, etc. For this reason, it is generally recommended to limit the use of high concentration glucose solutions unless volume overload should be controlled. Moreover, glucose-sparing strategies have recently prevailed to preserve peritoneal membrane and to prevent glucose toxicity-associated complication.

15.4 Comprehensive Understanding of Dialysis Adequacy

As seen in the ADEMEX study and the Hong Kong study, further increase in small solute clearance beyond some point did not improve clinical outcomes. In fact, urea and creatinine may be merely markers of kidney function, and there are more uremic toxins besides small solutes. Less importance of small solute clearance was also observed in patients undergoing hemodialysis. The Hemodialysis Study Group conducted a randomized controlled trial in 1846 patients to evaluate whether high dose of dialysis could improve survival compared with standard dose (Eknoyan et al. 2002). They failed to demonstrate that increasing Kt/*V* urea up to 1.7 was beneficial in decreasing mortality and morbidity. The findings

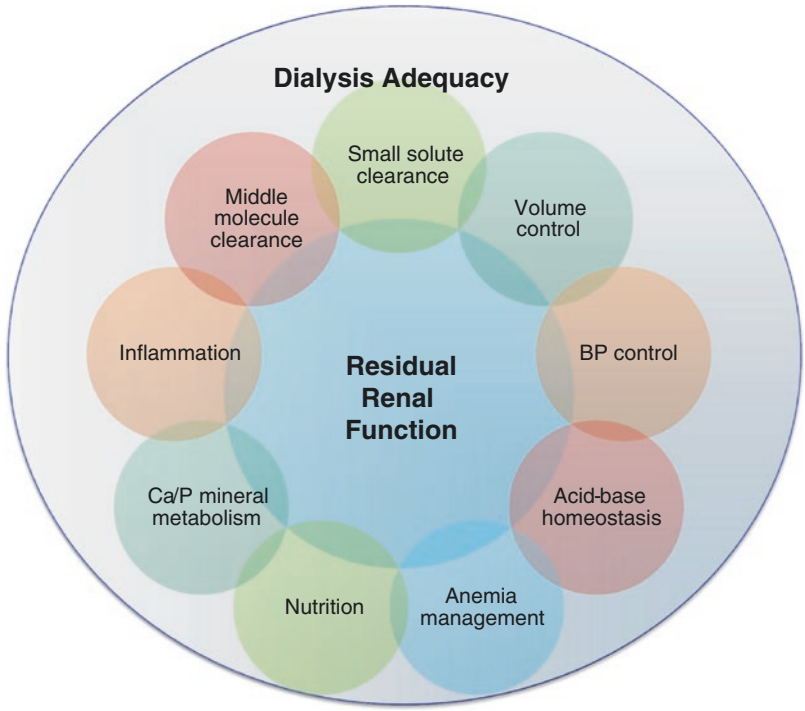

Fig. 15.6 Comprehensive understanding of dialysis adequacy

of the randomized controlled trials in dialysis patients suggest that there are more other factors that can determine clinical outcomes, and thus much attention should be paid to these factors after the minimum targets of Kt/*V* urea and CrCl are achieved. Therefore, we should comprehensively understand dialysis adequacy beyond small solute clearance. Dialysis adequacy cannot be determined by one biochemical marker. More importantly, it should encompass the management of fluid overload, blood pressure, acid-base disturbances, anemia, malnutrition, calcium-phosphorus mineral disturbances, inflammation, and middle molecule clearance (Fig. 15.6). To achieve these goals, RRF should be preserved because kidney is involved in all aspects of dialysis adequacy. It is no wonder why RRF is more associated with clinical outcomes than any other parameters. To corroborate this view, the current guidelines put much emphasis on the preservation of RRF and fluid overload management rather than small solute clearance. These are discussed in detail in Sects. 15. 5 and 15.6.

15.5 RRF

15.5.1 Survival Benefit of RRF

Recently, the importance of RRF has been highlighted through a number of studies. Its significant impact on patient survival was first reported in 1995 by Maiorca et al. (1995). They observed 68 CAPD and 34 HD patients in a prospective observational study for 3 years and found that persistence of RRF was associated with improved survival. In the following year, the CANUSA study first demonstrated the survival benefit with an increase in small solute clearance assessed by Kt/*V* urea. Five years later, the group reanalyzed the CANUSA data to evaluate relative contribution of RRF and peritoneal clearance to dialysis adequacy (Bargman et al. 2001). The results showed that each 5 L/week per 1.73 m^2 increment in GFR was associated with a 12% decrease in risk of death, but no association between peritoneal creatinine clearance and mortality was found. Furthermore, the original finding of the ADEMEX

study indicated no improvement in patient survival by increasing small solute clearance. Interestingly, in the multivariable analysis, residual renal Kt/*V* urea and CrCl were significantly associated with a reduced risk of mortality, whereas peritoneal Kt/*V* urea and CrCl were not. Subsequently published studies from the European cohort and the Asian cohort consistently have shown the survival advantage of RRF compared with no effect of peritoneal clearance on survival. As in PD patients, loss of RRF was a significant predictor of death in HD patients (Shafi et al. 2010).

15.5.2 Mechanistic Link Between RRF and Better Survival

15.5.2.1 Fluid Status, Blood Pressure, Cardiac Hypertrophy, and RRF

There have been a number of studies to explain mechanisms responsible for the improved survival conferred by RRF. As seen in Fig. 15.6, RRF plays an important role in the regulation of a variety of disturbances in dialysis patients. Fluid overload is a significant determinant of adverse outcomes and is highly associated with increased blood pressure, cardiac hypertrophy, and congestive heart failure in these patients. Ates et al. evaluated the effects of fluid and sodium removal on mortality in 125 PD patients (Ates et al. 2001). They observed an increased patient survival rate in proportion to the amount of sodium and fluid removal. In particular, a 3-year patient survival rate was highest in patients with fluid removal >2035 mL/24 h/1.73 m^2, whereas it was lowest in those with fluid removal <1265 mL/24 h/1.73 m^2. Their findings highlight the harmful effects of fluid retention on patient survival. Not surprisingly, fluid overload can be more easily controlled in patients with RRF than in anuric patients. In a cross-sectional study by Konings et al. (2003a, b), extracellular water content was significantly and inversely correlated with residual GFR. In addition, patients with residual GFR < 2 mL/min had higher extracellular water than those with residual GFR > 2 mL/min. This finding suggests that presence of RRF is advantageous for fluid management. Accordingly, blood pressure can be more controlled by maintaining fluid balance in patients with preserved RRF. Menon et al. performed a retrospective observational study to identify factors associated with uncontrolled blood pressure in 207 PD patients (Menon et al. 2001). In their study, declining RRF was significantly associated with high blood pressure. Moreover, fluid overload can contribute to the development of left ventricular hypertrophy. The prevalence of left ventricular hypertrophy is remarkably high, up to 75–90% in patients who initiate dialysis (Wang et al. 2002a, b, 2004a, b, c). It is well known that it is an independent predictor of cardiovascular events and death in dialysis patients (Silberberg et al. 1989). In a cross-sectional study by Wang et al., left ventricular hypertrophy index was significantly lower in patients with preserved RRF than anuric patients. However, this association was not observed for peritoneal clearance. Interestingly, sodium and fluid removal differ between the kidney and the peritoneum depending on presence or absence of RRF in patients undergoing PD. Cheng et al. evaluated fluid status by using bioimpedance analysis in 195 CAPD patients and found that sodium and fluid removal was greater by the kidney than by the peritoneum in patients with urine volume > 400 mL per day (Cheng et al. 2006). Conversely, peritoneal clearance in sodium and fluid removal became more important as RRF declined. Taken together, all these findings suggest that in the absence of RRF, patients are more likely to have fluid overload, high blood pressure, and cardiac dilatation, which ultimately result in the increased cardiovascular morbidity and mortality.

15.5.2.2 Middle Molecule and Phosphate Clearance and RRF

Middle molecule clearance has recently emerged as an important therapeutic target in dialysis patients. Among many middle molecules, β2-microglobulin (β2MG) has widely been investigated. Many studies have consistently shown that β2MG is a strong and independent predictor of mortality in ESRD patients. RRF is also associated with removal of middle molecules.

Bammens et al. conducted a longitudinal observational study to evaluate relative contribution of the peritoneum and the kidney to the clearance of small solutes and β2MG (Bammens et al. 2005). Renal clearance of urea and creatinine declined over time, while peritoneal clearance of these molecules increased. Interestingly, there was also a decline in renal clearance of β2MG, but its peritoneal clearance remained stable throughout the study period. These findings suggest that, for small solutes, peritoneal clearance can increase in compensation for loss of RRF. However, the elimination of middle molecule, β2MG, is less likely to be counterbalanced by the peritoneum.

Phosphate toxicity has been well recognized in CKD patients. In fact, phosphate promotes vascular calcification process, which in turn increases cardiovascular risk. Kidney is a major organ that regulates phosphate clearance. Accordingly, phosphate accumulates in the body as CKD progresses. It is well known that hyperphosphatemia is a significant predictor of mortality in CKD patients. Phosphate is a small molecule because its molecular weight is only 96 D. Phosphate itself is not water-soluble and thus theoretically cannot be removed by dialysis therapy. Interestingly, phosphate behaves like a middle molecule because it is surrounded by water molecules, making it water-soluble and thus dialyzable. Not surprisingly, RRF plays an important role in removal of phosphate (Wang et al. 2004a, b, c). Residual GFR is inversely correlated with serum phosphate levels in dialysis patients. Because middle molecule clearance is more affected by RRF than by the peritoneal clearance, phosphate control is much difficult in patients without RRF. Thus, presence of RRF has advantage of the elimination of phosphate and middle molecules.

15.5.2.3 Inflammation and RRF

Inflammation is another important predictor of adverse outcomes in dialysis patients. It is significantly associated with malnutrition, arteriosclerosis, and increased cardiovascular risk in these patients. Increased mortality rate is also observed in PD patients with increased CRP levels (Noh et al. 1998). There is evidence that loss of RRF can contribute to inflammation. In a cross-sectional study by Pecoits-Filho et al., residual GFR was inversely correlated with serum levels of inflammatory markers such as high-sensitive CRP and IL-6 (Pecoits-Filho et al. 2003). In addition, a prospective observational study by Wang et al. revealed that the combination of inflammation, loss of RRF, and cardiac hypertrophy was significantly associated with an increased risk of death in PD patients (Wang et al. 2004a, b, c). Although causality is uncertain, it can be presumed that loss of RRF and inflammation work together in a vicious cycle, eventually leading to the increased mortality.

15.5.2.4 Vascular Protection and RRF

The importance of RRF has also been recognized from a viewpoint of vascular protection. Endothelial dysfunction and arterial stiffness in CKD patients are of multifactorial origin including traditional and nontraditional risk factors. Many of these factors such as blood pressure, fluid overload, and inflammation are significantly associated with RRF as mentioned earlier. Thus, it can be presumed that vascular insufficiency is less severe in patients with preserved RRF compared to patients without RRF. In fact, endothelial dysfunction assessed by flow-mediated dilation was significantly correlated with residual GFR in PD patients (Han et al. 2012). In addition, another study demonstrated that brachial artery pulse wave velocity, a marker of arterial stiffness, was inversely associated with RRF (Huang et al. 2008). These findings suggest that preservation of RRF can be also helpful in protecting vascular function.

15.5.2.5 Nutritional Status and RRF

Malnutrition is a serious complication in dialysis patients. RRF is also associated with nutritional status. There are number of studies indicating significant association between RRF and parameters of nutritional status such as lean body mass, normalized protein catabolic rate, subjective global assessment score, dietary protein intake, serum albumin, and handgrip strength. The differential effects of RRF and peritoneal clearance on nutritional intake were demonstrated by Wang et al. In their findings, presence of RRF significantly contributed to better protein and calorie intake, whereas increased peritoneal solute clearance had no impact

on nutritional intake (Wang et al. 2002a, b). RRF also showed an inverse relationship with resting energy expenditure (Wang et al. 2004a, b, c), suggesting disturbed protein metabolism as kidney function declined. As mentioned earlier, loss of RRF can accelerate inflammatory status. Of note, inflammation is an important mediator that aggravates muscle wasting and anorexia. Presumably, malnutrition can be worsened by loss of RRF via exacerbated inflammation.

15.5.2.6 Peritonitis and RRF

The potential association between RRF and PD-related peritonitis has also been suggested. Several studies have shown that risk of PD-related peritonitis was lower in patients with preserved RRF (Perez Fontan et al. 2005; Han et al. 2007). Conversely, there is an opposite direction of the relationship indicating that peritonitis can accelerate loss of RRF (Szeto et al. 2007) possibly as a result of infection itself or the use of nephrotoxic antibiotics. Whichever comes first, peritonitis is significantly associated with morbidity and mortality in PD patients, and thus it should be prevented by using available strategies.

15.5.3 Strategies to Preserve RRF

Even though declining residual function in dialysis patients is inevitable after commencing dialysis, the diseased kidney can still carry out numerous functions. Therefore, nephrologists should attempt to preserve RRF. Conventionally, as in CKD patients prior to dialysis, avoidance of the use of nephrotoxic drugs and volume depletion is highly recommended. Much attention should be paid to dialysis patients with presence of RRF before the use of contrast dye. Blood pressure should be well controlled given the relationship between uncontrolled blood pressure and CKD progression. PD-related peritonitis should also be prevented and be promptly managed if it occurs, given the accelerated decline in RRF after peritonitis. However, there is lack of evidence as to whether all the conventional strategies can indeed be of help in the preservation of RRF. The rationales for the application of these to dialysis patients are largely speculative based on the results of the studies in non-dialysis CKD population.

In addition to the general management, there are more available options to prevent loss of RRF: (1) PD as the first therapy when commencing dialysis, (2) the use of renin-angiotensin system (RAS) inhibitors, and (3) the use of new PD solutions (Fig. 15.7). These strategies have been studied mostly in PD patients, and thus there has been more evidence for utilization of these in this population compared with HD patients.

15.5.3.1 PD as the First Dialysis Modality

In general, PD is known to preserve RRF better than HD. Although this concept has long been accepted, relevant studies to this are not randomized controlled trials, but mostly observational in nature, and thus the findings of these studies should be interpreted with caution. Moist et al. analyzed factors associated with loss of kidney function in 1843 dialysis patients using the US Renal Data System (USRDS) data and found that PD was associated with a 65% risk reduction of developing a urine volume < 200 mL per day compared to HD (Moist et al. 2000). In line with this result, the European cohort study also observed a similar finding. The Netherlands Cooperative Study on the Adequacy of Dialysis phase-2 (NECOSAD-2) study involved 522 incident dialysis patients treated with PD or HD from 32 dialysis centers nationwide (Jansen et al. 2002). The results showed that residual GFR declined faster in HD patients than in PD patients during a 12-month observation period. The better preservation of RRF by PD is well reflected in survival benefit of PD over HD, particularly during early period after dialysis initiation. Heaf et al. first suggested the better survival rate in PD patients than in HD patients up to 2 years after dialysis initiation (Heaf et al. 2002). Since then, many epidemiologic studies have consistently shown similar findings (McDonald et al. 2009; Weinhandl et al. 2010; Choi et al. 2013; Kumar et al. 2014). This phenomenon may be attributed to unseen confounding factors between patients on HD and PD, but many researchers believe that

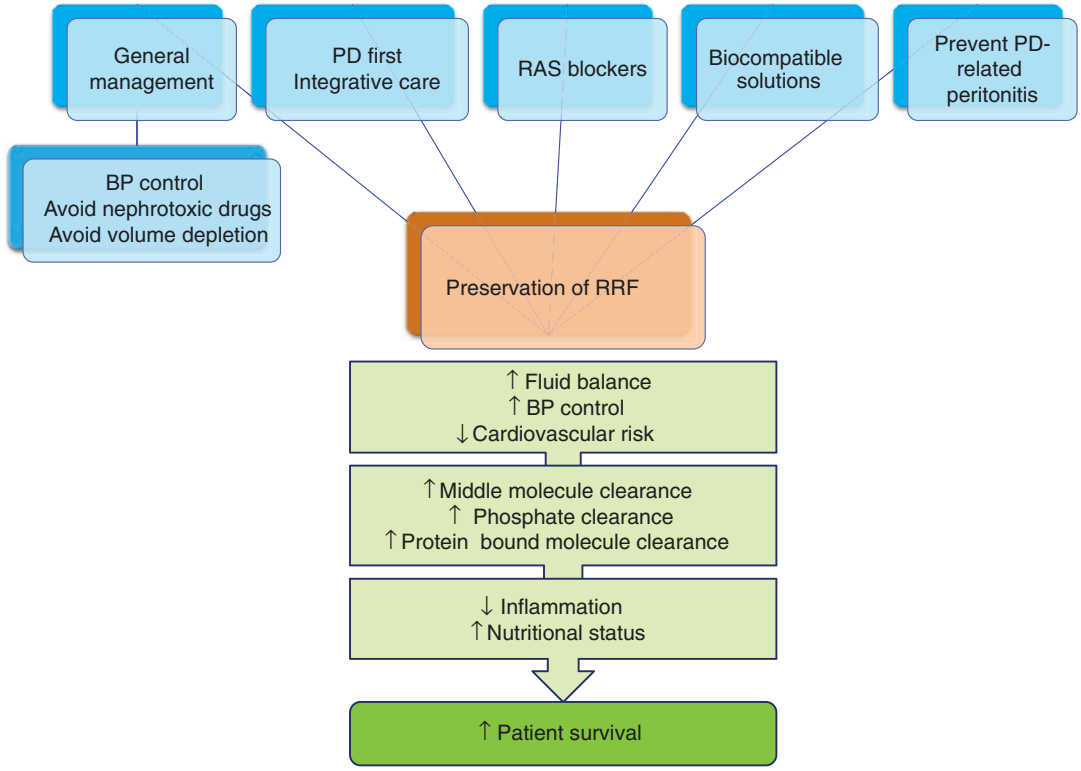

Fig. 15.7 Strategies to preserve RRF and beneficial effects of RRF

preserved RRF plays a significant role in the survival advantage of PD over HD during initial period of dialysis. Based on these results, some groups proposed an "integrative care approach" when commencing dialysis. This includes sequential utilization of PD first and then HD, given the favorable effect of PD on RRF. In fact, in a single-center retrospective analysis, this approach was associated with better patient survival compared to patients who started and remained on PD alone or HD alone (Van Biesen et al. 2000). However, further large-scale studies are required to confirm this finding.

The exact mechanisms for better maintaining kidney function by PD are unclear. Renal ischemia is considered a key explanation for this. Because HD is intermittently provided compared with continuous nature of PD, the volume gained during interdialysis period should be removed during only 3–4 h of HD treatment. For this reason, not surprisingly, renal ischemia occurs more frequently in HD than in PD. In addition, inflammatory mediators are released from extracorporeal circulation during HD treatment and exhibit nephrotoxic effects on the kidney. These together can eventually lead to faster loss of RRF in HD patients. During the past decades, HD technology has greatly advanced. Accordingly, there has been hope that the disadvantage of HD regarding faster deterioration of RRF can be overcome by the new advanced HD modalities. Nowadays, cellulose membrane, which is known as a main culprit for inflammatory cytokine production, has been replaced by a new biocompatible HD membrane. In addition, hemodiafiltration can provide more hemodynamic stability and more removal of inflammatory cytokines than conventional HD. Interestingly, two previous studies showed that a gap in a decline rate in RRF between PD and HD was decreased or null since biocompatible polysulfone membrane was utilized (Lang et al. 2001; McKane et al. 2002). Unfortunately, these studies are limited by small sample size or observational nature, and no other

studies have been conducted to examine this issue thereafter. Thus, evidence level is very low. Of note, recent randomized controlled trials failed to show that RRF was more preserved by hemodiafiltration as compared with conventional HD (Penne et al. 2010; Mostovaya et al. 2014). Further studies are required to investigate whether the use of new modalities can prevent rapid loss of RRF in HD patients.

15.5.3.2 The Use of RAS Blockers

RAS inhibitors have been proven to prevent progression of kidney disease in patients with CKD prior to dialysis. To date, there have been several randomized controlled trials to investigate whether these drugs could preserve RRF in dialysis patients. Most studies have been conducted in PD patients, whereas there was only one in HD patients. Li et al. conducted a prospective randomized controlled open-label trial in 60 PD patients and found that RRF declined slower in the angiotensin-converting enzyme inhibitor group than in the control group (Li et al. 2003). In addition, another randomized controlled open-label study of 34 PD patients showed that the use of an angiotensin receptor antagonist, valsartan, resulted in better preservation of RRF (Suzuki et al. 2004). However, a recent prospective randomized placebo-controlled double-blinded trial of 82 HD patients did not prove superiority of RAS inhibitor to placebo in the preservation of RRF (Kjaergaard et al. 2014). It is possible that hemodynamically negative effects of HD on RRF may overwhelm the renoprotective effects of RAS blockers. Nevertheless, given the importance of RRF, the use of RAS inhibitors can be incorporated as a therapeutic strategy to preserve RRF in dialysis patients.

15.5.3.3 The Use of New PD Solutions

During the past decades, there has been much concern on "glucose toxicity" of high glucose contents of PD solutions. These include deleterious effects of bioincompatible characteristics of the solutions on peritoneal membrane, systemic inflammation, and even RRF. Therefore, new neutral pH biocompatible solutions containing low glucose degradation products (GDPs), or non-glucose-based solutions such as icodextrin or amino acids, have been developed and commercially available. There is evidence to favor the use of the new solutions from a viewpoint of preserving RRF. The initial study by Fan et al. failed to show the beneficial effect of the new PD solutions on the preservation of RRF (Fan et al. 2008). However, in a prospective randomized controlled open-label trial by Kim et al., residual GFR and urine volume declined faster in the conventional solution group than in the biocompatible solution group during 1-year follow-up period (Kim et al. 2009). A subgroup analysis showed that the better preservation of RRF by biocompatible solutions was more pronounced in patients with residual GFR > 2 mL/min per 1.73 m^2. A subsequent study by Haag-Weber et al. included patients with residual GFR ≥ 3 mL/min per 1.73 m^2 and observed a similar finding (Haag-Weber et al. 2010). These findings were not entirely supported by the Balance in Australian and New Zealand (balANZ) trial (Johnson et al. 2010). This was a prospective randomized open-label multicenter study involving the largest number of patients regarding this issue. Overall decline rate in residual GFR did not differ between groups, but time to the development of anuria was significantly longer in the biocompatible solution group than in the conventional solution group. Interestingly, the biocompatible solution group also had significantly longer time to the first peritonitis episode compared to the control group. It is uncertain why biocompatible solutions exhibit the renoprotective effect on RRF. One potential mechanism is the decreased burden of GDPs due to the less systemic absorption via the peritoneum, which is considered the main factor that can generate inflammatory and oxidative damage to the kidney. In addition, as noted in the balANZ trial, delayed onset of peritonitis can also provide an alternative explanation for the beneficial effect of the biocompatible solutions, given the bidirectional relationship between RRF and peritonitis.

Icodextrin PD solution has also been developed with an aim to reduce glucose toxicity. Icodextrin is a glucose polymer and induces ultrafiltration by colloid osmosis. Since Davies

et al. first suggested the renoprotective effect of this solution, many studies have produced conflicting results regarding this issue. Cho et al. performed a systemic review of randomized controlled trials that had evaluated the effects of icodextrin solution and showed comparable effects on residual GFR or urine volume between icodextrin solution and conventional solutions (Cho et al. 2013). However, a change in RRF was not a primary outcome in all studies. Of note, a recent prospective randomized controlled multicenter trial by Chang et al. primarily focused on RRF and found that residual urine volume was more preserved in the icodextrin group than in the control group despite no difference in a decline rate in residual GFR between groups (Chang et al. 2016). The underlying mechanism for this effect is uncertain, but one potential explanation includes the presence of high-molecular-weight icodextrin metabolites in plasma, which in turn may increase plasma oncotic pressure and hence preserve plasma volume and renal perfusion.

There are no guidelines that recommend the use of biocompatible or icodextrin solutions for the purpose of preserving RRF. A systematic review of the new PD solutions appeared to favor the renoprotective effects of the biocompatible solutions compared to conventional solutions, whereas the net effect of icodextrin on RRF was inconclusive (Cho et al. 2013).

15.6 Fluid Overload Management

The current guidelines recognize well the importance of RRF and fluid overload in dialysis patients and thus put much emphasis on preserving RRF and maintaining euvolemia to achieve dialysis adequacy. As aforementioned, fluid overload is significantly associated with high blood pressure, left ventricular hypertrophy, and congestive heart failure. All are well-known cardiovascular risk factors, and thus uncontrolled fluid overload will eventually result in the increased cardiovascular morbidity and mortality. Adequate fluid balance is particularly important in anuric patients. In the prospective observational European APD Outcome Study (EAPOS), baseline peritoneal ultrafiltration <750 mL per day was significantly associated with an increased risk of death in anuric patients on APD (Brown et al. 2003). In line with this, the NECOSAD study group also showed that increased peritoneal ultrafiltration was significantly associated with better survival (Jansen et al. 2005). These findings together highlight the importance of fluid balance in dialysis patients.

15.6.1 Factors Causing Fluid Overload

15.6.1.1 Loss of RRF

There are many factors that can cause fluid overload in PD patients (Table 15.5). Not surprisingly, loss of RRF is a major contributor to the fluid overload. The importance and the preservation of RRF are discussed in detail above (see Sects. 15.5.2 and 15.5.3). Fluid overload can become a serious concern while RRF declines over time. In general, most dialysis patients eventually become anuric in several years after commencing dialysis. Therefore, regular monitoring of RRF and fluid status is required to maintain euvolemia. A corresponding increase in dialysis dose by increasing either frequency or volume of PD solution exchanges should be considered in compensation for loss of RRF.

15.6.1.2 Excessive Salt and Fluid Intake

Excessive salt intake and inadequate peritoneal ultrafiltration are also important causative factors for fluid overload. Failure to dietary restric-

Table 15.5 Causes of fluid overload in PD patients

1. Loss of RRF
2. Excessive salt and water intake
3. Insufficient peritoneal ultrafiltration
• Non-compliance with PD prescription
• Mechanical complications: Peritoneal fluid leak or catheter malfunction
• Peritoneal membrane failure
• Excessive fluid absorption during the long-dwell exchanges
4. Decompensated heart failure

tion is very common, up to 67% in PD patients (Griva et al. 2014a, b). Tzamaloukas et al. assessed clinical features of PD patients with fluid retention (Tzamaloukas et al. 1995). Symptomatic fluid retention was commonly observed in up to 30.7% of all patients and was associated with peripheral edema, pulmonary congestion, pleural effusion, and hypertension. Patients who did not adhere to dietary restriction and had excessive fluid and salt intake were more likely to have fluid retention and its associated problems. The authors also found that inadequate peritoneal ultrafiltration was another important factor associated with fluid retention. A previous study by Gunal et al. further substantiated these findings (Gunal et al. 2001). They performed a stepwise approach to achieve normal blood pressure in 47 hypertensive PD patients. Interestingly, 20 (42.5%) patients achieved a blood pressure of <140/90 mmHg after 4-week salt restriction alone of <4 g/day. Of the remaining 27 patients, increasing peritoneal ultrafiltration by using hypertonic glucose solutions combined with maintaining salt restriction additionally resulted in normal blood pressure in 17 (36.2%) patients. Together, 37 (78.7%) patients achieved a target blood pressure without adding antihypertensive medications. These findings highlight the importance of salt restriction and adequate peritoneal ultrafiltration in the management of fluid overload.

15.6.1.3 Insufficient Ultrafiltration

Non-compliance is another important cause of insufficient ultrafiltration. A recent systematic review study with respect to nonadherence issue reported the rates of nonadherence to dialysis exchanges to be approximately >20% of patients (Griva et al. 2014a, b). Factors associated with non-compliance are controversial between studies, but one small group study showed that patients who did not have a person to help exchange procedure were more non-compliant than those who were assisted by someone (Bernardini et al. 2000).

Inadequate peritoneal ultrafiltration can be also caused by mechanical complications and peritoneal membrane failure. Mechanical complications include peritoneal fluid leak associated with hernias and peritoneal-pleural shunt and catheter malfunction. These appear to occur more frequently during the early period after commencing dialysis (see Sect. 15.7, Complication of PD). Peritoneal membrane transport characteristics are an important determinant of peritoneal ultrafiltration. In this regard, PD prescription can be adjusted depending on membrane transport types. In general, patients with fast transport are vulnerable to fluid overload because osmotic gradient dissipates quickly after the dwell, and thus short and frequent exchanges are recommended in these patients. Membrane failure frequently occurs particularly in long-term PD patients. In clinical practice, peritoneal equilibration test should be done at least every 6 months to characterize and monitor membrane transport type. In fact, increasing D/P creatinine ratio at 4 h generally precedes the development of ultrafiltration failure (Davies et al. 1996). Therefore, much attention should be given to long-term PD patients who develop fluid overload without specific causes and exhibit a progressive increase in D/P creatinine ratio.

Insufficient ultrafiltration can occur as a result of excessive fluid absorption during the long-dwell exchanges. In this case, patients typically complain of the decreased net ultrafiltration after the night exchange in CAPD or the daytime exchange in APD.

15.6.1.4 Congestive Heart Failure

Cardiovascular disease is the most common cause of morbidity and mortality in dialysis patients. Not surprisingly, fluid management is difficult when heart failure occurs. A number of studies have shown that many circulating biomarkers and echocardiographic parameters could predict the future cardiovascular adverse outcomes even in asymptomatic dialysis patients. This led many physicians and researchers to acknowledge the need for monitoring of cardiac function. Accordingly, the KDOQI guidelines suggest that echocardiograms should be performed in all patients at the initiation of dialysis and at 3-yearly intervals thereafter (Evidence C).

15.6.2 Management of Fluid Overload

15.6.2.1 Regular Monitoring of Fluid Status

To maintain euvolemia, routine monitoring of RRF, fluid status, and peritoneal membrane function is mandatory. Detailed methods on evaluating RRF and peritoneal membrane function are described in other sections. To evaluate fluid status, physical examination and clinical assessment should be primarily performed, which are easily used in clinical practice. These include obtaining previous history and symptoms and examining signs of volume overload such as peripheral edema, elevated blood pressure, swollen jugular vein, and pulmonary congestion on chest X-ray. However, it is not easy to evaluate exact fluid status by physical examination alone because significant fluid overload can be present in the absence of detectable signs and symptoms.

To increase diagnostic accuracy of fluid overload, many assessment devices have been tested and validated such as trace dilution techniques, imaging studies, circulating biomarkers, and bioimpedance analysis. Theoretically, dilutional methods by using deuterium and bromide have high levels of reproducibility and accuracy and are considered gold standard methods to assess water contents of the body. However, these are very costly and cumbersome and thus have not been widely used in clinical practice.

Imaging studies such as intravenous collapse index and echocardiography can also be used, but have limitations in wide interpatient variability, operator dependency, and high variations depending on cardiac function. Circulating biomarkers such as atrial natriuretic peptide (ANP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and cyclic guanidine monophosphate (cGMP) have been reported to predict adverse outcomes in dialysis patients. However, these markers also have wide interpatient variability and are mostly secreted by the kidney. In addition, there is much concern about inability of these markers to discriminate fluid status.

Bioimpedance analysis is a relatively easy technique to assess fluid status. It can measure both extracellular and intracellular water contents and assess nutritional status. In addition, fluid status assessed by this method well correlates with the results determined by dilutional methods and is highly reproducible. However, it can underestimate volume removed from trunk and temperature, and ion effects and recumbent position can affect water contents assessed by this method. To date, there is no single test to precisely represent fluid status. A variety of tests together can be applied to increase accuracy, but cost-effectiveness and inconvenience should be taken into account. Regardless of which assessment methods are used, regular and serial measurements using the same method seem to be the most helpful and reliable way to determine the fluid status in an individual patient.

15.6.2.2 Management of Fluid Overload

Preservation of RRF

Table 15.6 presents a summary of management of fluid overload in dialysis patients. RRF should be preserved given its important role in fluid status. Preventive strategies against loss of RRF are described in detail above (see Sect. 15.5.5.3).

High-Dose Loop Diuretics

The use of diuretics is also a useful option to manage fluid overload, as long as sufficient RRF exists. In general, high loop diuretics are recommended in advanced stages of CKD given its pharmacodynamics. Dialysis therapy does not influence removal of diuretics (Sica 2012). Studies to evaluate the effects of diuretics are lacking in ESRD population. Favorable effects of high-dose furosemide on preservation of RRF were first suggested by Medcalf et al. (2001). They conducted a randomized controlled trial in 61 incident PD patients and found that urine volume and sodium excretion were greater in patients assigned to furosemide 250 mg compared to control group. In agreement with this finding, reanalysis of the data from the Dialysis

Table 15.6 Management of fluid overload

1.	Regular monitoring
	RRF
	Fluid status
	Peritoneal membrane function
2.	Preservation of RRF
3.	High-dose loop diuretics (in presence of RRF)
4.	Diet control
	Dietary counseling
	Salt and water restriction
5.	Enhanced compliance via education
6.	Increasing peritoneal ultrafiltration
	Proper use of hypertonic solutions
	Blood sugar control
	Awareness of long-term effects of hypertonic solutions
	Modification of PD prescription depending on types of ultrafiltration failure
7.	Preservation of peritoneal membrane function
	Prevention of PD-related peritonitis
	Avoidance of frequent use of high glucose concentration solution
	Biocompatible solution containing low GDPs
	Non-glucose-based solution (icodextrin, amino acids)

Outcomes and Practice Patterns Study (DOPPS) showed diuretic users were more likely to have RRF at 1 year after entering the study than non-users (Bragg-Gresham et al. 2007). In contrast, a small group study involving 62 PD patients alone failed to show beneficial effects of furosemide on preserving RRF (Flinn et al. 2006). Nevertheless, patients with presence of RRF have merits in many aspects. To date, the use of high-dose furosemide is widely accepted as a therapeutic option to maintain euvolemia.

Diet Control

Because excessive salt and water intake is the primary cause of fluid overload, dietary counseling can be helpful. Dietary restriction is not routinely recommended for all patients. However, it should be given to patients who have persistent edema and uncontrolled blood pressure. The effect of dietary restriction alone on normalization of blood pressure was demonstrated in small group studies as discussed above (Tzamaloukas et al. 1995).

Enhanced Compliance Via Education

Non-compliance to dietary restrictions or the prescribed peritoneal dialysis regimen can be improved through repeated education programs. Every PD facility should implement such program that can assess issues regarding inadequate dialysis. Home visit program is another good option to increase compliance and optimize dialysis effectiveness. This can be more effective particularly in patients who do not have someone to assist exchange procedure, elderly people, or physically disabled patients. In one small group case-control study in Italy, home visit program was associated with improved technique survival (Martino et al. 2014).

Increasing Peritoneal Ultrafiltration

Hypertonic PD solutions should be considered to use if fluid overload persists particularly in anuric patients. Some patients have concern about the use of high concentration glucose solution because of infusion pain, long-term deleterious effects of high glucose burden, or hyperglycemia in diabetic patients. Proper education should be delivered to these patients. Blood sugar levels in diabetic patients should be monitored and controlled because osmotic gradient across the peritoneal membrane induced by high concentration glucose solution use is required for fluid removal. PD prescription should be modified in patients with ultrafiltration failure depending on peritoneal membrane transport status. This is discussed in detail in Sect. 15.5.6.3 below.

Preservation of Peritoneal Membrane Function

To maintain consistently adequate ultrafiltration and clearance, strategies to preserve peritoneal membrane function should be employed. To this end, PD-related peritonitis should be prevented because peritonitis can directly give damage to the peritoneum. Severe and prolonged peritonitis which has not been resolved despite the proper use of antibiotics can eventually lead to structural and functional derangement of peritoneal membrane. Although hypertonic PD solutions are allowed for the management of fluid overload, avoidance of the frequent use of these solutions is

recommended to minimize glucose toxicity to the peritoneum. It is well known that long-term exposure to glucose is a main cause of peritoneal membrane failure. In addition, glucose absorbed during PD may induce weight gain, hyperglycemia, lipid abnormalities, and insulin resistance and thus increase cardiovascular risk. For this reason, "glucose-sparing strategies" have been recently proposed to lessen glucose toxicity. These approaches focus on fluid management with the reduced need for hypertonic solution use, salt and water restriction, the use of high-dose loop diuretics in the presence of RRF, preservation of RRF, and the use of non-glucose-based solutions.

The harmful effects of the conventional glucose-based solutions are mainly attributed to "bioincompatibility," which is characterized by GDPs, lactate, low pH, and high osmolality. Therefore, new neutral pH, bicarbonate-buffered biocompatible solutions containing low GDPs have recently been highlighted. In vitro and in vivo studies have demonstrated the strengths of the biocompatible solutions compared to conventional solutions with respect to the improved viability of peritoneal mesothelial and inflammatory cells, less accumulation of GDPs, reduced new vessel formation, and decreased fibrosis (Hoff 2003; Mortier et al. 2004; Fabbrini et al. 2006). However, whether these favorable findings from experimental studies can be translated into the better peritoneal membrane function is uncertain. Early studies showed that the use of new biocompatible solutions resulted in more peritoneal ultrafiltration volume than conventional solutions (Tranaeus 2000; Fan et al. 2008). However, these findings were not validated by many subsequent studies (Fang et al. 2008; Kim et al. 2009; Haag-Weber et al. 2010; Johnson et al. 2012; Lui et al. 2012). Interestingly, there may be reciprocal changes between RRF and peritoneal ultrafiltration; a decrease in RRF is compensated by an increase in peritoneal ultrafiltration or vice versa. Thus, it is possible that the effects of the biocompatible solutions on RRF or peritoneal ultrafiltration may not be caused by "biocompatibility" itself, but can simply vary depending on fluid status. However, the study duration was 1 or 2 years in most trials, thus further long-term studies are required to prove superiority of the new biocompatible solutions, particularly after RRF is lost.

Another option to decrease "glucose toxicity" is to use non-glucose-based solutions. In particular, icodextrin solution has been highlighted in terms of improving peritoneal ultrafiltration. Due to its high molecular weight (14–18 kD), icodextrin solution can induce peritoneal ultrafiltration by colloid osmosis, unlike conventional solutions by crystalloid osmosis. Ultrafiltration capacity of icodextrin solution is as much as that of 4.25% glucose solution in the long-dwell time up to 12–16 h. In fact, many studies have shown that the use of icodextrin solution improves fluid status by sustained increase in ultrafiltration (Posthuma et al. 1997, Plum et al. 2002, Davies et al. 2003, Konings et al. 2003a, b), even in patients with fast transport membrane (Lin et al. 2009). Possibly, it has also potential merits in preservation of RRF, improved lipid profiles, and less glucose burden.

The beneficial effects of these new solutions were adopted by the European Best Practice Guidelines. The committee suggests that the use of these solutions can be used particularly when there is concern on biocompatibility, glucose toxicity, or fluid balance (Evidence level B or C).

15.6.3 Fluid Management in Peritoneal Ultrafiltration Failure

There are three types of ultrafiltration failure depending on peritoneal membrane transport status. Therapeutic strategies should be individualized according to these types given the different pathophysiology of ultrafiltration failure (Fig. 15.8).

15.6.3.1 Fast Transport Status

This is known as type I ultrafiltration failure characterized by low ultrafiltration volume and fast transport status. It is most common among three types of ultrafiltration failure. High amount of glucose exposure and PD-related peritonitis are two main factors leading to this type of ultra-

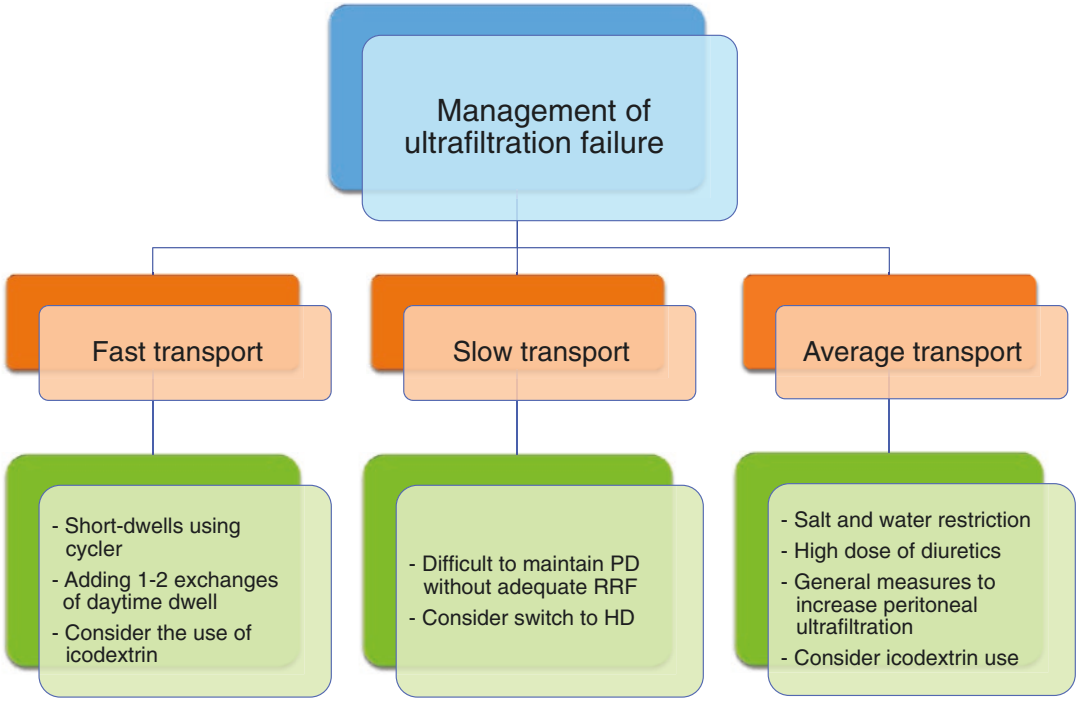

Fig. 15.8 Management of ultrafiltration failure according to peritoneal membrane transport type

filtration failure. Due to early osmotic dissipation in fast transport status, short and frequent exchanges are generally recommended. Best program in this case is, for example, the combined use of short 1–2-h dwells using cycler during the nighttime and additional long dwell of icodextrin solution during the daytime. Icodextrin solution exerts its maximal ultrafiltration during the 12–16-h dwell; thus the use of this solution is an ideal approach. In fact, icodextrin solution has been demonstrated to prolong technique survival in patients with ultrafiltration failure and fast transport status (Takatori et al. 2011).

Resting the peritoneum for 4 weeks is another option for ultrafiltration failure with fast transport as peritoneal membrane function can be restored to some degree following a temporary cessation of PD. The mechanism for this is unclear, but it can be presumed that increased vascularity can be resolved during the PD-free period.

15.6.3.2 Slow Transport Status

This type of ultrafiltration failure is referred to type II ultrafiltration failure. Possible causes for this ultrafiltration failure are peritoneal adhesions and scarring after a severe peritonitis or other intra-abdominal complication. Unfortunately, short exchanges or icodextrin solution use is not effective in patients with type II ultrafiltration failure. Transfer to HD is generally recommended because it is difficult to maintain PD unless patients have significant RRF.

15.6.3.3 Average Transport Status

Type III ultrafiltration occurs in patients with average transport status. It is caused by aquaporin deficiency or increased lymphatic reabsorption. Because there are no reliable drugs to restore aquaporin function or to decrease lymphatic absorption, general approach such as salt and water restriction, use of diuretics, and other methods to increase ultrafiltration can be employed. Of note, icodextrin induces ultrafiltration by colloid osmosis, which is not involved in aquaporin channels. Therefore, as in type I ultrafiltration failure, long dwell of icodextrin solution with short and frequent exchanges by APD can be useful in type III ultrafiltration failure.

15.7 Nutritional Status

Malnutrition, which is now interchangeably referred to protein-energy wasting (PEW), is common in PD patients on dialysis and has been recognized as an important risk factor for adverse outcomes in these patients. Therefore, it is widely acknowledged that nutritional issue should be a part of dialysis adequacy. To correctly define PEW, recent criteria by a panel of experts from the International Society of Renal Nutrition and Metabolism (ISRNM) have been proposed and are steadily gaining acceptance (Fouque et al. 2008). Based on these criteria, PEW can be diagnosed when at least three out of the four listed categories should be met and at least one test in each of the selected category should be included; four categories are serum biochemistry, body mass, muscle mass, and dietary intake. There are number of factors that are involved in the development of PEW in dialysis patients. These include inflammation, inadequate dialysis, insufficient nutrient intake, loss of protein during dialysis, chronic acidosis, hypercatabolic illness, and comorbid conditions. Given the multifactorial and complicated pathogenesis of PEW, a multidisciplinary approach should be provided through careful nutritional assessment, dietary counseling, delivery of adequate dialysis dose, proper nutritional support, correction of acidosis, and management of comorbid conditions (Han and Han 2012). Besides such general care, there are more factors that should also be taken into account in PD patients. As discussed earlier, RRF is significantly associated with nutritional status, thus preservation of RRF can be a therapeutic strategy to improve PEW. Peritonitis should also be prevented because appetite and nutritional status are impaired by recurrent peritonitis. Encouraging dietary intake and adequate nutritional support is of paramount importance due to insufficient calorie intake in PD patients and the substantial protein loss into the dialysate. Unfortunately, nutritional intervention trials to date have produced inconclusive findings because these have not been well controlled and are limited by short follow-up duration and small sample sizes. Further long-term prospective, randomized, controlled trials are warranted to clarify the beneficial effects of nutritional interventions. In the meantime, patients with PEW should be treated by using currently available therapeutic strategies (Table 15.7).

Table 15.7 Management of protein-energy wasting in patients on PD

1.	**General management**
	Maintain adequate dialysis dose
	Correct acidosis
	Manage comorbid or catabolic conditions
	Dietary counseling
	Encourage adequate food intake
	Daily energy intake 35 kcal/kg of body weight for patients <60 years and 30–35 kcal/kg body weight for patients >60 years
	Protein intake 1.2–1.3 g/kg body weight per day
	Oral nutritional supplements
2.	**PD-related therapies**
	Preserve RRF
	Prevent and treat peritonitis
	Maintain optimal fluid balance
	Utilize amino acid-based solutions

15.8 Middle Molecule Clearance

Small solutes are not sole uremic toxins. Enhancing the elimination of middle molecules should be incorporated to a therapeutic target in dialysis patients. β2MG is a representative middle molecule with a molecular weight of 11,000 D. The harmful effects of β2MG are well recognized as in carpal tunnel syndrome and β2MG-related amyloidosis. These complications frequently occur particularly in patients on long-term dialysis. Recent studies have identified β2MG as an independent prognostic factor of morbidity and mortality in both HD and PD patients. Cheung et al. reanalyzed the HEMO study data and found that a 10 mg/L increase in serum β2MG level was significantly associated with an 11% increase in risk of all-cause mortality in HD patients (Cheung et al. 2006). Similar findings were also observed in PD patients. In a prospective cohort study in Korea (Koh et al. 2015), patients in the highest tertile of β2MG level had higher mortality rate than patients in the lowest tertile. PD has conventionally been thought to have better removal of larger molecular

weight uremic toxins than intermittent HD. There are several reasons for this notion. First, peritoneal membrane is more porous than the cellulosic HD membrane. Second, middle molecule clearance is time dependent (Kim et al. 2001). Therefore, PD has advantage over intermittent HD in terms of removal of middle molecules. However, HD technology has consistently advanced, and convective therapy such as online hemodiafiltration has increasingly been used in clinical practice. These modalities have been reported to have superior removal of β2MG to conventional HD. There has been lack of studies to evaluate which dialysis modality between HD and PD is better in middle molecule clearance. Evenepoel et al. compared dialytic clearance of β2MG between high-flux HD and PD (Evenepoel et al. 2006). The results showed that β2MG clearance was significantly higher in patients receiving high-flux HD than in patients receiving PD. When different PD modalities were compared to HD, serum β2MG level was significantly lower in high-flux HD group than in APD group. However, there was no significant difference in serum β2MG level between high-flux HD group and CAPD group. Presumably, short and frequent exchanges in APD might result in insufficient removal of larger molecules. Because HD is an intermittent therapy, it is difficult to maintain consistently lower serum β2MG levels as compared to continuous PD therapy despite the superior capacity of middle molecule removal by high-flux dialysis. Considering the theoretical merits of PD with respect to removal of middle molecules, convective therapy using more porous HD membrane and extended duration of HD treatment are required to remove middle molecules more effectively. This notion is supported by a previous study by Raj et al. (2000). They compared β2MG clearance between conventional thrice a week HD and nocturnal HD. Two dialysis modalities used the same high-flux dialyzer. β2MG clearance was significantly higher, and serum predialysis β2MG level was lower in nocturnal HD group than in conventional HD group. To date, there is no randomized controlled trial to investigate the optimal level of β2MG or whether lowering β2MG level can result in better survival. In addition, the current guidelines do not recommend the routine monitoring of β2MG or other middle molecules in dialysis patients. Nevertheless, given the fact that β2MG exhibits deleterious effects and is a strong predictor of death, much effort should be made to increase β2MG clearance.

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Peritonitis and Exit-Site Infection

16

Bum Soon Choi

16.1 Introduction

Infection-related complication in patients with peritoneal dialysis (PD) is a leading complication. Among infection-related complications, peritonitis is the most common cause of death and hospitalization. Although less than 5% of peritonitis episodes result in death, peritonitis is a major contributing cause to 16% of deaths on PD. It is also the most common cause of treatment failure, accounting for nearly 30% of the cases (Ghali et al. 2011; Pérez Fontan et al. 2005; Davenport 2009; Szeto et al. 2003; Brown et al. 2011; Boudville et al. 2012; Daugirdas et al. 2015). Therefore, it is important to have interest in diagnosis, treatment, and prevention of peritonitis. Exit-site infection is an important complication of long-term PD, occurring on average at a rate of 0.48 episodes per patient-year. A patient with an exit-site infection that progresses to peritonitis or who presents with an exit-site infection in conjunction with peritonitis will usually require catheter removal. Intensification of exit-site cleaning with antiseptics is advised (Daugirdas et al. 2015; Li et al. 2016).

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16.2 Peritonitis

The discussion that follows is an adaptation of the International Society for Peritoneal Dialysis (ISPD) recommendations by Li et al. (2016).

16.2.1 Peritonitis Rate

Every program should monitor, at least on a yearly basis, the incidence of peritonitis. Parameters monitored should include overall peritonitis rate (standardly reported as number of episodes per patient-year), peritonitis rates of specific organisms (reported as absolute rates, i.e., as number of episodes per year), percentage of patients per year who are peritonitis-free, and antimicrobial susceptibilities of the infecting organisms. Nonetheless, the overall peritonitis rate should be no more than 0.5 episodes per year at risk, although the rate achieved depends considerably on the patient population (Li et al. 2016).

16.2.2 Pathogenesis of Peritonitis

Potential routes of infection are intraluminal (bacteria to gain access to the peritoneal cavity via the catheter lumen, coagulase-negative staphylococci or diphtheroids), periluminal (bacteria present on the skin surface can enter the

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peritoneal cavity via the peritoneal catheter tract, *Staphylococcus aureus* or *Pseudomonas aeruginosa*), bowel source (bacteria of intestinal origin can enter the peritoneal cavity by migrating across the bowel wall, *Escherichia coli* and *Klebsiella* species), hematogenous (less commonly, peritonitis is due to bacteria that have seeded the peritoneum from a distant site by way of the bloodstream, streptococci and staphylococci), and transvaginal (uncommon, but ascending infection may occur from the vagina via the uterine tubes into the peritoneum, *Candida* peritonitis) (Daugirdas et al. 2015).

16.2.3 Diagnosis of Peritonitis

Peritonitis always is diagnosed when at least two of the following are present: (1) clinical features consistent with peritonitis (i.e., abdominal pain and/or cloudy dialysis effluent) (Fig. 16.1); (2) dialysis effluent white cell count >100/μL or >0.1 × 10^9/L (after a dwell time of at least 2 h), with >50% polymorphonuclear; and (3) positive dialysis effluent culture.

PD patients presenting with cloudy effluent is presumed to have peritonitis and treated as such until the diagnosis can be confirmed or excluded. PD effluent is tested for cell count, differential, Gram stain, and culture whenever peritonitis is suspected. Differential diagnosis of cloudy effluent includes culture-positive infectious peritonitis, infectious peritonitis with sterile cultures, chemical peritonitis, calcium channel blockers, eosinophilia of the effluent, hemoperitoneum, malignancy (rare), chylous effluent (rare), and specimen taken from "dry" abdomen.

16.2.4 Identification of Causative Organism

Blood-culture bottle is the preferred technique for bacterial culture of PD effluent. Bedside inoculation of 5–10 mL effluent in two (aerobic and anaerobic) blood-culture bottles has a reasonable sensitivity, and the culture-negative rate is typically around 10–20% (Alfa et al. 1997; Azap et al. 2006). Centrifugation of 50 mL PD effluent at 3000×*g* for 15 min, followed by resuspension of the sediment in 3–5 mL supernatant and inoculation on solid culture media or standard blood-culture media, increases the yield by 5–10 times but is more cumbersome (Sewell et al. 1990; Chow et al. 2007).

Fig. 16.1 Purulent dialysate (Courtesy Yong-Lim Kim, Korea)

Specimens should arrive at the laboratory within 6 h. If immediate delivery to the laboratory is not possible, the inoculated culture bottles should ideally be incubated at 37 °C. Sampling and culture methods are reviewed and improved if more than 15% of peritonitis episodes are culture-negative.

16.2.5 Treatment

16.2.5.1 Initial Management (Fig. 16.2)

Empirical antibiotic therapy is initiated as soon as possible after appropriate microbiological specimens have been obtained. Empirical

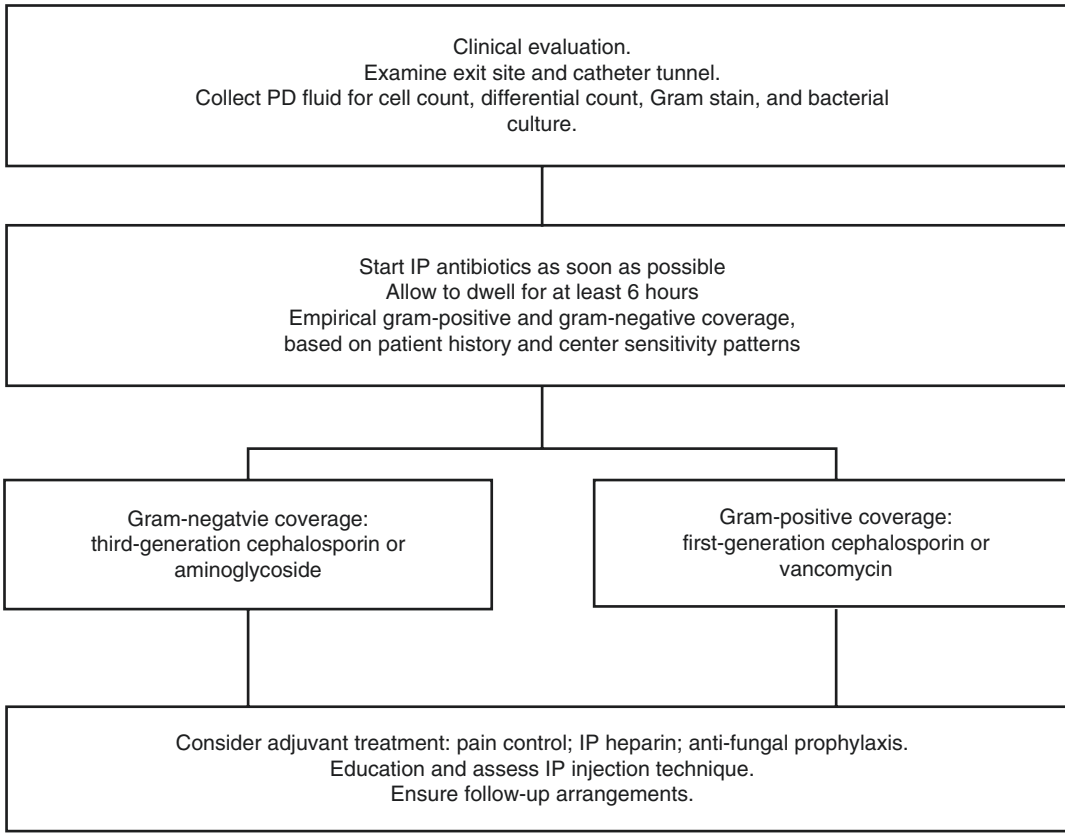

Fig. 16.2 Initial management of peritonitis (reproduced from Li et al. 2016)

antibiotic regimens are center-specific and cover both gram-positive and gram-negative organisms. Gram-positive organisms are covered by vancomycin or a first-generation cephalosporin and gram-negative organisms by a third-generation cephalosporin or an aminoglycoside (Li et al. 2016).

16.2.5.2 Dosage of Antibiotics (Tables 16.1 and 16.2)

Intraperitoneal (IP) antibiotics are the preferred route of administration unless the patient has features of systemic sepsis. IP aminoglycoside is administered as daily intermittent dosing, and prolonged courses of IP aminoglycoside are avoided. IP vancomycin is administered intermittently and the serum vancomycin level is kept above 15 μg/mL. IP cephalosporin is administered either continuously (in each exchange) or on a daily intermittent basis (Li et al. 2016).

16.2.5.3 Subsequent Management of Peritonitis

Antibiotic therapy is adjusted to narrow-spectrum agents, as appropriate, once culture results and sensitivities are known. The management algorithms for gram-positive cocci and gram-negative bacilli identified in dialysis effluent are summarized in Figs. 16.3 and 16.4, respectively (Li et al. 2016).

Refractory peritonitis is defined as failure of the effluent to clear after 5 days of appropriate antibiotics. Catheter removal is indicated in case of refractory peritonitis, or earlier if the patient's clinical condition is deteriorating, in order to preserve the peritoneum for future PD as well as preventing morbidity and mortality. Prolonged attempts to treat refractory peritonitis by antibiotics without catheter removal are associated with extended hospital stay, peritoneal membrane damage, increased risk of fungal peritonitis, and excessive mortality (Choi et al. 2004).

Table 16.1 Intraperitoneal antibiotic dosing recommendations for treatment of peritonitis (reproduced from Li et al. 2016)

	Intermittent (1 exchange daily)	Continuous (all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg daily	LD 25 mg/L, MD 12 mg/L
Gentamicin	0.6 mg/kg daily	LD 8 mg/L, MD 4 mg/L
Netilmicin	0.6 mg/kg daily	MD 10 mg/L
Tobramycin	0.6 mg/kg daily	LD 3 mg/kg, MD 0.3 mg/kg
Cephalosporins		
Cefazolin	15–20 mg/kg daily	LD 500 mg/L, MD 125 mg/L
Cefepime	1000 mg daily	D 250–500 mg/L, MD 100–125 mg/L
Cefoperazone	No data	LD 500 mg/L, MD 62.5–125 mg/L
Cefotaxime	500–1000 mg daily	No data
Ceftazidime	1000–1500 mg daily	LD 500 mg/L, MD 125 mg/L
Ceftriaxone	1000 mg daily	No data
Penicillins		
Penicillin G	No data	LD 50,000 unit/L, MD 25,000 unit/L
Amoxicillin	No data	MD 150 mg/L
Ampicillin	No data	MD 125 mg/L
Ampicillin/sulbactam	2 g/1 g every 12 h	LD 750–100 mg/L, MD 100 mg/L
Piperacillin/tazobactam	No data	LD 4 g/0.5 g, MD 1 g/0.125 g
Others		
Aztreonam	2 g daily	LD 1000 mg/L, MD 250 mg/L
Ciprofloxacin	No data	MD 50 mg/L
Clindamycin	No data	MD 600 mg/bag
Daptomycin	No data	LD 100 mg/L, MD 20 mg/L
Imipenem/cilastatin	500 mg in alternate exchange	LD 250 mg/L, MD 50 mg/L
Ofloxacin	No data	LD 200 mg, MD 25 mg/L
Polymyxin B	No data	MD 300,000 unit (30 mg)/bag
Quinupristin/dalfopristin	25 mg/L in alternate exchange[a]	No data
Meropenem	1 g daily	No data
Teicoplanin	15 mg/kg every 5 days	LD 400 mg/bag, MD 20 mg/bag
Vancomycin	15–30 mg/kg every 5–7 days[b]	LD 30 mg/kg, MD 1.5 mg/kg/bag
Antifungals		
Fluconazole	IP 200 mg every 24–48 h	No data
Voriconazole	IP 2.5 mg/kg daily	No data

LD loading dose in mg, *MD* maintenance dose in mg, *IP* intraperitoneal, *APD* automated peritoneal
[a]Given in conjunction with 500 mg intravenous twice daily
[b]Supplemental doses may be needed for APD patients

Terminology of peritonitis is as follows: (1) recurrent peritonitis, an episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism; (2) relapsing peritonitis, an episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode; and (3) repeat peritonitis, an episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism. Timely catheter removal is considered for relapsing, recurrent, or repeat peritonitis episodes. When compared to non-relapsing episodes, relapsing ones are associated with a lower rate of cure, more ultrafiltration problems, and higher rate of technique failure (Szeto et al. 2009;

Table 16.2 Systemic antibiotic dosing recommendations for treatment of peritonitis (reproduced from Li et al. 2016)

Drug	Dosing
Antibacterials	
Ciprofloxacin	Oral 250 mg BD[a]
Colistin	IV 300 mg loading, then 150–200 mg daily[b]
Ertapenem	IV 500 mg daily
Levofloxacin	Oral 250 mg daily
Linezolid	IV or oral 600 mg BD
Moxifloxacin	Oral 400 mg daily
Rifampicin	450 mg daily for BW <50 kg
	600 mg daily for BW ≥50 kg
Trimethoprim/sulfamethoxazole	Oral 160 mg/800 mg BD
Antifungals	
Amphotericin	IV test dose 1 mg; starting dose
	0.1 mg/kg/day over 6 h; increased to target dose
	0.75–1.0 mg/kg/day over 4 days
Caspofungin	IV 70 mg loading, then 50 mg daily
Fluconazole	Oral 200 mg loading, then 50–100 mg daily
Flucytosine	Oral 1 g/day
Posaconazole	IV 400 mg every 12 h
Voriconazole	Oral 200 mg every 12 h

BD twice a day, *IV* intravenous, *BW* body weight
[a]Ciprofloxacin 500 mg BD may be needed if residual glomerular filtration rate is above 5 mL/min
[b]Expressed as colistin base activity (CBA)

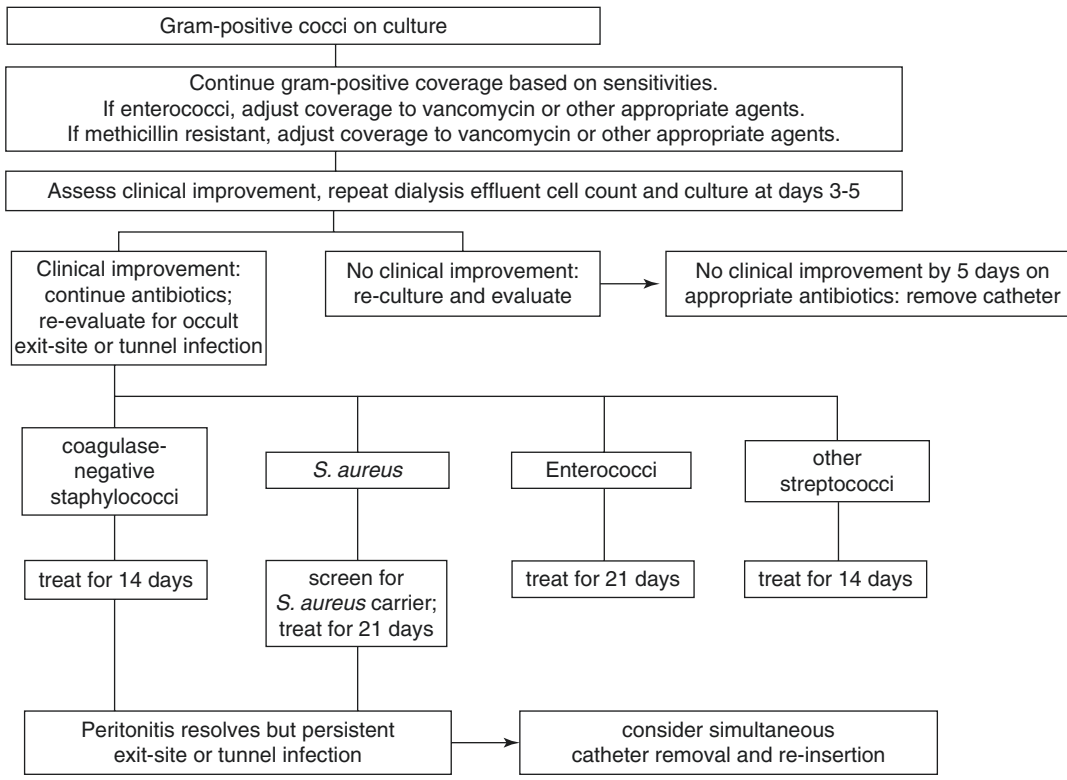

Fig. 16.3 Management algorithm for gram-positive cocci identified in dialysis effluent (reproduced from Li et al. 2016)

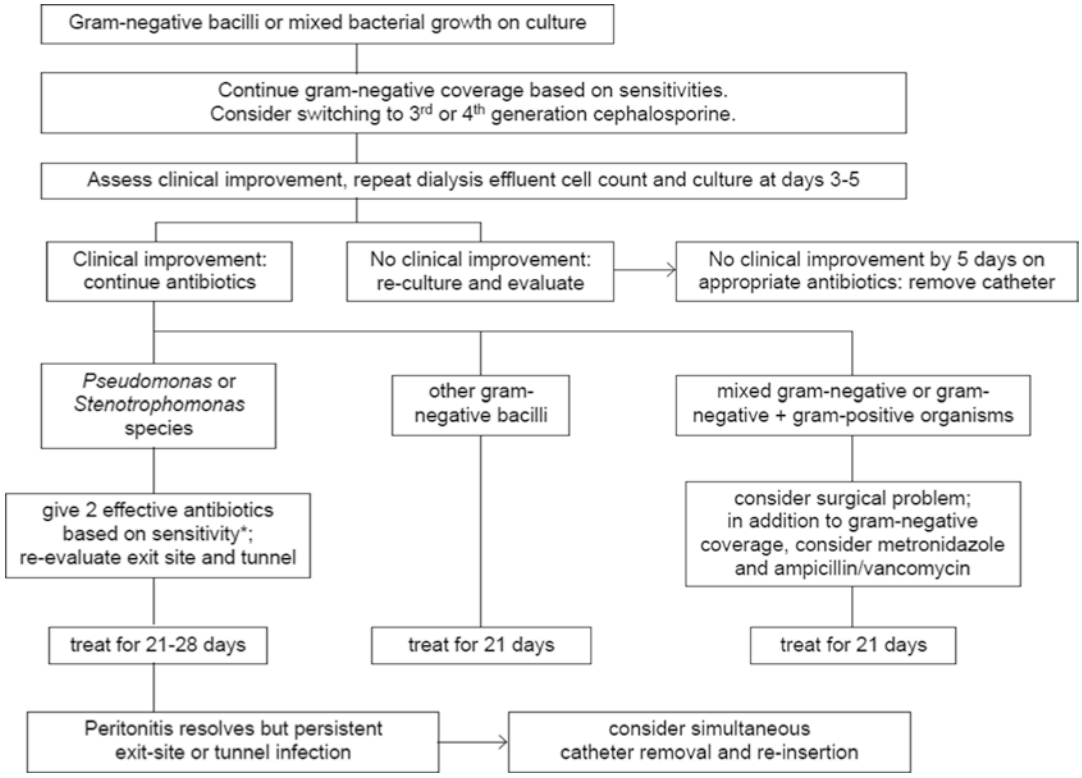

Fig. 16.4 Management algorithm for gram-negative bacilli or mixed bacterial growth identified in dialysis effluent (reproduced from Li et al. 2016)

Lane et al. 2010). Recurrent peritonitis episodes had a worse prognosis than relapsing ones (Szeto et al. 2009; Burke et al. 2011).

Coagulase-Negative *Staphylococcus*

Coagulase-negative *staphylococci* generally are treated with IP cephalosporins or vancomycin, according to antimicrobial susceptibility, for a period of 2 weeks (Li et al. 2016). Many patients with *S. epidermidis* peritonitis have mild clinical symptoms and respond well to treatment as outpatients (Szeto et al. 2008; Camargo et al. 2014; Fahim et al. 2010). The patient's exchange technique should be reviewed to prevent another episode.

Enterococcus Species

Enterococcal peritonitis is treated for 3 weeks with IP vancomycin. Adding IP aminoglycoside for severe enterococcal peritonitis is suggested. For peritonitis due to vancomycin-resistant *Enterococcus* (VRE), treatment for 3 weeks with IP ampicillin is suggested, if the organism is susceptible or with alternative antibiotics (linezolid, quinupristin/dalfopristin, daptomycin, or teicoplanin, based on antimicrobial susceptibilities) if the organism is ampicillin-resistant (Li et al. 2016).

Streptococcal Species

Streptococcal peritonitis is treated with appropriate antibiotics, such as IP ampicillin, for 2 weeks (Li et al. 2016). Peritonitis episodes caused by *streptococci* usually respond well to antibiotic treatment (Shukla et al. 2006; O'Shea et al. 2009), but viridans streptococcal peritonitis is more likely to be refractory (Chao et al. 2015). Cefazolin and vancomycin are often effective.

Staphylococcus Aureus

Staphylococcus aureus peritonitis is treated with effective antibiotics for 3 weeks (Li et al. 2016). Peritonitis episodes caused by *Staphylococcus aureus* are often secondary to exit-site or tunnel infection, although touch contamination is also common. If the bacterial isolate is methicillin-sensitive, a first-generation cephalosporin is the drug of choice (Szeto et al. 2007; Govindarajulu et al. 2010). If the isolate is methicillin-resistant, IP vancomycin is the drug of choice, but teicoplanin and daptomycin can be used as alternatives (Lin et al. 2011).

Corynebacterium Peritonitis

Corynebacterial peritonitis is treated with effective antibiotics for 3 weeks (Li et al. 2016). In a retrospective study, *Corynebacterium* peritonitis often resulted in relapse or repeat episodes, catheter removal, permanent hemodialysis transfer, and death (Barraclough et al. 2009). For patients with concomitant exit-site or catheter tunnel infection caused by *Corynebacterium*, early catheter removal should be considered (Li et al. 2016).

Pseudomonas Peritonitis

Pseudomonas peritonitis is treated with two antibiotics with different mechanisms of action and to which the organism is sensitive (e.g., IP gentamicin or oral ciprofloxacin with IP ceftazidime or cefepime) for 3 weeks. *Pseudomonas* peritonitis with concomitant exit-site and tunnel infection is treated with catheter removal (Li et al. 2016). Carbapenems, such as imipenem, meropenem, and doripenem, are valid alternatives, especially if the bacterial isolate is resistant to cephalosporin and antipseudomonal penicillins.

Other Gram-Negative Bacteria

Non-*Pseudomonas* gram-negative peritonitis is treated with effective antibiotics for at least 3 weeks (Li et al. 2016). SPICE organisms (*Serratia*, *Pseudomonas*, indole-positive organisms such as *Proteus* and *Providentia*, *Citrobacter*, and *Enterobacter*) have amp-C beta-lactamases, which inactivate cephalosporins, and have a high risk of relapse (Szeto et al. 2006).

Extended-spectrum beta-lactamases (ESBLs) are resistant to all cephalosporins but usually susceptible to carbapenems (Wong et al. 2007; Feng et al. 2014). Carbapenem-resistant *Enterobacteriaceae* (CRE)/ Klebsiella pneumoniae carbapenemase (KPC)-producing bacteria are usually resistant to all classes of beta-lactams, usually resistant to fluoroquinolones, variably susceptible to aminoglycosides, but usually susceptible to polymyxin and colistin (Wong et al. 2007; Zhang et al. 2014).

Isolation of a *Stenotrophomonas* species, while infrequent, requires special attention, as it is sensitive to only a few antimicrobial agents (Szeto et al. 1997; Tzanetou et al. 2004).

Polymicrobial Peritonitis

If multiple enteric organisms (multiple gram-negative or mixed gram-negative/gram-positive organisms) are grown from PD effluent, surgical evaluation is obtained immediately when there is no prompt clinical response and the patient is treated with metronidazole in conjunction with IP vancomycin and either IP aminoglycoside or IP ceftazidime for a minimum period of 3 weeks (Li et al. 2016).

If multiple gram-positive organisms are grown from PD effluent, we suggest that patients be treated with effective antibiotics for 3 weeks (Li et al. 2016).

Culture-Negative Peritonitis

Negative effluent cultures on day 3 warrant a repeat dialysis effluent WBC count with differential. If the culture-negative peritonitis is resolving at day 3, discontinue aminoglycoside therapy and continue treatment with gram-positive coverage (e.g., first-generation cephalosporin or vancomycin) for 2 weeks. If the culture-negative peritonitis is not resolving at day 3, special culture techniques are considered for isolation of unusual organisms (Li et al. 2016). In contrast, if there is suboptimal response after 5 days of empirical antibiotics, catheter removal should be strongly considered.

Fungal Peritonitis

Immediate catheter removal is suggested when fungi are identified in PD effluent. Treatment

with an appropriate antifungal agent is continued for at least 2 weeks after catheter removal (Li et al. 2016).

Tuberculous Peritonitis

Diagnosis should be considered in any patient with refractory or relapsing peritonitis with negative bacterial cultures. Similar to bacterial peritonitis, most cases of tuberculous peritonitis have PMN in the dialysis effluent at initial presentation, but lymphocytosis in the dialysis effluent usually becomes obvious later. Ziehl-Neelsen stain examination of the PD effluent is often unrevealing, and conventional culture technique (e.g., Löwenstein-Jensen agar) is slow and not sufficiently sensitive (Li et al. 2016). Overall diagnostic yield could be improved by centrifuging a large volume of effluent (50–100 mL), followed by culturing the sediment in both solid and fluid media. Alternatively, mycobacterial DNA PCR can be performed (Lye 2002).

Treatment protocol should be based on general protocols for treatment of tuberculosis but is often started with four drugs: rifampicin, isoniazid, pyrazinamide, and ofloxacin. Many patients respond to antituberculous therapy without catheter removal (Ahn et al. 2003; Ram et al. 2013; Akpolat 2009).

Nontuberculous Mycobacterial Peritonitis

Data on peritonitis caused by nontuberculous mycobacteria are limited but may be increasing (Kunin et al. 2014; Song et al. 2012). Over half of the isolates are rapidly growing species, such as *M. fortuitum* and *M. chelonae*, and often become positive on routine bacteriologic cultures in 3–5 days (Song et al. 2012). Treatment regimen for nontuberculous mycobacterial peritonitis is not well established and requires individualized protocols based on susceptibility. The type and duration of antibiotic therapy are variable, and the optimal treatment regimen is poorly defined and depends on species and drug susceptibilities. Catheter removal is usually necessary, and experience with non-removal is limited (Song et al. 2012; Renaud et al. 2011; Jiang et al. 2013).

16.2.5.4 Catheter Removal and Reinsertion

PD catheters may be removed for refractory peritonitis, relapsing peritonitis, refractory exit-site and tunnel infection, or fungal peritonitis. Catheter removal may also be considered for repeat peritonitis, mycobacterial peritonitis, or multiple enteric organisms (Li et al. 2016). It is appropriate to consider return to PD for many patients who have had their catheter removed for refractory, relapsing, or fungal peritonitis. If reinsertion of a new catheter is attempted after a PD catheter is removed for refractory, relapsing, or fungal peritonitis, it should be performed at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms (Li et al. 2016).

16.2.5.5 Special Consideration for Automated Peritoneal Dialysis (APD)

Intermittent IP dosing could be given in the day dwell of APD patients. However, extrapolation of data from CAPD to APD may result in significant underdosing in APD patients because rapid exchanges in APD may lead to inadequate time to achieve therapeutic levels. Alternatively, APD patients may switch temporarily to CAPD. However, it is not always practical to switch because patients may not be familiar with the exchange technique and this practice is associated with an increased risk of technique failure and fluid overload (Li et al. 2016; de Moraes et al. 2014).

16.2.5.6 Adjunctive Treatments

Some patients with PD-related peritonitis could be managed on an outpatient basis. The decision to hospitalize a patient depends on many factors, including hemodynamic status of the patient, severity of signs and symptoms, and, for APD patients, the type of treatment schedule chosen, as well as the ability to provide IP antibiotics as an outpatient and the reliability of the patient (Li et al. 2016). Antifungal prophylaxis is recommended when PD patients receive antibiotic courses to prevent fungal peritonitis (Strippoli et al. 2004).

Depending on the severity of symptoms, some patients would require analgesics for pain control. At the initial presentation and before IP antibiotics are initiated, one or two rapid PD exchanges are often performed for pain relief, although there are no data supporting this approach (Ejlersen et al. 1991).

Cloudy effluent may benefit from the addition of heparin 500 units/L IP to prevent occlusion of the catheter by fibrin. Intraperitoneal urokinase has been advocated for the treatment of biofilm, which may be the cause of refractory or relapsing peritonitis (Tong et al. 2005; Gadallah et al. 2000).

Reduction in ultrafiltration is commonly observed, and fluid overload is a frequent complication. Temporary use of hypertonic exchanges and short dwell times may be needed to maintain adequate fluid removal (Chow et al. 2014). Blood glucose monitoring with appropriate adjustments of insulin dosage may be needed. Protein loss during peritonitis is also increased. Screening for malnutrition should be undertaken in patients with prolonged peritoneal inflammation (Li et al. 2016).

16.2.6 Prevention of Peritonitis

Exit-site and catheter tunnel infections are major predisposing factors to PD-related peritonitis (van Diepen et al. 2012). Approximately one-fifth of peritonitis episodes are temporally associated with exit-site and tunnel infections. Early detection of ESI and prompt management with appropriate antibiotics are logical steps to minimize the risk of subsequent peritonitis.

16.2.6.1 Catheter Placement

Systemic prophylactic antibiotics are administered immediately prior to catheter insertion (Li et al. 2016). Although first-generation cephalosporin may be slightly less effective than vancomycin, the former is still commonly used because of the concern regarding vancomycin resistance. Each PD program should determine its own choice of antibiotic for prophylaxis after considering the local spectrum of antibiotic resistance.

16.2.6.2 Catheter Design and Connection Methods

There is no specific recommendation on catheter design for prevention of peritonitis. Disconnect systems with a "flush before fill" design are used for continuous ambulatory PD (Li et al. 2016).

16.2.6.3 Training Programs

The latest ISPD recommendations for teaching PD patients and their caregivers are followed (ISPD guideline/recommendations: a syllabus for teaching peritoneal dialysis to patients and caregivers) (Figueiredo et al. 2016). PD training is conducted by nursing staff with the appropriate qualifications and experience.

Indications for PD retraining include following prolonged hospitalization; following peritonitis and/or catheter infection; following change in dexterity, vision, or mental acuity; following change to another supplier or a different type of connection; or following other interruptions in PD (e.g., period of time on hemodialysis) (Li et al. 2016).

16.2.6.4 Exit-Site Care

Topical application of antibiotic (mupirocin or gentamicin) cream or ointment is recommended to the catheter exit site. Prompt treatment of exit-site or catheter tunnel infection is to reduce subsequent peritonitis risk (Li et al. 2016).

16.2.6.5 Bowel and Gynecological Source Infection

Antibiotic prophylaxis is recommended prior to colonoscopy and invasive gynecologic procedures. Optimal antibiotic regimen has not been determined by any clinical study (Li et al. 2016).

16.2.6.6 Other Modifiable Risk Factors

There are a number of other modifiable risk factors for PD peritonitis: social/environmental factor (smoking, living distantly from PD unit, pets), medical problem (obesity, depression, hypokalemia, hypoalbuminemia, absence of vitamin D supplementation, invasive interventions), dialysis-related factor (prior hemodialysis, PD against patient's choice, training, bioincompatible

fluids, wet contamination), or infection-related factor (nasal *Staphylococcus aureus* carrier status, previous exit-site infection) (Li et al. 2016).

16.3 Exit-Site Infection

Purulent drainage from the exit site indicates the presence of infection (Fig. 16.5). Erythema may or may not represent infection (Daugirdas et al. 2015).

The discussion that follows is an adaptation of the ISPD recommendations by Li et al. (2010).

16.3.1 Pathogenesis of Exit Infection

The most serious and common exit-site pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Other bacteria (diphtheroids, anaerobic organisms, nonfermenting bacteria, streptococci, nontuberculous mycobacteria, *Legionella*, yeasts, and fungi) can also be involved (Li et al. 2010).

16.3.2 Treatment of Exit Infection

Staphylococcus aureus and *Pseudomonas aeruginosa* infections must be treated aggressively; these organisms frequently lead to peritonitis. Oral antibiotic therapy is generally recommended, with the exception of methicillin-resistant *Staphylococcus aureus* (MRSA) (Li et al. 2010). Oral antibiotics used in exit-site and tunnel infection are shown in Table 16.3. Oral antibiotic therapy has been shown to be as effective as intraperitoneal (IP) antibiotic therapy.

16.3.2.1 Empiric Antibiotic Therapy of Exit Infection

Empiric antibiotic therapy may be initiated immediately. Healthcare team may decide to defer therapy until the results of the exit-site culture can direct the choice of antibiotic. Empiric therapy should always cover *Staphylococcus aureus*. If the patient has a history of *Pseudomonas aeruginosa* exit-site infections, empiric therapy should be with an antibiotic that will cover this organism (Li et al. 2010).

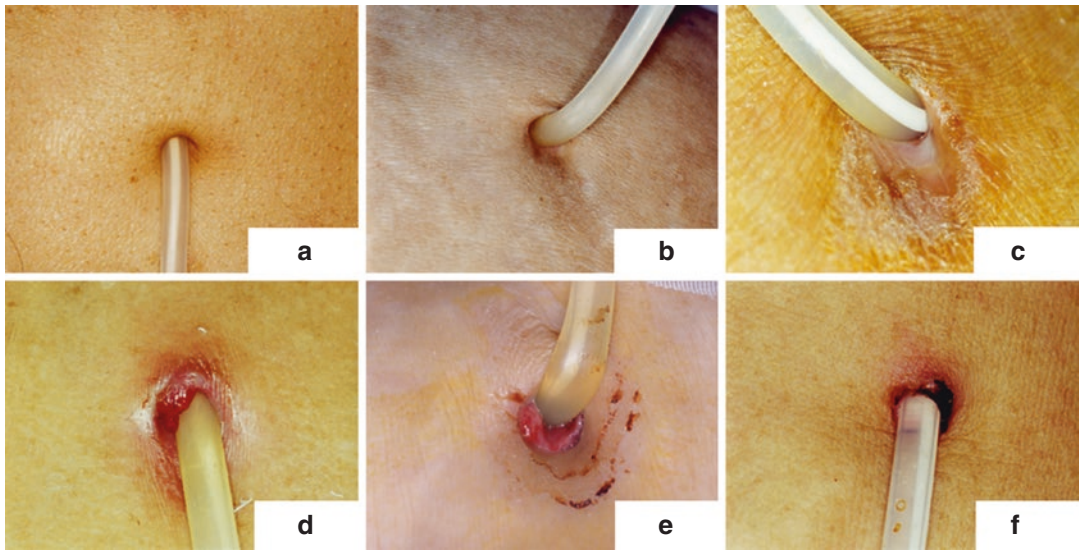

Fig. 16.5 Exit-site infection (**a**), normal (**b**), good (**c**) equivocal (**d**) acutely inflamed, (**e**) chronically inflamed (**f**), traumatic (Courtesy Yong-Lim Kim, Korea)

Table 16.3 Oral antibiotics used in exit-site and tunnel infection (reproduced from Li et al. 2010)

Amoxicillin	250–500 mg bid
Cephalexin	500 mg bid to tid
Ciprofloxacin	250 mg bid
Clarithromycin	500 mg loading dose, then 250 mg bid or qd
Dicloxacillin	500 mg qid
Erythromycin	500 mg qid
Flucloxacillin (or cloxacillin)	500 mg qid
Fluconazole	200 mg qd for 2 days, then 100 mg qd
Flucytosine	0.5–1 g/day titrated to response and serum trough levels (25–50 mg/mL)
Isoniazid	200–300 mg qd
Linezolid	400–600 mg bid
Metronidazole	400 mg tid
Moxifloxacin	400 mg daily
Ofloxacin	400 mg first day then 200 mg qd
Pyrazinamide	25–35 mg/kg 3 times per week
Rifampicin	450 mg qd for <50 kg; 600 mg qd for >50 kg
Trimethoprim/sulfamethoxazole	80/400 mg qd

bid 2 times per day, *qd* every day, *tid* 3 times per day, *qid* 4 times daily

16.3.2.2 Subsequent Management of Exit Infection

Gram-Positive Organism Exit-Site Infections

Gram-positive organisms are treated with oral penicillinase-resistant (or broad spectrum) penicillin or a first-generation cephalosporin. Recommendations for frequently used oral antibiotics are shown in Table 16.3 (Cervelli 2007). In slowly resolving or particularly severe *S. aureus* exit-site infections, rifampicin 600 mg daily may be added. Rifampicin should never be given as monotherapy. To prevent unnecessary exposure to vancomycin and thus emergence of resistant organisms, vancomycin should be avoided in the routine treatment. Clindamycin, doxycycline, and minocycline are sometimes useful for the treatment of community-acquired MRSA and other organisms (Li et al. 2010).

Pseudomonas aeruginosa Exit-Site Infections

Particulaly, *Pseudomonas aeruginosa* exit-site infection is difficult to treat and often require prolonged therapy with two antibiotics. Oral fluoroquinolones are recommended as the first choice, preferably not as monotherapy since resistance develops rapidly. If resolution of the infection is slow or if there is recurrent *Pseudomonas aeruginosa* exit-site infection, a second antipseudomonal drug, such as, but not limited to, IP aminoglycoside, ceftazidime, cefepime, piperacillin, imipenem–cilastatin, or meropenem, should be added (Li et al. 2010).

16.3.2.3 Special Consideration of Exit Infection

Many organisms can cause exit-site and tunnel infections, including microorganisms belonging to the normal skin flora, such as corynebacteria (Piraino et al. 1986; Schiffl et al. 2004). Therefore, culture with sensitivity testing is important in determining antibiotic therapy. Ultrasonography of the exit site is a useful adjunctive tool in the management of exit-site and tunnel infections (Fig. 16.6) (Kwan et al. 2004).

Antibiotic therapy must be continued until the exit site appears entirely normal. Two weeks is the minimum length of treatment time; treatment

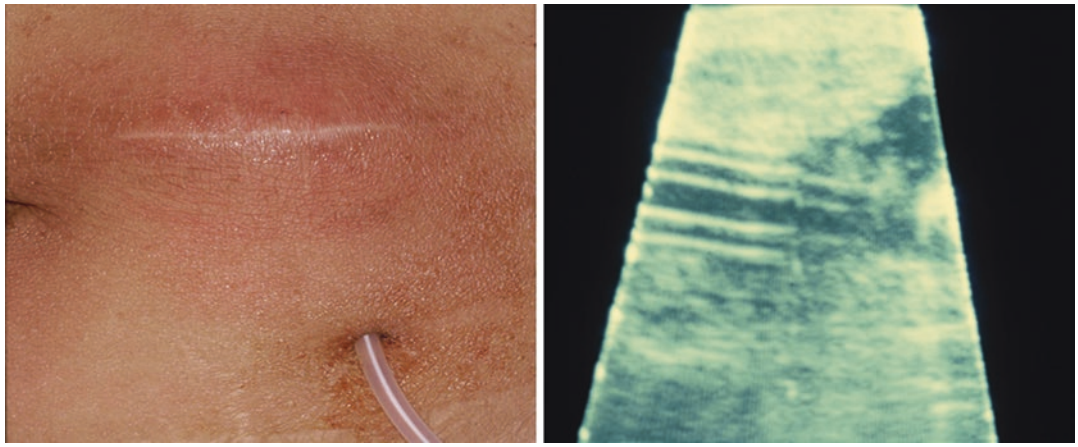

Fig. 16.6 Tunnel infection (Courtesy Yong-Lim Kim, Korea)

for 3 weeks is probably necessary for exit-site infections caused by *Pseudomonas aeruginosa* (Li et al. 2010). If prolonged therapy (e.g., longer than 3 weeks) with appropriate antibiotics fails to resolve the infection, the catheter can be replaced as a single procedure under antibiotic coverage (Lui et al. 2000; Yoshino et al. 2004). If the cuffs are not involved, revision of the tunnel may be performed in conjunction with continued antibiotic therapy (Li et al. 2010).

In general, catheter removal should be considered earlier for exit-site infections caused by *Pseudomonas aeruginosa* or if there is tunnel infection. A patient with an exit-site infection that progresses to peritonitis or who presents with an exit-site infection in conjunction with peritonitis with the same organism will usually require catheter removal (Li et al. 2010). The exception is peritonitis due to coagulase-negative *Staphylococcus*, which is generally readily treated. In selected cases, cuff shaving may be considered an alternative to catheter replacement for tunnel infection (Yoshino et al. 2004).

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Complication of PD (Except Infection)

17

Hitoshi Sugiyama, Toshio Yamanari, and Hiroshi Morinaga

17.1 Introduction

Peritoneal dialysis is an established form of renal replacement therapy. With its increasing popularity, we are now encountering a variety of complications. Noninfectious complications are usually less common as compared with infectious complications such as bacterial peritonitis. In this article, we discuss some of the common noninfectious complications of peritoneal dialysis such as chyloperitoneum, hemoperitoneum, herniation, hydrothorax, acid-base and electrolyte disorders, and encapsulating peritoneal sclerosis. Since noninfectious complications are less common than infectious complications, diagnosis might be delayed due to lack of awareness. The awareness of these complications thus will help us in early diagnosis and treatment in patients with peritoneal dialysis.

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17.2 Chyloperitoneum

The influx of triglyceride-rich chylomicrons into the peritoneal cavity occurs due to the interruption of the lymphatic drainage from the gut to the main lymphatic trunks. The compromise of the integrity of these lymphatic channels most commonly occurs as the result of neoplasms, in particular malignant lymphoma (Press et al. 1982).

After a fat-rich meal, long-chain fatty acids are incorporated into chylomicrons, which enter the lymphatic circulation. Chyloperitoneum is therefore an intermittent event that occurs after the ingestion of fat and which clears sometime afterward. Because medium-chain triglycerides are not absorbed through the lymphatic channels, chylous complications have been treated by prescribing a diet in which fat is delivered in this form (Hashim et al. 1964), thus obviating the need for lymphatic drainage of triglycerides.

In patients who are not on peritoneal dialysis (PD), chylous ascites is likely to present as increasing abdominal girth and peripheral edema (Press et al. 1982). For PD patients, chyloperitoneum presents as milky-white effluent, which can be mistaken for peritonitis.

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Chyloperitoneum has been reported to be present at the time of the insertion of the peritoneal catheter (Porter et al. 1991) or in the days to months after its insertion. The diagnosis is suggested by the white, milky appearance of the dialysate in conjunction with the absence of any indications of peritonitis. Lipoprotein electrophoresis shows lipid staining at the origin, which is a characteristic of chylomicrons (Porter et al. 1991). When the dialysate is separated into layers upon standing, the supernatant is positively stained for fat by Sudan black and can be dissolved with ether (Porter et al. 1991). The triglyceride level of the dialysate is greater than the plasma triglyceride level, which is a characteristic of intestinal lymph.

The etiology of chyloperitoneum is unknown. In each case, there must be communication between the peritoneal lymphatics and the peritoneal cavity. The dialysis catheter or its trocar may cut a lymph vessel. Multiple previous episodes of peritonitis could result in peritoneal adhesion and lymphatic obstruction. In non-dialyzed patients, bacterial peritonitis has been implicated in the pathogenesis of chylous ascites and encapsulating peritonitis (Leport et al. 1987).

In patients with extensive retroperitoneal lymphoma, the episodes of cloudy dialysate are likely representative of chyloperitoneum. This phenomenon should be part of the differential diagnosis of culture-negative peritonitis.

Calcium channel blockers, including certain dihydropyridine-type calcium channel blockers, have been reported to induce chyloperitoneum in patients undergoing PD as a rare complication of PD (Suzuki et al. 2005; Yamamoto et al. 2010; Yoshimoto et al. 1993, 1998). The mechanisms by which calcium channel blockers lead to chyloperitoneum remain unclear. The reasons why not all PD patients who receive these agents develop chyloperitoneum and why there are differences in the incidence of chyloperitoneum among the different types of calcium channel blockers are also unknown. It has been hypothesized that calcium channel blockers may cause some alterations in the permeability of the peritoneal membrane or impaired resorption by dilating small vessels in the small bowel and mesentery and cause exudation of lymph into the peritoneal cavity by dilating the intestinal lymphatic system.

17.3 Hemoperitoneum

Hemoperitoneum is seen in patients receiving peritoneal dialysis (PD) because the PD catheter provides a clear window to the peritoneum (Fig. 17.1) (Lew 2007). Gynecological phenomena may account for the majority of cases. The intra-abdominal pathology of solid organs such as the kidney, liver, and spleen, as well as the gastrointestinal tract, is recognized. Characteristic to PD patients, hemoperitoneum may be associated with the catheter itself, uremic bleeding, or peritonitis. The presence of blood in dialysis effluent is stressful to patients with PD and a cause of concern to medical practitioner. For example, as little as 2 mL of blood can result in 1 L of dialysis effluent being noticeably blood tinged (Nace et al. 1985). A successful PD program requires nephrologists, PD nurses, and patients to assess and manage hemoperitoneum in a systematic manner.

Hemoperitoneum has a wide differential diagnosis (Table 17.1). Menstruation is a common and benign cause of blood in the peritoneal cavity. In a recent review of hemoperitoneum, bleeding due to menstruation was the most common cause, accounting for one third of the benign episodes of hemoperitoneum (Greenberg et al. 1992). The majority of regularly menstruating women undergoing PD experience repeated hemoperitoneum.

There are two mechanisms by which menstruation can lead to hemoperitoneum in patients receiving PD. If endometrial tissue is present in the peritoneal cavity, it will shed simultaneously with the intrauterine endometrium, and bloody dialysate will occur simultaneously with the menstrual flow. The other mechanism is that the shed uterine tissue and blood move out of both the uterine cervix and in a retrograde manner through the fallopian tubes into the peritoneal cavity. The peritoneal bleeding may start a few days prior to the appearance of blood in the vagina (Blumenkrantz et al. 1981). It has been

Fig. 17.1 Hemoperitoneum, probably due to anticoagulant therapy with warfarin in a patient undergoing PD

suggested that the timing of menstrual pain matches the appearance of peritoneal blood rather than the vaginal menstrual flow; thus, peritoneal blood may be an important cause of dysmenorrhea (Blumenkrantz et al. 1981).

Women of reproductive age may also experience hemoperitoneum coincident with ovulation (Greenberg et al. 1992; Harnett et al. 1987). It is suggested that the source of blood is bleeding from the ovary, which occurs with the rupture and release of the ovum. Other ovarian sources of bleeding include ruptured cysts with sufficient to bleeding to necessitate transfusion (Fraley et al. 1988). The episodes of hemoperitoneum associated with menstruation and ovulation are recognized by their periodicity and occurrence in women of reproductive age. While this cause of blood in the dialysate is considered benign, there are potential complications. The blood loss can exacerbate anemia due to chronic kidney disease, and for this reason alone anovulant therapy may be indicated.

A reported association between hemoperitoneum and *Staphylococcus epidermidis* peritonitis suggests that the bloody dialysate may provide a rich growth medium for intraperitoneal bacteria. Other investigators, however, have been unable to document an increased frequency of peritonitis in relation to menstruation-generated hemoperitoneum (Greenberg et al. 1992).

In non-menstruating patients, hemoperitoneum must be carefully investigated. There are a number of surgical causes of blood in the peritoneal cavity, including cholecystitis (Nace et al. 1985), rupture of the spleen (de los Santos et al. 1986), and pancreatitis (Greenberg et al. 1992).

Table 17.1 Causes of hemoperitoneum in peritoneal dialysis

	References
Gynecologic	
Menstruation	Press et al. (1982) and Hashim et al. (1964)
Ovulation	Hashim et al. (1964)
Bleeding ovarian cysts	Hashim et al. (1964), Porter et al. (1991) and Leport et al. (1987)
Neoplastic	
Renal cell carcinoma	Suzuki et al. (2005)
Adenocarcinoma of the colon	Suzuki et al. (2005)
Polycystic kidney disease	Yamamoto et al. (2010)
Hematologic	
Idiopathic thrombopenic purpura	Leport et al. (1987)
Anticoagulant therapy	Leport et al. (1987)
Peritoneal membrane disease	
Peritoneal calcification	Yoshimoto et al. (1993)
Radiation-induced peritoneal fibrosis	Yoshimoto et al. (1998)
Sclerosing peritonitis	Leport et al. (1987)
Gastrointestinal	
Acute cholecystitis	Lew (2007)
Post-colonoscopy	Leport et al. (1987) and Lew (2007)
Catheter-induced splenic rupture	Nace et al. (1985)
Pancreatitis	Leport et al. (1987)
Miscellaneous	
Leakage from extra-peritoneal hematoma	Leport et al. (1987)
Splenic rupture	Greenberg et al. (1992)
Extracorporeal lithotripsy	Blumenkrantz et al. (1981)

In these cases, it should be apparent that the patient has a painful abdomen, and localized tenderness in association with bloody effluent requires an urgent surgical consultation. Hemoperitoneum due to splenic rupture, which occurs in association with PD, is very unusual. However, hemoperitoneum due to a ruptured spleen has been reported in chronic leukemia patients undergoing PD (Wang et al. 1998).

In non-dialysis patients there may be episodes of peritoneal bleeding that never come to medical attention because they are not observed. Peritoneal dialysis patients, on the other hand, have a window into the peritoneal cavity and otherwise asymptomatic peritoneal bleeding is readily apparent. This explains the hemoperitoneum that is observed following colonoscopy (Nace et al. 1985; Greenberg et al. 1992), in patients with coagulation disorders (Greenberg et al. 1992), polycystic kidney disease (PKD) (Blake and Abraham 1988), in patients with leakage from a hematoma outside the peritoneal cavity (Greenberg et al. 1992), and following extracorporeal lithotripsy for kidney stones (Husserl and Tapia 1987).

In patients with PKD, bleeding into a cyst can be associated with hematuria or hemoperitoneum (Blake and Abraham 1988). A case of bloody effluent in a PKD patient receiving PD was described. In this case, however, the bleeding was painless, which would be unusual if a kidney cyst had ruptured into the peritoneal cavity. Moreover, leukocytosis was observed in the dialysis effluent. These unusual features led to further investigations, which revealed that the patient had renal cell carcinoma (Twardowski et al. 1992). Bloody dialysate has also been mentioned in association with adenocarcinoma of the colon (Twardowski et al. 1992), presumably from the serosal spread of the tumor.

Recurrent hemoperitoneum may be a forerunner of peritoneal membrane disease. Bloody effluent has been described in association with hyperparathyroidism in patients with peritoneal calcification (Francis et al. 1990), in patients with radiation-induced peritoneal injury (Hassell et al. 1984), and as the presenting abnormality in patients who develop sclerosing peritonitis (Greenberg et al. 1992).

In patients with hemoperitoneum, there is a risk of the intraperitoneal blood coagulating in the catheter lumen. Thus, it has been recommended that intraperitoneal heparin (500–1000 U/L) be administered for as long as the dialysate still has visible blood or fibrin. In the clinical setting, intraperitoneal heparin does not worsen the bleeding or lead to systemic anticoagulation. In some instances of hemoperitoneum, the use of rapid exchanges with dialysate at room temperature leads to the rapid resolution of the bleeding. It is hypothesized that the relatively cool dialysate induces peritoneal

vasoconstriction and that this leads to hemostasis (Goodkin and Benning 1990).

17.4 Hernia

The risk of abdominal hernia is significantly higher in peritoneal dialysis (PD) patients than it is in hemodialysis patients (Fig. 17.2) (Lee et al. 2015). The presence of dialysis fluid in the peritoneal cavity leads to increased intra-abdominal pressure (IAP). Pressure within the abdomen increases in proportion to the volume of dialysate that is instilled (Twardowski et al. 1986). The supine patient generates the lowest IAP for a given volume of peritoneal fluid, while coughing in the sitting and upright positions results in the greatest pressure. In addition, a given activity can generate higher IAPs in patients who are older or more obese (Twardowski et al. 1986). A recent study in a small modern cohort examined the outcomes of large (in size) PD patients. However, it

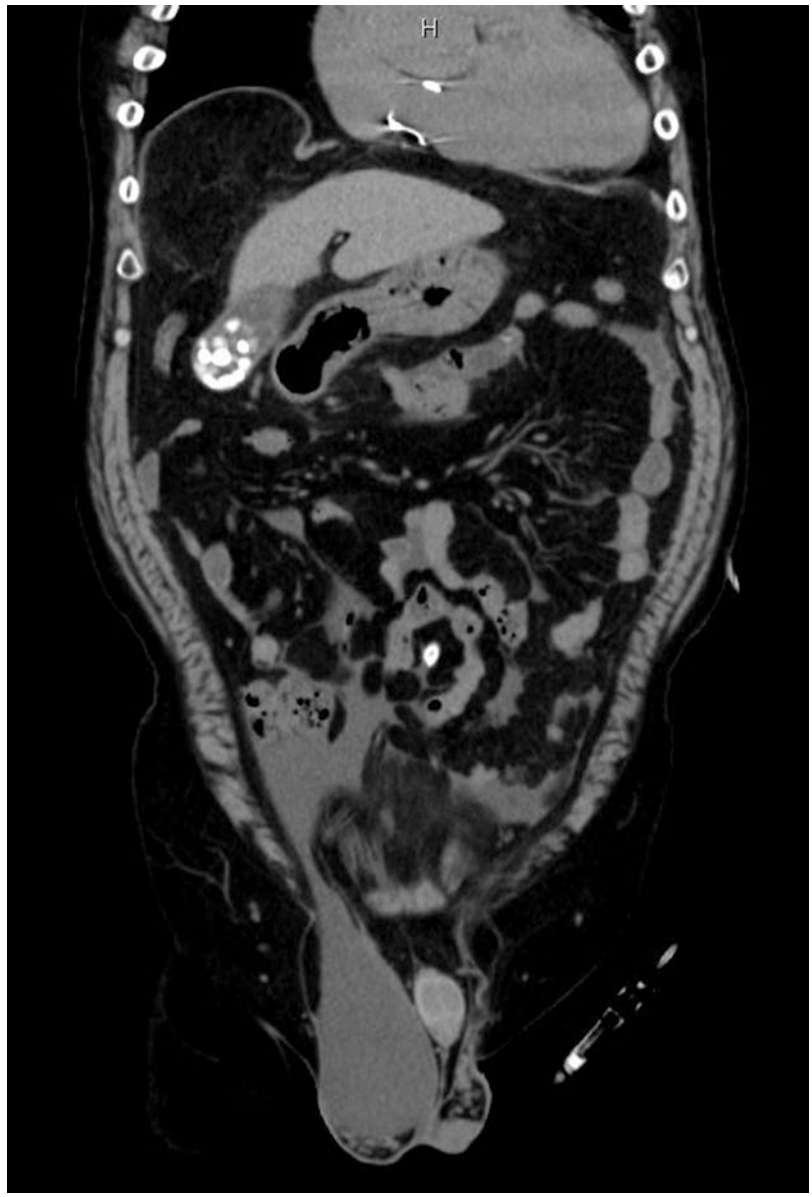

Fig. 17.2 A CT scan of indirect inguinal hernia exhibiting peritoneal fluid connecting the peritoneal cavity with the testis in a PD patient (coronal plane)

demonstrated that hernias and leaks were more common in patients weighing less than 90 kg than they were in obese patients (Ananthakrishnan et al. 2014). Another report demonstrated that the frequency of hernia in childhood PD patients was 8.6% (Kim et al. 2015a).

In accordance with Laplace's law, tension on the abdominal wall increases with the instillation of dialysate, as a result of the increase in IAP. An increase in the abdominal pressure and abdominal wall tension may lead to the formation of hernias in patients with congenital or acquired defects in or around the abdomen. Areas of weakness are very important in the pathogenesis of hernias. Indeed, the IAP in hernia patients is no different from the IAP in patients without hernias (Durand et al. 1992). The causes of hernias in PD patients have been described (Table 17.2). The most common types of hernia are incisional or occur through the catheter placement site (Digenis et al. 1982; O'Connor et al. 1986); other studies have reported that inguinal (Kauffman and Adams 1986) or umbilical (Wetherington et al. 1985) hernias occur most frequently. Asymptomatic hernias are probably quite common and may not be detected until a complication, such as bowel strangulation, occurs.

Table 17.2 Hernia in patients on peritoneal dialysis

	References
Umbilical	Harnett et al. (1987), Fraley et al. (1988) and de los Santos et al. (1986)
Inguinal	Harnett et al. (1987), Fraley et al. (1988), de los Santos et al. (1986) and Wang et al. (1998)
Catheter incision site	Fraley et al. (1988)
Ventral	de los Santos et al. (1986)
Epigastric	Harnett et al. (1987 and Fraley et al. (1988)
Incisional	Harnett et al. (1987), Fraley et al. (1988) and Blake and Abraham (1988)
Cystocele	Harnett et al. (1987)
Foramen of Morgagni	Harnett et al. (1987) and Husserl and Tapia (1987)
Richter's	Twardowski et al. (1992)
Enterocele	Harnett et al. (1987)

A review found that 11.5% of PD patients developed a hernia over 5 years of follow-up. Patients with hernias tend to be older, female, and multiparous. They also tend to experience a higher frequency of postoperative leak at the time of catheter insertion (Digenis et al. 1982) and to have undergone a previous hernia repair (O'Connor et al. 1986).

Patients with polycystic kidney disease (PKD) may be predisposed to hernia formation, either as a result of the higher IAP caused by large kidneys or as a manifestation of a generalized collagen disorder (Modi et al. 1989). The mean time for the development of a hernia is 1 year, and the risk increases by 20% for each year that a patient is on PD (O'Connor et al. 1986).

A major potential area of weakness is the abdominal incision for the implantation of the dialysis catheter. When this incision is made in the midline, there is a predilection for an incisional hernia to develop because this is an anatomically weak area (Apostolidis et al. 1988). Changing to a paramedian incision through the rectus muscle is associated with rates of perioperative leak and hernia formation (Spence et al. 1985).

Another area of potential weakness for herniation is the processus vaginalis. After the migration of the testis in fetal life, the processus vaginalis normally undergoes obliteration. In many cases, however, this does not occur, and the increased abdominal pressure during PD may push the bowel into the processus vaginalis, resulting in an indirect inguinal hernia. Male pediatric patients may be predisposed to this complication. If they develop a unilateral inguinal hernia, both sides should probably be prophylactically repaired (Khoury et al. 1991).

Most hernias present as a painless swelling (Digenis et al. 1982). The bowel has been reported to herniate through the diaphragm at the foramen of Morgagni and to present as a retrosternal air-fluid level (Ramos et al. 1982). The most troublesome complications are incarceration and strangulation of bowel. This can occur through almost any kind of hernia, but especially small ones. It may present as a tender lump (Power et al. 1981), recurrent gram-negative peritonitis,

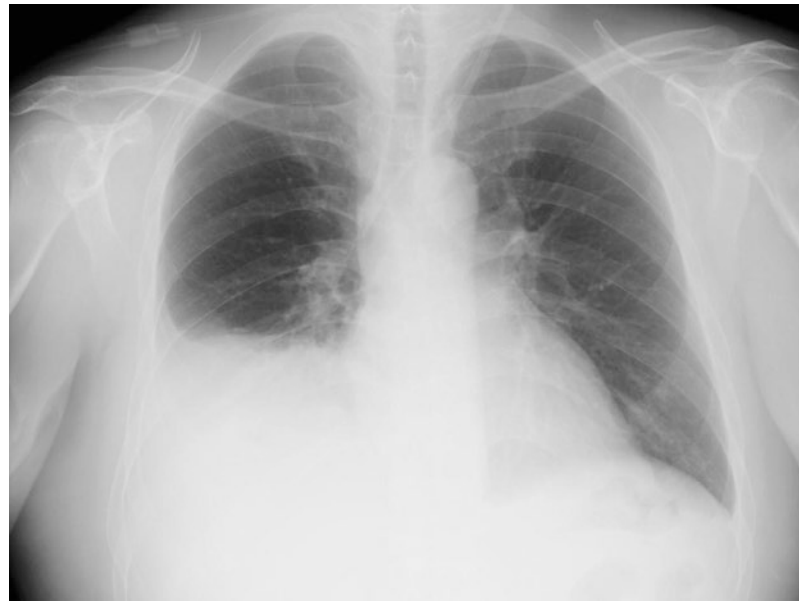

Fig. 17.3 A chest X-ray film showing moderate pleural effusion on the right side in a PD patient

bowel obstruction, or perforation (Digenis et al. 1982). Bowel incarceration or strangulation can mimic peritonitis (Power et al. 1981), and this complication must be kept in mind, particularly if the site of herniation is not obvious.

Hernias deserve surgical repair. Although large ventral hernias carry little measurable risk of bowel incarceration (Moffat et al. 1982), they are unsightly and prone to becoming enlarged. The other types of hernias should be repaired because of the risk of bowel incarceration and strangulation. After surgery, the patient can be temporarily maintained on low volume intermittent PD to allow time for wound healing. If hernias recur, other options include changing the patient to nighttime cycler dialysis, where dialysis is performed with the patient in the supine position, under a lower IAP, or with lower volumes of dialysate but more frequent exchanges.

17.5 Hydrothorax

Increased intra-abdominal pressure can result in the leakage of dialysis fluid across the diaphragm and into the pleural space. The accumulation of dialysis fluid in the pleural cavity is called hydrothorax. Hydrothorax commonly presents on the right side in peritoneal dialysis (PD) patients (Fig. 17.3) (Saha and Singh 2007). It is not clear how often hydrothorax occurs in patients receiving PD, but most studies estimate that the incidence is less than 5%, which would make it a less frequent consequence of an increased IAP than abdominal hernia (Maher and Schreiner 1965; Nomoto et al. 1989). However, it is possible that hydrothorax occurs more frequently but does not come to medical attention if the patient is asymptomatic or if minor complaints of shortness of breath are overlooked.

17.5.1 Pathogenesis

A defect in the diaphragm must be present to allow the flux of dialysis fluid from the peritoneal cavity into the pleural cavity. Autopsy studies have revealed the localized absence of muscle fibers in the hemidiaphragm (Lieberman et al. 1966). The missing muscle fibers are replaced with a disordered network of collagen. One or more defects in the tendinous part of the hemidiaphragm have been observed (Lieberman et al. 1966).

In pediatric patients receiving PD who develop hydrothorax, diaphragmatic eventration rather

than hernia has been described at surgery (Bjerke et al. 1991).

It is likely that these defects in the musculotendinous part of the diaphragm are not rare occurrences. Rather, they may only come to medical attention when there is fluid in the abdominal cavity under increased pressure in a manner similar to patent processus vaginalis. This explains why hydrothorax has been described in patients receiving PD and in those with liver disease or with ovarian cancer and ascites.

The extent of the deficiency in the hemidiaphragm varies among patients. Patients with a clear preexisting connection between the peritoneal cavity and the pleural space are probably the same patients who develop hydrothorax with their first-ever infusion of dialysis fluid. In contrast, some patients develop hydrothorax months to years after the start of PD. Presumably, those patients have attenuated tissue separating the pleural space from the peritoneal cavity, and it may take repeated exposure to an increased IAP or an episode of peritonitis to remove the barrier between the two cavities.

17.5.2 Diagnosis

Small pleural effusions can be asymptomatic and are detected by routine chest radiography. Larger pleural effusions can lead to respiratory embarrassment.

The shortness of breath that results from pleural effusion can be mistaken for congestive heart failure. The patient may choose more hypertonic dialysis solutions in an effort to increase ultrafiltration. In patients with hydrothorax, however, increased ultrafiltration will lead to an even greater IAP with further flux of the dialysate into the pleural space, worsening the symptoms. Thus, a history of complaints of dyspnea that appears to worsen with hypertonic dialysate should suggest the possibility of hydrothorax, particularly if the volume of effluent that returns is less than normal. On physical examination, the absence of breath sounds and stony dullness to percussion in the lung base is consistent with pleural effusion. There are few reports on tension hydrothorax (Rossoff 1990).

Chest X-ray shows pleural effusion, which occurs on the right side in most patients. It is assumed that the diaphragm defect occurs more frequently on the right side; however, the reason for this is unknown. Alternatively, the heart may cover any defects that might be present in the left hemidiaphragm.

Clearly, other causes of pleural effusion should be ruled out, including local parenchymal lung disease, congestive heart failure, and pleuritis. The scenario wherein a patient develops a large right-sided pleural effusion within the first few dialysis sessions is strongly suggestive of hydrothorax. However, when a patient on PD for months develops peritonitis, fluid overload, and pleural effusion, it can be more difficult to make the correct diagnosis.

Thoracentesis can be helpful for making a correct diagnosis in patients in whom the etiology of pleural effusion is uncertain. If the pleural effusion is composed of dialysate, the glucose concentration is very high (usually >40 mmol/L), and the fluid has a low protein concentration consistent with a transudate.

Even when the diagnosis is certain, thoracentesis should be performed for patients who are short of breath from hydrothorax. The evacuation of one or more liters of fluid can be expected to lead to a significant improvement in the patients' respiratory status.

In the absence of thoracentesis, the presence of peritoneal-pleural communication can be confirmed by isotopic scanning. Between 3 and 10 mCi of technetium-labeled macroaggregated albumin or sulfur colloid is instilled into the peritoneal cavity along with the usual volume of dialysis fluid. The patient should move around to ensure the mixing of the radioisotope and dialysate and to increase the IAP. Subsequent scanning detects the movement of the isotope above the hemidiaphragm. Although this usually is detectable in the first few minutes, sometimes late pictures (up to 6 h) need to be taken. This method is convenient but is not completely foolproof. Defects have been found in the diaphragm at surgery in patients in whom isotopic scanning was negative (Mestas et al. 1991).

17.5.3 Treatment

Thoracentesis is recommended for the immediate treatment of hydrothorax if respiratory compromise is present. Otherwise, the discontinuation of PD often leads to the rapid and dramatic resolution of pleural effusion (Nomoto et al. 1989). In a small number of patients, the effusion is very slow to resolve, suggesting the possibility of one-way or ball-valve type communication between the peritoneal and pleural spaces. In such cases, thoracentesis may be helpful for hastening the resolution of the pleural effusion.

Subsequent treatment depends on whether the patient is going to continue on PD. The occurrence of hydrothorax is occasionally so distressing to the patient that the patient requests a transfer to hemodialysis. In this case, the communication between the peritoneal cavity and the pleural space should be of no consequence, and nothing further needs to be done after the resolution of effusion.

If the patient is going to continue PD, there are several different options.

Temporary hemodialysis (2–4 weeks) with a subsequent return to PD: There may be a transient loss of the integrity of the cell layers overlying a diaphragmatic defect, especially in the presence of peritonitis. If PD is temporarily discontinued and the mesothelium is allowed to reconstitute itself over the defect, it is possible that the peritoneo-pleural communication may become resealed. It is less likely that this would be effective in patients demonstrating pleural leak at the first dialysis session; however, this phenomenon has even been reported after a 2-month hiatus from hemodialysis. It has been suggested that the dialysate in the pleural space may act as a sclerosing agent and prevent subsequent leaks (Rutland and Kalowski 1992).

Temporary hemodialysis with a return to a PD regimen with lower intra-abdominal pressure: Patients who experience hydrothorax on PD are sometimes able to resume PD using a cycler. Even though the supine position might be thought to be conducive to the movement of fluid into the pleural cavity, the reduction in IAP afforded by this posture seems to more than compensate for possibility (Townsend and Fragola 1982). The use of smaller dialysis volumes with more frequent exchanges is helpful in minimizing the increase in IAP.

The obliteration of the pleural space: Previous studies have reported the successful obliteration of the pleural cavity. In this case, the leaves of the pleura stick together and prevent the re-accumulation of pleural fluid. Different agents can be used to induce the obliteration of the pleural space. Oxytetracycline (20 mg/kg) has been administered via a thoracostomy tube (Nomoto et al. 1989; Benz and Schleifer 1985). It is important that the patient remains supine for up to 24 h and assumes different positions, including head down, to ensure that all of the pleural surfaces are exposed to the agent. The patient should also receive analgesia, as this procedure can be painful. Talc has also been successfully applied for the obliteration of the pleural cavity in a PD (Posen and Sachs 1979). The obliteration of the pleural cavity has also been accomplished by the instillation of 40 mL of autologous blood. The patient should be maintained, if possible, on hemodialysis for a few weeks to allow the obliteration of the pleural cavity to take place. More than one instillation of blood may be necessary, but the benefit of the blood is that it appears to be a relatively painless procedure in comparison to the use of talc or tetracycline (Hidai et al. 1989). There are reports from Japan of the use of OK-432, a hemolytic streptococcal preparation, and the use of *Nocardia rubra* cell wall skeleton to obliterate the pleural cavity (Nomoto et al. 1989). Finally, the instillation of a combination of aprotinin-calciumchloride-thrombin and fibrin glue in the drained pleural cavity was reported to have successfully prevented recurrent hydrothorax in a patient in whom treatment with other agents had been unsuccessful (Vlachojannis et al. 1985).

Operative repair: At thoracotomy, communication between the peritoneal cavity and the pleural space may be visualized. Sometimes blebs or blisters are quickly recognized and can be sutured and reinforced with Teflon felt patches. It is recommended that two to three liters of dialysate be infused into the peritoneal cavity through the

dialysis catheter. The diaphragm is inspected from the pleural side to check for the seepage of dialysate through holes or blisters. It is important that the surgeon be patient as it may take time for seepage to be recognized (Allen and Matthews 1991). In the case of eventration of the diaphragm, as reported in the pediatric literature, plication with nonabsorbable sutures can be an effective surgical repair. These patients are able to return to PD (Bjerke et al. 1991).

In summary, hydrothorax is a well-described but relatively uncommon complication of PD. The diagnosis is relatively simple once the possibility of peritoneal-pleural communication has been investigated. Thoracentesis may be necessary to confirm the diagnosis and is mandated by respiratory embarrassment. As described above, several treatment options are available if the patient is willing to continue with PD.

17.6 Acid-Base and Electrolyte Disorders

17.6.1 Disorders of Water Metabolism

In patients with end-stage renal disease, the serum sodium concentration depends on the relative amount of salt and water being ingested and the amount of salt and water removed by dialysis. Sodium flux into the peritoneal cavity of peritoneal dialysis (PD) patients is caused by diffusion and convection. Because sodium is sieved by the peritoneal membrane, the fluid entering the peritoneal cavity by osmotically driven flow is hyponatremic, more water than salt flows from plasma to the peritoneal cavity (Ahearn and Nolph 1972). In theory, this flux should leave the patient with a relative water deficit; thus, the patient should become hypernatremic. However, hypertonicity is a powerful stimulant of ADH secretion, which in turn stimulates thirst. The patient then drinks water or some other hypotonic fluid until tonicity is restored. In fact, PD patients may actually demonstrate plasma sodium concentrations that are slightly lower than normal. There are a number of reasons for the relative water excess, including an increased water intake or the low sodium concentration of the dialysis solution (Lindholm et al. 1986). Infants undergoing PD who are fed normal infant formula may be prone to hyponatremia because the amount of sodium lost through ultrafiltration is greater than that gained from the ingestion of formula. Moreover, the proprietary infant formulas have a high water to sodium ratio, leading to water accumulation and hyponatremia (Paulson et al. 1989).

In a recent study, tolvaptan (15 mg daily), a vasopressin type 2 receptor antagonist, was administered to 15 PD patients (Mori et al. 2013). In 11 of 15 patients, the urine volume increased to more than 400 mL daily. A significant increase in diluted urine was observed, as indicated by a reduction in the specific gravity or osmolality of the urine, or both. The urinary excretion of urea nitrogen and sodium was significantly increased. Increases in the renal Kt/V were observed, but the peritoneal Kt/V was unchanged. A significant increase in creatinine clearance was also observed. The data suggest that tolvaptan not only stimulates water diuresis but also natriuresis, without reducing the residual renal function (RRF) in PD patients. Thus, tolvaptan could be a beneficial tool for controlling body fluid and maintaining the RRF in PD patients; however, the long-term effects of this agent are unclear.

Cardiovascular (CV) disease is the leading cause of morbidity and mortality in PD patients. As for the impact of hyponatremia on the prognosis, the cumulative incidence of new-onset CV events after the initiation of PD in patients with a time-averaged serum sodium level of $\leq$138 mEq/L was significantly higher than in it was in patients with a TA-Na level of >138 mEq/L during a mean follow-up period of 43.2 months, among 441 incident patients who had started PD (Kim et al. 2015b). An increase in the time-averaged serum sodium level was associated with a significantly lower risk of CV events after adjustment for multiple confounding covariates. However, whether the correction of hyponatremia provides additional protection from the development of CV events in PD patients remains to be addressed in future interventional studies.

A study of insulin-dependent diabetics with hyperglycemia revealed that it was possible for the serum tonicity of patients on hemodialysis to nearly normalize, whereas patients with PD remained hypertonic due to the continued loss of water (in the excess of solute) into the dialysate. In hyperglycemia, the increased extracellular glucose has a normalizing effect on the osmotic flux of water from the intracellular compartment. The fall in the serum sodium concentration, which results from this movement of water into the extracellular compartment, can be predicted. In patients on hemodialysis, however, the reduction in the serum sodium concentration is greater than that observed in hyperglycemic patients who are not on dialysis. On the other hand, patients on PD behave more like non-dialysis patients. One explanation is that the hemodialysis patient drinks water in response to increased plasma osmolality; in the absence of ongoing osmotic diuresis, this is able to lower plasma tonicity. In contrast, PD patients undergo a continuous loss of water with an excess of sodium, which mimics the effect of the osmotic diuresis that is seen in hyperglycemic patients with a normal renal function. The excess loss of water can perpetuate the hyperosmolar state (Tzamaloukas and Avasthi 1986).

17.6.2 Potassium Metabolism Disorders

In PD patients, a low serum potassium concentration can be a more prevalent problem. In contrast, hemodialysis patients who are noncompliant with their prescribed diet may have problems with hyperkalemia on non-dialysis days. Hypokalemia is found in 10–36% of PD patients (Spital and Sterns 1985). The effects can be profound, as reported in the case of a diabetic PD patient who presented with vomiting and diarrhea (Rostand 1983). Ongoing losses of potassium in the dialysate may contribute to hypokalemia in some PD patients. However, other factors, such as the cellular uptake and bowel losses, may play a role. Muscle biopsy studies show that the muscle potassium content is increased in PD patients, presumably reflecting the intracellular uptake of potassium (Lindholm et al. 1986).

It is recommended that the serum potassium concentration be maintained at >3.0 mmol/L in asymptomatic patients and >3.5 mmol/L in patients on digoxin or with a history of cardiac arrhythmias (Bargman and Jamison 1986). Potassium supplementation should be strictly monitored in dialysis patients because of the absence of a renal reserve to excrete excess potassium. Potassium chloride can be added to the dialysate to diminish the concentration gradient for the diffusion of potassium into the dialysis fluid. In the acute setting, up to 20 mmol/L of KCI can be added to the dialysate with a low incidence of side effects. This dose has been reported to increase the plasma potassium concentration by an average 0.44 mmol/L over 2–3 h. However, the effect of this hyperkalemic solution on the peritoneal membrane is unknown; thus, this treatment should be used only in urgent settings (Spital and Sterns 1985).

Hyperkalemia is occasionally seen in acute PD patients. It has been reported to occur after acute PD (Vaamonde et al. 1975) and has been attributed to the breakdown of glycogen with the consequent release of potassium. Other factors that may affect extrarenal potassium disposal, such as insulin deficiency, converting enzyme inhibitors, and beta-blockers, should be considered.

17.6.3 Acid-Base Balance

In healthy individuals, the kidneys help to maintain the acid-base balance via the excretion of acid and the generation of new bicarbonate. As the kidneys fail, however, the net acid excretion diminishes and metabolic acidosis develops. It is therefore important that the buffer is replenished in any form of dialysis.

In the early years of PD, bicarbonate was employed as buffer. However, bicarbonate reacts with calcium chloride leading to precipitation of calcium carbonate. Thus, other less reactive buffers have been used, and the experience with lac-

tate and acetate has continued. Dialysate containing glucose must be kept at pH 5–6 to prevent caramelization. At equimolar concentrations of acetate and lactate, the titratable acidity of acetate is higher than that of lactate. Thus, when instilled into the peritoneal cavity, solutions containing acetate remain acidic for longer than lactate-based solutions (Pedersen et al. 1985). The prolonged acidity of the solution may explain reports of abdominal pain and chemical peritonitis with the use of acetate-based dialysate (Pedersen et al. 1985). The serum lactate level remains low in patients receiving lactate-containing dialysate. Patients receiving equimolar amounts of acetate-containing dialysate, on the other hand, demonstrate abnormally high levels of plasma acetate (La Greca et al. 1981). This finding suggests that less lactate is absorbed or it is more efficiently metabolized than acetate. Patients receiving lactate show normal serum bicarbonate levels (La Greca et al. 1981), suggesting that adequate amounts of lactate are being absorbed and converted to bicarbonate. The dialysate lactate is composed of both the easily metabolized L isomer and the slowly metabolized D isomer. Both isomers are absorbed from the dialysate in equal amounts. The lack of accumulation of the D isomer in the blood suggests that it is metabolized to a significant extent (Richardson and Roscoe 1986); however, previous investigations have suggested otherwise (Rubin et al. 1982). The fate of the absorbed D-lactate is a matter of concern because of reports of cerebral dysfunction in patients with high blood levels of this isomer (Graves 1987). During IPD, there is a net gain in the body buffer of approximately 80 mmol. This is the result of lactate absorption surpassing bicarbonate loss from plasma to dialysate. High rates of ultrafiltration mitigate this effect via both the increased loss of bicarbonate and the diminished absorption of lactate. Presumably, convective forces are involved in this phenomenon (Richardson and Roscoe 1986).

The use of lactate has its drawbacks. In patients with lactic acidosis, its use may worsen the metabolic derangement (Conte et al. 1986). In this setting, the use of specially prepared bicarbonate-based solutions (Foulks and Wright 1981), or a proportioning system similar to that used in bicarbonate-based hemodialysis (Feriani et al. 1985), is recommended. Lactate may be an inappropriate buffer in patients with hepatic failure. In this setting, lactate may not be sufficiently converted to bicarbonate, leading to acidosis and the accumulation of lactate (Vaamonde et al. 1975).

PD patients may develop metabolic or respiratory alkalosis. Metabolic alkalosis can result from a reduction in the extracellular fluid volume, as reported in the treatment phase of hyperglycemia (Garella 1984) or from the frequent use of hypertonic dialysis solutions (Gault et al. 1971). In patients with respiratory alkalosis, the normally functioning kidneys defend against alkalemia by excreting bicarbonate. PD patients have no such mechanism. Furthermore, the constant infusion of buffer in the patients with respiratory alkalosis can lead to serious alkalemia (Kenamond et al. 1986).

Respiratory alkalosis may appear during the initial stages of dialysis. When an acidotic patient commences dialysis, the infusion of buffer will correct the extracellular acidosis. However, because the bicarbonate anion crosses the blood-brain barrier relatively slowly, the cerebrospinal fluid that bathes the respirator center will remain relatively acid. This cerebrospinal fluid acidosis will continue to stimulate the respiratory drive and maintain hyperventilation despite the pH of the extracellular fluid being normal. Thus, respiratory alkalosis will develop as a response to hyperventilation (Posner and Plum 1967). This phenomenon poses only a minor problem in PD patients because the conversion of lactate to bicarbonate occurs slowly enough to allow for the equilibration of cerebrospinal fluid with extracellular fluid.

The measured level of bicarbonate in PD patients is significantly higher than that in hemodialysis patients (Vashistha et al. 2013), suggesting that the therapy provides a more complete correction of metabolic acidosis than intermittent hemodialysis. Survival data suggest that the serum bicarbonate concentration should be maintained at >22 mEq/L in all ESRD patients,

irrespective of the mode of dialysis (Vashistha et al. 2013). On the other hand, low serum bicarbonate levels in PD patients reflect inadequate dialysis (Tattersall et al. 1995).

17.7 Encapsulating Peritoneal Sclerosis (EPS)

Encapsulating peritoneal sclerosis (EPS), previously known as sclerosing encapsulating peritonitis (Nomoto et al. 1996), is a serious complication of peritoneal dialysis (PD) (Brown et al. 2009; Kawanishi et al. 2004; Nakao et al. 2014; Nakayama et al. 2014). The disease, which was first reported in Gandhi et al. (1980), consists of progressive inanition, vomiting, intermittent bowel obstruction, and the decreased peritoneal transport of water and solutes. It has mainly been reported from Europe (Bradley et al. 1983; Grefberg et al. 1983; Rottembourg 1983); however, sporadic cases have been found elsewhere. At surgery or postmortem examination, the small intestine is found to be bound or encapsulated by a thick fibrous layer, which renders the peritoneal surface opaque. The fibrous layer resembles a so-called thick shaggy membrane (Rottembourg 1983), marble (Pusateri et al. 1986), cocoon, or fruit rind and may or may not peel off the bowel relatively easily (Daugirdas and Gandhi 1984). The bowel exposed after peeling off the fibrous layer may appear normal (Daugirdas and Gandhi 1984). A different form of sclerosing peritonitis has been described in which the diffuse sclerosing process extends transmurally with the incorporation of the inner circular muscular layer and the myenteric plexus of the small bowel in the process of fibrosis (Hauglustaine et al. 1984).

Patients with this disease show a poor prognosis, with a mortality rate of at least 50% (Pusateri et al. 1986). The poor prognosis is probably due to severe malnutrition and recurrent bowel obstruction. The mortality rate of patients whose symptoms lead to laparotomy was close to 80% (Pusateri et al. 1986). The diagnosis of bowel obstruction may be delayed because the process of fibrosis does not allow the bowel to distend (Bradley et al. 1983).

EPS appears to be a distinct and devastating syndrome, and the name should not be used interchangeably with peritoneal sclerosis. The latter term should be reserved for the finding of non-encapsulating sclerosis and the fibrous adhesions associated with ultrafiltration failure. This condition is seen in patients who undergo prolonged PD or who have recurrent episodes of peritonitis, but it may be present at the initiation of dialysis. Indeed, the lack of rigorous differentiation between these two entities may confuse any attempt to define the etiological factors, particularly among different dialysis centers.

The cause of EPS is uncertain and numerous possibilities have been suggested (Table 17.3). The original reports came from centers in which the dialysate buffer was primarily acetate rather than lactate (Rottembourg 1983; Slingeneyer et al. 1983). It has been suggested that acetate may irritate the peritoneal membrane and perhaps initiate the fibrosing process (Oreopoulos et al. 1983). Acetatecontaining dialysate exposes the mesothelium to concentrations of this buffer anion that are 350–450 times that normally found in the peritoneal cavity (Dobbie 1992). However, EPS has also been reported in patients who undergo dialysis with lactate (Daugirdas et al. 1986); however, in some cases the disease in question may be peritoneal sclerosis (Daugirdas et al. 1986) or transmural bowel fibrosis (Hauglustaine et al. 1984).

Recurrent peritonitis or subclinical grumbling peritonitis (Ing et al. 1983) has been suggested as a cause of this distressing syndrome; however, many patients have clearly never had clinically detectable peritonitis or the incidence of peritonitis has been relatively low (Slingeneyer et al. 1983). Alternatively, it is possible that one severe episode of peritonitis might condition the peritoneal milieu to initiate the development of this syndrome.

Some researchers have hypothesized that the use of a bacterial filter in the dialysis tubing may be linked to the high incidence of EPS. They suggested that bacteria trapped upstream of the filter secrete pyrogen, which crosses the filter and enters the peritoneal cavity, where it stimulates macrophages to secrete interleukin-1 (Shaldon

Table 17.3 Possible causes of development of encapsulating peritoneal sclerosis (EPS)

	References
Acetate-containing dialysate	Francis et al. (1990), Hassell et al. (1984) and Goodkin and Benning (1990)
Recurrent peritonitis	Hassell et al. (1984), Lee et al. (2015) and Twardowski et al. (1986)
Plastic particles	Goodkin and Benning (1990))
Formaldehyde	Goodkin and Benning (1990)
Bacterial filter causing upstream multiplication of bacteria with pyrogen release into peritoneum stimulating interleukin-1 production	Ananthakrishnan et al. (2014)
Multiple abdominal surgeries	Twardowski et al. (1986)
Unrecognized subclinical peritonitis with fastidious bacteria or fungi	Kim et al. (2015a)
IP contamination with chlorhexidine in alcohol sprayed on connector	Durand et al. (1992 and Digenis et al. 1982)
Hypertonic acidic dialysate	Goodkin and Benning (1990)
Catheter	Goodkin and Benning (1990 and O'Connor et al. (1986)
Beta blockers	Francis et al. (1990), Goodkin and Benning (1990) and Kauffman and Adams (1986)
High interdialytic peritoneal content of fibrinogen	Wetherington et al. (1985)

et al. 1984). This lymphokine stimulates fibroblast proliferation and can therefore accelerate the fibrosing process. Once again, however, bacterial filters were only used for some EPS patients.

The large molecular weight of interleukin-1 would impede its transport through or around mesothelium to affect the more deeply situated fibroblasts. In addition, histologically, the loss of the normal cellular constituents appears to be more important than fibroblast proliferation in the pathogenesis of peritoneal fibrosis and sclerosis (Dobbie 1992). Indeed, rather than fibroblast proliferation, it may be the loss of plasminogen activation from the damaged mesothelial cells that impairs normal fibrinolysis and which allows fibrosis (Dobbie 1992). Markedly elevated levels of type I and type III procollagen have been found in the peritoneal fluid of a patient who subsequently developed peritoneal fibrosis (Joffe and Jensen 1991).

A retrospective analysis in one dialysis unit demonstrated that all of the patients who developed EPS were members of a subgroup in which 0.5% chlorhexidine in 70% alcohol had been used to spray the connectors at each exchange (Junor et al. 1985). The authors studied the short-term effects of this antiseptic in a rat model and demonstrated inflammation in the submesothelial tissues. The incidence of EPS in this unit has diminished since the antiseptic protocol was changed. On the other hand, a study in Y-set patients observed no difference in the peritoneal transport characteristics of patients with or without accidental hypochlorite infusion or in the same patients before and after this infusion (De Vecchi et al. 1992). However, in the first study the patients had regular exposure to the potential contaminant, chlorhexidine, as part of their connector care. In contrast, the patients in the latter study were only exposed to the disinfectant once. Thus, the studies are not comparable.

The presence of the dialysis catheter in the peritoneal cavity could promote an inflammatory or foreign-body response. In this regard, a similar type of encapsulating peritoneal sclerosis has been described in patients with ascites in whom LeVeen shunts have been implanted (Greenlee et al. 1979). Given the number of patients with implanted silastic catheters, the EPS-type response is very rare. It is interesting, however, that localized fibrosis and peritoneal pseudocyst formation may develop in relation to the peritoneal dialysis catheter. This phenomenon has also been observed in patients with a ventriculoperitoneal shunt (Namasivayam 1991).

Other factors include the use of beta-blockers, which have been linked to peritoneal sclerosis (Clark and Terris 1983). Finally, there are many potentially toxic factors related to dialysis itself,

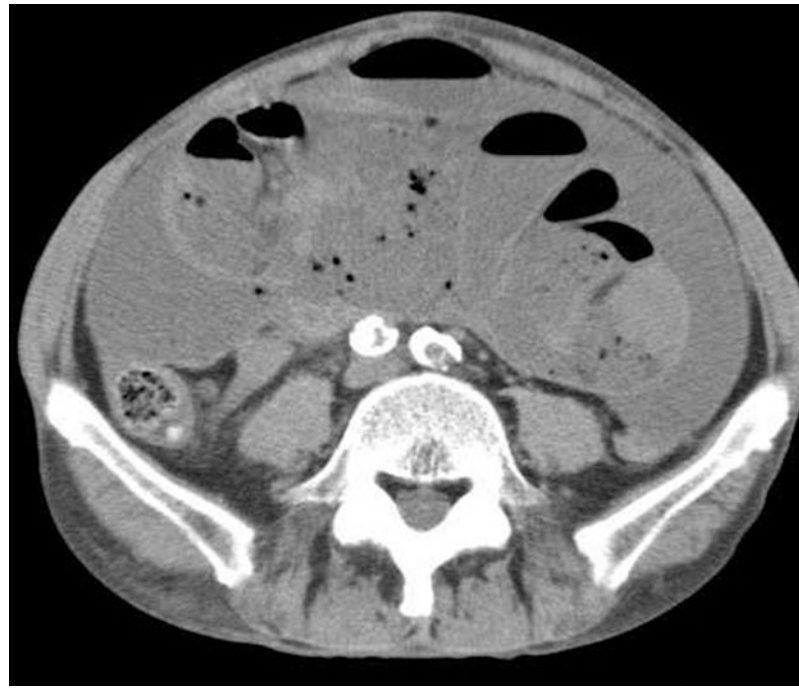

Fig. 17.4 A CT scan of the abdomen in a patient with EPS. Note the thickened, dense peritoneal membrane encapsulating the small intestine, which contains fluid and air

including hypertonicity and acidity of the dialysate. Taken together, there is no single factor which can be implicated in the pathogenesis of EPS. It is likely that the etiology is multifactorial.

The radiological picture may be suggestive of EPS (Fig. 17.4). Ultrasound examinations have revealed changes in EPS, including increased small bowel peristalsis, tethering of the bowel to the posterior abdominal wall, echogenic strands, and new membrane formation (Hollman et al. 1991). CT scans reveal the characteristics of advanced disease. In the early stages loculated ascites, adherent bowel loops, the narrowing of the bowel lumen, and the thickening of the peritoneal membrane may be a marker of the subsequent development of EPS; however, these changes may also represent those seen with peritoneal fibrosis (Korzets et al. 1988). CT screening is not indicated for asymptomatic PD patients, since EPS may occur within a year of a normal CT scan (Goodlad et al. 2011). Abdominal symptoms in long-term PD patients can be associated with CT scan abnormalities. These patients may be at increased risk of EPS after stopping PD.

After the report on the potential relationship between chlorhexidine and the development of EPS, the use of this antiseptic has declined. Indeed, the peritoneal mesothelium has been reported to be sensitive to the cytotoxic effects of a wide variety of substances (Dobbie 1992). The use of any agent that might enter the peritoneum must be tempered with consideration of its long-term effects on this delicate membrane.

The surgical treatment of EPS was fraught with hazard and can lead to severe bleeding. In cases of life-threatening obstruction or necrosis of the bowel, however, the surgeon has no other choice but to operate. The rate of postoperative mortality was previously high. It has been suggested that primary anastomosis is best avoided in cases of bowel resection. Instead, one suggestion is that the bowel be put to rest and the patient receives parenteral alimentation before anastomosis is attempted (Kittur et al. 1990). However, recent reports showed surgical enterolysis (adhesiolysis) in 239 surgical procedures in 181 patients with favorable outcomes (Kawanishi et al. 2011). Although there were previously many negative viewpoints on the use of surgery in the treatment of EPS, surgery has been

accepted in the face of the increasing number of cases (Kawanishi 2012).

A very important, but as of yet unsolved, management problem is whether patients with early but definite EPS should be transferred to hemodialysis or deliberately maintained on PD. The rationale for the latter decision is to keep the bowel loops separate from one another while they are afloat in dialysate so there is no opportunity for the bowel and peritoneal membrane to become matted down in the posterior peritoneum. Some patients with EPS appeared to develop the disease after they were transferred to hemodialysis. One patient who received a transplant, and presumably immunosuppression, died from intestinal obstruction (Lo et al. 1990). Similarly, it has been noted that the onset of symptomatic EPS appeared soon after transfer to another treatment modality (Slingeneyer 1987). Thus, it is possible that the dry peritoneum can accelerate the encapsulating process. If peritoneal transport is sufficient, a case could be made to continue PD instead. However, there are too few cases documented to put forth any firm recommendations.

A report has suggested that the use of prednisone and azathioprine in patients with EPS led to an improved outcome with the recovery of the bowel function (Junor and McMillan 1993). The report was observational and the number of patients was small. Thus, it is not clear whether the benefit was derived from immunosuppression or from the anti-inflammatory effect of corticosteroids.

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Part IV

Summary of Dialysis Related Guidelines

18 Preparation and Timing of Dialysis Initiation

Seong Eun Kim

When GFR <30 or GFR >15 and before their CKD becomes symptomatic

	Education	Preparation for permanent access before initiation of HD
KDOQI 2015	GFR <30 (NG)	At least 6 months (2006, B)
JSDT 2015	GFR 15–30 (1D)	At least 1 month (2C)
ERBP 2011	GFR >15 and before their CKD becomes symptomatic (1C)	GFR >15 and before their CKD becomes symptomatic (1C)

When GFR <15

Decision to initiate maintenance dialysis	
KDOQI 2015	Uremic signs and/or symptoms
	Protein-energy wasting
	Metabolic abnormalities
	Volume overload hard to manage with medical therapy alone (not graded)
JSDT 2015	Renal failure symptoms
	Daily life activities
	Nutritional status
	Which are not relievable without hemodialysis treatment (1D)
	Should be initiated prior to GFR of 2 mL/min/1.73 m^2, even if no symptoms (2C)
	Should be considered if GFR <10 mL/min/1.73 m^2, even if asymptomatic (2D)

Decision to initiate maintenance dialysis	
ERBP 2011	Symptoms or signs of uraemia, inability to control hydration status or blood pressure or a progressive deterioration in nutritional status (1A)
	A planned start to dialysis, while still asymptomatic in high-risk patients whose renal function is deteriorating rapidly and close supervision is not feasible (1C)

Dialysis membrane

Dialysis membrane and flux	
KDOQI 2015	Biocompatible, either high- or low-flux hemodialysis membranes for intermittent hemodialysis (1B)
JSDT 2015	High-performance membrane dialyzers should be used
KHA-CARI 2013	Either synthetic or cellulosic membranes be used for symptomatic intradialytic hypotension (1C)
	High-flux membranes to remove molecules such as beta-2 microglobulin (1A)
	Possible survival benefits from high-flux membranes (1A):
	On dialysis for more than 3.7 years
	Diabetic and serum albumin below 40 g/L

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Dialysis membrane and flux	
ERBP 2009 after MPO	Synthetic high-flux membranes in high-risk (serum albumin <40 g/L) (level 1A: strong recommendation, based on high-quality evidence)
	Synthetic high-flux membranes even in low-risk (level 2B: weak recommendation, low- quality evidence)

Measuring hemodialysis dose

Dose expression and measuring interval	
KDOQI 2006	The frequency of treatments should be included in the expression of dose. (A) At regular intervals no less than monthly. (A) (Kurea td)/Vurea (abbreviated as Kt/V (B))
JSDT 2015	Dialysis dose is expressed by the single-pool Kt/V for urea (spKt/V) (1B)
	At least once a month
	The therapeutic efficacy of dialysis is evaluated regularly using both short-term and medium- to long-term indices (1B)
	1. Intradialytic hemodynamics and the efficiency of removing small solutes are used as the short-term indices
	2. Predialysis serum β2M concentration, nutritional status, and QOL are used as the medium- to long-term indices (maximum predialysis serum β2M concentration <30 mg/L (2C))

Dialysis, time, and frequency

Time and frequency	
KDOQI 2015	A bare minimum of 3 h per session (thrice weekly) (1D)
	May be reduced in patients with significant residual native kidney function (not graded)
JSDT 2015	Minimal dialysis time 4 h or longer (1B)
ERBP 2007	At least three times per week and the total duration at least 12 h per week (evidence level III)
	For patients with renal function, weekly dialysis dose at least equivalent to an SRI of 2 (evidence level IV)
Additional sessions or longer times	
KDOQI 2015	Large weight gains
	High ultrafiltration rates
	Poorly controlled blood pressure
	Difficulty achieving dry weight
	Poor metabolic control (such as hyperphosphatemia, metabolic acidosis, and/or hyperkalemia) (not graded)

Time and frequency	
JSDT 2015	1. Symptoms of cardiac failure or hemodynamic instability during dialysis
	2. Hypertensive despite fluid removal, the administration of antihypertensive agents, and the restriction of salt intakes
	3. Hyperphosphatemic despite dietary controls and phosphate control
ERBP 2007	Hemodynamic or cardiovascular instability (evidence level II)
	Hypertensive despite maximum possible fluid removal (evidence level III)
	Impaired phosphate control (evidence level III)
	Malnourished patients (opinion)

Target dialysis dose

Thrice weekly HD	
KDOQI 2015	Target spKt/V of 1.4/session
	Minimum delivered spKt/V of 1.2 (1B)
JSDT 2015	Minimal adequate dose 1.2 (1B)
	Target dose 1.4 or higher (2B)
ERBP 2007	Target eKt/V at least 1.2
	Higher doses, up to 1.4 should be considered in females and those patients with high comorbidity (evidence level III)
Other than thrice weekly	
KDOQI 2015	Target standard Kt/V of 2.3 volumes per week
	Minimum delivered dose of 2.1
	(ultrafiltration and residual kidney function)
	(not graded)

Volume and blood pressure control (optimization of DW)

Volume and blood pressure control	
KDOQI 2006	Ultrafiltration rate that allows for optimal balance among achieving euvolemia, adequate blood pressure control, and solute clearance, while minimizing hemodynamic instability and intradialytic symptoms (not graded)
	Recommend both reducing dietary sodium intake and adequate sodium/water removal with hemodialysis
JSDT 2015	Body weight gain after maximum interdialytic period ≤6% (2B)
	Ultrafiltration rate ≤15 mL/kg/h (2B)
	Receive guidance on limitations of salt and water intake (1B)

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