SECTION 12

The patient on dialysis

CHAPTER 254

Uraemic toxins: overview

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Introduction

As chronic kidney disease (CKD) progresses, a gradual dose-dependent dysfunction of most organ systems occurs, called the *uraemic syndrome* (Vanholder and De Smet, 1999). This ultimately results in the malfunctioning of the entire body, and as symptoms become more prominent, survival and quality of life can only be maintained by replacing kidney function by dialysis or transplantation. The functional disturbances are to a large extent attributed to the retention of uraemic solutes, which, with normal renal function, are removed from the body by the normal kidneys via the urine. The uraemic syndrome consists of a myriad of functional disturbances, such as anaemia, metabolic bone disease, insulin resistance, inflammation, hypercoagulation, fluid overload, and hypertension. However, the most concerning one is cardiovascular disease (CVD), which, among the population with end-stage renal failure, remains responsible for > 50% of mortality.

Classification of uraemic toxins

A gradual retention of a large number of organic metabolites of proteins, fatty acids, and carbohydrates characterizes the progression of renal failure, whereby partial metabolism and elimination by other than renal pathways may compensate for the loss of renal clearance. Some of the retained compounds are proven toxins. An additional role can be attributed to changes in tubular secretion, reabsorption, and metabolic breakdown, which all are altered when renal mass decreases. Renal and non-renal metabolism of solutes and non-renal clearance may in turn be inhibited following uraemic retention.

Uraemic retention products are arbitrarily subdivided according to their molecular weight (MW) (Vanholder and De Smet 1999). Low-MW molecules are characterized by an MW up to 500 Da (e.g. urea (MW 60) and creatinine (MW 113)). They can further be subdivided into protein-bound and non-protein-bound molecules. Substances with an MW range > 500 Da are called middle molecules (e.g. parathyroid hormone (PTH; MW 9424) and beta-2 microglobulin (B2M; MW 11,818)). Recent reviews point out that removal of small water-soluble compounds is important for 'acute mortality' (e.g. related to hyperkalaemia, sodium removal), but that for the chronic cardiovascular problems of the uraemic syndrome, the protein-bound solutes and the middle molecules seem to play a more essential role (Vanholder et al., 2008). Whereas the small water-soluble compounds are easily removed by whatever dialysis strategy, the protein-bound toxins and middle molecules require more sophisticated strategies.

Most important uraemic retention solutes

Several uraemic retention solutes influence biological functions. Other compounds have no proven direct toxicity, but may be useful markers of uraemic retention. An overview of the pathologically most relevant uraemic retention solutes with their MW is given in Table 254.1. It should be acknowledged that inorganic compounds such as water and potassium exert toxicity as well. In what follows, we will concentrate on the organic retention compounds.

Due to the multitude of known uraemic retention compounds, we will discuss only a selection of the pathophysiologically most relevant solutes.

Low-molecular-weight molecules

Non-protein-bound molecules

Creatinine

Creatinine belongs to the larger group of guanidines (see below) but because of its specific value as a marker of renal function, this compound is discussed separately.

Although creatinine is retained during the progression of renal failure it is only held responsible for a few side effects, such as chloride channel blocking in mouse spinal cord neurons (De Deyn and Macdonald 1990; D'Hooge et al., 1992) and the reduction of the contractility of cultured myocardial cells (Weisensee et al., 1993).

Guanidines

Guanidino compounds (GCs) are structural metabolites of arginine. Increased guanidine levels have been determined in serum, urine, cerebrospinal fluid, and brains of uraemic patients (De Deyn et al., 1995).

The neurotoxicity of several GCs is extensively described (De Deyn et al., 2009); their potential cardiovascular impact was, until recently, mainly attributed to asymmetric dimethylarginine (ADMA), which inhibits nitric oxide synthase (NOS), an endothelial-protective enzyme (Kielstein et al., 2004). However, GCs have also been shown to enhance baseline immune function and lipopolysaccharide (LPS)-stimulated intracellular tumour necrosis factor alpha (TNF-α) by normal monocytes (Glorieux et al., 2004b). Moreover, these compounds have been related to decreased protein binding of homocysteine, another compound with vessel-damaging potential (Perna et al., 2004).

A holistic and standardized evaluation of 10 GCs in different *in vitro* models showed that especially symmetric dimethylarginine (SDMA), formerly considered biologically inert, contributes to biological effects related to cardiovascular complications in uraemia

Table 254.1 An overview of the pathologically most relevant uraemic retention solutes

Compound	MW (Daltons)	Toxic
Low molecular weight (< 500 Da)		
Non-protein-bound		
Guanidines:		
ADMA/SDMA	202	+
Creatinine	113	+/–
Creatine	131	+
Guanidinoacetic acid	117	+
Methylguanidine	73	+
Guanidinosuccinic acid	175	+
ß-guanidinopropionic acid	131	+
γ-guanidinobutyric acid	145	+
Dimethylarginine	202	+
Guanidine	59	+
Oxalic acid	90	+/–
Purines:		
Hypoxanthine	136	+
Uric acid	168	+
Xanthine	152	+
Urea	60	+/–
Protein-bound		
AGEs:		
3-deoxyglucosone	162	+
Pentosidine	135	+
CML	188	+
Imidazolone	203	+
CMPF	240	+
Homocysteine	135	+
Indole-3-acetic acid	175	+
Indoxyl sulfate	251	+
p-Cresyl sulfate	188	+
p-Cresyl glucuronide	283	+/–
Middle molecules (> 500 Da)		
Adrenomedullin	5729	+
AOPP		+
$ß_2$-microglobulin	11,818	+
Complement factor D	23,750	+
Cytokines	15,000–30,000	+
DIP II	24,000	+
Endothelin	4283	+
FGF-23	26,000	+
GIP I	28,000	+
GIP II	25,000	+
Ig light chains	25,000	+
Leptin	16,000	+
Neuropeptide Y	4272	+
Parathyroid hormone	9225	+
Resistin	12,500	+
Retinol binding protein	21,200	+

ADMA/SDMA = asymmetric/symmetric dimethylarginine; AGEs = advanced glycation end products; AOPP = advanced oxidation protein products; CML = carboxymethyl lysine; CMPF = 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid; DIP II = degranulation inhibiting protein II; FGF-23 = fibroblast growth factor-23; GIP I/II = granulocyte inhibiting protein I/II.

(Bode-Boger et al., 2006; Schepers et al., 2009, 2010, 2011). These effects may be involved in altering the prevalence of CVD in CKD, as confirmed by clinical data pointing to an *in vivo* association of SDMA with interleukin (IL)-6 and TNF-α in CKD at different stages (Schepers et al., 2009). Both SDMA and ADMA are only weakly correlated to estimated glomerular filtration rate (eGFR) (Eloot et al., 2011) suggesting other factors are influencing their concentration (tubular secretion, metabolism).

Finally, although GCs are water-soluble, they might have a different kinetic behaviour from urea because of their larger distribution volume which makes them more difficult to remove (Eloot et al., 2005, 2008a). A two-compartmental kinetic model demonstrated that prolonged dialysis and increased dialysis frequency are effective in significantly reducing concentration of the GCs compared to standard haemodialysis (HD) (Eloot et al., 2009).

Oxalic acid

Increased plasma oxalic acid synthesis in CKD results from diminished excretion of precursors of oxalic acid, glycolic acid, and ascorbic acid (vitamin C). Ascorbic acid administration after HD causes an increase in plasma oxalic acid levels (Ono, 1986), which are an important factor for calcium oxalate deposition in uraemia (Worcester et al., 1986) and for inhibition of proliferation of endothelial cells thus preventing re-endothelialization (Recht et al., 2004), and a trigger for polymorphonuclear cells and platelets to damage endothelium (Boogaerts et al., 1983).

Purines

Uric acid, xanthine, and hypoxanthine are the most important purines retained in uraemia. The purines disturb calcitriol production, metabolism (Hsu et al., 1991; Vanholder et al., 1993), and sensitivity to calcitriol of immune competent cells (Glorieux et al., 1998). Uric acid is a stimulator of the renin–angiotensin (Ang) system and of endothelin-1 (ET-1) in mesangial cells. This leads to the production of Ang-II and ET-1, causing increases in glomerular cell proliferation which could be responsible for the glomerulosclerosis and renal damage observed in long-term hyperuricaemia (Albertoni et al., 2011).

A recent study by Goicoechea et al. suggests that treatment with allopurinol of patients with moderate CKD decreases inflammation and progression of renal disease and reduces cardiovascular and hospitalization risk (Goicoechea et al., 2010).

Xanthine and hypoxanthine have been implicated as modulators of neurotransmission, poor appetite, and weight loss (Simmonds et al., 1987). Both purines induce vasoconstriction (Yang et al.,

1994) and disturb endothelial barriers (Berman and Martin, 1993). Uric acid is a small water-soluble compound that is removed by HD from the plasma in a similar way as urea (Vanholder et al., 1992), but removal from the intracellular compartment is by far not as efficient (Langsdorf and Zydney, 1993). Dialytic removal of xanthine and hypoxanthine shows no correlation with that of urea and creatinine (Vanholder et al., 1992).

Urea

Urea is a 60 Da water-soluble compound which is considered not really toxic by itself (Johnson et al., 1972). Two large controlled clinical studies, the ADEMEX and the HEMO-study, could not demonstrate an impact of enhanced urea removal on survival outcome (Eknoyan et al., 2002; Paniagua et al., 2002). However, a recent study showed that increased levels of urea can cause insulin resistance *in vitro* and *in vivo* (mice) as a consequence of increased reactive oxygen species (ROS) generation (D'Apolito et al., 2010). Urea is also the precursor of some guanidines (see above). Urea may also be a source of generation of cyanate and isocyanic acid, and these might be at the origin of carbamylation, resulting in structural and functional changes of amino acids and proteins (Fluckiger et al., 1981; Haley and Ward, 1986; Kwan et al., 1991; Kairaitis et al., 2000; Kraus and Kraus, 2001; Zhang et al., 2004).

Urea is generally used as a marker of solute retention and removal in dialysed patients. However, it is clear that urea removal is not representative for the removal of a host of other uraemic retention solutes, essentially the middle molecules and the smaller but protein-bound and/or lipophilic compounds. Even if dialytic removal from the plasma is similar, as is the case for other small, water-soluble, non-protein-bound compounds such as creatinine or uric acid (Vanholder et al., 1992), the shift from intracellular to the plasma might occur at a different rate (Langsdorf and Zydney, 1993), again resulting in divergent kinetics. Similarly, effective removal of small GCs was markedly different from urea, due to larger distribution volumes (Eloot et al., 2005).

Protein-bound molecules

Advanced glycation end-products

Advanced glycation end-products (AGEs) are generated through a non-enzymatic reaction between reducing sugars and free amino groups of proteins, lipids, or nucleic acids. This reaction is also known as the Maillard or browning reaction. Pathologic effects are related to their ability to promote oxidative stress and inflammation by binding with cell surface receptors or cross-linking with body proteins, altering their structure and function. In addition to AGEs that form within the body, AGEs also exist in foods. Cellular proteolysis forms AGE-free adducts from these proteins, which normally have high renal clearance, but this capacity declines markedly in CKD, leading to substantial increases in plasma AGE-free adducts (Thornalley 2005), inducing an increase in leucocyte oxidative stress (Witko-Sarsat et al., 1998). Specific AGE compounds known to be retained in uraemia exert proinflammatory effects by enhancing monocyte free radical production (Glorieux et al., 2004a). Binding of AGE compounds to its receptor, RAGE, extracts them from the circulation and/or induces biological responses (Dobler et al., 2006). Other RAGE ligands have been reported, such as the extracellular newly identified RAGE-binding protein (EN-RAGE), S100A12 (Hofmann et al., 1999), which is twice as much elevated in HD patients compared with healthy controls; they positively correlate with carotid intima media thickness in HD patients (Mori et al., 2009). A recent cross-sectional study found a strong association between plasma S100A12 protein level and the prevalence of CVD in HD patients (Shiotsu et al., 2011).

Homocysteine and S-adenosylhomocysteine

Homocysteine (Hcy), a sulphur-containing amino acid, is produced by the demethylation of dietary methionine. Moderate hyperhomocysteinaemia is an independent risk factor for CVD in the general population (Boushey et al., 1995). Patients with chronic kidney failure have serum Hcy levels two- to fourfold above normal. Hcy increases the proliferation of vascular smooth muscle cells (VSMCs) (Kielstein et al., 2008), induces endothelial dysfunction, and generation of oxidative oxygen species (Massy et al., 2001) responsible for nuclear factor kappa B (NF-κB) activation (Au-Yeung et al., 2006), atherogenesis (Matthias et al., 1996), and disruption of anticoagulant function (Harpel et al., 1996). Studies evaluating the potential of folic acid or 5-methyltetrahydrophosphate (MTHF) to decrease Hcy levels emanated in contradictory results (Touam et al., 1999; van Guldener et al., 2000). Furthermore, recent intervention studies, both of primary and secondary prevention, in the general population and in CKD patients, appeared to be negative (Jamison et al., 2007; Albert et al., 2008), possibly due to several shortcomings (Lonn, 2008). The original hypothesis that high Hcy levels might be causal in the genesis of cardiovascular risk might be wrong. Its precursor molecule, S-adenosylhomocysteine (AdoHcy), has been proposed as more reliable marker for CVD (Valli et al., 2008). Accumulation of AdoHcy leads to inhibition of methyltransferases. DNA of uraemic patients was found to be hypomethylated compared to normal, and DNA hypomethylation significantly correlated with plasma Hcy levels (Ingrosso et al., 2003). Research on Hcy-related single gene expression may lead to a better understanding of its contribution to premature CVD via down- or upregulation of genes important in the atherosclerotic process.

Indoxyl sulfate

Indoles are produced by colonic bacteria as degradation products of the amino acid tryptophan. Further hydroxylation results in 3-hydroxyl-indole, the majority of which is sulfated by hepatic enzymes to indoxyl sulfate (IS) (Wikoff et al., 2009). IS is normally excreted into urine, but accumulates in CKD patients and circulates mostly linked to albumin. IS was first associated with a profibrotic effect in kidneys and a role in the progression of renal failure (Niwa and Ise, 1994; Niwa, 2010). Subsequently, IS has also been linked to endothelial damage, inhibition of endothelial regeneration and repair, and endothelial and vascular smooth muscle cell (VSMC) free radical production (Dou et al., 2004, 2007; Yamamoto et al., 2006; Muteliefu et al., 2009; Brunet et al., 2011). However, chronic exposure to IS significantly inhibits VSMC proliferation (Mozar et al., 2011). IS has a profibrotic and prohypertrophic effect on cardiac fibroblasts and a proinflammatory effect on monocytic cells (Lekawanvijit et al., 2010) and is an endogenous agonist for the human aryl hydrocarbon receptor, a transcription factor involved in the regulation of multiple cellular pathways (Schroeder et al., 2010). Administration of IS to hypertensive rats reduces renal Klotho expression, through production of ROS and activation of NF-κB in proximal tubular cells, promotes cell senescence, and renal fibrosis (Adijiang et al., 2010, 2011; Shimizu et al., 2010, 2011).

In HD patients, IS is associated with markers related to atherosclerosis (Taki et al., 2007) and cardiovascular outcomes (Barreto et al., 2009).

Protein binding hampers dialytic removal of IS and alternative removal strategies should be considered. The oral adsorbent AST-120 (Kremezin®) decreases serum and urine concentration of IS in rats, thereby restraining the progression of renal failure (Miyazaki et al., 2000; Aoyama and Niwa 2001). AST-120 retards the development of acquired renal cystic disease and aortic calcification (Ishikawa et al., 2002), and ameliorates tubulointerstitial injury by reducing the expression in the kidneys of intercellular adhesion molecule (ICAM)-1, osteopontin, transforming growth factor (TGF)-β1, and clusterin in uninephrectomized rats (Aoyama and Niwa, 2001).

Prospective clinical studies in humans with AST-120 demonstrated decreased plasma concentration of IS (Schulman et al., 2006), postponement of the start of dialysis, and better outcomes once dialysis is initiated (Ueda et al., 2008).

p-Cresyl sulfate and p-cresyl glucuronide

The amino acids tyrosine and phenylalanine, generated from nutritional proteins, are metabolized by intestinal flora into 4-hydroxyphenylacetic acid, which is decarboxylated to *p*-cresol. During the passage of *p*-cresol through the intestinal mucosa, a cytosolic sulfotransferase metabolizes *p*-cresol into *p*-cresyl sulfate (pCS), its main conjugate. Another conjugate, *p*-cresyl glucuronide (pCG), is formed by glucoronidase in the liver which however results in markedly lower total concentrations through pCS (de Loor et al., 2005; Evenepoel et al., 2009).

Most pioneering research on phenolic uraemic retention compounds focused on the concentration and toxicity of the mother compound, *p*-cresol. This was due to the fact that previously measured *p*-cresol values were the result of pCS hydrolysis as a consequence of sample deproteinization by acidification. Nevertheless, previously held conclusions about the relationship to overall and cardiovascular mortality in dialysis patients as well as to the development of infection probably are still valid, as there is very likely a correlation between former *p*-cresol estimations and current pCS measurements (Vanholder et al., 2011). pCS induces baseline leucocyte activation (Schepers et al., 2007) and increases endothelial microparticle release (Meijers et al., 2009), suggesting its contribution to the propensity for vascular damage in renal disease patients. Moreover, recent cohort studies showed that free pCS is a predictor of survival in CKD (Liabeuf et al., 2010) and that serum total pCS is correlated to the severity of coronary artery disease (Wang et al., 2010). Total and free pCS show a very weak correlation with eGFR, pointing to other factors affecting their concentration (Eloot et al., 2011).

Middle molecules

Advanced oxidation protein products

Oxidative stress, defined as a disequilibrium between the generation of free radicals and the activity of the antioxidant systems, plays a significant role in the development of inflammatory syndrome associated with CKD. In addition to glycation, proteins are vulnerable to ROS. Oxidation of amino acid residues such as tyrosine, which leads to formation of dityrosine, protein cross-linking, and protein aggregation, is but one example of ROS-mediated protein damage *in vitro*. Human serum albumin-advanced oxidation protein products (HAS-AOPPs) can trigger oxidative burst and cytokine synthesis in neutrophils and monocytes (Witko-Sarsat et al., 1998). Part of the AOPP, consists out of oxidized fibrinogen. Oxidized fibrinogen is bound to Apo(a) of Lp(a) causing inhibition of fibrinolysis and thereby promoting atherosclerosis and CVD(Selmeci, 2011).

A significant association of plasma AOPP levels with common carotid artery intima media thickness (CCA-IMT) and CCA wall-to-lumen ratio was observed in uraemic patients (Drueke et al., 2002).

However, caution is recommended with the classical methods for measuring AOPP concentration (Witko-Sarsat et al., 1996), as they can be biased by an unpredictable background noise created to a large extent by triglycerides and coagulation factors (Valli et al., 2007).

β_2 microglobulin and AGE-modified β_2 microglobulin

B2M (MW 11,800 Da) is a component of the major histocompatibility antigen. Uraemia-related amyloid is to a large extent composed of B2M and is essentially found in the osteoarticular system and the carpal tunnel, although deposition can be systemic as well. Uraemia-related amyloidosis most often becomes clinically apparent after several years of CKD and/or in the aged, although its prevalence has definitely decreased, due to modifications in dialysis removal strategies and improvements in dialysis water quality (Schwalbe et al., 1997). AGE-modified B2M has been identified in amyloid of haemodialysed patients (Niwa et al., 1996) and enhances monocytic migration and cytokine secretion (Miyata et al., 1994), TNF-α mRNA expression and production, suggesting that foci containing AGE-B2M may initiate inflammatory response, leading to bone and joint destruction while eNOS mRNA and protein expression by human umbilical vein endothelial cells (HUVECs) is decreased (Rashid et al., 2004). Both native B2M and AGE-modified B2M have been shown to enhance bone resorption in neonatal mice and net calcium efflux from mouse calvariae. These actions are attributed to stimulation of osteoclastogenesis, probably via upregulation of TNF-α and IL-1β expression (Menaa et al., 2008).

Long-term HD with large-pore membranes and addition of convective dialysis strategies to diffusion results in a progressive decrease of predialysis B2M concentrations although the levels remain far above normal, even after intensive removal therapy (Canaud et al., 1992; Locatelli et al., 1996; Li et al., 2010). A longer duration of HD session results in a more effective removal of B2M (Eloot et al., 2008; Raj et al., 2000). Long-term dialysis with large pore dialysers results in a lower prevalence of dialysis-related amyloidosis and/or carpal tunnel syndrome (Chanard et al., 1989; Koda et al., 1997). Whether this benefit is attributable to a better removal of B2M or to lower complement, lower leucocyte activating capacity, or to protection against the transfer of dialysate impurities into the bloodstream (e.g. lipopolysaccharides) (Schwalbe et al., 1997), is not evident, since most of the dialysers associated with a lower incidence of amyloidosis have all three above mentioned properties. Structural conformational intermediates of B2M, which are present in different proportions in normal subjects and patients with CKD, have different amyloidogenic properties, and are more difficult to remove by dialysis (Uji et al., 2009). Several devices with strong adsorptive capacity for B2M have been developed (Ronco et al., 2001).

In a subanalysis of the HD (HEMO) study, serum B2M levels were directly related to patient outcome and infectious or non-cardiovascular mortality (Cheung et al., 2008). This was

confirmed in an observational trial with high-flux dialysis where serum B2M was a predictor for all-cause and non-cardiovascular mortality (Okuno et al., 2009). In a proteomic analysis for biomarkers of peripheral vascular disease in a general population without renal dysfunction, B2M was selected as the most appropriate index molecule (Wilson et al., 2007). Serum B2M was found to be associated with arterial stiffness in the general population (Saijo et al., 2005) and was an independent predictor of mortality in a population aged between 65 and 84 years (Shinkai et al., 2008). Hence, B2M might not only be a marker of middle molecule retention and removal, but also a pro-active compound playing a role in inflammation and vascular damage.

Complement factor D

Plasmatic concentration of complement factor D increases in uraemia. Complement factor D exerts specific protease activity on its natural substrate, complement factor B, which results in activation of the alternative complement pathway, contributing to the inflammatory state of CKD patients (Deppisch et al., 2001).

Cytokines

Under normal conditions, cytokines are not detectable in body fluids or tissue. In CKD stage 5, mean concentrations of most cytokines are higher due to both increased production and decreased renal clearance. In addition, the dialysis procedure itself may further stimulate cytokine production. In general, cytokines are classified according to their pro- (TNF-α, IL-1, IL-6, IL-18, interferon-gamma (IFN-γ)) or anti-inflammatory (IL-4, IL-10, IL-13, TGF-β) properties. From that point of view, the balance between opposing cytokines may be more important than the absolute concentration of a single cytokine. All available evidence suggests that the pro-inflammatory cytokine system activity is elevated in CKD stage 5 patients (Kimmel et al., 1998), and might contribute to the strong associations between atherosclerosis, malnutrition, and inflammation (Kaizu et al., 1998, 2003; Stenvinkel et al., 1999). Vascular endothelial dysfunction is associated with IL-6 and TNF-α in a predialysis population (Bolton et al., 2001). IL-6 is a predictor of all-cause and cardiovascular mortality in CKD and a dialysis population (Pecoits-Filho et al., 2002; Panichi et al., 2004; Tripepi et al., 2005; Barreto et al., 2010). In dialysis, TNF-α is associated with mortality (Kimmel et al., 1998; Futh et al., 2004). Accumulation of TNF-α may contribute to the development of neurological and haematological complications in uraemia.

Endothelin

Many studies have demonstrated a link between ET and cardiorenal pathology (Barton, 2008; Longaretti and Benigni, 2009; Neuhofer and Pittrow, 2009). ET-1 production is increased in hypertension and CKD (Ohta et al., 1991) and stimulates vasoconstriction, inflammation, and fibrosis (Pollock and Pollock 2005; Dhaun et al., 2008; Tran et al., 2009). ET blockade reduces hypertension and improves proteinuria, blood pressure, and arterial stiffness in patients with proteinuric nephropathy (Dhaun et al., 2009, 2011; Epstein and Anderson, 2009). ET is a promising target in the treatment of resistant hypertension and CKD, with additional potential benefits on atherosclerosis and the metabolic syndrome. The nature and mechanisms of drug side effects require elucidation before the potential of this new class of drugs can be fully realized (Kohan 2010).

Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF-23) (26 kDa) is a peptide hormone secreted by osteoblasts and osteocytes in response to hyperphosphataemia and calcitriol. FGF-23 is the main regulator of phosphate homeostasis by inducing phosphaturia and inhibiting 1α-hydroxylase in the kidney. FGF-23 plays a role in the inhibition of parathyroid secretion. Interaction between FGF-23-FGF-receptor complex and co-factor Klotho is mandatory for these actions. *In vitro*, HUVECs cultured in high phosphate with FGF-23 had an increased expression of E-selectins and VCAM, indicating an activation of the vascular endothelium (Stevens et al., 2011), independent of Klotho.

FGF-23 is elevated in early CKD before PTH and phosphorus (Gutierrez et al., 2005; Ix et al., 2010; Isakova et al., 2011b). FGF-23 is associated with vascular calcifications in dialysis (Nasrallah et al., 2010; Srivaths et al., 2011) and CKD patients (Kanbay et al., 2010) and with left ventricular hypertrophy in CKD (Gutierrez et al., 2009). FGF-23 is independently associated with mortality in CKD (Isakova et al., 2011c) and dialysis patients (Gutierrez et al., 2008). In kidney transplant patients, elevated FGF-23 is an independent risk of kidney transplant loss and mortality (Wolf et al., 2011). The effects of dietary intervention and phosphate binders on FGF-23 still need to be determined (Isakova et al., 2011a; Vervloet et al., 2011).

FGF-23 will probably become an important parameter in the detection and follow-up of mineral and bone disease in CKD, but its position still needs to be defined, mainly regarding its pathophysiological role in mortality and CVD, which possibly occurs in part independently of Klotho and phosphorus metabolism.

Immunoglobulin light chains

Immunoglobulin light chains (IgLCs) are part of intact immunoglobulins and contribute to antigen recognition. IgLCs are synthesized by B cells and metabolized primarily by the kidneys. Polyclonal free IgLCs (25 kDa) accumulate in the serum of patients with CKD, and their concentration progressively increases with CKD stage (Hutchison et al., 2008). In parallel, polyclonal IgLCs appear in the urine (Hutchison et al., 2008). Free IgLCs exert biological effects on immune cells, such as neutrophil and mast cells (Cohen and Horl 2009).

Leptin

Leptin is a 16 kDa plasma protein which regulates eating behaviour. An increase in serum leptin in kidney failure is mostly attributed to decreased renal elimination and is almost entirely limited to the free fraction, but its biochemical role in renal failure remains inadequately defined.

Increased leptin is associated with low protein intake and loss of lean tissue in CKD (Young et al., 1997;Stenvinkel et al., 2000). Erythropoietin treatment results in a decline of leptinaemia and improvement of nutritional status (Kokot et al., 1998). However, leptin levels are also elevated in obese individuals and are hence not necessarily related to reduced appetite. Female gender and obesity are important factors that affect serum leptin in CKD stage 5 patients (Stenvinkel et al., 1999).

With respect to inflammation, a relation with C-reactive protein (CRP) and secretion of pro-inflammatory cytokines has been demonstrated (Heimburger et al., 1997; Axelsson et al., 2006). Leptin induces tissue factor expression, an agonist in the clotting cascade

playing a key role in thrombosis and inflammation. Don et al., on the other hand, suggested that leptin may be depressed during inflammation and may actually act as a negative acute-phase reactant (Don et al., 2001). Low serum leptin concentration was also shown to be an independent predictor of cardiovascular and infectious mortality in HD patients (Scholze et al., 2007).

Parathyroid hormone

PTH (MW 9000 Da), gives rise to an increase in intracellular calcium, which results in functional disturbances of virtually every organ system (Rodriguez and Lorenzo, 2009). PTH is one of the few substances that have been causally linked to uraemic neuropathy (Di et al., 1982). It also plays a role in fibroblast activation (Amann et al., 1994) and has been related to uraemic pruritus.

In observational studies, both low and high PTH levels have been associated with increased mortality (Pontoriero et al., 2010), suggesting toxicity of a too high level, but also the necessity of some hormone to avoid vascular damage.

Hyperparathyroidism results from phosphate retention, decreased production of calcitriol (1,25 $(OH)_2$ vitamin D_3) and/or hypocalcaemia, and possibly also from acidosis (Movilli et al., 2001).

Resistin

Resistin is a 12.5 kDa protein mainly expressed in human macrophages and released predominantly by human visceral white adipose tissue macrophages (Curat et al., 2006). Serum concentrations of resistin are markedly increased in CKD (Axelsson et al., 2006). In patients with CKD, resistin levels correlate with CRP and TNF-α, suggesting a role in the subclinical inflammation associated with CKD (Yaturu S et al., 2007). Resistin attenuates neutrophil chemotaxis and decreases stimulated oxidative burst. From this point of view, resistin can contribute to the suboptimal immune response in uraemic patients (Cohen et al., 2008). On the other hand, resistin was present in human atherosclerotic lesions (Burnett et al., 2005), increases endothelial cell adhesion molecule expression (Skilton et al., 2005), and positively correlates with leucocyte counts, high sensitivity CRP, and ET-1 (Hu et al., 2007). Therefore, resistin may also be involved in the development of coronary artery disease by influencing systemic inflammation and endothelial activation. Whether or not resistin is associated with insulin resistance in CKD remains controversial.

Retinol binding protein

Retinol binding protein (RbP) (21 kDa) is a low-MW protein of the lipocalin family. In circulation it is bound to transthyretin for > 98%. RbP is the main binding protein for retinol in circulation (Theodosiou et al., 2010). It is also recognized as an adipokine and plays a role in obesity and insulin resistance (Graham et al., 2006; Axelsson et al., 2009). In CKD, concentrations are elevated (Ziegelmeier et al., 2007; Frey et al., 2008; Henze et al., 2010). In a population with diabetes mellitus type 2, RbP has been linked to CVD (Cabre et al., 2007). More research needs to be done to determine the specific role of RbP in inflammation and CVD in CKD.

Factors influencing uraemic solute concentrations

Conventional HD easily removes small water-soluble compounds, such as urea and creatinine, which are the usual markers of uraemic retention and removal. The removal pattern of urea and creatinine is markedly different from that of many other uraemic solutes with proven toxicity. To protect patients against the cardiovascular as well as other side effects of the uraemic syndrome, it seems in accordance with our current pathophysiological concepts to pursue the removal of protein-bound and middle molecules as much as possible.

Protein-bound solutes

Application of high-flux HD has no considerable impact on the removal of the protein-bound solutes (Lesaffer et al., 2000). *Convective strategies*, on the other hand, increase removal compared to diffusive removal, with postdilution haemodiafiltration (HDF) being superior to both predilution HDF and predilution haemofiltration (Meert et al., 2009). In contrast, Krieter et al. could not detect a difference in removal of the protein-bound solutes, pCS and IS, between post-HDF and high-flux HD (Krieter et al., 2010).

Daily HD was shown to decrease the predialysis concentration of protein-bound solutes, as compared to a classical alternate-day dialysis regimen (Fagugli et al., 2002). Long extended dialysis on the other hand had no impact on the protein-bound solutes concentration (Basile et al., 2010)

Peritoneal dialysis (PD) seemed to be inferior to high-flux HD in removing protein-bound molecules, in spite of a better preserved residual renal function and considerable transperitoneal albumin loss. In spite of this lower removal with PD, plasma concentrations of protein-bound solutes were also lower in PD patients, pointing to possible differences in intestinal generation and/or metabolism (Vanholder et al., 2009). Whatever the mechanisms, since free plasma concentration determines toxicity, the latter finding seems to be pathophysiologically more relevant than the lower clearance with PD.

Much is expected from *adsorptive strategies* to enhance removal of the protein-bound solutes. One option is fractionated plasma separation and adsorption (Prometheus®). Indeed, a pilot study showed effective removal of protein-bound solutes but was hampered by troublesome coagulation problems (Meijers et al., 2008). Removal of protein-bound solutes was also enhanced by adding sorbent to the dialysate (Meyer et al., 2007).

Since the *intestine* is a major source of uraemic toxin generation and/or uptake, administration of pre- and probiotics could contribute to the decrease in plasma levels (Schepers et al., 2010) as was recently suggested by reduced generation rates of pCS after administration of the prebiotic oligofructose-inulin to HD patients (Meijers et al., 2010). In addition, oral sorbents may be administered to bind solutes and prevent their intestinal absorption. Currently, AST-120 (Kremezin®) is the only therapeutic sorbent of especially indolic and phenolic compounds (Schulman et al., 2006) with an impact on outcome parameters shown in a number of studies (Ueda et al., 2007, 2008; Akizawa et al., 2009). Data analysis of a large multicentre controlled trial on AST-120 did not confirm its nephroprotective effect (Schulman et al., 2014). A recent study showed disappointing correlations of protein-bound solute concentration and eGFR, pointing to the fact that concentration is dependent on many other factors such as tubular secretion and metabolism (Eloot et al., 2011).

Middle molecules

In contrast to what has been observed for the protein-bound solutes, removal of *middle molecules* can be accomplished by

applying dialysis *membranes with a large enough pore size* (so-called high-flux membranes) even in a HD setting. Removal through large pores can be further enhanced by applying convection; the amount of cleared middle molecules is correlated to the quantity of plasma water removed and replaced in an equivoluminous manner (Lornoy et al., 2000). The relative increase in adequacy due to convection becomes more pronounced as the MW of the compounds increases. Among convective strategies, both postdilution HDF and predilution haemofiltration are superior to predilution HDF for removal of middle molecules (Meert et al., 2009). More recent high-flux membranes are more efficient in removing middle molecules than previous prototypes, even if the polymers are the same (Meert et al., 2011).

Of note, partial removal via the kidneys, as long as *residual renal function* is preserved, becomes relatively more important as the MW of the compounds to be removed increases and/or the molecules in question are difficult to remove by dialysis for other reasons (e.g. protein binding). As a consequence, dialytic strategies which preserve residual renal function, such as PD or high-flux HD, are preferable in this context. A recent evaluation in the CONTRAST study confirmed an effective lowering of B2M levels by HDF but especially in patients without residual kidney function (Penne et al., 2010).

Removal of the middle molecules can be further enhanced by increasing *dialysis frequency* and/or with prolonging the dialysis session (Raj et al., 2000). Applying the Genius® dialysis system, B2M removal into the dialysate increased almost twofold, only by increasing dialysis time from 4 to 8 hours, in spite of an unaltered Kt/V urea (Eloot et al., 2008b), very likely as more B2M is allowed to move from extra-plasmatic compartments to the plasma and from there to the dialyser if dialysis time is prolonged.

Patient outcome

A number of recent data suggest an improvement of outcomes when increasing membrane pore size in a HD setting; the differences were found in secondary or subgroup analyses (Cheung et al., 2003; Delmez et al., 2006; Krane et al., 2007). In the MPO study, superiority of the high-flux membrane was found in the subgroup with serum albumin < 4 g/dL, which composed approximately 75% of the studied population and was the group for which the study was originally designed (Locatelli et al., 2009).

More recently, a number of studies concentrated on convective strategies. In an observational trial, Canaud et al. found a better survival for on-line HDF with large exchange volumes (>15 L) (Canaud et al., 2006). In a small controlled trial, survival was better at the borderline of significance for on-line HF (Santoro et al., 2008). In a large controlled trial, convective strategies were superior regarding haemodynamic stability (Locatelli et al., 2010). Three recent controlled trials compared on line HDF to either low-flux (Contrast) (Grooteman et al., 2012) or high-flux HD (Turkish) (Ok et al., 2013) and with HD (ESHOL) (Maduel et al., 2013). No differences could be observed at primary analysis, but at secondary analysis a lower mortality risk was shown in patients who had reached a high exchange volume of > 20 L.

The combined pathophysiological evidence with these clinical outcome studies suggests that increasing dialyser pore size has a positive impact on outcomes and might be preferred as a mode of dialysis (Tattersall et al., 2010). Adding convection might further improve outcomes if a large enough volume is exchanged.

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CHAPTER 255

Haemodialysis: overview

Jonathan Himmelfarb

Introduction

Haemodialysis is a medical procedure where the blood volume circulates extracorporeally through a dialysis membrane and is returned to the patient via the vasculature, during which time there is diffusion of molecules in solution along an electrochemical concentration gradient. In clinical haemodialysis, the semipermeable dialysis membrane separates the blood from a solution of prescribed electrolyte composition known as the dialysate. The use of long-term dialysis for treatment of irreversible kidney failure and amelioration of the uraemic syndrome dates back to the 1960s, when Belding Scribner and colleagues developed a repeatedly usable vascular access device using Teflon-coated plastic tubes. These and many other pioneering advances led to early successes in carefully selected populations of predominantly young, relatively fit patients with kidney failure. This in turn prompted a dramatic expansion of the use of haemodialysis as a life-sustaining treatment, and today haemodialysis is the most frequently used treatment for end-stage kidney disease in the United States, Europe, and worldwide. The expanded use of haemodialysis as kidney replacement therapy transformed the profession of nephrology and the care of people living with severe kidney disease, and also created a new field of medical science, which has been referred to as 'the physiology of the artificial kidney' (Himmelfarb and Ikizler, 2010).

Mechanisms of solute removal during haemodialysis

The ultimate goal of any renal replacement therapy is to replace the normal function of the kidney, thereby alleviating the uraemic syndrome and providing patients with opportunities for increased well-being and rehabilitation. Haemodialysis relies on mechanical methods to remove uraemic toxins from the blood, balance fluid and electrolyte levels, and correct acid–base disturbances. Measuring the clearance of solutes that accumulate in uraemia has become the mainstay of quantifying dialysis therapy, and determining whether the delivered dose of dialysis is 'adequate'. Solute clearance is defined as the plasma volume from which the solute is completely removed over time, and is often expressed in units of millilitres per minute. During haemodialysis, most solute removal occurs via diffusion, which is defined as the movement of particles from areas of higher concentration to areas of lower concentration through random motion. The characteristics that most affect diffusion rates from blood into the dialysate are solute concentration and molecular weight. Small molecules, such as urea, diffuse quickly, whereas larger molecules, such as albumin or beta 2-microglobulin, diffuse much more slowly. In addition to diffusion, solutes may also pass through pores in the membrane by a convective process, also known as 'solute drag' which is characterized by the movement of molecules within fluids. Convection also occurs when a transmembrane pressure is applied to the blood side of a membrane forcing plasma water through the pores in the membrane, a process known as haemofiltration or ultrafiltration. The achievement of electrolyte homeostasis and acid–base balance during dialysis is most often accomplished by varying the prescription of dialysate, by adjusting the concentrations of potassium, sodium, chloride, bicarbonate, calcium, and other dialysate constituents.

Trends in outcomes with haemodialysis

Over time, haemodialysis has become a much safer medical procedure than in the past. For example, serious adverse events and death directly related to the dialysis procedure itself are now rare events. Increased patient safety has resulted from a combination of technical advances that have reduced complications attributable to the procedure itself, implementation of quality control standards and regulations, and the use of multidisciplinary care teams. Technical advances include availability of multiple vascular access options, development of hollow fibre dialysers, improved dialysate delivery systems, more reliable intradialytic monitoring devices, and automated safety mechanisms. Many other technical improvements have been routinely implemented; these include the standard use of bicarbonate-based dialysate, improvements in water quality designed to reduce endotoxin exposure, more rigorous water quality standards with backup systems for protection against system failure, and more precise volumetric ultrafiltration control. Improvements in hollow fibre haemodialysis membrane design have more effectively replicated the permselectivity of the native kidney glomerular filtration barrier. Computer-controlled sodium and bicarbonate modelling can be employed, and several online devices now allow dynamic intradialytic monitoring of the blood flow rate, changes in the haematocrit (to measure vascular refilling during ultrafiltration), and changes in dialysate electrical conductivity (which is used to estimate the amount of solute being removed). Automated dialysate temperature control maintains a constant body temperature during dialysis, which may reduce the incidence of hypotension. In addition, lowering dialysate temperature can help achieve haemodynamic stability and reduce intradialytic hypotension.

Globally, the prevalence of end-stage renal disease (ESRD) treated with haemodialysis is steadily increasing. Factors contributing to this trend include the ageing population, as well as steadily increasing rates of diabetes and hypertension in both low- and high-income regions of the world. In many low-income countries,

there are significant challenges in determining accurate estimates of the disease burden from ESRD, and data on use of maintenance haemodialysis is incomplete. In high- and middle-income countries, more data from registries and other sources are available. Historically the most complete data is available for the United States, from the United State Renal Data Registry (USRDS). By 2011, > 400,000 patients were undergoing maintenance dialysis in the United States, with the vast majority (~ 85–90%) receiving haemodialysis. Diabetes mellitus is the most common cause of need for maintenance haemodialysis, accounting for > 45% of all cases.

There has been steady improvement in achieving quality measures, which has led to a noticeable improvement in demographic-adjusted mortality outcomes over the past three decades. Nevertheless, in the United States, the median life expectancy of patients receiving haemodialysis is only 3 years and for an individual ≥ 65 years of age with diabetes it is only 18–22 months. Mortality rates are particularly high in the first 120 days after initiating dialysis. Hospitalization rates have remained high, averaging almost 13 hospital days and two admissions per patient-year. Thirty-day hospital readmission rates are also high. Cardiovascular and infectious complications are by far the leading causes of morbidity and mortality for patients on haemodialysis, with sudden death as a dominant direct cause of cardiovascular mortality.

International comparisons of crude mortality rates have consistently demonstrated higher mortality rates in the United States than in Europe or Japan. However, the substantial differences in demographics, case-mix factors, completeness of data ascertainment, and access to kidney transplant seriously limit the validity of these comparisons. For example, data from the World Health Organization mortality database illustrate that differences in background cardiovascular disease mortality rates associate very strongly with transnational dialysis mortality rates. Yet data from the Dialysis Outcomes Practice Patterns Study (DOPPS) do suggest that the relative risk for mortality may still be higher for the United States compared with Japan or Europe. Practice pattern variation in length of treatment times and use of fistulae for vascular access have been suggested as contributors to regional variation in haemodialysis outcomes.

Trends in initiation of haemodialysis

The demographics of the population treated with haemodialysis have changed dramatically over time, both in developed and developing nations. The gradual relaxation of stringency in the selection of patients for dialysis treatment has led to an increasing proportion of frail, elderly patients, often with extensive underlying cardiovascular disease and diabetes mellitus as a cause of ESRD. In developed countries, there has been a concomitant demographic trend to initiate dialysis at higher levels of residual kidney function, particularly in elderly individuals. Recent USRDS data suggest that this trend may be reversing, resulting in a recent decline in the number of new patients undergoing haemodialysis.

To date, the Initiating Dialysis Early and Late (IDEAL) study is the only randomized clinical trial to examine the association of kidney function at the time of initiation of dialysis with clinical outcomes (Cooper et al., 2010). The IDEAL study randomized adult patients with creatinine clearance of 10–15 mL/min/1.73 m^2 to either begin dialysis treatment early (10–14 mL/min/1.73 m^2; N = 404) or late (5–7 mL/min/1.73 m^2; N = 424). However, there was substantial intratrial crossover, as19% of subjects assigned to start dialysis early started later, and 76% of subjects assigned to start dialysis late started early, and thus the median difference in time to dialysis initiation was only 5.6 months. In the primary analysis, there was no significant difference in time to death, cardiovascular or infectious events, or complications of dialysis. Investigators could not achieve the desired separation in creatinine clearances at the time of initiation of dialysis that they intended due to patient symptomatology. The most common reason attributed by the study investigators for initiating dialysis early was uraemia. Thus, this clinical trial suggests that patient symptoms and clinician judgement are of paramount importance in decision-making for the initiation of dialysis.

Trends in treatment time and frequency of dialysis

It should be noted that patients undergoing conventional maintenance haemodialysis have the equivalent of < 10% of normal kidney function, even measured as clearance of small molecules such as urea. Larger solutes, protein-bound solutes, and solutes that are not readily accessible to the circulation are even less well removed by haemodialysis. Furthermore, the mechanical clearance of uraemic solutes during haemodialysis does not address the many other endocrine- and immune-regulating functions of the kidney. Thus, despite our many technological advances in the field of haemodialysis over the past half century, haemodialysis does not completely replace kidney function but rather serves as a substitute. Treatment time is an important component of the dialysis prescription, which can influence both the ability to remove solutes and to safely remove accumulated excess fluid without engendering intradialytic hypotension. More frequent dialysis can increase the clearance of highly protein-bound solutes, and also 'sequestered' solutes that do not equilibrate rapidly from intracellular stores to the plasma space. There is currently great interest in ascertaining from controlled trials whether longer and/or more frequent dialysis can improve outcomes, and would be accepted by most patients.

Future directions

The National Institutes of Health-supported Kidney Research National Dialogue recently asked the scientific community to formulate and prioritize dialysis research objectives. Identified priorities included the study of health-related quality of life and patient-centred outcomes, as well as nutritional issues in dialysis patients, decreasing deleterious cardiovascular, vascular access, and other adverse patient outcomes, identifying uraemic toxins, and determining best technical practices, especially for distinct patient populations. While many of the essential components of haemodialysis have not significantly changed since the 1960s, we have entered a new era in biomedical engineering that emphasizes interdisciplinary and translational research (Himmelfarb, 2006). Applications of molecular cell biology, developmental biology, and computational biology will support new types of therapeutic device development. Thus, the prospects for development of novel renal replacement therapies are bright. Innovative therapies that are currently being evaluated include development of wearable artificial kidneys, hybrid renal assist devices that combine cellular therapy with plasma separation, membraneless

dialysis, and genetic engineering to increase cellular detoxification potential. Nanotechnology may be applicable to dialytic therapies. The development of novel renal replacement therapies will inform new approaches to improving patient outcomes. However, substantive improvements for dialysis patients will likely require major technological breakthroughs, which will be predicated on an improved understanding of uraemic toxicity and related complications.

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CHAPTER 256

Haemodialysis: vascular access

Michael Allon

Timing of access placement

Ideally, the permanent vascular access should be ready for cannulation when the patient initiates dialysis. Achieving this elusive goal requires close collaboration among nephrologists, access surgeons, and interventional radiologists in patients with chronic kidney disease (CKD) stage 4 or 5 (Allon et al., 1998; Polkinghorne et al., 2009; Lee et al., 2011). To optimize vascular access outcomes, the patient should be under the care of a nephrologist for several months preceding initiation of dialysis, receive adequate education about access options, and undergo fistula surgery in a timely fashion. Having a dedicated access coordinator as a liaison among the different disciplines is helpful in promoting a team approach to streamline the process. A substantial proportion of fistulas fail to mature after being created, and many require one or more percutaneous or surgical revisions before they are suitable for cannulation (Allon, 2007a). The average maturation time of successful fistulas has been about 3–4 months in several observational studies from the United States (Allon et al., 2001; Oliver et al., 2001; Maya et al., 2004; Lee et al., 2007). The Dialysis Outcomes and Practice Patterns Study (DOPPS) observed substantial differences in time from fistula surgery to cannulation among countries, with a median interval as high as 3 months in the United States and United Kingdom, 6 weeks in Germany, and only approximately 4 weeks in Italy and Japan (Rayner et al., 2003). The explanation for these wide variations is not readily apparent. Additional time is required in those patients with a failed fistula, in whom a second access needs to be created and mature successfully.

Owing to these considerations, placement of a fistula should occur at least 6 months prior to the anticipated date of end-stage renal disease (ESRD) to optimize the chance of having a mature fistula upon initiation of dialysis (National Kidney Foundation, 2006). Unfortunately, predicting time to ESRD initiation is notoriously difficult. At one extreme, some patients with CKD stage 4 receive a fistula and then fail to progress to ESRD for several years. At the other extreme are patients who appear to have stable renal function and then unexpectedly have a precipitous decline in kidney function requiring initiation of dialysis with a catheter. Guidelines by several organizations have suggested glomerular filtration rate (GFR) thresholds between 15 and 25 mL/min for fistula placement, with little hard evidence to support specific recommendations. Patient age is a key determinant of progression to ESRD (O'Hare et al., 2007a, 2007b). In the younger age groups, progression to dialysis is much more likely than death without dialysis. Conversely, among older patients, death without dialysis is much more likely than initiation of dialysis. The impact of age on likelihood of future ESRD has important implications for access planning. If the access placement guidelines were to be followed in every patient with CKD stage 4, the predicted ratio of unnecessary to necessary fistula surgery would vary from a low of 0.5 in the youngest age group to a high of 8 in the oldest age group (Fig. 256.1). The decision about timing of access placement also needs to incorporate the personal preferences of the individual patient, which may differ from those of the treating nephrologist (O'Hare et al., 2010; Demoulin et al., 2011).

Choice of vascular access

Until the mid 1990s, fistula use in US haemodialysis patients was extremely low, as compared with its use in Europe (24 vs 80%) (Pisoni et al., 2002). The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, as well as the Fistula First initiative, have aggressively promoted fistula use in the United States during the past 15 years. The dialysis networks and large dialysis organizations in the United States have reinforced the written guidelines by frequent feedback to the nephrologists, access surgeons, and dialysis units about their benchmarks. These efforts have been highly successful, resulting in a progressive increase in the proportion of haemodialysis patients with fistulas in the United States from 24% to 56% over the past few years (Lynch et al., 2011). In contrast, the proportion of US patients initiating haemodialysis with a catheter has actually increased from 65% to 80%. The reasons for the high catheter use among incident US haemodialysis patients are complex, and attributable to a fragmented healthcare system, financial disincentives, and patient factors (Allon et al., 2011). Patients receiving medical care in the US Veterans Affair Medical Centers or Department of Defense have insurance coverage prior to initiation of dialysis, and are more likely to initiate dialysis with a fistula, as compared to patients without such health care coverage (Hurst et al., 2010).

Initially, there was concern that the pressure to increase fistula use would result in a progressive increase in catheter use in prevalent US haemodialysis patients. Fortunately, this has not occurred. After an initial increase in catheter use, the proportion stabilized, and has even decreased modestly (Allon, 2011; Lynch et al., 2011). Nevertheless, the extremely high proportion of patients initiating dialysis with catheters is distressing.

Several studies have documented a higher mortality among patients initiating dialysis with a catheter, as compared with those starting with a fistula or graft (Dhingra et al., 2001; Pastan et al., 2002; Allon et al., 2003; Xue et al., 2003; Polkinghorne et al., 2004). Of note, the excess death hazard in patients initiating dialysis with catheters holds true not just for infection-related causes, but also for cardiovascular aetiologies. Causality between catheter use and

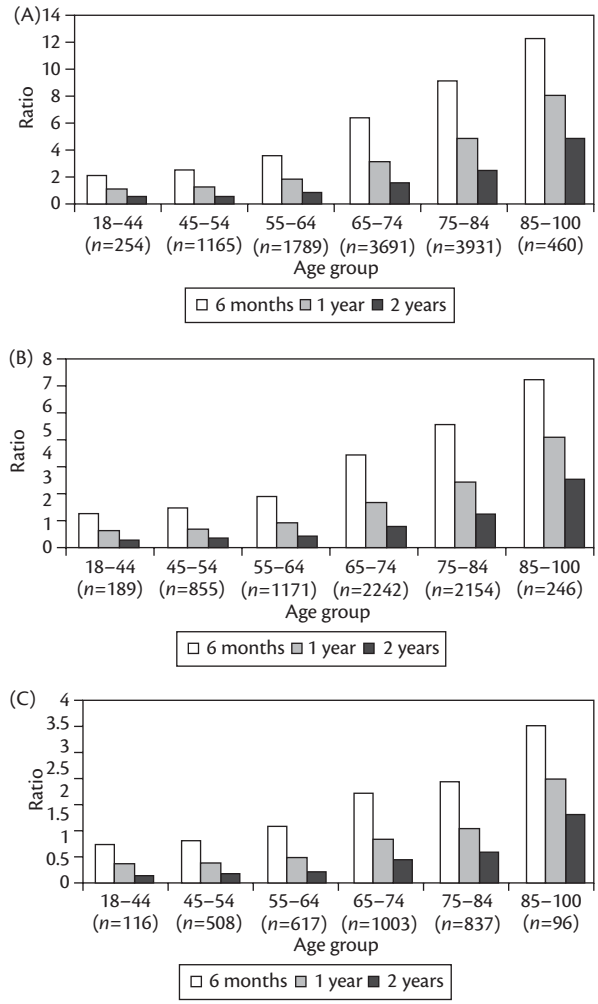

Fig. 256.1 Ratio of unnecessary to necessary permanent access surgeries at different theoretical referral eGFR thresholds by age and length of follow-up. (A) Referral threshold eGFR < 25 mL/min/1.73 m^2. (B) Referral threshold eGFR < 20 mL/min/1.73 m^2. (C) Referral threshold eGFR < 15 mL/min/1.73 m^2. Reproduced from *Kidney Int* 2007; 71:555–561. Reprinted by permission from Macmillan Publishers Ltd: *Kidney International*, A M O'Hare, D Bertenthal, L C Walter, A X Garg, K Covinsky *et al*., When to refer patients with chronic kidney disease for vascular access surgery: should age be a consideration?, 71/6, copyright 2007.

mortality is difficult to establish, as patients initiating dialysis with a catheter are also older and have higher co-morbidity. Consequently, it is not clear whether the higher death rate is due to complications of catheter use, or whether catheter use is simply a marker for patients already at higher risk of death. Two studies evaluating the impact of change in vascular access on subsequent risk of death provided more compelling evidence of causality (Allon et al., 2006; Lacson et al., 2009). Both studies observed that patients initiating dialysis with a catheter and switching to a permanent access (fistula or graft) had a lower mortality than those remaining catheter dependent. Conversely, patients initiating dialysis with a permanent access and subsequently switching to a catheter had a higher mortality than those who continued to use a permanent access. Finally, a change from catheter to permanent access is also associated with improvements in erythropoietin responsiveness and nutritional markers (Wystrychowski et al., 2009).

The vascular access guidelines are emphatic in stating that fistulas are superior to grafts because they last longer, require fewer interventions, and are less costly to maintain (National Kidney Foundation, 2006). These conclusions are largely drawn from 'as treated' analyses of patients who are already using their fistulas or grafts for dialysis. The conclusions differ when one uses 'intent to treat' analysis of patients referred for creation of a new access (Allon, 2007a; Allon and Lok, 2010). The latter scenario is more complex, as it needs to consider primary access failures (fistulas and grafts which are never suitable for dialysis), time to access maturation, and duration of catheter dependence, with its associated complications, in patients who have already initiated dialysis with a catheter. This type of analysis generally favours grafts during the early follow-up period and fistulas in the late follow-up period. Specifically, grafts are superior to fistulas because they have a lower primary failure rate, require fewer interventions to achieve suitability for dialysis, entail shorter catheter dependence, and incur fewer episodes of catheter-related bacteraemia until the permanent access is in use. Conversely, among vascular accesses that are successfully used for dialysis, fistulas are clearly superior to grafts because they last longer and require far fewer interventions to maintain their long-term patency. Thus, the relative merits of fistulas and grafts depend on a number of factors, such as whether the patient has started dialysis prior to access surgery, the likelihood of fistula non-maturation, and the patient's life expectancy (Allon and Robbin, 2008; Allon and Lok, 2010). At one extreme, a young pre-dialysis patient with low co-morbidity, low likelihood of fistula non-maturation, and a life expectancy of many years is an ideal candidate for a fistula. At the opposite extreme, an elderly patient with high co-morbidity, who has already started dialysis with a catheter, who has a high risk of fistula non-maturation, and who has a life expectancy < 2 years may be better suited to receiving a graft. Many patients fall between the two extremes, and the proper decision requires exercising clinical judgement rather than blind adherence to guidelines. A recent single-centre study compared fistula outcomes in patients older and younger than 70 years (Richardson et al., 2009). Cumulative fistula survival at 1 year was substantially lower in the older group (38% vs 68%). Likewise, patient survival at 1.5 years was also lower in the older group (50% vs 74%). Finally, of 35 elderly patients who died, only 35% ever had their fistula used for dialysis. These grim statistics suggest that fistula placement may be inadvisable in some elderly patients, in whom grafts may be a more viable option.

Remarkably, despite the extreme relevance of this question, only two randomized clinical trials have compared the outcomes of fistulas and grafts. The first study compared forearm grafts and radiocephalic fistulas in patients with marginal vessel size (arterial diameter 1–2 mm and vein diameter < 1.6 mm) (Rooijens et al., 2005). Cumulative 1-year fistula survival was significantly lower in the fistula group (52% vs 79%). The second study enrolled patients who were not candidates for a radiocephalic or brachiocephalic fistula to receive a transposed brachiobasilic fistula or a forearm graft (Keuter et al., 2008). Primary 1-year access survival was superior in the fistula group (46% vs 22%), although cumulative access survival was similar (89% vs 85%). Unfortunately, there are no randomized studies comparing the outcomes of grafts and brachiocephalic fistulas in patients who are not candidates for a forearm fistula. Until such a study is performed, the decision about vascular access relies on clinical judgement (Fig. 256.2). It is evident that a subset of patients may be better served by receiving a graft rather than a

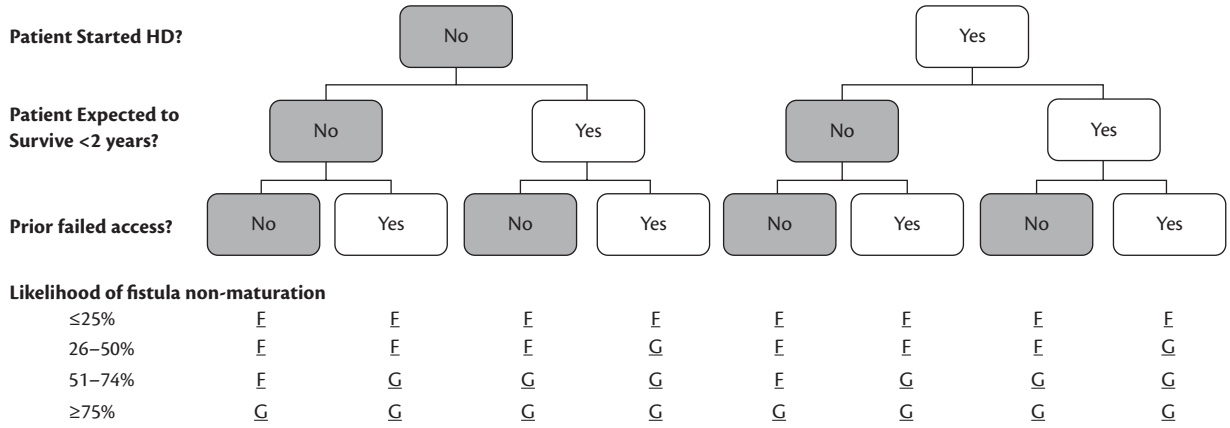

Fig. 256.2 An algorithmic guide to choosing an appropriate haemodialysis vascular access for patients. This protocol requires the nephrologist and access surgeon to consider three important clinical factors: timing of access surgery relative to initiation of haemodialysis, life expectancy of the patient, and prior failed vascular access. This information, along with the likelihood of AVF non-maturation, is used to determine the most appropriate vascular access for that patient. F = fistula; G = graft.
Reproduced from Allon, M. and Lok, C. E. (2010). Dialysis fistula or graft: the role for randomized clinical trials. *Clin J Am Soc Nephrol*, 5, 2348–54.

fistula. Fistula non-maturation has been repeatedly associated with certain patient characteristics, including older age, female sex, and cardiovascular disease (Allon and Robbin, 2002; Lok et al., 2006). If the patient has already initiated dialysis, fistula non-maturation may result in prolonged catheter dependence with its associated complications, including bacteraemia and central vein stenosis. When the patient's life expectancy is < 2 years and likely fistula non-maturation > 50%, a cogent argument can be made to place a graft in preference to a fistula (Allon and Lok, 2010). The case is particularly compelling in patients with a prior failed fistula.

Most studies have demonstrated lower non-maturation rates for fistulas placed in the upper arm, as compared with those in the forearm (Allon and Robbin, 2002; Peterson et al., 2008). Among upper arm fistulas, transposed brachiobasilic fistulas have a lower non-maturation rate than brachiocephalic fistulas, but require more extensive surgery (Maya et al., 2009). Thigh grafts have cumulative survival rates similar to that, or possibly better than that of, upper extremity grafts (Miller et al., 2003; Ram et al., 2010).

Preoperative vascular mapping

The premise of preoperative vascular mapping is that careful selection of suitable arteries and veins for fistula creation will maximize the chances of fistula success (National Kidney Foundation, 2006). Most centres utilize sonographic mapping, although some use venograms to assess vein suitability. Malovrh et al. demonstrated that selection of arteries or veins with a diameter < 1.5 mm was associated with inferior outcomes as compared to fistulas created with a diameter > 1.5 mm (Malovrh, 1998). Currently, most centres require a minimum arterial diameter of 2.0 mm, a minimum vein diameter of 2–3 mm, and absence of stenosis or thrombosis in the draining vein. A venogram should be performed in selected patients with clinical suspicion of central vein stenosis (Allon and Robbin, 2002). Although preoperative vascular mapping is widely touted as a tool that improves fistula outcomes, there is surprisingly little solid evidence to support this premise. Several observational studies have compared fistula outcomes with routine preoperative mapping to outcomes achieved during a prior historical period using physical examination alone (Silva et al., 1998; Ascher et al., 2000; Allon et al., 2001; Gibson et al., 2001). These studies consistently demonstrated increased fistula placement, but provided contradictory conclusions regarding the benefit of preoperative mapping on fistula maturation. Whereas one study observed a lower fistula non-maturation rate when preoperative vascular mapping was utilized (Silva et al., 1998), two others showed no benefit (Allon et al., 2001; Gibson et al., 2001). In a fourth study, the proportion of patients receiving a fistula increased from 61% to 73%, but fistula non-maturation increased concurrently from 27% to 43% (Patel et al., 2003). Only one randomized clinical trial has evaluated the impact of preoperative vascular mapping on fistula outcomes (Ferring et al., 2010). In this British study, patients referred for a new fistula were allocated to preoperative vascular ultrasound or clinical evaluation alone prior to access surgery. Those receiving preoperative vascular mapping had a significantly lower immediate technical failure than those undergoing only clinical evaluation (3.6% vs 11.3%). However, after excluding immediate surgical failures, fistula non-maturation rates were similar between the two randomized groups (17.9% vs 19.8%). In other words, the primary benefit of preoperative mapping was avoidance of fistulas that would clot immediately. Unfortunately, it was of limited value in decreasing non-maturation of fistulas that did not fail within 24 hours of their creation.

One might expect preoperative mapping to be particularly beneficial in patients with suboptimal vessels who are at high risk for fistula non-maturation (older patients, females, and those receiving a forearm fistula). However, a large single-centre observational study concluded that discrepancies in fistula maturation persisted in these high-risk groups despite implementation of routine preoperative mapping (Peterson et al., 2008). Using higher vascular diameter thresholds is not likely to be of benefit. Once the minimum threshold of 2.0 mm for arteries and 2.5 mm of veins is achieved, progressive increases in the preoperative vein diameter is not associated with improved fistula maturation, and would simply reduce the proportion of patients eligible for fistula creation (Maya et al., 2009).

Access monitoring and pre-emptive angioplasty

Most grafts and fistulas fail as a result of recurrent thrombosis. When clotted grafts are treated by percutaneous thrombectomy, imaging

almost always demonstrates concurrent haemodynamically significant stenosis at the graft–vein anastomosis, or less commonly in the draining vein or central vein (Allon, 2007a). This finding suggests that detection of underlying stenosis in a timely fashion and pre-emptive angioplasty may prevent graft thrombosis and potentially prolong cumulative graft longevity. A number of non-invasive methods for detection of significant graft stenosis have been validated. These include measurement of static dialysis venous pressures, access flow monitoring, and Duplex ultrasound. Routine use of each of these surveillance methods can detect haemodynamically significant graft stenosis in a timely fashion. The positive predictive value of an abnormal graft surveillance test for significant stenosis is 70–100% in multiple studies (Allon and Robbin, 2009). Moreover, several observational studies have reported a 40–80% reduction in the frequency of graft thrombosis after the implementation of graft surveillance with pre-emptive angioplasty, as compared to historical control period without surveillance (Schwab et al., 1989; Besarab et al., 1995; Safa et al., 1996; Allon et al., 1998; Cayco et al., 1998; McCarley et al., 2001). Taken together, these observations have led to published recommendations encouraging routine surveillance with pre-emptive angioplasty to improve graft outcomes (National Kidney Foundation, 2006).

Whereas abnormalities of graft surveillance have a relatively high positive predictive value for significant stenosis, they are much less useful in predicting thrombosis. The reason for this discrepancy is that only a subset of stenotic grafts is destined to clot. In one prospective evaluation of grafts with > 50% stenosis at the venous anastomosis documented by angiography, only approximately 30% thrombosed during 6 months of subsequent follow-up without pre-emptive angioplasty (Lumsden et al., 1997). Similarly, two studies performed regular graft surveillance by flow monitoring or static dialysis venous pressure measurements without prophylactic intervention. In both studies, only 30–40% of grafts with abnormal surveillance measurements indicating significant stenosis actually clotted during the subsequent 6 months of follow-up (McDougal and Agarwal, 2001; Dember et al., 2002). It is presently unknown why some grafts with stenosis clot, whereas others remain patent. There are also no available tests to reliably distinguish between the two groups. Thus, any graft surveillance programme necessarily results in pre-emptive angioplasty in all patients with proven graft stenosis, a large number of which are probably superfluous. In addition, surveillance does not always identify grafts with significant stenosis before they clot. In fact, approximately 25% of grafts that clot do so without having had an abnormal surveillance test preceding the thrombosis (Smits et al., 2001). This proportion is even higher among patients with new grafts.

To date, six randomized clinical trials have evaluated the benefit of graft surveillance and pre-emptive angioplasty (Lumsden et al., 1997; Moist et al., 2003; Ram et al., 2003; Dember et al., 2004; Malik et al., 2005; Robbin et al., 2006) (Fig. 256.3). In each study, patients were allocated to an interventional arm (periodic stenosis surveillance with static dialysis venous pressure measurements, access flow, or duplex ultrasound), or to a control arm (clinical monitoring only). The frequency of angioplasty was always higher in the surveillance group than in the control group, confirming that surveillance indeed resulted in more frequent angioplasty. Five of the six studies evaluated graft thrombosis as an endpoint, and none found a difference in time to thrombosis between the two randomized groups. Likewise, of the five studies evaluating cumulative graft survival, only one observed a beneficial effect. A meta-analysis of the randomized studies reported no significant benefit of surveillance with pre-emptive angioplasty on thrombosis-free graft survival or cumulative graft survival (Tonelli et al., 2008).

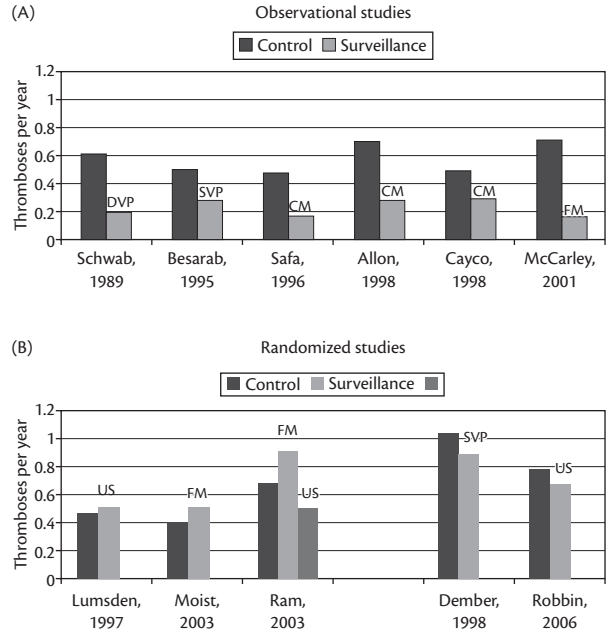

Fig. 256.3 (A) Observational studies reporting on the frequency of graft thrombosis occurring during a historical control period and following implementation of stenosis monitoring or surveillance. Thrombosis decreased during the intervention period in all the studies. (B) The frequency of graft thrombosis in the graft surveillance group and the control group observed in randomized clinical trials. The rate of thrombosis was not significantly different between the randomized groups in these studies.
Reproduced from Allon, M. (2007). Do we really need periodic monitoring of vascular access for hemodialysis? *NephSAP*, 6, 111–16.

The lack of benefit of surveillance and pre-emptive angioplasty on graft outcomes may reflect the limited short-term benefit of angioplasty. Flow monitoring is frequently used to detect haemodynamically significant stenosis in grafts, with angioplasty resulting in an acute increase in access flow. Two studies reported that the access flow was back to the pre-angioplasty value in 20% of patients at 1 week and in about 40% at 1 month (Schwab et al., 2001; Moist et al., 2003), confirming a high frequency of early graft restenosis. Vascular access angioplasty results in aggressive neointimal hyperplasia and rapid re-stenosis (Chang et al., 2004). The benefit of angioplasty may be improved by using stents to provide a rigid scaffold that keeps the vein open longer. Observational studies have provided contradictory results about the impact of vascular stents in improving graft patency (Yevzlin and Asif, 2009). A recent randomized clinical trial of 190 patients with haemodynamically significant stenosis at the graft–vein anastomosis allocated patients to deployment of a covered graft-stent or conventional balloon angioplasty. Protocol angiograms were performed at 2 and 6 months to evaluate for re-stenosis (Haskal et al., 2010). Recurrence of lesion-specific restenosis at 6 months was lower in the stent group than in the angioplasty group. Likewise, loss of access circuit patency was lower in the stent group. Unfortunately, graft thrombosis at 6 months did not differ between the two groups. To extend these results, a larger randomized study (RENOVA) is currently

being conducted. This trial has enrolled 270 patients with graft stenosis, and will determine graft patency at 12 months and frequency of graft interventions in patients treated with graft-stents or balloon angioplasty (<http://clinicaltrials.gov/ct2/show/NCT00677235>). An interim analysis reported improved graft patency and fewer interventions for stenosis in patients randomized to graft-stents, but did not report on the frequency of graft thrombosis (Haskal, 2013). A similar randomized study (REVISE) is being performed to compare the outcomes of stenosed grafts treated with a different type of stent-graft to those obtained with conventional balloon angioplasty. The ongoing REVISE Study is enrolling 280 patients with 2 years of follow-up (<http://clinicaltrials.gov/ct2/show/NCT00737672>). These ongoing studies have generated optimism that covered stent-grafts may represent an important advance in improving long-term graft outcomes (Kerlan and LaBerge, 2010), but a recent commentary urged caution in jumping on the 'stent bandwagon' before the results of longer-term follow-ups are available (Salman and Asif, 2010).

Much less has been published on the potential benefit of access surveillance for fistulas. The benefit may be more difficult to demonstrate, as the frequency of access stenosis and thrombosis is several-fold lower for fistulas than for grafts (Allon and Robbin, 2002). As is the case for grafts, flow monitoring has a high positive predictive value for haemodynamically significant stenosis. To date, only one randomized clinical trial has evaluated the impact of surveillance and pre-emptive angioplasty on fistula outcomes (Tessitore et al., 2004). This study observed better fistula longevity in patients receiving routine surveillance. Of note, unlike the randomized graft trials, the patients in the fistula trial underwent both angioplasty and surgical revision.

In summary, although circumstantial evidence makes graft surveillance and pre-emptive angioplasty a potentially attractive approach to improving graft outcomes, the randomized clinical trials do not support the value of this approach. This topic will continue to generate considerable controversy until a definitive, large multicentre clinical trial is published (White et al., 2005; Besarab, 2006; Allon and Robbin, 2009).

Assessing and intervening in non-maturing fistulas

Creation of a fistula requires direct anastomosis between a high-pressure artery and a low-pressure vein. Once the vein is exposed to the high arterial pressure, it dilates and increases its blood flow by as much as 10-fold within 24 hours, with a further increase over the subsequent few weeks (Yerdel et al., 1997; Malovrh, 1998; Robbin et al., 2002). The single biggest hurdle to increasing fistula use is the high proportion of fistulas that fail to mature sufficiently to be suitable for dialysis (Allon and Robbin, 2002). Whereas studies from the 1970s and 1980s reported a fistula non-maturation rate of about 10%, more recent studies have reported a much higher rate, ranging between 20% and 50% (Allon and Robbin, 2002). A recent large American multicentre clinical trial reported that approximately 60% of fistulas were not suitable for dialysis within 6 months of their creation (Dember et al., 2008). About one-third of the failed fistulas clotted within 6 weeks of their creation, and the remainder did not mature adequately to be suitable for haemodialysis. The high fistula non-maturation rate is not unique to the United States. A recent prospective study of 491 fistulas created in the Netherlands observed a 40% primary failure rate (Huijbregts et al., 2008).

Future suitability for dialysis can be assessed 4–6 weeks following fistula creation. An experienced dialysis nurse can often evaluate fistula maturation by clinical evaluation alone (Robbin et al., 2002). However, postoperative sonograms provide valuable adjunctive information to predict fistula suitability for dialysis. Two studies documented that the combination of an access blood flow > 500 mL/min and a vein diameter > 4 mm predicted a > 90% likelihood of fistula suitability (Robbin et al., 2002; Singh et al., 2008). Conversely, fistula suitability was observed in only approximately 35% of patients who met neither sonographic criterion. In addition to assisting in prediction of fistula success, the postoperative sonogram can also identify anatomic lesions in immature fistulas, which may promote fistula maturation once they are addressed. These abnormalities may include juxta-anastomotic stenosis, presence of large accessory veins, and excessive depth of the fistula from the skin. Stenosis can be corrected by angioplasty or surgical revision, accessory veins can be ligated surgically or embolized, and excessively deep fistulas can be transposed closer to the skin to permit safe cannulation. Several uncontrolled series have reported a high success rate in salvaging immature fistulas with percutaneous or surgical interventions (Beathard et al., 1999; Turmel-Rodrigues et al., 2001; Miller et al., 2003; Asif et al., 2005, 2006; Falk, 2006; Nassar et al., 2006). One study compared the outcomes of sonographically immature fistulas with underlying anatomic lesions that were corrected or not corrected. Suitability for dialysis was achieved in 78% of patients undergoing targeted fistula interventions, as compared with 31% of those who declined subsequent interventions (Singh et al., 2008). As compared with fistulas that mature with 0 or 1 interventions, those requiring two or more interventions to achieve maturation have significantly shorter cumulative survival and require more interventions to maintain their long-term patency (Lee et al., 2011).

Pharmacologic interventions to improve fistula and graft outcomes

Both intimal hyperplasia and thrombosis play a role in vascular access failure. Our current approach to achieving and maintaining vascular access patency for dialysis is purely mechanical: access stenosis is treated by balloon angioplasty or stent deployment and clotted accesses are treated by mechanical thrombectomy (Allon, 2007a). There has been great interest in pharmacologic interventions to interfere in the pathogenesis of intimal hyperplasia and thrombosis (Allon, 2009a).

Thrombosis is a common cause of early fistula failure, occurring in about 20% of patients with new fistulas. Antiplatelet agents may reduce this complication and potentially increase fistula maturation. Several small, randomized clinical trials observed a reduction in early fistula thrombosis in patients treated with antiplatelet agents, as compared with those receiving placebo (Kaufman, 2000). The Dialysis Access Consortium (DAC) study was a large, multicentre, randomized clinical trial which assigned 877 patients receiving a new fistula to treatment with clopidogrel or placebo for 6 weeks postoperatively (Dember et al., 2008). The patients receiving clopidogrel had a nearly 40% lower frequency of early fistula thrombosis. Unfortunately, failure of fistulas to achieve suitability for dialysis was similar (~ 60%) in both treatment arms. An

ongoing randomized, double-blinded clinical trial in Australia and New Zealand (FAVOURED) is assigning 1200 patients with new fistulas to aspirin, fish oil, both drugs, or placebo for 3 months postoperatively, and assessing early fistula thrombosis, as well as fistula suitability for dialysis (Irish et al., 2009).

Several randomized studies have evaluated pharmacologic interventions to improve graft outcomes. A single-centre, randomized clinical trial allocated patients with new grafts to receive aspirin, dipyridamole, both drugs, or placebo (Sreedhara et al., 1994). Patients treated with dipyridamole, with or without aspirin, had a 40–50% lower frequency of graft thrombosis. To confirm the results of this pilot study, the DAC graft study randomized 649 patients with new grafts to treatment with dipyridamole plus aspirin or placebo (Dixon et al., 2009). The primary unassisted graft patency (absence of angioplasty or thrombosis) at 1 year was significantly (but modestly) higher in the active drug group (28% vs 23%). However, the cumulative graft survival did not differ between the two treatment arms. Another randomized clinical trial allocated 200 patients with grafts to clopidogrel plus aspirin or placebo (Kaufman et al., 2003). The active drug did not lower the frequency of graft thrombosis, but significantly increased haemorrhagic complications. A Canadian double-blinded randomized clinical trial assigned 107 patients with new grafts to low intensity warfarin (target international normalized ratio 1.4–1.9) or placebo (Crowther et al., 2002). Warfarin treatment did not reduce graft thrombosis, but was associated with life-threatening haemorrhage in 10% of the patients.

Plasma homocysteine levels are markedly elevated in haemodialysis patients and the risk of graft thrombosis is associated with homocysteine concentrations (Shemin et al., 1999). Thus, a plausible hypothesis is that pharmacologic reduction of homocysteine levels may improve graft outcomes. However, two randomized clinical trials in which patients received high doses of folic acid to lower plasma homocysteine, did not observe a reduction in access thrombosis (Wrone et al., 2004; Jamison et al., 2007). A very small (N = 24) single-centre, randomized clinical trial observed a significant reduction in graft thrombosis among patients treated with fish oil (Schmitz et al., 2002). A larger, multicentre trial randomized 201 haemodialysis patients with new grafts to receive fish oil or placebo. Patients treated with fish oil had longer primary unassisted graft survival, and required fewer angioplasties and thrombectomies to maintain long-term graft patency (Lok et al., 2012).

Aggressive intimal hyperplasia is the major cellular mediator in the pathogenesis of access thrombosis (Roy-Chaudhury et al., 2001, 2006). Antiproliferative agents would seem to be an attractive approach to reduce intimal hyperplasia and thereby prevent access stenosis and failure, but their use is limited by the potential for systemic toxicity (Allon, 2009a). This concern has generated a growing interest in local drug delivery systems that would provide a high concentration of antiproliferative drug to the target area (graft–vein anastomosis), while minimizing the risk of systemic toxicity (Li et al., 2008). None of the local delivery systems are commercially available at this time.

Graft and fistula infections

Fistula infections occur far less frequently than graft infections (Allon and Robbin, 2002; Maya et al., 2009). Both present with evidence of localized infection (erythema, heat, tenderness or drainage at the access site). The infection occasionally arises from contamination at the initial surgery, but is more commonly introduced from the skin during access cannulation. Treatment usually requires systemic antibiotics, as well as surgical excision of the graft. In two large series, patients required an average of 7 days of hospitalization to manage graft infection (Minga et al., 2001; Harish and Allon, 2011). In selected patients, graft infection may be sufficiently localized to permit partial excision of the graft with creation of a bypass graft, permitting continued cannulation of the access. Graft infections usually occur relatively early after graft creation, with about 50% of infections occurring within 6 months, and the remainder spread out over a period of years (Harish and Allon, 2011). A recent study highlighted important differences between infected thigh and upper extremity grafts (Harish and Allon, 2011). As compared with upper extremity graft infections, thigh grafts infections were more common (14% vs 9%), more likely to be caused by Gram-negative rods (31% vs 4%), more likely to result in metastatic infections (15% vs 3%), and were associated with more prolonged catheter dependence (319 vs 237 days).

Buttonhole cannulation of fistulas has become more popular in recent years, in an attempt to decrease pain with cannulation, prevent needle infiltrations, and avoid pseudoaneurysms. Prior to cannulation through the buttonhole, it's imperative for the dialysis nurse to remove the scab overlying the subcutaneous tunnel and reapply a disinfectant to the cannulation site. Failure to do so has been associated with clusters of bacteraemic episodes, some of them complicated by metastatic infections (Nesrallah et al., 2010; Labriola et al., 2011). Such infections can be prevented by ongoing dialysis staff education (Labriola et al., 2011) or by applying mupirocin ointment at the buttonhole site (Nesrallah et al., 2010). A recent Canadian randomized clinical trial allocated haemodialysis patients with fistulas to buttonhole cannulation or conventional rope ladder cannulation. The frequency of fistula infection was more than twofold higher in patients undergoing buttonhole cannulation (MacRae et al., 2012). Moreover, unassisted fistula patency was shorter in patients undergoing buttonhole cannulation (MacRae et al., 2014). These observations suggest that buttonhole cannulation of fistulas should be abandoned in most patients with fistulas (Zimmerman and Lok, 2012).

Non-infectious dialysis catheter complications

Dialysis catheters are a necessary evil in dialysis patients, either as a bridge until a permanent access is placed and suitable for dialysis, or as a long-term access in patients who have exhausted all potential sites for permanent access (fistula or graft) (Schwab and Beathard, 1999). The major complications of catheters are dysfunction, central vein stenosis, and infection. The effective dialysis blood flow is lower with catheters than with fistulas or grafts, often leading to suboptimal delivery of dialysis. One study observed a higher likelihood of inadequate dialysis (Kt/V < 1.2) among catheter-dependent patients, as compared to patients using fistulas or grafts (Lee et al., 2005). The KDOQI guidelines recommend that a catheter deliver a minimal dialysis blood flow of 300 mL/min to ensure an adequate dialysis dose, and that catheters providing a lower blood flow should be treated (National Kidney Foundation, 2006). This recommendation has been challenged by one study, which reported that 22% of patients with dialysis blood flows < 300 mL/min could still achieve adequate

dialysis, particularly women and smaller patients (Moist et al., 2006). Thus, treatment of catheters with lower dialysis blood flows may be indicated only when it is associated with inadequate dialysis.

Subclavian catheters should be avoided if at all possible, due to their high likelihood of causing central vein stenosis, even after a short duration of use. The right internal jugular vein is the preferred site of insertion of tunnelled dialysis catheters, due to the lack of angulation of veins between the right internal jugular vein and the right atrium. When this is not feasible, a left internal jugular catheter can be placed, but it has decreased patency than the right internal jugular catheter (Jain et al., 2009; Shingarev et al., 2013). Catheter dysfunction presenting immediately after placement suggests incorrect placement, and can be resolved by repositioning of the catheter. When catheter dysfunction arises after a prior period of good function, the most likely problem is a thrombus in the distal tip of the lumen. Severe catheter dysfunction manifests with inability to aspirate blood from the catheter lumen upon initiation of dialysis. Milder cases present with suboptimal dialysis blood flows and excessively negative arterial blood pressures when the nurse attempts to increase the blood flow. Initial manoeuvres to trouble-shoot catheter dysfunction include changing the patient's position, switching the arterial and venous lines, or forceful flushing of the catheter lumens. When the dysfunction persists despite such manoeuvres, the nurse instils a thrombolytic solution (tissue plasminogen activator or urokinase) into each catheter lumen. Although the definition of catheter patency has varied among reported studies, thrombolytic instillation restores catheter patency in 60–95% of cases. Catheter dysfunction frequently recurs rapidly (within ~ 4 weeks) after treatment with a thrombolytic agent, and may respond to another thrombolytic instillation (Daeihagh et al., 2000; Little and Walshe, 2002). When catheter dysfunction persists despite thrombolytic instillation, the catheter can be exchanged for a new one over a guidewire. Patients whose catheter dysfunction persists after exchange may have a fibrin sheath, which can be demonstrated by fluoroscopy. Heparin-coated catheters have similar cumulative survival to that obtained with non-coated catheters (Jain et al., 2009).

Tunnelled femoral dialysis catheters are used in patients with bilateral central vein stenosis, but have a much higher rate of dysfunction than do internal jugular catheters. In one study, the median survival of femoral catheters (from initial placement to exchange) was only 2 months, as compared with 10 months for internal jugular catheters (Maya and Allon, 2005). Femoral catheters also deliver lower dialysis blood flows than do internal jugular catheters, often resulting in inadequate dialysis. Kinking during hip flexion (when the patient is sitting) may contribute to femoral catheter dysfunction. In one study, 26% of patients with femoral catheters developed symptomatic ipsilateral deep vein thrombosis requiring anticoagulation (Maya and Allon, 2005). Whereas central vein thrombosis has also been visualized in 26% of patients with internal jugular vein catheters (Wilkin et al., 2003), the thrombosis is usually asymptomatic.

An anticoagulant solution (heparin or citrate) is instilled into the catheter lumens after each dialysis session to prevent catheter thrombosis during the interdialytic interval. Heparin is the primary anticoagulant used in the United States, whereas citrate is used preferentially in Europe and Canada. There remains ongoing controversy about the optimal type and dose of anticoagulant. Several studies have compared the frequency of thrombolytic instillation and catheter exchange due to dysfunction between patients receiving heparin locks and those with citrate locks. A retrospective study comparing patients with heparin and citrate locks observed no difference in the frequency of thrombolytic instillation or catheter survival (Grudzinski et al., 2007). In contrast, a prospective, non-randomized study observed a lower requirement for thrombolytic instillation and catheter exchange due to dysfunction among patients treated with citrate locks (Lok et al., 2007). Finally, two randomized clinical trials observed no significant difference in catheter dysfunction between heparin and citrate locks (Dogra et al., 2002; Weijmer et al., 2005).

Despite careful instillation of the prescribed volume of heparin into the catheter lumen, about 20% of the solution immediately leaks into the bloodstream and has been associated with systemic bleeding complications (Sungur et al., 2007; Markota et al., 2009). A relatively high concentration of heparin lock solution (> 5000 units/mL) was used in the past for dialysis catheters, but a recent position paper urged adopting a lower concentration (1000 units/mL) to minimize haemorrhagic complications (Moran and Ash, 2008). Three observational studies noted a two- to threefold higher requirement for thrombolytic instillation with the lower heparin lock concentration, but no difference in the frequency of catheter exchange due to dysfunction (Holley and Bailey, 2007; Thomas et al., 2007; Maya et al., 2010). The overall cost of heparin and tissue plasminogen activator (tPA) to maintain catheter patency was lower with a 1000-unit/mL heparin lock as compared to the 5000-unit/mL lock in one study (Maya et al., 2010).

A recent double-blinded, randomized clinical trial evaluated the benefit of prophylactic thrombolytic locks on dialysis catheter patency (Hemmelgarn et al., 2011). This Canadian study allocated 225 patients with new, tunnelled catheters to receive conventional heparin (5000-unit/mL) locks thrice weekly or to receive tPA locks once a week and heparin after the other two weekly sessions. Catheter dysfunction was reduced by about 50% in the group receiving weekly tPA locks. In addition, the frequency of bacteraemia was decreased by about two-thirds in the tPA group. Although the benefit of prophylactic tPA locks appears attractive, the high cost of this drug will likely curtail widespread adoption of this protocol in outpatient dialysis units.

Central vein stenosis is a common complication of catheters (Agarwal et al., 2007). It is often asymptomatic, but in selected patients may present with diffuse ipsilateral upper extremity oedema. The symptoms may arise in some cases only after creation of a permanent vascular access on the side of a previously unsuspected central vein stenosis. Central vein stenosis should be treated only in symptomatic patients. The benefit of angioplasty is short-lived with a 20% patency at 1 year, and the outcomes are no better after stent deployment (Maya et al., 2007). Pacemakers and defibrillators may also be an important cause of central vein stenosis in haemodialysis patients. These devices are typically placed transvenously, but an epicardial approach may prevent central vein stenosis (Asif et al., 2011). Upper extremity fistulas created on the same side as the dialysis catheter have decreased secondary survival as compared to fistulas on the contralateral side (Shingarev et al., 2012).

Catheter-related infections

Infection is the most serious complication of dialysis catheters. These infections fall into three broad categories: exit site infection, tunnel infection, and catheter-related bacteraemia (Allon 2004,

2007a; Lok and Mokrzycki, 2011). Exit site infection manifests with erythema, swelling, tenderness, or purulent drainage from the catheter exit site. A trial of local antiseptic ointment or oral antibiotics is reasonable as the initial approach. If this is unsuccessful, the catheter should be removed. Tunnel infections manifest with severe pain and erythema along the subcutaneous tunnel, in conjunction with purulent drainage from the exit site. Prompt catheter removal and debridement of the subcutaneous tunnel is mandatory in patients with a tunnel infection. Catheter-related bacteraemia is diagnosed in patients with suspected bacteraemia (fever, rigors, or non-specific symptoms of infection), positive blood cultures obtained from the catheter and from a peripheral vein, and absence of evidence for an alternative source of infection. Peripheral blood cultures are frequently not feasible in haemodialysis patients, and many dialysis centres substitute cultures obtained from the dialysis bloodline (Allon, 2009b). Most episodes of catheter-related bacteraemia resolve without major sequelae, but 5–10% are complicated by major metastatic infections, such as endocarditis, osteomyelitis, septic arthritis, or epidural abscess. Patients with relatively mild symptoms can be treated as outpatients, whereas those with severe sepsis or metastatic complications require hospitalization. About 5% of patients with catheter-related bacteraemia present with concurrent purulent exit site infection, which is seen almost exclusively with Gram-positive infections (Sychev et al., 2011). The frequency of catheter-related bacteraemia varies greatly among dialysis units. In one prospective single-centre study, bacteraemia occurred in 35% of catheter-dependent patients at 3 months, and in 48% at 6 months (Lee et al., 2005). *Staphylococcus aureus* catheter-related bacteraemia is more likely to result in metastatic infection, require hospitalization, and be associated with treatment failure (Poole et al., 2004; Mokrzycki et al., 2006; Al-Solaiman et al., 2011).

Catheter-related bacteraemia requires administration of intravenous antibiotics for 2–3 weeks. Empiric antibiotics need to be selected to cover the likely organism. In the United States, where Gram-negative organisms are relatively common and *Staphylococcus* infections are frequently methicillin resistant, the empiric antibiotic regimen typically includes vancomycin plus an aminoglycoside or third-generation cephalosporin. In many European and Asian dialysis centres, the infecting organism is almost always methicillin-sensitive *Staphylococcus epidermidis*, so empiric therapy with a first-generation cephalosporin may be adequate. Once the infecting organism and its sensitivities are available, the patient should be switched to a more narrow-spectrum antibiotic regimen. When systemic antibiotics are administered without doing something about the infected catheter, the bacteraemia recurs in approximately 75% of cases once the course of antibiotics is completed (Allon, 2004). There are three major options for dealing with the infected catheter (Allon, 2009b). First, the infected catheter can be removed promptly, a temporary catheter used for dialysis, and a new tunnelled catheter placed once the repeat cultures are negative. Second, if the patient's fever and symptoms resolve within 2–3 days of initiating antibiotics, the infected catheter can be exchanged for a new one over a guidewire. Third, an antibiotic-anticoagulant solution (antibiotic lock) can be instilled into the catheter lumens at the end of each dialysis session, in conjunction with the systemic antibiotics. When an antibiotic lock is used, the catheter is retained if the symptoms and bacteraemia resolve, but replaced if the symptoms or bacteraemia persist or recur. Each of these management options results in approximately 75% cure of bacteraemia at 90 days.

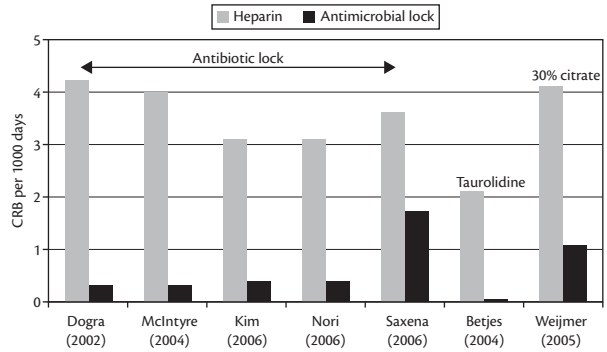

Fig. 256.4 Summary of frequency of catheter-related bacteraemia with antimicrobial locks versus heparin locks in published randomized clinical trials. Five trials used an antibiotic lock, one used taurolidine, and one used 30% citrate. In each study, the catheter-related bacteraemia frequency was 50–100% lower in the group with antimicrobial lock, as compared with the heparin controls.
Reproduced from Allon, M. (2008). Prophylaxis against dialysis catheter-related bacteremia: a glimmer of hope. *Am J Kidney Dis*, 51, 165–8.

There has been great interest in pharmacologic approaches to prevention of catheter-related bacteraemia. In patients with non-tunnelled catheters, the infection is introduced into the bloodstream by one of two pathways: along the outside of the catheter or through the catheter lumen. Tunnelled dialysis catheters have a Dacron cuff which acts as a mechanical barrier on the outside of the catheter. As a consequence, the frequency of bacteraemia is significantly lower with tunnelled dialysis catheters (Allon, 2004). Even in patients with tunnelled catheters, bacteria from the chest wall skin are introduced by contamination during dialysis hookups and form a biofilm on the inner surface of the lumen, which is a potential source of bacteraemia. Application of an antibiotic ointment (mupirocin or polysporin) at the exit site reduces catheter-related bacteraemia (Johnson et al., 2002; Lok et al., 2003). Likewise, several randomized clinical trials have shown a dramatic (50–100%) reduction in the frequency of catheter-related bacteraemia by use of an antibiotic (gentamicin, cephalosporin, or minocycline) or antimicrobial (30% citrate, taurolidine, or methylene blue) lock solution after each dialysis session (Dogra et al., 2002; Betjes and van Agteren, 2004; McIntyre et al., 2004; Weijmer et al., 2004; Kim et al., 2006; Nori et al., 2006; Saxena et al., 2006; Maki et al., 2011) (Fig. 256.4). Long-term use of prophylactic antibiotic locks in dialysis catheters may lead to antibiotic-resistant bacteraemias (Allon, 2008), and this occurrence has been documented in a large observational study using prophylactic gentamicin locks (Landry et al., 2010). Presumably, such a complication would not arise with antimicrobial lock solutions that are not antibiotics. A recent randomized study documented a significant lowering of catheter-related bacteraemia in patients receiving weekly prophylactic thrombolytic catheter instillation (Hemmelgarn et al., 2011). Finally, a recent observational study documented a 64% reduction in mortality in patients receiving prophylactic gentamicin catheter locks (Moore et al., 2014).

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CHAPTER 258

Haemodialysis: prescription and assessment of adequacy

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Introduction

The development of haemodialysis for the treatment of chronic kidney disease was a remarkable step in medicine that moved what was once a universally fatal organ failure to a condition that is regarded as treatable (Scribner et al., 1960). Over the decades since that remarkable advancement, mechanical methods of blood purification to correct the uraemic condition have gained a prominent and often expected role in the care of the patient with end-stage kidney failure. Even so, patients with end-stage kidney disease still experience high rates of morbidity and mortality, at times surpassing other chronic conditions such as cancer (Centers for Disease Control and Prevention, 2007; United States Renal Data System, 2011). The goal of haemodialysis should be not only to maintain life but also to restore the afflicted individual to a state of health, thus rehabilitating them so that they can lead a meaningful, fulfilling life. Currently utilized methods of haemodialysis, while effective at acutely reversing the uraemic condition, often fall short of the goal of rehabilitation. This observation, among others, has led many scientists and physicians to suspect that contemporary dialytic therapy is inadequate and has led to vigorous pursuit of the question: what is the adequate dose of dialysis? While extensive effort has been devoted to the pursuit of this question, it has yet to be definitively answered to the satisfaction of the scientific community. The following adequacy chapter will predominantly focus on currently popularized and frequently utilized methods for measurement of dialysis dose with the stipulation that the reader understands that the determination of the adequate dose of dialysis is an evolving field and in clinical practice should require more diligence than simple surveillance of urea clearance. The adequacy of volume management, which is arguably of equal importance to the adequacy of uraemic retention solute clearance, is covered in other chapters within this text.

Dose of dialysis: historic background

Much of the fundamental knowledge about clearance of solute during haemodialysis is described in the first thorough publication discussing the kinetics of haemodialysis in 1951 (Wolf et al., 1951). In these studies from Albany Medical College, New York, a Brigham–Kolff type artificial kidney with a cellophane membrane was utilized. In a very intuitive approach, authors attempted to compare the function of the artificial kidney with the function of the normal kidney. The newly coined term 'dialysance' was described to be the minute rate exchange of a substance between the blood and the dialysate; the equivalent of native renal clearance for the artificial kidney. It was recognized that dialysance of various molecules differed depending upon the size and charge of the molecule. With increasing surface area of membrane as well as with increasing blood flow, the dialysance of all molecules was increased despite their specific characteristics. Also recognized was the rate of excretion in the artificial kidney, which is proportional to the difference between the blood and bath concentration. At this time in history, haemodialysis was still a therapy that was only utilized at specialized medical centres and large variation existed between centres as to the type of dialysis apparatus and dialysis membrane utilized.

In 1964, there was an attempt to quantify the performance characteristics of different dialysers (Michaels, 1966). In this work it was suggested that the overall efficiency of a membrane device is dependent upon two independent parameters, the ratio of flow rates (of blood and dialysate) and the rate constant (K) for solute transport between fluids. K would be dependent upon the characteristics of the membrane such as surface area, membrane thickness, pore size, and local fluid velocity. Recognizing these relationships led to the development of mathematical and graphical models allowing the estimation of the expected clearances at differing flow rates using a constant (KoA) for a particular dialyser at different blood and dialysate flows. Today the mass transfer permeability area coefficient or KoA is provided on dialyser specification sheets and predominantly has utility in comparing performance characteristics between dialysers and in calculations performed with urea kinetic modelling. The concept of the KoA is discussed in further detail below.

In the early 1960s, the development of the arteriovenous shunt and advancing dialysis technology made the treatment of chronic renal failure a more realistic possibility (Scribner et al., 1960; Hegstrom et al., 1962; Murray et al., 1962). Early determinations of the dose of dialysis were largely speculative, based on clinical observation and bound by logistical and financial constraints. Among other developments, in order for researchers to advance dialysis therapy and gain broader acceptance of dialysis for chronic renal failure, there would need to be a correlation between dialyser performance and patient outcome. The first attempt to do so came from the group at the University of Washington, Seattle, in the form of the square metre per hour hypothesis, first described in 1971 (Babb et al., 1971). The basis for this hypothesis rested on the speculation that 'middle molecules' or molecules with a molecular weight (MW) that was greater than urea, are the main

culprits responsible for the uraemic condition. The middle molecule hypothesis stemmed from the observation that patients on peritoneal dialysis with higher urea levels did not develop neuropathy. This observation compared with under-dialysed haemodialysis patients who did develop neuropathy, occasionally in the setting of lower blood urea nitrogen (BUN) levels. The cuprophane haemodialysis membranes in use at that time were not particularly permeable to middle molecules whereas the peritoneal membrane does allow diffusion of middle molecules through pores of varying sizes (Babb et al., 1973). It was also recognized, and later confirmed, that preserved residual function seen in many peritoneal dialysis patients is likely to play a significant role in middle molecule clearance (Bargman et al., 2001). In haemodialysis patients, based on elaborate studies of neurologic function in individuals with uraemia, they noted that neuropathy could be improved with increasing dialysis time and speculated that this improvement was due to enhanced middle molecule clearance (Teschan et al., 1974; Bourne et al., 1975; Ginn et al., 1975). The square metre per hour hypothesis stemmed from these observations as a complicated mathematical analysis of the process of diffusive clearance of middle molecules. This hypothesis demonstrated that clearance of middle molecules is more dependent upon membrane surface area and time length of dialysis rather than blood and dialysate flow rates. The interpretation of this hypothesis is suspected to have led many at that time to believe that surface area is the main determinant of middle molecule clearance and if you can increase surface area of a dialyser you could decrease time on dialysis and maintain the same clearances, spurring much focus on improvement of dialyser design to maximize surface area. The square metre per hour middle molecule hypothesis was further refined in 1975 through the proposal of the dialysis index (Babb et al., 1975). A ratio of the calculated weekly amount of solute removal versus the minimum weekly amount of solute to be removed, the dialysis index, attempted to describe the adequacy of a dialysis treatment by the amount of middle molecule removal using dialyser vitamin B_{12} clearance values as a surrogate marker for middle molecules and a minimum clearance threshold of 30 L/week/1.73 m^2 body surface area. This mathematical model which required measurement of vitamin B_{12} levels did not gain widespread acceptance.

Also early in the study of dialysis adequacy in 1971, the litre-kilogram concept was developed (Kopp et al., 1971). Researchers appropriately noticed that up until this point, therapy was commonly defined in terms of time on dialysis alone. This was recognized to be unsatisfactory because equal treatment times did not always mean equal clearance due to changes in various parameters, for example, blood flow variations during the treatment. To overcome this source of error one could measure the total blood volume that goes through the dialyser and adjust the goal amount processed to the weight of the patient. In this way, each patient can be dialysed for a particular duration defined by the number of turns of the roller pump needed to achieve the goal volume rather than on absolute time-based duration. Higher weight would require more blood volume processed, which translated into longer dialysis, therefore, dialysis time was uniquely adjusted to the patient rather than a 'one-size-fits-all' approach. Later, in 1997, a strong correlation was established between blood volume processed by the dialyser and Kt/V_{urea} (Ahmad, 1997). Monitoring blood volume processed presents a simple measure of dialysis that is not dependent upon laboratory analysis. The theory behind this approach may still be valid even when utilizing modern dialysis technology; the dose of dialysis can be more appropriately prescribed when related to the patient's overall volume of clearance rather than focused on any one particular solute.

Further work to normalize the dose of therapy to body volume would continue in 1972 from the University of Minnesota (Kjellstrand et al., 1972). Researchers introduced the term Nkj, which is very similar to the concept of Kt/V where the clearance effectiveness of a dialysis membrane could be determined by plotting the concentration decay as a fraction of the initial pre-dialysis concentration. Describing an equation with terms for the patient's body weight, time of dialysis, and dialyser clearance they proposed a dimensionless variable resulted from $c \times t/W$, where c is clearance, t dialysis time, and W weight. The result of this equation was termed the 'cleared blood number' or Nkj. The authors saw the advantage of the calculated Nkj number as a way to compare different dialysis techniques for substances of differing MW and to adjust for the body weight of the patient.

Popular opinion of the time would subsequently focus specifically on the blood clearance of small molecule urea and study into the adequacy of dialysis would steer away from a focus on middle molecules. Also in 1972, the concept of urea kinetic modelling was introduced (Sargent and Gotch, 1975). Urea kinetic modelling describes mass balance concepts in a complex mathematical analysis where urea concentration is a function of generation rate, volume of distribution, dialysis time, intradialytic interval, dialyser clearance, and residual kidney function. Iterative computer programs are utilized to calculate the most likely solutions to the model input variables. These programs were utilized to determine dose of dialysis necessary to maintain a specific time averaged urea concentration during the National Cooperative Dialysis Study (NCDS) (Lowrie et al., 1981), results of which were published in 1981 as the first attempt at a prospective evaluation of the effect of the dose of dialysis on patient mortality. Subsequent mechanistic analysis of the NCDS (Gotch and Sargent, 1985) and comparison of protein catabolic rate with Kt/V_{urea} would reveal a stepwise relationship between Kt/V_{urea} and outcome and would also highlight the importance of adequate nutrition on outcome. For a protein intake of > 0.8 g/kg/day a Kt/V value of > 0.8 was estimated to provide adequate therapy. To allow some buffer, inadequate therapy was described as a Kt/V of < 0.7 and adequate dialysis > 1.0. Advantage of higher Kt/V values was not demonstrated in this limited data set. Around the same time, prospective studies of the dose of dialysis as measured by the sum of dialysis and residual renal urea clearance and its effect on neurobehavioral parameters, including electroencephalogram measurements, established the minimum dose of dialysis at which neurobehavioral impairments did not occur; 2900 mL/L/week (equivalent to a glomerular filtration rate (GFR) of approximately 12 mL/min). This work should have established a threshold level below which the delivered dose of dialysis could not drop, however, the optimal dose of dialysis remained unclear (Teschan, 1983).

In the late 1980s, what has been described as the 'American tragedy' was recognized by the international nephrology community (Shinaberger, 2001). When comparing dialysis registries, the United States had the highest rate of mortality of all industrialized nations in the world. At an international symposium in Dallas, Texas, in 1989, the reasons for this discrepancy were discussed (Anonymous, 1990). While patient-specific factors and differing transplant rates among nations might explain some of the

variation, it was also noted that dialysis time in the United States was significantly shorter than in other nations. Under-dialysis was suspected to be contributing to the excess mortality of Americans. Many were left to conclude that shortened dialysis procedures justified by urea-based measures of dialysis adequacy were favoured by American practitioners inappropriately.

Most of the work described up until this point has focused on measurements of solute on the blood side of the circuit to determine clearances and adequacy. Many of these determinations rely on complex mathematical models and are limited by often inappropriate assumptions regarding kinetic behaviour of the solute and dialysis membranes. Alternatively, mass of solute removed could be measured directly from the dialysate. This was described in 1982 through the concept of direct dialysis quantification where urea was measured directly from the spent dialysate (Ellis et al., 1984). Under currently utilized dialysis techniques this would require collection of large amounts of dialysate fluid (> 120 L) or utilization of a calibrated dialysate collection device. Assessing the quantity of urea removed as the ratio of urea removal to the total body content of urea rather than relying on clearance methods was also described in the solute removal index (Keshaviah, 1994). Simplified and less cumbersome measurement methods have been presented in terms of mass balance indexes of urea clearance (Raj et al., 1998). Despite their potential, the direct methods of measurement of urea removal in the dialysate did not gain widespread acceptance over blood-based clearance models.

The late 1980s and 1990s were witness to further efforts to refine methods for measurement of dialysis adequacy through analysis of urea clearance by measurement of pre- and post-dialysis urea levels. Crucial to the more widespread use of Kt/V_{urea}, urea kinetic modelling concepts were simplified by development of easy to use logarithmic equations with input variables of pre- and post-dialysis BUN, ultrafiltration volume, and body weight (Daugirdas, 1990, 1993; Daugirdas and Depner, 1994; Garred et al., 1994). Thus, Kt/V could be calculated without the use of complex iterative computer programs. The urea reduction ratio was introduced as an even simpler and easily understandable method for calculating the dose of dialysis (Lowrie, 1991). The urea reduction ratio is still commonly used by dialysis facilities and regulatory agencies worldwide. The concept of clearance and dialysis time product (Kt) was developed out of the realization that volume (V), a proxy for body mass, has survival implications of its own (Lowrie et al., 1999). Therefore, confounding can be present in the calculation of Kt/V urea when dividing Kt (dialysis dose) by patient weight (V).

There was also an improved understanding of the compartmental effects of urea distribution in the body by recognition and quantification of post-dialysis urea rebound. Many methods relied on the 'single-pool' model of urea distribution where urea is evenly distributed in the body water and moves throughout body compartments easily. In dialysis this is known to be an incorrect assumption as urea rebound occurs after dialysis due to the equilibration of various body compartments over the immediate post-dialysis period. This improved knowledge would lead to formulas for equilibrated Kt/V urea; calculations that could allow post-urea level to be drawn immediately after dialysis but still estimate the amount of rebound that will occur during the process of equilibration (Fig. 258.1) (Tattersall et al., 1996; Daugirdas et al., 1999; Smye et al., 1999). The equations for equilibrated Kt/V proved useful for the Hemodialysis (HEMO) study (Eknoyan et al., 2002) performed in 2002.

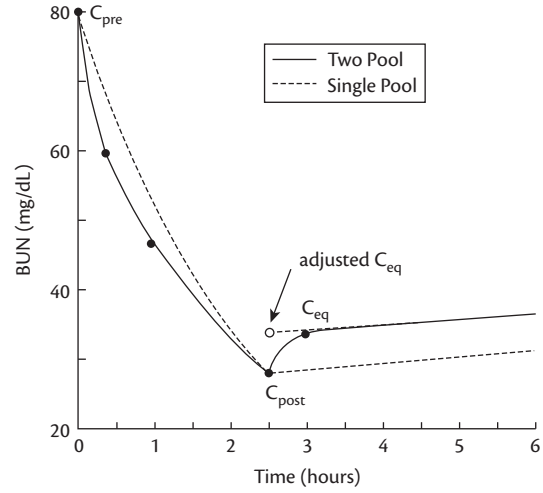

Fig. 258.1 Post-dialysis urea rebound, comparison of the single-pool and the double-pool model.

Reprinted from *Controlled Clinical Trials*, 21/5, Tom Greene, Gerald J. Beck, Jennifer J. Gassman, Frank A. Gotch, John W. Kusek, Andrew S. Levey, Nathan W. Levin, Gerald Schulman, Garabed Eknoyan, Design and Statistical Issues of the Hemodialysis (HEMO) Study, 502–525, Copyright 2000, with permission from Elsevier.

Measurement of Kt/V urea in dialysis patients would be brought into question by recognized limitations, often results were at odds with clinical experience. Again comparing peritoneal dialysis and patients on haemodialysis, a paradox was noted between patients on peritoneal therapies receiving much lower weekly Kt/V compared with patients on haemodialysis with higher weekly Kt/V yet both groups have similar outcomes. While earlier researchers attempted to explain this paradox through the middle molecule hypothesis, others attempted to explain it through the peak concentration hypothesis (Keshaviah et al., 1989). Drawing parallels to aminoglycoside toxicity in native kidneys, the peak concentration hypothesis suggested that more important to uraemic toxicity is the peak concentrations of uraemic toxins as opposed to time averaged concentrations. This theory also exposed the limitations of comparing an intermittent therapy such as haemodialysis with a continuous process such as peritoneal dialysis or residual renal function. Further methods to standardize the Kt/V amongst differing treatment techniques would follow. The equivalent renal urea clearance, described as the ratio of urea generation (mg/min) and the time averaged concentration (mg/mL) was a method developed to convert Kt into a time averaged clearance, in other words, a clearance that would be equivalent to continuous renal function (mL/min) (Casino and Lopez, 1996). This method has the added advantage of adjusting for residual renal function. Further methods to standardize the Kt/V, by describing it as a more continuous clearance similar to native kidney function were subsequently developed and allowed comparisons between differing dialysis modalities and frequencies (Fig. 258.2) (Gotch, 1998; Leypoldt et al., 2004).

Lastly and perhaps most importantly, while urea-based measures of dialysis adequacy have failed to demonstrate a correlation with outcome (Eknoyan et al., 2002), impressive long-term survival rates have been realized in Tassin, France where extended dialysis regimens are utilized and control of blood pressure is superior (Charra et al., 1996). It has been suggested that perhaps survival itself is the

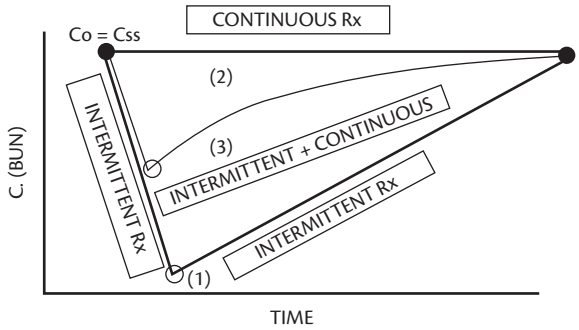

Fig. 258.2 The three concentration profiles in dialysis therapy.
Reproduced with permission from Gotch, F. A. (1998). The current place of urea kinetic modelling with respect to different dialysis modalities. *Nephrol Dial Transplant*, 13 Suppl 6, 10–14.

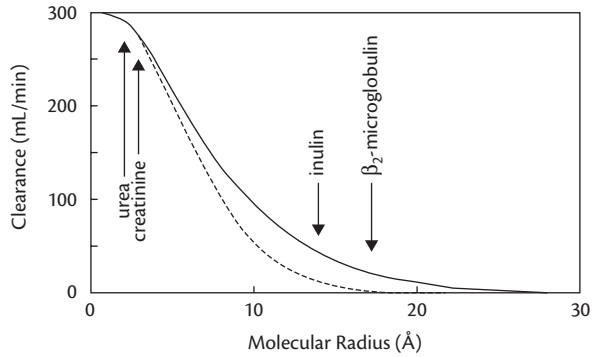

Fig. 258.3 Solute clearance by molecular radius using low-flux (dashed line) and high-flux dialysers (solid line).
Reproduced with permission from Leypoldt, J. K. (2000). Solute fluxes in different treatment modalities. *Nephrol Dial Transplant*, 15 Suppl 1, 3–9.

most appropriate index of dialysis adequacy (Charra et al., 1992). The haemodialysis product, which is the product of the hours per dialysis session and the number of sessions per week squared, has also been proposed as a simple index of dialysis adequacy based upon improved survival seen with longer, more frequent dialysis (Scribner and Oreopoulos, 2002).

Uraemic retention solutes

When renal function declines, the excretory capacity of the kidney fails and the body accumulates substances which would normally be discarded in the urine by glomerular filtration or tubular secretion. In order to understand whether a prescribed dialysis therapy is adequate, it becomes important for the practising clinician to understand the toxins which need to be removed with the therapy. Historically the first solute recognized to be retained in persons with kidney failure was urea, hence the terms uraemia and uraemic syndrome. Urea, easily measureable as BUN, has appropriately served as a surrogate marker for the uraemic condition but it is important to note that urea itself is not responsible for the toxicity witnessed in the setting of the uraemic condition (Johnson et al., 1972). Scientific developments have revealed that numerous compounds of varying size and origin are progressively retained with decline in kidney function, many of these molecules having inherent properties quite different from urea. While work is continuing in this field, at the time of this writing, our knowledge of many of these retention solutes and their removal during dialysis is quite limited. Our knowledge about the source of these toxins is also evolving. It is believed that the majority of uraemic retention solutes are generated during the course of normal protein metabolism or by modifications of amino acids in the gastrointestinal tract by microbial flora, but it is also possible that toxins gain entry into the body via alternate pathways or metabolic processes (Vanholder and De Smet, 1999; Schepers et al., 2010; Aronov et al., 2011).

Uraemic retention solutes have classically been categorized based on MW. Size comparison has utility in evaluating expected solute clearance (also known as dialysance) during dialysis. As will be discussed in detail below, the removal of a solute from the body during dialysis is dependent on many modifiable factors such as membrane characteristics (Fig. 258.3), dialysis technique (Figs 258.4 and 258.5), and patient specific factors. Dialysance of a particular solute is also affected by the unique characteristics of the solute and its resident environment such as MW, solubility, shape, charge, protein binding, Gibbs–Donnan equilibrium, and volume of distribution. When assessing the adequacy of dialysis it is important to recognize that many uraemic retention solutes, particularly middle molecules, large molecules, and protein-bound molecules, do not behave in the same manner as urea during dialysis (Figs 258.3, 258.4, and 258.5) (Vanholder et al., 2003).

Small molecules

Small molecules, with a MW (g/mol) of < 500, pass relatively easily across dialysis membranes. Movement of small molecules during dialysis is predominantly dependent upon diffusion; therefore, clearance of small molecules is governed largely by solute gradients established by the amount of blood (Qb) and dialysate (Qd) that is delivered to the dialysis membrane. Urea (MW 60) is the prototypical small molecule that accumulates in renal failure. Urea is the product of protein metabolism. During normal metabolic processes breakdown of protein leads to the formation of ammonia. Ammonia is toxic to the body if allowed to accumulate. The liver handles the detoxification of ammonia by converting it to urea through the urea cycle. Urea can then be excreted by the kidneys. In other words, urea is the body's way of getting rid of

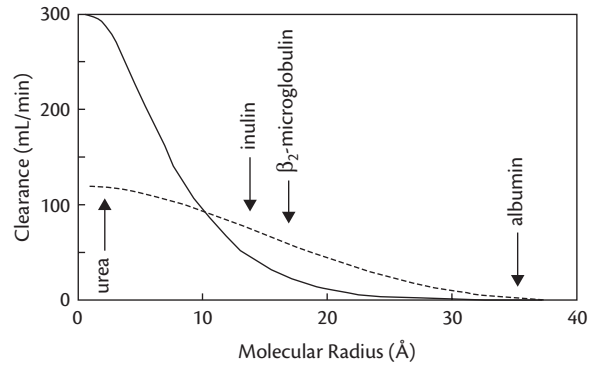

Fig. 258.4 Solute clearance by molecular radius during haemodialysis (solid line) compared with post-dilution haemofiltration (dashed line).
Reproduced with permission from Leypoldt, J. K. (2000). Solute fluxes in different treatment modalities. *Nephrol Dial Transplant*, 15 Suppl 1, 3–9.

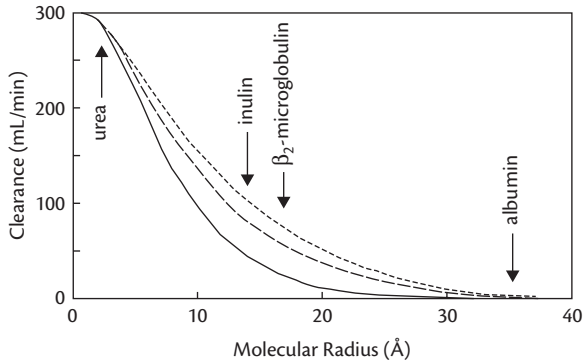

Fig. 258.5 Solute clearance by molecular radius during haemodialysis (solid line) and haemodiafiltration with ultrafiltration rate of 80 mL/min (dashed line) and 120 mL/min dotted line.

Reproduced with permission from Leypoldt, J. K. (2000). Solute fluxes in different treatment modalities. *Nephrol Dial Transplant*, 15 Suppl 1, 3–9.

ammonia which would otherwise be toxic. Recall that the native kidney also rids the body of some ammonia through the excretion of acid (ammoniagenesis); however, the bulk of ammonia generated in the body is dealt with by the liver and urea cycle. Urea is sometimes described as an 'ineffective osmole'. This terminology is often a source of confusion for many practitioners. It should be noted that this is not because urea does not exert any osmotic pressure, just like any particle dissolved in fluid, it does have osmotic pressure. What the term 'ineffective osmole' refers to is the ability of urea to distribute completely in the total body water passing cellular membranes with relative ease. In this way, it does not exert an osmotic pressure between the intracellular and extracellular space like many other small molecules, for example, sodium. However, with the artificial dialysis procedure, gradients do develop between body compartments and urea can exert osmotic pressure which can become clinically significant. This is evidenced clinically after rapid clearance of the vascular space of urea subsequently promoting hypotension, haemodynamic collapse, or intracellular oedema (cerebral oedema/dialysis disequilibrium syndrome). Urea movement between body compartments, such as between the interstitium and vascular space, can be affected by patient specific factors. For example, lower blood pressure before dialysis leads to slower urea transfer and oedematous states have been associated with unpredictable rates of urea transfer (Kjellstrand et al., 1994). Examples of some other small molecules that can accumulate during kidney failure are creatinine (MW 113), phosphates (MW ~ 95), and electrolytes such as sodium (MW 23) and potassium (MW 39) (Table 258.1).

Table 258.1 Examples of uraemic retention solutes and the methods which are currently available to increase their removal (Vanholder et al., 2003, 2008; Schepers et al., 2010; Aronov et al., 2011)

Solute type	Size (Da)	Examples	Most effective means of removal
Small molecules	<500	Urea, creatinine, sodium, potassium, uric acid, oxalate, asymmetrical dimethylarginine	Diffusive clearance (dialysis) Increase the speed of dialysis—faster blood flow (Qb) and/or dialysate flow (Qd)
Middle molecules	500–60,000	3-deoxyglucose β_2-microglobulin *p*-Cresol Indoxyl sulphate Advanced glycation end products Oxidation products Cytokines Interleukins Cystatin C Atrial natriuretic peptide Tumour necrosis factor κ and λ light chains Parathyroid hormone Dinucleoside polyphosphates	Increase dialysis time Increase dialyser surface area, pore size, pore density (high-flux dialyser) Convective clearance (haemofiltration)
Protein bound	Variable	Fructoselysine Hippuric acid Homocysteine Indoxyl sulphate Retinol binding protein Phenol *p*-Cresol	Increase dialysis time Increase dialysate flow Sorbent technology Albumin dialysis
Gut derived	Variable	Phenylacetyl-l-glutamine 5-hydroxyindole Indoxyl glucuronide *p*-Cresol Indoxyl sulphate Urea	Nutritional modifications Maintenance of GI motility Potential in the future: Oral sorbents, absorbents Antibiotics or probiotics

Middle molecules

Classically, middle molecules were described to have MWs in the range of 300–2000 but more recent classifications have simplified the issue by adding all compounds of MW 500–60,000, the upper number of this range being the approximate size barrier of the glomerular basement membrane (Babb et al., 1981; Vanholder et al., 2003). By nature of their size relative to the dialysis membrane pore size and pore density, middle molecules have a more limited dialysance than small molecules. Most middle molecules identified to be toxic in the uraemic condition are peptides of various shape, size, charge, and level of protein binding; all properties which make their kinetic behaviours during dialysis unique (Mann et al., 2002). The classic, prototypical surrogate middle molecule is vitamin B_{12} (MW 1470) (Babb et al., 1975). Another larger middle molecule frequently measured for research purposes is beta-2-microglobulin (MW 12,000). Clearance of middle molecules is dependent upon membrane surface area, dialysis time, and membrane pore size (Table 258.1) (Babb et al., 1971; Mandolfo et al., 2003). Middle molecules are only removed during dialysis after passage through larger pores on the dialysis membrane. There are relatively few large pores in most standard dialysers, thus, both surface area and time are seen as more important in middle molecule clearance. This compares

to small molecule clearance, where solute has access to more pores leading to more dependence on flow rates or speed of dialysis. Dialysers with a higher density of large pore sizes (high-flux dialysers, super high-flux dialysers, or protein leaking dialysers) are more efficient at middle and large molecule removal (De Vriese et al., 2003; Evenepoel et al., 2006). Convective therapies, particularly in the post-filter dilution mode, are considered more effective at removal of middle molecules than purely diffusive methods, probably related to solute drag during convective clearance (Tattersall, 2007). There is some suggestion that movement of middle molecules from the extravascular to intravascular space occurs at a slower rate relative to the movement of small molecules such as urea, another factor contributing to the need for increased duration of dialysis time in order to achieve middle molecule clearance (Popovich et al., 1975; Clark et al., 1999). Membrane absorption may also play a significant role in the clearance of middle molecules, particularly during the initial stages of dialyser use (Wernert et al., 2006).

Protein binding

Uraemic retention solutes do not exist exclusively as the nephrologist would prefer them; as free and unbound compounds floating in the plasma space. Rather, they are distributed throughout the body, a fraction existing in free form in the plasma, but the majority bound and sequestered by various proteins and body compartments (Watanabe et al., 2011). The binding of a uraemic toxin to the predominant plasma protein, albumin (MW 66,000), effectively makes it impermeable to the dialysis membrane when compared to free unbound solute (Lesaffer et al., 2000). Examples of commonly studied protein-bound uraemic retention solutes include *p*-cresol and indoxyl sulphate (Table 258.1) (Brunet et al., 2003; Martinez et al., 2005; Meijers et al., 2009). Removal of protein-bound uraemic toxins during dialysis is typically slow and incomplete. Even so, there are some strategies that can be employed to improve removal of protein-bound toxins. Clearance of some protein-bound uraemic retention solutes has been shown to increase with increasing dialysate flow rate (Meyer et al., 2004; Luo et al., 2009). The observation of dependence of protein-bound solute removal on dialysate concentration points towards a predominant reliance on diffusion of free molecule for clearance. This observation appears to agree with others that have demonstrated equivalent removal of substances that are protein bound during comparable diffusive methods of clearance and lack of improvement with the addition of standard volume convective therapies (Krieter et al., 2010). This is not to say that convective therapies do not clear protein-bound uraemic retention solutes; particularly large-volume convective therapies (60 L) seem effective in increasing removal of protein-bound uraemic retention solutes, perhaps again by decreasing the concentration of free unbound solute (Bammens et al., 2004). Various exciting and unique strategies have been suggested to improve removal of protein-bound substances during dialysis such as sorbent-based therapies and albumin dialysis (Stange et al., 1993; Meyer et al., 2007; Sarnatskaya et al., 2007; Kruse et al., 2011). These innovative approaches to dialysis are currently not the standard of care but may become more important as technology progresses.

Gut-derived solutes

Uraemic retention solutes can be derived from exogenous intake, endogenous production, or from gastrointestinal microbial metabolism. Examples of sources of exogenous intake include normal food nutrients, preservatives, known environmental toxins, or drugs (Table 258.1). Alternatively, production of solute could be endogenous as seen in compounds, such as urea, formed during protein metabolism. Flora metabolism of various compounds such as amino acids and fermentation of various sugars is also likely to play a role in the production of uraemic retention solutes. Previously mentioned protein-bound uraemic compounds *p*-cresol and indoxyl sulphate are, at least in part, produced as a result of microbial processing of amino acids in the colon. Indole is a product of metabolism of amino acid tryptophan and is later metabolized to indoxyl sulphate in the liver. Phenolic compounds such as *p*-cresol are a result of breakdown of phenylalanine (Schepers et al., 2010). In a study of end-stage renal disease (ESRD) patients post colectomy compared with ESRD patients with a normal colon, composition of uraemic retention compounds was different, suggesting a colonic contribution, some of which has yet to be characterized (Aronov et al., 2011). Many of these seemingly gut-derived uraemic retention compounds are not easily removed during the dialysis process and therefore present a future target for improvement in dialytic therapy. Oral absorbents and agents to modify gastrointestinal bacterial flora or motility have also been proposed as a potential treatment strategy (Simenhoff et al., 1977; Yokoyama et al., 1982; Hida et al., 1996; Evenepoel et al., 2009; Goto et al., 2011).

Solute removal during dialysis

Haemodialysis is often considered by clinicians as a form of 'renal replacement therapy'. Over the years of witnessing outcomes in patients with extended dialysis vintage it has become clear that the term 'renal replacement therapy' is a misnomer. In fact, haemodialysis does not replace all functions of the native kidney. For example, certain endocrine and immunologic tasks of the native kidney are lost in the state of renal failure and remain so despite the dose of dialysis delivered. The key role of haemodialysis is to provide removal of uraemic retention solutes from the body, an enterprise which has allowed for effective treatment of the uraemic syndrome. This technique is limited in that it does not replace the entirety of native kidney function but nevertheless remarkable because in the absence of kidney function and clearance provided by dialytic methods, the end-stage uraemic condition would be fatal.

Understanding molecular movement is relevant to the understanding of solute removal during haemodialysis. Diffusion describes movement of solute across a semipermeable membrane from an area of higher concentration to an area of lower concentration. Diffusion of solute across the dialyser and into the dialysate is the predominant method of solute clearance that occurs during standard haemodialysis. Convection describes the movement of molecules suspended within fluids and is also often termed 'solute drag'. During convection a given amount of solute which is dissolved in a given volume of solvent is cleared after a pressure gradient forces the solvent through the pores of a semipermeable membrane. If the solute is smaller than the pore size of the membrane it will be dragged along with the solvent into the effluent. Convective clearance is at play during routine ultrafiltration and also if haemofiltration is utilized, the latter example usually representing a larger volume of clearance necessitating replacement fluid administration compared to the relatively minimal convective clearance seen with routine ultrafiltration for volume management. During both diffusion and convection, movement of molecules can

be dependent upon membrane pore size with molecules that are larger than the pore not passing the membrane. The sieving coefficient describes the membrane passage of a certain solute and is determined by dividing the solute concentration in the effluent by the solute concentration in the blood. Solute with a sieving coefficient of 1 (e.g. sodium) easily passes the dialysis membrane whereas a sieving coefficient of 0 indicates no movement across the membrane (e.g. albumin in a standard flux haemodialysis membrane).

Clearance concept in haemodialysis

The definition of clearance is the volume from which a substance is completely removed usually specified per unit time (mL/min). Clearance in the native kidney is typically described in terms of GFR (mL/min). The GFR is regulated by the mechanical forces across the capillary wall such as capillary wall transmural pressure, oncotic pressure, and by the native properties of the capillary wall endothelium such as surface area and pore size. The hollow fibre capillary in a typical haemodialyser is subject to similar forces. Clearance during dialysis is governed by dialyser transmembrane pressure, oncotic forces and membrane specific characteristics such as surface area, membrane thickness, and pore size. Clearance of a solute during dialysis is often termed dialysance. During haemodialysis the physiological processes of diffusion, convection (ultrafiltration) and to a lesser extent membrane surface absorption all play a role in the clearance of uraemic retention solutes. Note that the volume of a substance cleared has a relationship with time where increased time will lead to larger volume of clearance if the rate of removal is kept constant. It is also important to recognize that clearance does not describe the amount (mass) of solute removed, it simply describes a volume that has been liberated of a particular solute, usually expressed per unit time.

Mass balance and clearance

Clearance equations as applied to native kidney function and to dialysis quantification (dialysance) are a derivation of mass balance relationships. The law of conservation of mass states that matter can be neither created nor destroyed. In the human body mass balance can be appreciated over time if the generation, intake, and output of such mass with relation to the body volume are described. In the uraemic condition, the change (Δ) in mass of a particular uraemic retention solute over time will be equal to the mass input into the body plus mass generated by the body minus the mass that has left the body:

$$\Delta \text{Mass}_{\text{body}} = \left(\text{Mass}_{\text{input}} + \text{Mass}_{\text{gen}} - \text{Mass}_{\text{output}}\right)\Delta t \qquad (258.1)$$

The above relationship can be expressed as applicable to uraemic retention solute removal by the native kidney or dialysis (Gotch, 1998). $\text{Mass}_{\text{body}}$ is equal to the concentration in the body multiplied by volume of distribution, $\text{Mass}_{\text{input}}$ into the body can be lumped together with mass generated (G), and $\text{Mass}_{\text{output}}$ is equal to the concentration multiplied by the clearance:

$$\Delta\left(C * V\right) / \Delta t = G - K * C \qquad (258.2)$$

Rewritten as a derivative:

$$V\left(dC\right) / dt + C\left(dV\right) / dt = G - K * C \qquad (258.3)$$

This equation describes V as the volume of distribution, C concentration, t time, G generation rate, and K clearance. Note that in steady-state conditions, where the concentration does not change over time and the volume does not change over time, the left side of Equation 258.3 is equal to zero. Therefore, after rearrangement of the equation, the relationship between concentration, generation and clearance is appreciated in the steady state:

$$K = G / C \qquad (258.4)$$

As can be seen from this equation, clearance of uraemic solutes is inversely proportional to concentration in the steady state. The above observation is useful in the quantification of continuous clearances such as native kidney function and peritoneal dialysis. For example, in the case of creatinine, a uraemic retention solute with a constant generation rate, it can be seen that if the glomerular filtration rate (K) was to drop by half, the concentration of creatinine would double. It is from this relationship that the commonly utilized renal clearance equation is derived:

$$\text{Volume cleared} = UV / P \qquad (258.5)$$

where U is urine concentration, V is urine volume, and P is plasma concentration. Again, this equation assumes that the patient is in the steady state, without any change in solute concentration over time. One could see how volume cleared during dialysis can be calculated similarly to native kidney clearance by substituting dialysate volume (mL) for V and dialysate solute concentration for U. Adding time to the equation would yield a clearance (mL/min) or in the case of dialysis, a dialysance (mL/min). Unfortunately, this simple relationship would only apply to the steady-state condition, a stipulation that is not satisfied with intermittent dialysis sessions.

Describing intermittent clearances provided with commonly utilized haemodialysis techniques as a clearance per treatment rather than a continuous clearance synonymous to GFR requires a different approach. Firstly, collection of the entire volume of dialysate as a surrogate for the urine during a treatment is cumbersome and unrealistic in clinical practice. Subsequently, the calculation of clearance based on measures of dialysate concentration has largely been ignored. Secondly, the steady-state condition is not satisfied utilizing intermittent methods of dialysis. Urea is rapidly removed from the body at clearances that far exceed the capacity of a normal kidney during dialysis followed by a period of slow accumulation during the interdialytic period (Fig. 258.1). Popular methods of measurement of dialysis adequacy have attempted to work around the former shortcoming by focusing on blood side measurements to estimate clearance as a measure of the dose of dialysis. The latter restriction has been addressed by mathematical models attempting to correct for different frequencies of dialysis treatment by converting the intermittent nature of haemodialysis into a renal equivalent continuous clearance such as time averaged urea concentration and standard Kt/V (described below).

Dialyser clearance and KoA

Native kidneys vary in their efficiency of removal of the daily solute load amongst different persons by virtue of differences in GFR. Similarly, differing dialysers can vary in their efficiency of removal of uraemic retention solutes. With the artificial kidney, the term efficiency refers to a dialyser's ability to facilitate removal of uraemic

retention solutes. High-efficiency dialysers have membrane properties that allow them to be more effective at removal of solute compared with low-efficiency dialysers. The expected clearance of a dialyser can be determined by *in vitro* studies and usually is provided by the manufacturer in dialyser specification sheets in the form of calculated clearances of various solutes (urea, creatinine, phosphorus, vitamin B_{12}) at various blood flow rates (Qb 200, 300, 400, 500 mL/min) and a pre-set dialysate flow rate (usually 500–800 mL/min). The clearance provided by a dialysis membrane is dependent upon various membrane characteristics such as surface area, pore size, pore density, and membrane thickness. These clearance values can be useful for comparison of the expected clearances provided by different dialysers with urea representing small molecule clearance and vitamin B_{12} representing middle molecule clearance.

Another method for comparison of the performance of different dialysers is provided by the KoA urea. This is a theoretical clearance of urea provided at infinite blood and dialysate flows. In other words, the KoA urea gives you an idea of the maximum ability of the dialyser to clear small molecule urea when not limited by blood and dialysate flow rates. In this way, it is a reflection of clearance provided by membrane properties alone such as surface area and pore size. A higher value for KoA indicates a more efficient membrane. Manufacturers of haemodialysers will usually provide KoA urea values, calculated using Equation 258.6 (Michaels, 1966):

$$\begin{aligned}\text{KoA} &= \left[Q_b * Q_d\right] / \left[Q_b - Q_d\right] * \ln\left[\left(1 - K_d / Q_b\right) / \left(1 - K_d / Q_d\right)\right] \text{KoA} \\ &= \left[Q_b * Q_d\right] / \left[Q_b - Q_d\right] * \ln\left[\left(1 - K_d / Q_b\right) / \left(1 - K_d / Q_d\right)\right]\end{aligned} \quad (258.6)$$

where Q_b is the blood flow, Q_d dialysate flow, and K_d the dialyser clearance. The KoA equation allows the calculation of expected clearances using a dialyser at varying blood and dialysate flows, however, it should be recognized that the manufacturer provided clearance values can be useful to help compare performance, but cannot reliably be used to calculate the dose of dialysis. The problem with relying on KoA to calculate the dose of dialysis is that it does not take into account potential differences between delivered and prescribed dose of dialysis. Also, the complex relationship seen in combination convective and diffusive methods of clearance is ignored. Further, blood flow (Q_b) needs to be corrected for solute containing blood water. Clearance will be altered as haematocrit increases and less water is available for diffusion. This limitation is more of an issue in modern times after the introduction of erythropoietin agents for the treatment of anaemia which have corrected the majority of the deficit in haematocrit, a situation that was not the case when original experiments of KoA took place. KoA measurements are often performed *in vitro* with solution (not blood) which tends to overestimate clearances. While originally believed that KoA is constant for a given dialyser, it has more recently been shown that KoA can vary based on the dialysate flow rate, possibly related to differences in dialysate flow distribution (Bhimani et al., 2010).

Urea-based measures of dialysis adequacy

Popular methods to quantify the dose of dialysis have mostly focused on blood measurement of urea before and after dialysis. Easily measured urea values obtained before and after dialysis can be input into mathematical constructs which result in a dialysis index that can then be used to assess the adequacy of dialysis by quantifying the amount of dialysis delivered. The ideal dialysis index is simple, intuitive, works with different dialysis modalities, accounts for residual renal function, and, most importantly, is validated against patient outcomes. The methods of dialysis adequacy assessment described below each meet some of these criteria but no single dose measure has satisfied all.

Methods for measurement of blood urea nitrogen

Accurate measurement of pre- and post-dialysis BUN level is important to ensure proper interpretation of dialysis adequacy. The pre-dialysis urea sample should be drawn prior to the patient being placed on dialysis and without any influence of dilution from heparin or saline. This is easily accomplished immediately after placement of the dialysis needles if the patient has an arteriovenous access. If the patient has a catheter, care should be taken to discard the lumen dwell content, a discard volume of 5 mL is usually sufficient. The post-dialysis sample should be drawn at the end of the dialysis procedure. In the post-dialysis period there is a time of equilibration of urea between various body compartments. The first and shortest period of equilibration is known as access recirculation. Access recirculation occurs over a matter of seconds when previously dialysed blood which has returned to the venous portion of the dialysis access is taken up by the arterial needle and sent back through the extracorporeal circuit, decreasing the efficiency of the dialysis procedure. This phenomenon takes place in the dialysis access itself and is more predominant in the setting of a dysfunctional dialysis access and high blood flows. Keeping the possibility of access recirculation in mind, methods have been developed to help ameliorate falsely low BUN levels due to access recirculation. One such method is the slow-blood-flow method (Hemodialysis Adequacy 2006 Work Group, 2006). At the completion of dialysis, dialysate flow and ultrafiltration are turned off (or if unable to turn off ultrafiltration completely the ultrafiltration rate can be reduced to 50 mL/hour), the blood pump is slowed to 100 mL/min for 15–30 seconds, and the sample is subsequently obtained. Alternatively, the stop-dialysate-flow method can be utilized (Geddes et al., 2000). With this method dialysate flow and ultrafiltration are turned off, 3 minutes are allowed to pass without any changes in the blood flow rate and blood is subsequently sampled. The idea behind this method is that by stopping the dialysate for the 3-minute period, the dialysate compartment will equilibrate with the blood compartment yielding identical dialyser blood inlet and outlet concentration. Both methods have been found to be equally effective in eliminating access recirculation. The stop-dialysate-flow method may yield slightly lower indexes of dialysis adequacy if a significant amount of tissue equilibration of urea occurs in the 3-minute period when dialysate flow is stopped (Hemodialysis Adequacy 2006 Work Group, 2006).

Urea reduction ratio

The amount of urea removed during a dialysis session can be described as a fractional reduction of urea, calculated using Equation 258.7:

$$\text{URR} = C_0 - C / C_0 \quad (258.7)$$

where C_0 is the urea concentration before dialysis and C is the urea concentration at the end of dialysis (Lowrie, 1991). The result multiplied by 100 will yield a percentage urea reduction. The urea

reduction ratio is simple, intuitive and has been embraced as a measure of dialysis dose adequacy by various regulatory agencies. While appropriate for the measurement of intermittent clearances as seen in standard haemodialytic therapy, it is not applicable to continuous clearances such as peritoneal dialysis and comparison between haemodialysis strategies of differing frequency and duration would be limited. This is because when the level of kidney replacement increases or continuous clearance is provided, the urea reduction ratio trends towards zero. As can be seen in the equation above, there is no accounting for residual renal function, ultrafiltration, or urea generation during dialysis. In contrast to other indexes of dialysis adequacy, the urea reduction ratio is not normalized to body size.

The urea reduction ratio has not been validated as a reliable measure of outcome in prospective studies. Retrospective analyses have been able to demonstrate an inverse relationship between urea reduction ratio and odds for death (Owen et al., 1993). However, this inverse relationship does not seem to hold up in patients with high urea reduction ratios as there seems to be a paradoxical relationship between high urea reduction ratio (> 75%) and increased risk of death. This has been demonstrated in a reverse J-shape curve between mortality and urea reduction ratio (Chertow et al., 1999). This paradoxical relationship may be explained by nutritional factors and patient body size. Mortality in dialysis patients is strongly correlated with body weight, with larger patients demonstrating survival advantage. There is an inverse relationship with urea reduction and weight where patients with lower body weight more frequently have elevated urea reduction ratios (Frankenfield et al., 1999; Kopple et al., 1993). These data indicate that the urea reduction ratio should not be interpreted as a predictor of outcome alone without taking into account the confounding effect of protein calorie malnutrition or body size. There also seems to be differences in the relationship between urea reduction ratio and mortality among different demographic groups (Owen et al., 1998). These observations have drawn into question the utility of the urea reduction ratio as a measure of outcome.

Kt/V

Imagine the body as a container, or box, within which solid and liquid resides. The solid we will ignore for now and instead focus on the liquid because the liquid, or total body water, is the space in which urea resides and is of interest to the clinician performing dialysis. Now imagine that this box containing water with urea dissolved in it is connected to a circuit in series with a dialyser. As the liquid is pumped out of the box and through the dialyser, urea is removed or cleared from the liquid which is then returned to the box. Over time, the urea level in the box will fall, however the rate of removal of urea will slow as the concentration of urea in the box falls (see indirect relationship between clearance and concentration as described in Equation 258.4). We can call the clearance, or volume from which urea is completely removed over time, K, mL/min. If we multiply this clearance (K, mL/min) by the by time (t, min) then we are left with a volume cleared (mL) or total volume taken from the box that was cleaned of urea. If the box contains 42 L (approximate total body water of a 70 kg man), providing a Kt of 42 L would mean that we have cleared a volume equal to the volume of the box, though it does not mean that the fluid in the box is free of urea. This is because over time the efficiency of the clearance will decrease with decreasing concentration of urea in the box. Therefore, the curve of urea concentration in the box plotted against time would display

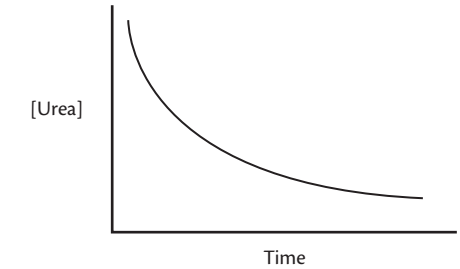

Fig. 258.6 The urea disappearance curve during haemodialysis in a single-pool model follows an exponential pattern.

an exponential pattern where the concentration of urea in the box approaches zero over time (Fig. 258.6). If Kt (mL) is divided by volume in the box (V, mL) then the result is a dimensionless expression of Kt/V. The Kt/V_{urea} in this situation can be thought of as the number of times that a volume equal to the volume of the box is completely cleared of urea in a given dialysis session. In this example, a Kt/V equal to 1 would mean that 42 L was cleared of urea. In order to express the fractional reduction of urea with a dialysis treatment, a kinetic equation can be described by the exponential curve of urea disappearance during dialysis in a single-pool recirculating model (Gotch and Sargent, 1985; Daugirdas, 1995):

$$C = C_0 e^{-Kt/V} \tag{258.8}$$

$$Kt/V = -\ln\left(C/C_0\right) \tag{258.9}$$

where C is the post-dialysis urea concentration, C_0 is the pre-dialysis urea concentration, K is clearance, t time, V volume of distribution of urea, *e* is a mathematical constant—the base of the natural logarithm, approximately equal to 2.71828, also known as Euler's number or the limit of $(1 + 1/n)^n$—and ln is the natural logarithm or $\log_e(x)$. The natural logarithm of number x is the power to which *e* would have to be raised to equal x, that is, $\ln(e^x) = x$. This equation is the simplified solution to the differential equation listed in Equation 258.3. It effectively models the removal of a substance from the body where that substance decreases in an exponential fashion, describing the disappearance curve of urea during a dialysis session.

The concept of single-pool (spKt/V) urea relies on the assumption that urea is evenly distributed in a single pool of body water which has even access to the dialyser. Due to the extremely efficient nature of a modern dialysis treatment session where urea is removed from the plasma space at a rate that exceeds equilibration from outside the plasma space, this assumption no longer holds true. In deference to the single-pool model, urea is distributed in varying concentration throughout the body during dialysis, evidenced by the rebound phenomenon of equilibration at the end of dialysis when urea moves from tissue areas of lower perfusion back into the vascular space. This is sometimes referred to as two-compartment distribution or the double-pool model where one compartment is considered the vascular space and the other compartment is everything outside of the vascular space (Daugirdas and Smye, 1997). The original logarithmic equations of spKt/V are also flawed in that they do not take into account any fluid removed during the dialysis procedure, which would have an effect on the size of the volume of distribution and alter the concentration of the urea which in turn affects the clearance. Further,

the simplified single-pool model described in Equation 258.9 does not account for urea generation, albeit minimal, that occurs during the dialysis session. More advanced formulas have attempted to account for fluid removed with dialysis and estimate urea generation during dialysis (Daugirdas, 1990; Garred et al., 1994). Listed in Equation 258.10 is an example of a commonly utilized formula for single-pool Kt/V, often referred to as a second-generation equation (not to be confused with the double pool-model, discussed below under equilibrated Kt/V) (Daugirdas, 1993):

$$\text{spKt / V} = -\ln\left(\text{R} - 0.008 * \text{t}\right) + \left(4 - 3.5 * \text{R}\right) * \text{UF / W} \qquad (258.10)$$

where R is the post-dialysis BUN divided by pre-dialysis BUN, t is the dialysis session length in hours, UF is the ultrafiltrate volume in litres, and W is the post-dialysis weight in kilograms. In general, a single-pool Kt/V of 1.2 is equivalent to a 65% urea reduction. Most clinical guidelines recommend achieving a minimum single-pool Kt/V urea of 1.4 (European Best Practice Guidelines Expert Group on Hemodialysis, 2002; Hemodialysis Adequacy 2006 Work Group, 2006).

The main disadvantage of using simplified single-pool equations for calculation of dialysis dose is that unlike formal urea kinetic modelling, useful information about protein catabolic rate is not resulted. Information regarding discrepancy between delivered and prescribed dose may not be appreciated in the way they would with urea kinetic modelling. The equation is also prone to error if utilized outside standard thrice-weekly 4-hour dialysis in regimens of short, long, or frequent dialysis. To accurately measure the spKt/V using the above equations, the decrease in BUN during the dialysis treatment must be significant otherwise error is introduced due to mathematical variance. This inherent property makes the spKt/V models above inappropriate for frequent haemodialysis regimens such as daily or nocturnal dialysis. Further, these equations would not be appropriate to calculate continuous clearances such as delivered with peritoneal dialysis where the urea concentration remains at a relative steady state. In such steady-state situations, simple clearance calculations can be undertaken because the volume of effluent dialysate is known. Lastly, there is no adjustment for urea equilibration, or the rebound elevation of urea that occurs after dialysis if the post-dialysis BUN level is drawn as is routinely done, immediately following the treatment session.

Equilibrated Kt/V

In order to circumvent the problem of the unrealistic single-pool model of urea distribution, dialysis samples could be drawn an hour after dialysis to allow adequate time for urea to equilibrate equally between all body compartments (Fig. 258.2). This approach takes time and is not practical for the typical dialysis staff or patient. The equilibrated (eKt/V), occasionally referred to as the double-pool Kt/V, was developed to estimate and adjust the single-pool Kt/V for post urea rebound in lieu of the more painful, time consuming alternative.

Post-dialysis urea rebound is largely believed to have three phases, access recirculation, cardiopulmonary recirculation, and urea redistribution from less accessible body compartments. The phenomenon of disparate urea content in various body compartments is particularly evident with the use of an arteriovenous dialysis access. The first phase, access recirculation, usually resolves in a period of 10–15 seconds after the blood pump is stopped or slowed to 50–100 mL/min (Kapoian et al., 1997). Cardiopulmonary recirculation refers to the distribution of dialysed blood to the heart and quickly back to the dialysis access through the cardiopulmonary circuit, bypassing slower areas of circulation that would allow for more even distribution of urea. The effect of cardiopulmonary recirculation is largely absent about a minute after dialysis (Schneditz et al., 1992). The third component, the slow movement of urea from areas of lower perfusion and cellular spaces, can take up to 30–60 minutes following the completion of dialysis, depending upon the patient (Tattersall et al., 1996).

Urea rebound is variable between patients. Dialysis related factors such as blood flow, amount of ultrafiltration performed, and patient-related factors such as age, heart function, muscle mass, and blood pressure can affect the amount of urea rebound experienced (Pedrini et al., 1988; Daugirdas et al., 2004). For example, muscle is thought to contain about 60% of the total body water yet blood flow to the muscle during dialysis is relatively low which contributes to a rebound in urea level after dialysis (Daugirdas, 1995). In contrast, organs receive a large amount of cardiac output but relatively less body water. Due to these gradients established during dialysis, in the post-dialysis period when organ blood combines with muscle blood, one would expect a urea rebound. The rate of dialysis can affect the amount of urea rebound. Rate of dialysis can be expressed as K/V. Higher K/V would be more prone to rebound phenomena. The difference between single-pool Kt/V and actual Kt/V after equilibration is allowed to occur has been described in Equation 258.11 (Daugirdas and Schneditz, 1995):

$$\Delta\text{Kt / V} = a\left(\text{K / V}\right) - b \qquad (258.11)$$

Values of *a* and *b* can be determined through linear regression analysis of ΔKt/V and K/V based on pre- and post-dialysis blood urea levels using Equation 258.10 to calculate Kt/V and dividing the result of equation 10 by time (t) to calculate K/V. The variable *a* represents the slope of the line, and *b* the intercept. The slope of the line, *a*, is dependent upon the degree of urea redistribution in the body among intracellular/extracellular space and various organ compartments and upon blood flow to muscle and bone based on predictions of cardiac output and vascular access flow:

$$\Delta\text{Kt / V} = 0.6\left(\text{K / V}\right) - 0.03 \qquad (258.12)$$

In the following equations, time of dialysis and the value of the single-pool Kt/V are added which converts the change in Kt/V to an adjusted, equilibrated Kt/V. These equations are commonly utilized to calculate the equilibrated Kt/V (Daugirdas, 1995):

$$\text{eKt / V} = \text{spKtV} - 0.6\left(\text{spKtV / T}\right) + 0.03 \qquad (258.13)$$

$$\text{eKt / V} = \text{spKtV} - 0.47\left(\text{spKtV / T}\right) + 0.02 \qquad (258.14)$$

where spKtV is the result of the single-pool Kt/V as calculated from Equation 258.10 above and T is equal to dialysis time in hours. The difference in urea distribution during cardiopulmonary recirculation between different dialysis access types necessitates two equations. Equation 258.13 should be used in patients in which cardiopulmonary recirculation is present (those with an arteriovenous access) and Equation 258.14 is for patients where there is no arterial

mixing of blood and measurements of urea are strictly venous, such as patients with a typical venous dialysis catheter. Alternative methods to calculate equilibrated Kt/V are discussed elsewhere (Smye et al., 1994; Tattersall et al. 1996; Leypoldt et al., 2004).

Practice guidelines recommend a minimum equilibrated Kt/V ≥ 1.2 which is roughly equivalent to a single-pool Kt/V of 1.4 (European Best Practice Guidelines Expert Group on Hemodialysis, 2002). This seems to be an appropriate goal for the prevention of under-dialysis even though there is no evidence that eKt/V correlates strongly with outcome when in the range of 1.1–1.5 (Tattersall et al. 1996). The key advantage of the equilibrated Kt/V is avoidance of the error generated in single-pool methods which overestimate of dialysis dose due to urea rebound. This advantage is particularly evidenced when the treatment time is short and the dialysis technique efficient (short, fast dialysis). It should be recognized that the equation provides an approximation based on population data and the coefficients involved are not always accurate for every patient. For example, if blood flow to the muscle is lower in a particular patient then the coefficient of 0.6 should be less. Other limitations of the single-pool model described above are still applicable to the equilibrated Kt/V and should be kept in mind during interpretation of the results.

Standard Kt/V

The methods described above have utility in describing the kinetics of urea removal during an intermittent dialysis session and are predominantly designed for thrice-weekly intermittent dialysis. More frequent methods of dialysis require a different approach where the dose of dialysis is expressed independently of the frequency of dialysis as a continuous clearance. This concept relies on the steady-state assumption where clearance of a solute is equal to the generation of solute. Recall from mass balance relationships in the steady-state (Equation 258.4) clearance is inversely proportional to solute concentration and directly affected by the solute generation rate. Therefore under a steady-state assumption, urea generation and time averaged urea concentration can be input into Equation 258.4 to calculate a continuous clearance:

$$K = G / TAC_{urea} \tag{258.15}$$

This expression has been termed the equivalent renal urea clearance (EKR) (Casino and Lopez, 1996). Alternatively, the average peak or predialysis urea could be input into Equation 258.4 in lieu of the time averaged urea concentration. In this way, the K (mL/min) could become the hypothetical continuous renal urea clearance that would achieve the mean predialysis urea concentration. Utilizing the average predialysis or peak urea concentration results in a lower clearance than if the TAC_{urea} was utilized, is more comparable to peritoneal dialysis methods (Keshaviah et al., 1989) and has been termed the 'standard' clearance (K) (Gotch, 1998):

$$\text{Standard } K = G / C_m \tag{258.16}$$

where C_m is the mean predialysis urea concentration. Adding the parameter of time (min) and normalizing to volume of distribution (mL) yields the dimensionless standard weekly Kt/V (stdKt/V), with the time interval being set at one week (10,080 minutes):

$$stdKt / V = G / C_m * 10080 / V \tag{258.17}$$

The standard Kt/V can be calculated from pre- and post-dialysis urea levels with urea kinetic modelling to calculate urea generation (G) or can be approximated with Equation 258.18 (Leypoldt, 2004). This equation utilizes the equilibrated Kt/V and therefore takes into account post urea rebound. Fluid removal during dialysis or residual renal function is neglected and the equation assumes that the dialysis schedule is symmetrical within the week. Even so, the prerequisite for symmetrical dialysis sessions within a week does not seem to affect the results when the treatment sessions are delivered in an asymmetrical fashion and the equation can be used reliably regardless of treatment symmetry (Daugirdas and Tattersall, 2010):

$$stdKt/V = \frac{10{,}080\dfrac{1-e^{-eKt/V}}{t}}{\dfrac{1-e^{-eKt/V}}{eKt/V}+\dfrac{10{,}080}{Ft}-1} \tag{258.18}$$

where F is the number of treatments in the week and eKt/V is the equilibrated Kt/V. This method of calculation underestimates the true clearance (K) during dialysis because of fixed volume assumptions. It does not account for ultrafiltration in two ways: (1) the convective clearance of solute that happens during ultrafiltration is not appreciated, and (2) the change in concentration of urea due to fluid accumulation between dialysis diluting the urea concentration is not appreciated. Further, residual renal function, which can contribute significantly to the patient's overall clearance of uraemic retention solutes is ignored. Equation 258.19 was modelled from patient data in order to account for ultrafiltration during dialysis and residual renal function (Daugirdas et al., 2010):

$$\begin{aligned} stdKt / V = {} & S / \left(1 - \left(0.74 / F\right) * UFw / V\right) \\ & + Kru * \left(0.974 / \left(spKtV + 1.62\right) + 0.4\right) * 10080 / V \end{aligned} \tag{258.19}$$

where S is the result of Equation 258.18, F the number of dialysis sessions per week, UFw is the weekly fluid removal in litres, spKtV single-pool Kt/V, and V volume of distribution.

The utility of standardizing the Kt/V to a continuous weekly clearance can be appreciated mostly when comparing patients on different dialysis regimens. Urea kinetic modelling and the logarithmic equations described above for single-pool and equilibrated Kt/V work well for thrice-weekly dialysis but are not designed for use with more frequent dialysis sessions. For example, a patient dialysing three times weekly may achieve an eKt/V of 1.2. If the dialysis regimen was increased to four times weekly, it would not be surprising to see the eKt/V drop to 0.9, despite a greater dose of dialysis delivered over the week on account of the extra day of dialysis (see Fig. 258.1). Superficial analysis of the difference between these two values for eKt/V could lead one to erroneously suspect that a lower eKt/V indicates less dialysis delivered. Alternatively, inputting the numbers into Equation 258.16 would yield a higher standard Kt/V for the four-times-weekly regimen. In other words, to compare dialysis adequacy between different dialysis modalities of differing treatment duration, the standard Kt/V or the equivalent renal urea clearance is the preferable method. Clinical practice guidelines recommend achieving an equivalent renal urea clearance (EKR) of 15 mL/min (Casino and Lopez, 1996; European Best Practice Guidelines Expert Group on Hemodialysis, 2002) or a standard

Kt/V of 2.0 (Hemodialysis Adequacy 2006 Work Group, 2006). It is reasonable to aim for a higher goal of 2.12 if the standard Kt/V is calculated by urea kinetic modelling to account for error introduced by neglected interdialytic volume gain (Daugirdas et al., 2010).

Urea kinetic modelling

Utilizing computer programs to perform iterative mathematics that attempt to describe urea kinetic behaviour during dialysis is known as formal urea kinetic modelling. Considering urea distribution under the single-pool model, and assuming that urea is freely and equally distributed throughout the total body water, the change in urea in the body over time could be described as previously illustrated in Equation 258.3. The steady-state condition of mass balance, where inputs are equal to outputs, does not apply given the intermittent nature of typical thrice-weekly dialysis and therefore the left side of the equation must be considered. Solving Equation 258.3 leads to the expression in Equation 258.20 (Sargent and Gotch, 1980):

$$C = C_0\left[\frac{V - B\cdot t}{V}\right]^{\left(\frac{K_r + K_d + B}{B}\right)} + \frac{G}{K_r + K_d + B}\left[1 - \left[\frac{V - B\cdot t}{V}\right]^{\left(\frac{K_r + K_d + B}{B}\right)}\right] \quad (258.20)$$

where V is post-dialysis urea distribution volume, G urea generation, K_r native kidney urea clearance, B is the change in V during dialysis, and K_d is dialyser urea clearance (Sargent and Gotch, 1975; Hemodialysis Adequacy 2006 Work Group, 2006). Iterative computer programs based on Equation 258.20, and others, can be used to predict the urea concentrations that would be expected using *in vitro* clearance data which provides dialyser K (from manufacturer specifications or KoA), estimated V (based on total body water estimations from anthropometric nomograms or roughly 58% of body weight) and dialysis time. If three urea values are known,—pre(C_o) dialysis urea concentration for two subsequent treatments and post(C) dialysis urea concentration of the second treatment—rates of urea generation can be calculated. Input variables of pre- and post-dialysis urea, dialyser K, and time allows calculation of a modelled V which can then be compared with the estimated V. Urea generation (G) can also be calculated. From model output variables of G and V, Kt/V and protein catabolic rate (PCR) can be calculated. Modelled values obtained compared to expected values obtained yield insight into discrepancy between prescribed and delivered dose of dialysis. Modelling kinetics with two urea measurements (pre- and post-dialysis BUN for a single session) is possible and more frequently utilized in clinical practice as it does not require an extra lab draw. The two-draw method requires an iterative process over the period of a week rather than over one dialysis session and is limited by the often erroneous assumption that predialysis urea level is consistently the same (Depner and Cheer, 1989).

Generation of urea: normalized protein catabolic rate (nPCR, nPNA)

Serum urea level is dependent upon mass balance relationships with input of urea into the system described as urea generation, G, mg/min. Because urea generation, under steady-state conditions when the patient is neither catabolic nor anabolic, is dependent upon dietary protein intake, measurement of urea generation can be utilized as a marker of nutrition. Due to the close relationship of urea level with dietary protein intake, assessment of dialysis adequacy could be considered to be incomplete without an assessment of nutritional intake. As an example, consider the dialysis patient with subclinical uraemia which is limiting nutritional intake due to nausea. Often in this setting predialysis urea levels will be low due to decreased protein intake. Low predialysis urea could represent optimal dialysis or, if the uraemic condition is present it is more likely to reflect low dietary protein intake. Indexes of adequacy such as Kt/V urea or urea reduction ratio may appear abnormal and serve as a cue to the clinician that more dialysis is necessary; however, this is not universally the case. In certain settings, limited protein intake can also yield indexes of dialysis adequacy that are within goal range. In such cases, analysis of nutritional parameters such as the normalized protein catabolic rate (nPCR) along with subjective clinical assessment of the patient are key to the proper interpretation of adequacy indexes. Nutritional status of dialysis patients is likely to have a significant impact on clinical outcome. Low dietary protein intake has been associated with increased mortality in dialysis patients (Kalantar-Zadeh et al., 2003; Araujo et al., 2006). In particular, trends of declining protein catabolic rate over time in a dialysis patient portend a poor prognosis whereas increasing protein catabolic rate over time is associated with improved survival (Shinaberger et al., 2006). The recommended protein intake for patients on maintenance haemodialysis is 1.2 g/kg/day with at least 50% of the protein being of high biological value; meaning that the protein has amino acid composition similar to human protein (National Kidney Foundation, 2000).

Use of the term protein catabolic rate is considered to be a misnomer by some because not all protein in dialysis patients is lost to catabolism. Some of it is lost in dialysate and urine. Subsequently, the total amount of protein breakdown is believed to be larger than what is apparent through urea generation. The term protein equivalent of total nitrogen appearance or protein nitrogen appearance (PNA) has been suggested as more appropriate (National Kidney Foundation, 2000). For the purpose of the reader, PCR and PNA should be considered synonymous. Recall that urea is often measured in the laboratory as BUN, which is a measure of urea nitrogen not urea level. Total nitrogen appearance (TNA) is dependent upon losses from residual renal function, stool, skin and dialysate losses as well as urea generation during the interdialytic period. Urea generation (G, mg/min) during the interdialytic period can be calculated by quantifying the rise in urea between dialysis sessions (Gotch and Sargent et al., 1985):

$$G = \Delta C * V / \theta \quad (258.21)$$

where ΔC is the difference between the urea concentration at the end of the dialysis session and the beginning of the next session, V is the volume of distribution of urea, and θ is the interdialytic time interval in minutes. This expression assumes a steady state of urea generation with no other outputs in the interdialytic period. The protein catabolic rate (PCR) is derived by the following expression (Borah et al., 1978; Sargent et al., 1978):

$$PCR = 6.25\left(N_o + N_{cat}\right) \quad (258.22)$$

where N_o is nitrogen(g) output and N_{cat} is nitrogen(g) catabolized. The PCR is usually expressed in grams per day. The constant 6.25 is a reflection of biologic protein consisting on average of 16% nitrogen. By multiplying nitrogen levels by 6.25 the result is subsequently converted to a protein-equivalent of nitrogen. Outside of research settings it is difficult to measure total nitrogen inputs and outputs in order to solve Equation 258.22. Therefore, based upon linear regression data from elaborate studies of nitrogen balance in dialysis patients, the following relationship has been established between urea generation and PCR, with G in g/day (Borah et al., 1978):

$$G = 0.154 * PCR - 1.7 \quad (258.23)$$

An alternate equation has been described that is solved for PCR with the units for G converted to mg/min and the intercept of the regression equation scaled to volume of distribution (V) (Gotch and Sargent, 1985):

$$PCR = 9.35G + 0.294V \quad (258.24)$$

Normalized PCR (nPCR) takes into account the volume of distribution of urea and is expressed in grams per kilogram per day. Kilograms refers to litres of total body water derived from anthropometric formulae or more simply by dividing the ideal body weight by 0.58 (Gotch and Sargent, 1985; National Kidney Foundation, 2000).

$$nPCR = 0.58(PCR / V) \quad (258.25)$$

In the standard situation where the two-blood-draw method, as opposed to the three-draw method, is utilized and urea is measured before and after a single dialysis session, the ΔC of the interdialytic period is unknown and therefore G is unknown. As a work around recall, as discussed above, that G, and V, can be calculated through urea kinetic modelling allowing for calculation of nPCR. Alternatively, other equations have been developed to calculate the nPCR based upon linear regression data of predialysis urea level and Kt/V (Depner and Daugirdas, 1996). The following equations also adjust for differences in interdialytic time interval and are most accurate in anuric patients.
Thrice-weekly dialysis:

$$\text{Beginning of week}: C_o / [36.3 + 5.48KTV + 53.5 / KTV] + 0.168 \quad (258.26)$$

$$\text{Midweek}: C_o / [25.8 + 1.15KTV + 56.4 / KTV] + 0.168 \quad (258.27)$$

$$\text{End of week}: C_o / [16.3 + 4.30KTV + 56.6 / KTV] + 0.168 \quad (258.28)$$

Twice-weekly dialysis:

$$\text{Beginning of week}: C_o / [48 + 5.14KTV + 79 / KTV] + 0.168 \quad (258.29)$$

$$\text{End of week}: C_o / [33 + 3.6KTV + 83.2 / KTV] + 0.168 \quad (258.30)$$

where C_o is the pre-dialysis BUN in mg/dL and KTV is the Kt/V which can be calculated by urea kinetic modelling or as a result of the simpler equations described above. Equilibrated Kt/V (Equation 258.13 or 258.14) would be the most appropriate input for KTV because if single-pool methods for input of KTV are utilized then post-dialysis urea rebound will be neglected and nPCR will appear falsely high. For patients with significant residual renal function, the following equations should be utilized to adjust the Co upward, accounting for the clearance of urea through the kidneys. The result C_o' (adjusted BUN, mg/dL) can then be input into the appropriate equation (Equations 258.26–30) (Depner and Daugirdas, 1996):

$$\text{Thrice weekly dialysis}: C_o' = C_o / [1 + (0.7 + 3.08 / KTV) K_r / V] \quad (258.31)$$

$$\text{Twice weekly dialysis}: C_o' = C_o / [1 + (1.15 + 4.56 / KTV) K_r / V] \quad (258.32)$$

where Kr is the residual renal urea clearance in mL/min and V is volume of distribution in L. Goal nPCR should be above 1.0 g/kg/day. nPCR < 0.8 should raise suspicion for protein calorie malnutrition and has been associated with poor outcome (Gotch and Sargent, 1985; Shinaberger et al., 2006).

The results of calculations of the protein catabolic rate as described above should always be interpreted with an understanding of its inherent limitations in mind. Perhaps the most relevant limitation is the requirement for the patient to be in steady state of nitrogen balance. This is not always the case, for example, in acutely ill patients where muscle stores are catabolized to meet metabolic demands and conversely in the illness recovery stage when anabolism leads to increased protein storage in the muscle. Also, urine urea nitrogen levels are not consistent and vary with dietary intake. For accurate analysis of the PCR, measurement of the contribution of urea loss in the urine should be performed concurrently, a process that requires cumbersome urine collections. Unmeasured pathways of nitrogen excretion such as skin and respiration are also not accounted for. Lastly, there is some controversy as to the method of normalizing the PCR to body weight, a process which can be misleading in obese, oedematous or malnourished patients (National Kidney Foundation, 2000).

The problem with urea-based measures of dialysis adequacy

Analysis of the disappearance of urea from the blood during a dialysis session via the methods described above has gained widespread acceptance as a reliable measure of the dose and adequacy of haemodialytic therapy. Even so, there are notable caveats that should be kept in mind when interpreting urea-based measures of dialysis adequacy. The uraemic condition is complicated and at the time of this writing, poorly understood. Urea serves as a surrogate marker of the uraemic condition but it does not describe the totality of the uraemic condition. Notably missing from urea-based measures of dialysis adequacy is assessment of middle molecule solutes, large solutes, protein-bound, and gut-derived uraemic retention compounds. These myriad compounds are becoming increasingly recognized as pathologic in the uraemic condition (Vanholder et al., 2009). Urea indices provide information only about small molecular solute clearance. Urea kinetic modelling assumes that urea is a valid marker and the clinical significance of urea-based measures of dialysis adequacy has yet to be validated by outcome studies (Barth, 1993). The following summarizes potential sources of error in the

calculation of dialysis dose utilizing urea-based measures of dialysis adequacy:

- Manufacturer's K (KoA) overestimates clearance provided by dialyser. Based on *in vitro* studies. No adjustment for haematocrit, recirculation, or loss of dialyser surface area and volume due to clotting.
- Recirculation/urea rebound if not accounted for can lead to inappropriately elevated adequacy indexes
- Assumes that haemodialysis treatments delivered throughout the month are similar to the treatment that was delivered on the day that the laboratory studies were drawn. In reality, dose of dialysis delivered during non-lab draw sessions is less (Arici et al., 1998; Brimble et al., 2002).
- Sampling procedure of BUN pre and post dialysis session can be variable and prone to error if not performed correctly.
- Shortened dialysis time due to treatment interruptions can lower the delivered dose of dialysis but is not accounted for in many of the methods.
- Modelling of urea disappearance is only feasible in the setting of intermittent dialysis sessions where the drop of BUN between the pre- and post-dialysis session is significant. Mathematically, accuracy is lost as treatment sessions become more frequent.
- Urea generation is dependent upon dietary protein intake, therefore analysis of indexes of urea can be confounded by protein calorie malnutrition.
- Implicit assumption that generation of uraemic toxins is a function of the volume of distribution (V). Assumption that urea is freely and equally distributed within the total body water.
- Based on the premise that V is simply a dilutent for urea and does not have any other clinical meaning, this probably is not true. V correlates with mortality with larger patients generally enjoying a survival advantage (Leavey et al., 1998; Kopple et al., 1999; Pifer et al., 2002; Kalantar-Zadeh et al., 2010). In other words, Kt/V and V are independently and significantly associated with survival. Patients with lower body size require higher Kt/V to achieve the same outcome (Ginn et al., 1975). Dividing Kt by V failed to normalize results across all body sizes as an index is supposed to do; the expected relationships do not seem to hold up at the extremes of body size. This has been shown to be significant in women with a smaller V (Spalding et al., 2008) as well as big men, particularly when residual renal function drops off (Kuhlmann et al., 1999).

Key studies of the optimal dialysis dose

The NCDS in 1981 was a seminal early study seeking to provide a means for quantitative measurement of the optimal dose for thrice-weekly dialysis (Lowrie et al., 1981). Investigators compared time averaged urea clearances (TAC_{urea}) with long or short treatment durations using a factorial randomized study design. Patients were divided into four groups based on their TAC_{urea} and dialysis time (Table 258.2). TAC_{urea} provides a value for the mean concentration of urea over a dialysis cycle. Investigators found that the patients in groups (2 and 4) with higher TAC_{urea} had more frequent hospitalizations, most commonly due to nausea, anorexia, and other uraemic symptoms. As a result, more patients were withdrawn from the high TAC_{urea} groups for medical reasons likely related to uraemia and under dialysis. With regards to the length of therapy, in the high TAC_{urea} patients (groups 2 and 4), the short duration dialysis group (group 4) was hospitalized more frequently than the long duration dialysis group (group 2) (Fig. 258.7). The benefit of longer dialysis was not seen in the two groups with low TAC_{urea} (groups 1 and 3). The NCDS findings were widely interpreted as suggesting that to prevent morbidity, clearance of urea is more important than dialysis treatment time. This lead to the assumption by many clinicians, particularly in the United States, that dialysis time could be shortened so long as urea clearance remained adequate. Notable caveats of the NCDS study include relatively low urea clearances across all groups, a patient population that was healthier when compared to the dialysis population in more recent times and the small size of the study which was underpowered to make mortality comparisons.

Table 258.2 NCDS Study Groups

Group	Td (h)	Predialysis BUN (mg/dL)	TAC_{urea} (mg/dL)	Patients (%)
1. Long Td, low BUN	4.5–5.0	60–80	50	86
2. Long Td, high BUN	4.5–5.0	110–130	100	46
3. Short Td, low BUN	2.5–3.5	60–80	50	69
4. Short Td, high BUN	2.5–3.5	110–130	100	31

BUN = blood urea nitrogen; TAC_{urea} = time averaged concentration of BUN; Td = dialysis time.

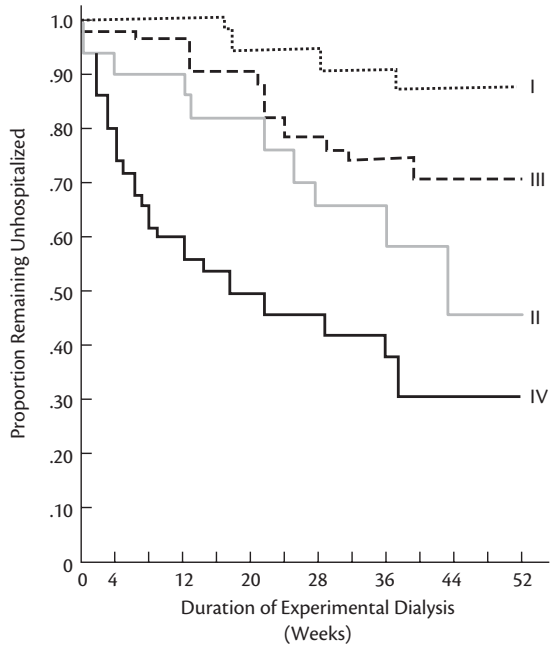

Fig. 258.7 NCDS study. Proportion of patients who remained free of hospitalization by treatment group (see Table 258.2).
Reproduced with permission from Lowrie, E. G., Laird, N. M., Parker, T. F., *et al.* (1981). Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. *N Engl J Med*, 305(20), 1176–81.

Following the NCDS study, numerous large observational studies, most of them performed in the 1990s, challenged the NCDS findings and suggested that higher Kt/V urea values and higher flux dialysis is associated with better outcomes (Held et al., 1991, 1996; Hornberger et al., 1992; Owen et al., 1993; Collins et al., 1994; Locatelli et al., 1996; Koda et al., 1997; Port et al., 2001). Subsequently, there was a trend towards lengthening dialysis time and the utilization of high-flux membranes.

The HEMO study in 2002 sought to evaluate the effect of dialysis dose and membrane flux on death from any cause (Eknoyan et al., 2002). In a schedule of thrice-weekly dialysis, investigators used a two-by-two factorial design to randomize patients to high-dose or low-dose groups and high-flux or low-flux groups. In order to account for urea rebound effects post dialysis, equilibrated Kt/V was used as the method of measurement of dialysis adequacy. Investigators achieved an equilibrated Kt/V (eKt/V) in the low-dose group of 1.16 and 1.53 in the high-dose group. The low-flux and high-flux groups had similar mean eKt/V at 1.34. No significant improvement in survival or hospitalization was seen between standard dose, high-dose, low-flux, or high-flux dialysis groups (Fig. 258.8). Health-related quality of life, nutritional parameters, and functional status were also not different between groups (Rocco et al., 2004; Unruh et al., 2004). The results of the HEMO study were surprisingly negative in contrast to the earlier observational data of the 1990s. Even so, it is notable that on secondary analysis of the HEMO study, high-flux dialysis was associated with improved cardiovascular (Cheung et al., 2003) and cerebrovascular outcomes (Delmez et al., 2006).

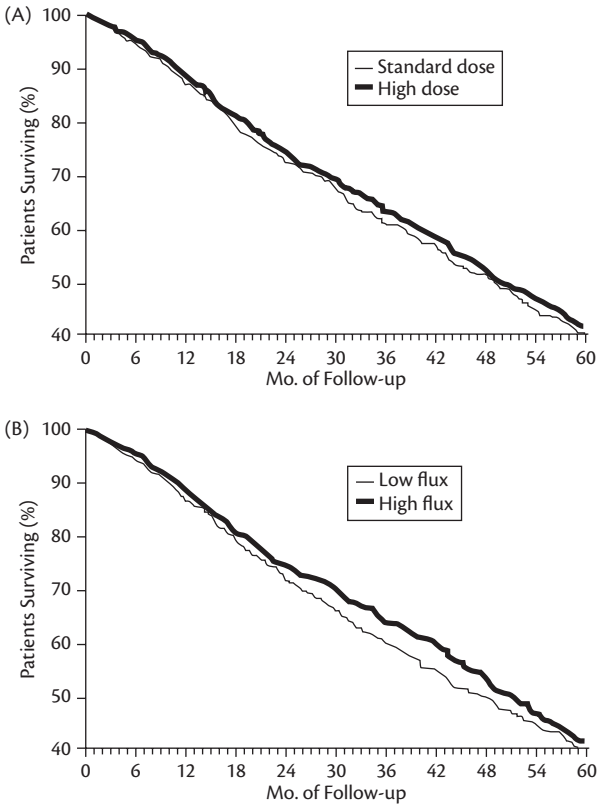

Fig. 258.8 Survival curves for the treatment groups in the HEMO study.
Reproduced with permission from Eknoyan, G., Beck, G. J., Cheung, A. K., *et al.* (2002). Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*, 347(25), 2010–19.

The Membrane Permeability Outcome (MPO) study (Locatelli et al., 2009) was also undertaken with a goal of evaluating the effect of membrane permeability (flux) on outcomes. Patients were randomized to dialysis with low-flux or high-flux membranes and stratified according to their serum albumin level (albumin < 4 g/dL or albumin > 4 g/dL). Both groups were treated with a minimum single-pool Kt/V of 1.2. Findings revealed that patients in the low-albumin group (< 4 g/dL) had significantly higher survival rates when treated with a high-flux dialyser. Further, high-flux dialysers in secondary analysis seemed to improve survival of diabetics regardless of serum albumin. This survival benefit was not seen in patients with higher serum albumin levels or across the group as a whole.

Effect of extended duration of dialysis therapy on patient outcome was not assessed in the aforementioned clinical trials. In 2010, data from the Frequent Hemodialysis Network (FHN) trial (Chertow et al., 2010) was released to help address the issue of the appropriate duration of dialysis. The rational for the currently used duration of dialysis (three times weekly) is based on limited studies, logistic practicality, cost, and patient acceptance rather than on sound science. The FHN randomized subjects to in-centre haemodialysis six times weekly compared with standard thrice-weekly dialysis with the hypothesis that more frequent dialysis would improve outcomes. As expected, solute clearance was improved in the frequent dialysis group (weekly standard Kt/V 3.54 vs 2.49). Results revealed that more frequent dialysis was associated with improvement in left ventricular mass, physical composite heath score, hypertension, and phosphorus control. The study was only conducted for 12 months and was underpowered to detect any differences in mortality. There was no difference in the rates of hospitalizations with more frequent dialysis.

Extended duration dialysis can also be provided through nocturnal dialysis programmes. Numerous observational studies have suggested benefit in nocturnal patients with regards to improvement in left ventricular mass, superior hypertension control, greater phosphorus clearance, enhanced nutritional parameters and improved quality of life (Mucsi et al., 1998; Pierratos, 1999; Hanly and Pierratos, 2001; Chan et al., 2002, 2005; Lockridge et al., 2004; Walsh et al., 2005; Sikkes et al., 2009). In a small prospective study from Canada, left ventricular mass was reduced in patients on nocturnal haemodialysis (30–48 hours per week of dialysis) (Culleton et l., 2007). Blood pressure control was superior using nocturnal therapy and mineral metabolism parameters were also better than the conventional control group (10.5–13.5 hours per week of dialysis). The FHN nocturnal trial is the largest prospective study of nocturnal dialysis to date (Rocco et al., 2011). This study was underpowered to meet statistical significance for outcomes of death, hospitalization, LV mass or composite physical health score; however, nocturnal dialysis did improve systolic blood pressure control and phosphorus control. Similar to the results found during the in-centre FHN trials, access complications were more common in the nocturnal haemodialysis group. Unfortunately this study does not appear to be useful in proving or disproving the utility of increased delivery of dialysis through nocturnal dialysis programmes. As can been inferred from the two prospective studies illustrated above, the study of frequent and nocturnal haemodialysis has been somewhat hampered by difficulty in recruitment of patients for these extended therapies.

Under-dialysis and failure to meet adequacy goals

Inadequate delivery of dialysis can be a significant cause of morbidity in dialysis patients. Under-dialysis usually presents subtly with lack of appetite that can progress to more severe problems such as protein calorie malnutrition. If under-dialysis is severe, patients experience the full range of symptoms associated with uraemia. Clues to under-dialysis lie in the history where patients may complain of pruritus or fatigue in addition to anorexia. Laboratory parameters and urea kinetic modelling may reveal measures of declining solute clearance or even inability to meet monthly adequacy goals. Decline in haemoglobin or resistance to erythropoietic medications may also be present. If protein calorie malnutrition progresses and is severe enough, patients can have low BUN and low phosphorus levels which indicate poor nutrition as opposed to good clearance with dialysis.

Under-dialysis is most commonly the result of a dysfunctional dialysis access or an inadequate dialysis prescription. Workup of under-dialysis should include a close review of the dialysis access for functional problems such as recirculation. In the setting of recirculation, dialysis efficiency is reduced due to blood which is leaving the extracorporeal circuit via the venous limb being taken up by the arterial inflow. In this situation, blood which has already been dialysed is sent through the dialyser repeatedly leading to a decrease in the overall effectiveness of the therapy systemically. Doppler ultrasonography can be used to evaluate a dysfunctional dialysis access and decide if further intervention is needed to repair or replace it. Identification of significant recirculation (> 15–20%) should prompt further investigation of the dialysis access. Recirculation rates tend to be higher when catheters are used for haemodialysis due to the nature of their configuration with the arterial inflow in close proximity of the venous return. Location of the venous catheter tip in the central vein can also have an effect on catheter recirculation. After careful evaluation and repair of haemodialysis access problems, treatment of under-dialysis involves increasing the dose of dialysis. This most readily can be accomplished by increasing the frequency of dialysis treatments, increasing blood and/or dialysate flows, or by increasing the duration of each dialysis treatment.

Future of dialysis adequacy assessment

Currently popularized methods of dialysis adequacy assessment rely on blood measurements of urea decline with treatment. The future of dialysis adequacy assessment is likely to see a shift to dialysate-based measures of adequacy. Dialysate-based measures of adequacy have an advantage in that they provide a bloodless source of information that can often be obtained in real time without the logistical inconvenience and cost of laboratory analysis. Continuous input and feedback regarding the adequacy of a dialysis session has the potential to ensure that the adequate dose is delivered during every dialysis treatment with errors involving urea kinetic modelling being largely abolished. Methods currently under study and likely to be a feature of newer dialysis machine models include measurement of dialysate conductivity, also known as ionic dialysance (Kuhlmann et al., 2001; Chesterton et al., 2006; Maduell et al., 2008), measurement of dialysate effluent ultraviolet absorbance (Uhlin et al., 2003, 2005, 2006; Castellarnau et al., 2010), or near infrared spectroscopy (Olesberg et al., 2004). Utilizing these methods has the potential to provide point-of-care information about the substances removed from the body and discarded in the dialysis effluent.

Advancement of our understanding of uraemic toxins and novel measurement methods should also have an effect on the analysis of the adequacy of dialysis dose. Expansion of indexes of dialysis adequacy to include alternate uraemic toxins such as middle molecules, protein-bound, and gut-derived uraemic retention solutes has the potential to improve our assessment of dialysis outcome.

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CHAPTER 259

Haemodialysis: acute complications

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Cardiovascular complications

Intradialytic hypotension

Intradialytic hypotension occurs in 10–30% of treatments, ranging from asymptomatic episodes to life-threatening organ hypoperfusion. Intradialytic and post-dialysis hypotension have been associated with increased mortality (Shoji et al., 2004; Flythe et al., 2015). The pathogenesis of intradialytic hypotension is complex (Daugirdas, 1991) and is summarized in Table 259.1. Causes include reduced effective circulating volume (usually a combination of excessive fluid removal/wrong dry weight, reduction in plasma osmolality/low sodium dialysate, and reduction in plasma refilling rate), acute or chronic heart failure, and impaired vasoconstriction or vasodilation (due to many causes including autonomic neuropathy, use of antihypertensives, dialysate with acetate buffer, food ingestion, dialyser reactions, and increased synthesis of nitric oxide).

The immediate treatment is to restore the circulating blood volume by placing the patient in the Trendelenburg position, reducing or stopping ultrafiltration, and infusing boluses of 0.9% isotonic saline (100 mL or more, as necessary). Salt-poor albumin offers no advantage over isotonic saline and costs more. A reduction in the blood flow rate has not been shown to be beneficial. If the blood pump rate is reduced transiently, particular attention should be paid to minimizing under-dialysis from such a practice. Since cardiac factors can precipitate intradialytic hypotension, in the presence of chest pain or dyspnoea, oxygen should be administered and an electrocardiogram should be performed to rule out ischaemia. Similarly, recurrent and unexplained episodes of hypotension might warrant an echocardiogram to rule out pericardial effusion due to pericarditis.

Preventive strategies include correction of anaemia and hypoalbuminaemia, treatment of heart failure or arrhythmias, avoidance of antihypertensive drugs before dialysis, and food before and during dialysis. Patients should be counselled to avoid excessive interdialytic weight gain, and accurate assessment of the patient's dry weight is required. Midodrine, an oral selective α_1-agonist, is a useful preventive therapy in patients with persistent unexplained intradialytic hypotension (Cruz et al., 1999).

Preventive strategies through modification of the dialysis procedure include the use of bicarbonate dialysate, volumetric control of ultrafiltration, sodium modelling, and short daily dialysis (Okada et al., 2005). Online blood volume monitoring and biofeedback techniques have also been used to improve intradialytic cardiovascular stability (Locatelli et al., 2005). Finally, dialysate cooling to 35.5–36°C, a measure that induces release of catecholamines resulting in vasoconstriction, may lessen hypotension (Cogliati, 2005).

Intradialytic hypertension

Intradialytic hypertension occurs in 8–30% of treatments (Chen et al., 2006), and has been associated with an increased risk of hospitalization or death (Inrig et al., 2007). Although its pathophysiology is poorly understood, intradialytic hypertension has multiple potential causes, including an ultrafiltration-induced surge in the sympathetic nervous system (Ligtenberg et al., 1999) or renin–angiotensin system in the setting of renovascular disease, intradialytic removal of antihypertensive drugs (e.g. angiotensin-converting enzyme inhibitors (ACEIs) and beta blockers), use of hypernatric (Sang et al., 1997) or hypercalcic dialysate (Locatelli et al., 2004), intravenous erythropoietin (through direct endothelin 1 release) (Phrommintikul et al., 2007), and endothelial dysfunction (Chou et al., 2006; Inrig et al., 2011).

Intradialytic hypertension requires medical intervention if the systolic blood pressure is > 180 mmHg. This is best treated with a centrally acting agent such as clonidine or a short-acting ACEI such as captopril. Successful treatment of hypertension over a longer period requires an accurate determination of the patient's dry weight and its achievement by gradual ultrafiltration over several weeks of dialysis. Sodium modelling can be instituted by targeting a serum sodium concentration of 135 mmol/L by the end of dialysis. Once the estimated dry weight has been achieved, optimization of the antihypertensive drug regimen is warranted by using minimally or non-dialysable medications such as angiotensin receptor blockers, calcium channel blockers, clonidine, and carvedilol.

Cardiac arrhythmias

Intradialytic arrhythmias are common and are often multifactorial in origin (Bailey and Kaplan, 1994; Kant, 1994). Left ventricular hypertrophy, ischaemic cardiomyopathy, uraemic pericarditis, and conduction system calcification are frequently encountered in adult dialysis patients. In addition, the use of numerous pharmaceutical agents with potential cardiotropism coupled to constant alterations in fluid, electrolyte, and acid–base homeostasis might precipitate intradialytic arrhythmias.

Preventive measures include the use of bicarbonate dialysate and careful attention to dialysate potassium and calcium levels. Use of zero potassium dialysate should be discouraged due to its

Table 259.1 Pathogenesis and causes of intradialytic hypotension

Excessive fluid removal	Ultrafiltration rate > 0.35 mL/min/kg > 20% decrease in plasma volume
Reduced plasma refilling rate	
Impaired vasoconstriction	*Patient related-factors* Autonomic neuropathy (e.g. diabetic, uraemic) Antihypertensive medications Lack of appropriate rise in plasma norepinephrine ('sympathetic failure') Decreased sensitivity of the renin–angiotensin and arginine vasopressin systems Food ingestion (splanchnic vasodilatation) Tissue ischaemia (adenosine mediated) Bacterial sepsis Intradialytic venous pooling Increase in core body temperature Anaemia *Dialysis-related factors* Acetate dialysate (adenosine-mediated) Low dialysate sodium and/or ionized calcium concentrations Complement activation (C3a and C5a-mediated) Cytokine generation (interleukin-1β and nitric oxide mediated)
Cardiac factors	Myocardial infarction Structural heart disease Arrhythmias Pericardial tamponade
Haemorrhage	
Dialyser reaction	
Air embolism	
Haemolysis	

arrhythmogenic potential, particularly in patients on digoxin. Serum digoxin levels should be regularly monitored and the need for the drug regularly reassessed, as this agent has been associated with increased mortality, especially among dialysis patients with low predialysis potassium levels (Chan et al., 2010).

Sudden death

Cardiac arrest during dialysis is rare, occurring at a rate of 7 per 100,000 haemodialysis sessions, but is more common in the elderly, diabetics, patients using central venous catheters (Karnik et al., 2001), and after a 2-day interdialytic interval (Foley et al., 2011). Some 80% of sudden deaths during dialysis are due to ventricular fibrillation and are more frequently observed after the long interdialytic interval on thrice-weekly dialysis (Chazan, 1987; Bleyer et al., 1999). Although ischaemic cardiomyopathy increases the risk of sudden death, other catastrophic intradialytic events need to be ruled out. The prompt recognition and treatment of life-threatening hyperkalaemia, often encountered in young, non-compliant patients, is imperative. Profound generalized muscle weakness may be a warning sign of imminent life-threatening hyperkalaemia. When cardiopulmonary arrest occurs during dialysis, an immediate decision must be made as to whether the collapse is due to an intrinsic disease or technical errors such as air embolism, unsafe dialysate composition, overheated dialysate, line disconnection, or sterilant in the dialyser have occurred. Air in the dialysate, grossly haemolysed blood, and haemorrhage due to line disconnection can be easily detected. However, if no obvious cause is identifiable, blood should not be returned to the patient, particularly if the arrest occurred immediately on initiation of dialysis. A patient exposed to formaldehyde may have complained earlier of burning at the access site. If the possibility of a problem with dialysate composition is remote, blood may be returned to the patient. However, blood and dialysate samples should be immediately sent for electrolyte analysis, the dialyser and bloodlines saved for later analysis, and the dialysis machine replaced until all its safety features have been thoroughly evaluated for possible malfunction. It should be a standard practice to have defibrillators in dialysis units.

Dialysis-associated steal syndrome

The construction of an arteriovenous fistula or graft frequently results in reduction of blood flow to the hand. Although clinically significant ischaemia does not usually develop, symptoms are by no means rare, particularly in diabetics and elderly patients with peripheral arterial disease. Dialysis-associated steal syndrome has been reported in 6.4% and 1% of patients with radiocephalic fistulas and grafts, respectively. The syndrome may present with numbness, pain, weakness or coolness of the hand, diminished pulses, acrocyanosis, and gangrene. It must be differentiated from dialysis-associated cramps, uraemic and diabetic neuropathies, amyloid neuropathy, reflex sympathetic dystrophy, and calciphylaxis. The evaluation involves pulse oximetry, plethysmography, Doppler ultrasound, and angiography (Kwun et al., 1979; Schanzer et al., 1992).

Treatment depends on the clinical severity of ischaemia and vascular access anatomy (Schanzer et al., 1992). Severe ischaemia can cause irreparable injury to nerves within hours and must be considered a surgical emergency. Mild ischaemia, manifested by mild pain during haemodialysis, subjective coldness and paraesthesias, and objective reduction in skin temperature but with no loss of sensation or motion, is common and generally improves with time (Vascular Access 2006 Work Group, 2006). Patients with mild ischaemia should undergo symptom-specific therapy (e.g. wearing a glove) and frequent physical examination, with special attention to subtle neurological changes and muscle wasting (Mattson, 1987). Failure to improve may require surgical intervention with banding, revision, or ligation. More serious manifestations such as fingertip necrosis require ligation of the fistula (Vascular Access 2006 Work Group, 2006). Fistula ligation provides immediate improvement in perfusion but results in the elimination of a site for vascular access and the immediate need to construct another one. Other techniques that do not sacrifice the access and yet improve distal perfusion include ligation of the artery distal to the origin of the fistula/graft with or without establishing an arterial bypass or narrowing of the fistula/graft to reduce flow, thereby improving distal perfusion. Percutaneous luminal angioplasty or laser recanalization is reserved for patients with inflow or outflow arterial disease. A modified brachiocephalic fistula extension technique, in which the median vein is anastomosed to the radial or ulnar artery just

below the brachial bifurcation, is thought to preserve part of the blood supply to the hand and prevent the arterial steal syndrome (Ehsan et al., 2005). Persistence of symptoms after an apparently successful correction of the vascular access flow should alert the clinician to other unrelated causes.

Neuromuscular complications

Muscle cramps

Muscle cramps occur late during dialysis in 5–20% of patients, and frequently involve the legs. They account for 15% of premature dialysis session discontinuations (Canzanello and Burkart, 1992). Electromyography shows increased tonic muscle electrical activity throughout dialysis, and serum creatinine kinase may be elevated.

Although the pathogenesis is unknown, dialysis-induced volume contraction and hypo-osmolality are common predisposing factors. Although the onset of muscle cramps often gives an indication that the target weight has been reached, hypomagnesaemia and carnitine deficiency may also play a role.

The acute management is directed at increasing plasma osmolality. Cessation of ultrafiltration is not useful. Infusion of 23.5% hypertonic saline (15–20 mL), 25% mannitol (50–100 mL), or 50% dextrose in water (25–50 mL) is equally effective. However, hypertonic saline may result in post-dialytic thirst, and both hypertonic saline and mannitol cause transient warmth/flushing during the infusion. Furthermore, large and repetitive infusions of mannitol can induce thirst, interdialytic weight gain, and fluid overload. Overall, dextrose in water is preferred, particularly in non-diabetics.

Preventive measures include dietary counselling about excessive interdialytic weight gain. In patients without clinical signs of fluid overload, it is reasonable to increase the dry weight by 0.5 kg and observe the clinical response. Quinine sulphate (260–325 mg) or oxazepam (5–10 mg) given 2 hours prior to dialysis may also be effective. Although in the United States the Food and Drug Administration regards quinine sulphate as both unsafe and ineffective for the prevention of cramps, this drug works very well in some patients, and in most parts of the world, it is used freely. The use of sodium gradient during dialysis is effective as well. Proposed strategies include starting with a dialysate sodium concentration of 145–155 mmol/L and a linear decrease to 135–140 mmol/L by completion of dialysis. A comparison of sodium modelling using an exponential, linear, or step programme has yielded similar results (Sadowski et al., 1993). Enalapril (5 mg) twice weekly may be effective, presumably by inhibiting angiotensin II-mediated thirst. Finally, stretching exercises, creatine monohydrate (Chang et al., 2002), and L-carnitine supplementation (20 mg/kg per dialysis session) may also be beneficial (Eknoyan et al., 2003). An intradialytic blood volume biofeedback control system has been shown to effectively reduce the incidence of muscle cramps (Basile et al., 2001).

Restless legs syndrome

The restless legs syndrome (RLS) is relatively common in haemodialysis patients, ranging from 6% to 62% (Winkelman et al., 1996; Jaber et al., 2011). It is characterized by achy or crawling paraesthesias, typically in the lower extremities, which are relieved by movement of the affected limb. Most patients with RLS suffer from sleep disturbances resulting in sleep fragmentation and sleep deprivation, anxiety, and depressive symptoms. The RLS has been linked to premature discontinuation of dialysis, impaired quality of life, increased risk of cardiovascular morbidity, and death (Unruh et al., 2004; La Manna et al., 2011). Treatment includes avoidance of potentially exacerbating substances, including antidepressants, dopamine antagonists, and caffeine. Pharmacological treatment of RLS in patients with kidney failure is challenging as pramipexole and ropinirole lack adequate safety data for use in this population. Other agents such as levodopa, gabapentin, and benzodiazepines might be considered. Daily haemodialysis is associated with a long-term decrease in the prevalence and severity of RLS (Jaber et al., 2011). The adoption of an intradialytic exercise aerobic training programme has shown some promise (Giannaki et al., 2013).

Dialysis disequilibrium syndrome

Despite a decline in its incidence, dialysis disequilibrium syndrome (DDS) is still observed sporadically in patients being initiated on haemodialysis with large-surface, high-flux dialysers, and short treatment time. Risk factors include young age, severe azotaemia, low dialysate sodium concentration, and pre-existing neurological impairment.

The DDS usually develops toward the end of dialysis but may be delayed for up to 24 hours. Patients display symptoms of restlessness, headache, nausea, vomiting, blurred vision, muscle twitching, disorientation, tremor, and hypertension. More severe manifestations include obtundation, seizures, and coma. Although cerebral oedema is a consistent finding on imaging studies and electroencephalographic findings are non-specific, this remains a clinical diagnosis, and is usually self-limited, although full recovery may take several days.

The pathogenesis of DDS remains poorly understood. The disputed reverse urea effect theory proposes that a transient osmotic disequilibrium occurs during dialysis as a result of a more rapid removal of urea from blood than from cerebrospinal fluid (Arieff, 1994). Other mechanisms include the intracerebral accumulation of idiogenic osmoles such as inositol, glutamine, and glutamate.

In high-risk patients, preventive measures include the use of volumetric-controlled machines, bicarbonate dialysate, sodium modelling, earlier recognition of uraemic states, and earlier initiation of dialysis. In addition, short and more frequent dialysis treatments are recommended using small surface-area dialysers and reduced blood flow rates. The target reduction in plasma urea should initially be limited to 30%. The prophylactic use of mannitol or anticonvulsants is not recommended.

Seizures

Intradialytic seizures occur in < 10% of patients and tend to be generalized but easily controlled. However, focal or refractory seizures warrant evaluation for focal neurologic disease, particularly intracranial haemorrhage. Causes of intradialytic seizures include intradialytic sustained hypotension, intracranial haemorrhage, ischaemic stroke, acid–base or electrolyte disturbances, hypertensive or uraemic encephalopathy, DDS, intradialytic removal of anticonvulsants, and use of epileptogenic drugs such as theophylline, meperidine, and erythropoietin.

Treatment of established seizures requires cessation of dialysis, maintenance of airway patency, and investigation for metabolic abnormalities. Intravenous diazepam, alprazolam or clonazepam, and phenytoin may be required. Intravenous 50% dextrose in water should be administered promptly if hypoglycaemia is suspected.

Headache

Dialysis headache is described as the onset of bifrontal discomfort during dialysis that may become intense and throbbing, accompanied by nausea and vomiting. It is usually aggravated by the supine position, but there are no typical visual disturbances. Although its aetiology has not been elucidated, dialysis headache may be a subtle manifestation of DDS; it may also be a manifestation of caffeine withdrawal due to intradialytic removal of caffeine.

Management consists of oral analgesics, and preventive measures include slow dialysis with reduced blood flow rates, use of bicarbonate dialysate, sodium and ultrafiltration modelling, coffee ingestion during dialysis, and use of reprocessed dialysers.

Haematological complications

Dialysis-induced complement activation and neutropenia

During dialysis with unsubstituted cellulose dialysers, which are infrequently used nowadays, the free hydroxyl groups present on the membrane activates the alternative complement pathway (Cheung, 1990). This results in activation and increased adherence of circulating neutrophils to the endothelial capillary pulmonary vasculature, leading to transient neutropenia that reaches a nadir after 15 minutes dialysis, followed by a rebound leucocytosis 1 hour later. Neutropenia has also been detected with other more widely used dialyser membranes including cellulose acetate and polysulphone, but to a lesser degree.

Intradialytic haemolysis

Acute haemolysis can be due to faulty dialysis equipment, chemicals, drugs, toxins, or patient-related factors (Eaton and Leida, 1985). With the advent of better dialysis equipment and the widespread use of deionization systems, traumatic red blood cell fragmentation caused by poorly designed blood pumps and methaemoglobinaemia caused by water contamination with chloramine or copper are rarely seen today. Nitrate/nitrite intoxication causing methaemoglobinaemia can occur sporadically in patients on home haemodialysis who use water from wells that are contaminated with urine from domesticated animals. Further, during dialyser reprocessing, formaldehyde retention can result in haemolysis by inducing formation of cold agglutinins or inhibition of red cell metabolism. Another potential cause of haemolysis includes the kinking of dialysis lines and catheters.

The diagnosis of acute haemolysis is self-evident when grossly translucent haemolysed blood is observed in the tubing. Patients with methaemoglobinaemia have nausea, vomiting, hypotension, and cyanosis, and oxygen therapy does not improve the black-coloured blood present in the extracorporeal circuit. Copper contamination should be suspected in the presence of skin flushing and abdominal pain or diarrhoea.

Evaluation should include reticulocyte count, haptoglobin, lactate dehydrogenase, blood smear, Coombs test, and measurement of methaemoglobin. Bone marrow examination and the survival of ^{51}Cr-labelled erythrocytes may be indicated if the haemolysis is persistent and unexplained. More importantly, analysis of tap water for chloramines and metal contaminants, and of the dialysis equipment for clues of increased blood turbulence are recommended.

Haemorrhage

Bleeding complications are commonly related to the use of intradialytic anticoagulation, which further confounds the uraemic bleeding diathesis (Remuzzi, 1988). Dialysis patients are prone to spontaneous bleeding at specific sites, such as the gastrointestinal tract (from angiodysplasias); subdural, pericardial, pleural, retroperitoneal, and hepatic subcapsular spaces; and the ocular anterior chamber. Dialysis patients are also frequently prescribed antithrombotic agents and anticoagulants for the treatment of ischaemic heart disease and cardiac arrhythmias, which further compounds the bleeding risk.

Intradialytic blood loss can result from arterial or venous needle disengagement from the access, separation of the venous or arterial line connections, central venous dialysis catheter perforation or dislodgment, or rupture of a dialysis membrane with or without malfunction of the blood leak detector. In addition, following traumatic insertion of a dialysis catheter, blood loss can result in pain and a mass from a rapidly expanding haematoma; chest, shoulder, or neck pain from intrapericardial blood loss; back, flank, groin, or lower abdominal pain/distention from retroperitoneal bleeding; or haemoptysis from pulmonary bleeding. Acute management includes the discontinuation of haemodialysis, pressure application for local haemostasis, haemodynamic support, oxygen administration, and surgical intervention if needed.

In addition to specific measures directed to the site of haemorrhage, reversal of uraemic platelet dysfunction is imperative. Strategies include the use of erythropoiesis-stimulating agents or blood transfusions to achieve a haematocrit > 30% in order to improve rheological platelets–vessel wall interactions, intravenous/subcutaneous 1-deamino-8-D-arginine vasopressin (DDAVP) at 0.3 micrograms/kg over 15–30 minutes; and/or intravenous infusion of cryoprecipitate. Tranexamic acid, a potent fibrinolytic inhibitor, has been used as an adjuvant treatment (Sabovic et al., 2003). For patients experiencing severe bleeding, it is advisable to consider heparin-free dialysis, using normal saline flushes every 15–30 minutes with ultrafiltration adjustments. The use of heparin-bound haemophan dialysers has been advocated in high-risk patients (Lee et al., 2004). Regional citrate anticoagulation is associated with a lower risk of haemorrhage, but adds a significant amount of complexity to the procedure, and is usually restricted to continuous renal replacement therapy in the critically ill (Morabito et al., 2014). Citrate-enriched dialysate has been proposed as an alternative to regional citrate anticoagulation for the maintenance intermittent haemodialysis setting (Cheng et al., 2011). In patients scheduled for elective surgery or invasive procedures, aspirin should be stopped a week earlier, the dose of anticoagulant reduced to minimum, and the haematocrit maintained at > 30%. In some cases, DDAVP and/or oestrogens may also be required. For patients with recurrent gastrointestinal bleeding from difficult-to-locate angiodysplasias in the small intestine, conjugated oestrogens have been proposed.

Thrombocytopaenia

Heparin-induced thrombocytopaenia (HIT) is an important clinical problem in dialysis patients, with a prevalence rate of 4%. Type 1 HIT is characterized by the development of mild thrombocytopaenia. Heparin can usually be continued, and the thrombocytopaenia resolves spontaneously. By contrast, type 2 HIT, resulting in more severe thrombocytopaenia, is immunoglobulin (Ig)-G-antibody

mediated and is characterized by arterial and venous thromboses, and dialysis circuit clotting. The antibodies are directed against the complex of heparin and platelet factor IV.

The diagnosis of type 2 HIT is complex and depends on multiple criteria including the degree, rapidity, and time of onset of thrombocytopaenia, the presence of thrombosis, and resolution of the symptoms after cessation of heparin (Finazzi and Remuzzi, 1996). The presence of heparin antibodies only acts as an adjunct to the diagnosis.

The treatment of HIT includes the complete withdrawal of all heparin products including flush solutions and catheter locks, and the use of heparinoids such as argatroban or danaparoid, or direct thrombin inhibitors such as lepirudin, a biosynthetic hirudin analogue. Lepirudin can be used as a 0.1–0.2 mg/kg intravenous bolus administered 5 minutes before dialysis initiation, with a target activated prothrombin time 1 hour into dialysis of 1.5–2.0 times normal (Wittkowsky and Kondo, 2000). In patients with dialysis catheters, at the end of dialysis, the venous and arterial ports of the catheter can be filled with lepirudin (1 mg/mL), according to the volumes indicated on the catheter.

Thrombocytopaenia may also be secondary to other drugs used during dialysis such as vancomycin, quinine sulphate, desferrioxamine, as well as a result of blood–membrane interactions, where the platelet count reaches a nadir 1 hour after dialysis initiation.

Pulmonary complications

Dialysis-associated hypoxaemia

In most patients, the arterial PaO_2 decreases by 5–20 mmHg during haemodialysis, reaching a nadir at 30–60 minutes, and resolves within 60–120 minutes following discontinuation of dialysis. This decrease is usually of no clinical significance to patients unless there is underlying cardiopulmonary disease.

Hypoventilation is the main implicated factor and is primarily central in origin due to a decrease in carbon dioxide production following acetate metabolism (specific to acetate dialysate), loss of carbon dioxide in the dialyser (with both acetate and bicarbonate dialysate), and rapid alkalinization of body fluids (specific to bicarbonate dialysate, particularly with large surface-area dialysers) (Cardoso et al., 1988). In addition, acetate-induced respiratory muscle fatigue can lead to hypoventilation, especially in critically ill patients. Furthermore, a commonly observed ventilation-perfusion mismatch may be due to pulmonary leucoagglutination (due to complement activation) and/or impaired cardiac output (due to acetate-induced myocardial depression).

In high-risk patients with fluid overload, preventive measures consist of using intradialytic oxygen supplementation, conventional bicarbonate dialysate, and biocompatible membranes. Optimizing haematocrit values and performing sequential ultrafiltration followed by haemodialysis may further reduce the likelihood of hypoxaemia.

Technical malfunctions

Air embolism

The most vulnerable source of air entry into the extracorporeal circuit is the pre-pump tubing segment, where significant sub-atmospheric pressures prevail. However, other sources need to be considered including intravenous infusion circuits especially with glass bottles, air bubbles from the dialysate, and dialysis catheters. High blood flow rates may allow rapid entry of large volumes of air despite small leaks.

Clinical manifestations depend on the volume of air introduced, the site of introduction, the patient's position, and the speed at which air is introduced (O'Quin and Lakshminarayan, 1982). In the sitting position, air entry through a peripheral vein bypasses the heart and causes venous emboli in the cerebral circulation. The acute onset of seizures and coma in the absence of precedent symptoms such as chest pain or dyspnoea is highly suggestive of air embolism. In the supine position, air introduced through a central venous line will be trapped in the right ventricle where it forms foam, interferes with cardiac output, and, if large enough, leads to obstructive shock. Dissemination of microemboli to the pulmonary vasculature results in dyspnoea, dry cough, chest tightness, or respiratory arrest. Furthermore, passage of air across the pulmonary capillary bed can lead to cerebral or coronary artery embolism. In the left Trendelenburg position, air emboli migrate to the lower extremity venous circulation, resulting in limb ischaemia, due to increased outflow resistance. Foam may be visible in the extracorporeal tubing and cardiac auscultation may reveal a peculiar churning sound.

In the event of clinically suspected air embolism, the venous line must be clamped and the blood pump stopped; the patient should be placed in the left Trendelenburg position, and receive cardiopulmonary support; there should be a consideration for aspirating air from the right ventricle with a right atrial catheter, and referring the patient for the hyperbaric oxygen chamber.

Prevention depends primarily on dialysis machines that are equipped with venous air bubble traps and foam detectors located just distal to the dialyser and a venous pressure monitor at the venous end. The detector is attached to a relay switch that simultaneously activates an alarm, shuts off the blood pump, and clamps the venous bloodline if air is detected. Therefore, dialysis should never be performed in the presence of an inoperative air detection alarm system. Glass bottles should be avoided since they create vacuum effects that can permit air entry into the extracorporeal system. Dialysis catheters should be aspirated and flushed with saline prior to connection. Dialyser rinsing, prior to use, should expand all compartments to remove residual air bubbles.

Incorrect dialysate composition

Incorrect dialysate composition occurs as a result of technical or human errors. Since the primary dialysate solutes are electrolytes, the dialysate concentration will be reflected by its electrical conductivity. Therefore, proper proportioning of concentrate to water can be achieved by the use of a meter that continuously measures the conductivity of the dialysate solution as it is being fed to the dialyser. Life-threatening electrolyte and acid–base abnormalities are avoidable if the conductivity alarm is functioning properly and the alarm limits are set correctly. However, in dialysis machines that are equipped with conductivity-controlled mixing systems, the system automatically changes the mixing ratio of the concentrates until the dialysate solution conductivity falls within the set limits. This may inadvertently lead to dialysate without any bicarbonate, with apparently acceptable conductivity. Therefore, if conductivity-controlled systems are used, it is safer to also check the dialysate pH prior to dialysis. Conductivity monitors can fail or can be improperly adjusted due

to human error. Therefore, it is important to add human monitoring of dialysate composition before every treatment, whenever a machine has been sterilized or transported, or whenever a new concentrate is used. Furthermore, many non-standardized solutions are available, some of which may be used with an inappropriate proportioning system. Therefore, it is also essential that the supplies match the machine-proportioning ratio for which they were prepared to obtain the appropriate final dialysate composition.

Hypernatraemia

Hypernatraemia occurs when the concentrate or the ratio of the concentrate-to-water is incorrect, and the conductivity monitors or the alarms are not functioning properly. Clinical manifestations of the ensuing hyperosmolar state include thirst, headache, nausea, vomiting, seizure, coma, and death. Aggressive treatment is mandatory and includes cessation of dialysis, hospitalization, and infusion of 5% dextrose in water. Dialysis should be resumed using a different machine, and the dialysate sodium level should be 2 mmol/L lower than the plasma level and isotonic saline should be concurrently infused. Dialysis against a sodium level 3–5 mmol/L lower than the plasma level may increase the risk of disequilibrium. Ultrafiltration with equal volume replacement with normal saline is another option.

Hyponatraemia

Failure to add concentrate, inadequate concentrate to water ratio, or conductivity monitor or alarm malfunction can cause hyponatraemia. Hyponatraemia can also occur during the course of dialysis with a proportioning system, if the concentrate container runs dry and the conductivity set limits are inappropriate. Acute hypo-osmolality causes haemolysis with hyperkalaemia and haemodilution of all plasma constituents. Symptoms include restlessness, anxiety, pain in the vein injected with the hypotonic haemolysed blood, chest pain, headache, nausea, and occasional severe abdominal/lumbar cramps. Pallor, vomiting, and seizures may be observed. Treatment consists of clamping the bloodlines and discarding the haemolysed blood in the extracorporeal circuit. High-flow oxygen and cardiac monitoring are imperative because of hyperkalaemia and potential myocardial injury. Dialysis should be restarted with a new dialysate batch containing low potassium, and high transmembrane pressure should be applied to remove excess water. Correction of plasma sodium concentration should be achieved by no more than 1–2 mmol/L/hour. Anticonvulsants are indicated for seizures. Successful correction of severe hyponatraemia has been reported using a single 3-hour haemodialysis session using a dialysate sodium concentration of 135 mmol/L without sustaining any adverse neurologic consequences despite a serum sodium correction rate of 3 mmol/L/hour (Oo et al., 2003). This suggests elevated blood urea levels might protect uraemic patients from the development of demyelinating syndromes when hyponatraemia is rapidly corrected.

Metabolic acidosis

Although acute intradialytic metabolic acidosis can be a manifestation of improper mixing of concentrates or failure of pH monitors, other causes need to be ruled out including diabetic or alcoholic ketoacidosis, lactic acidosis, toxic ingestions, or dilutional acidosis (Gennari, 2000). The diagnosis is usually suggested by the acute onset of hyperventilation during haemodialysis and is confirmed by laboratory evaluation. In most circumstances, correcting the underlying cause and using bicarbonate dialysate at 35–40 mmol/L are adequate measures.

Metabolic alkalosis

Severe intradialytic metabolic alkalosis is rare. Causes include errors in dialysate concentrates, reversing the connection of the bicarbonate and acid concentrate containers to the entry ports of the dialysis machine, pH monitor malfunction, or the use of regional citrate anticoagulation (Gennari and Rimmer, 1990). Furthermore, the combination of sodium polystyrene sulphonate and aluminium hydroxide can lead to absorption of alkali that is normally neutralized in the small intestine.

Acute treatment is rarely necessary unless a technical error has occurred. Usually, removal of the alkali source is sufficient. The administration of sodium chloride to dialysis patients with chloride-sensitive alkalosis will not repair the alkalosis. If a more rapid reduction in plasma bicarbonate is desired, the use of low bicarbonate (25–30 mmol/L) dialysate is usually effective. Other cumbersome but effective measures include modifying the dialysate bath by replacing alkali with chloride, substituting bicarbonate with acetate dialysate, using acid dialysate, or infusing hydrochloric acid.

Temperature monitor malfunction

Malfunction of the thermostat in the dialysis machine can result in the production of excessively cool or hot dialysate. Whereas cool dialysate is not dangerous and may have beneficial haemodynamic effects, overheated dialysate can cause immediate haemolysis and life-threatening hyperkalaemia, particularly if the dialysate temperature increases to >51°C. In such an event, dialysis must be stopped immediately and blood in the system be discarded. The patient should be monitored for haemolysis and hyperkalaemia. Dialysis should be resumed to cool the patient by using a dialysate temperature of 34°C to treat hyperkalaemia and to allow blood transfusions if necessary. Visual and audible alarms are mandatory to prevent this complication.

Clotting of dialysis circuit

Clotting of the extracorporeal circuit during dialysis is a common practical problem, and has many underlying causes, warranting a thorough investigation. Technical-induced factors include an inadequate or poor priming technique resulting in retention of air in the dialyser, and lack of or inadequate priming of the heparin infusion line. Such operator-induced errors are corrected through ongoing staff education and competency assessment. Incorrect heparin loading dose, insufficient time lapse after loading dose of heparin for systemic anticoagulation to occur, incorrect pump setting for constant heparin infusion, delayed start of the heparin pump, and failure to release the heparin line clamp are important correctible causes of clotting that should also be considered. Finally, vascular access-related problems from inadequate blood flow due to needle/catheter positioning or clotting, excessive access recirculation, and frequent interruption of blood flow due to inadequate delivery or machine alarm situations are additional causes that can result in clotting. Immediate management requires prompt recognition of the underlying cause and implementation of corrective actions

including ongoing heparin dose adjustment and if indicated, vascular access revision.

Dialysis reactions

During haemodialysis, blood is exposed to surface components of the extracorporeal circuit including the dialyser, tubing, sterilization processes, and other foreign substances related to the manufacturing and reprocessing procedures. This interaction between the blood and the extracorporeal system can lead to various adverse reactions (Jaber and Pereira, 1997).

Anaphylactic and anaphylactoid reactions

Clinical presentation

Anaphylaxis is the result of an IgE-mediated acute allergic reaction in a sensitized patient, whereas anaphylactoid reactions result from the direct release of mediators by host cells. Symptoms typically develop within the first 5 minutes of dialysis initiation, although a delay of up to 20 minutes may be observed. The symptoms vary in severity and include a burning or heat sensation throughout the body or at the access site; dyspnoea, chest tightness, stridor as a result of angio-oedema or laryngeal oedema; paraesthesias involving the fingers, toes, lips, or tongue; rhinorrhoea; lacrimation; sneezing or coughing; skin flushing; pruritus; nausea and vomiting, abdominal cramps; and diarrhoea. Predisposing factors include a history of atopy, elevated total serum IgE, eosinophilia, and the use of ACEIs. The aetiology of dialysis reactions is diverse and requires a thorough investigation. A summary of dialyser-related reactions is provided in Table 259.2.

Dialyser first-use reactions

The majority of these reactions are ascribed to the manufacturer's dialyser sterilant ethylene oxide (ETO), which is now rarely used. The potting compound that anchors the hollow fibres in the dialyser housing acts as a reservoir for ETO, and may impede its washout from the dialyser, leading to sensitization. When conjugated to albumin, ETO acts as an allergen. Using a radioallergosorbent test (RAST), specific IgE antibodies against the ETO–albumin complex are detected in two thirds of patients with such reactions. However, 10% of patients with no history of dialysis reactions have a positive RAST result.

Dialyser reuse reactions

As most residual ETO is washed out of the dialyser during first use, reuse reactions are likely to be due to the disinfectants introduced during dialyser reprocessing procedures. These agents include formaldehyde, glutaraldehyde, and peracetic acid/hydrogen peroxide (also known as Renalin®), and, in allergic patients, specific IgE antibodies against formaldehyde are occasionally detected.

Bradykinin-mediated dialyser reactions

These anaphylactoid reactions were originally described in the 1990s in Europe, occurring among patients dialysed with AN69 dialysers who were also taking ACEIs. Investigation of these incidents revealed that binding of factor XII to this sulphonate-containing, negatively charged AN69 membrane resulted in the formation of kallikrein and release of bradykinin, which, in turn, led to the production of prostaglandin and histamine, with subsequent vasodilatation and increased vascular permeability. ACE inactivates bradykinin, and, therefore, ACEI can prolong the biological activities of bradykinin (Coppo et al., 2000). These membranes have since been chemically modified, thereby reducing this risk.

Anaphylactoid reactions have also been observed in patients on ACEIs who were receiving dialysis with membranes that had been reprocessed. Peracetic acid/hydrogen was the disinfectant used, and the reactions abated once reprocessing was discontinued, despite continued use of ACEIs. It has been speculated that peracetic acid/hydrogen might oxidize the cysteine-containing proteins that are adsorbed on the dialyser membrane, leading to the formation of

Table 259.2 Pathogenesis, causes, treatment, and prevention of dialyser reactions

Reaction	Onset following dialysis initiation	Pathogenesis	Cause	Treatment	Prevention
Severe (life-threatening) reaction	5–20 minutes	Anaphylaxis (IgE mediated)	First-use dialyser (ethylene oxide)	Stop dialysis Do not return extracorporeal blood Epinephrine Corticosteroids Antihistamines	Rinse dialyser before use Use gamma-ray-, steam-, or electron beam-sterilized dialyser
			Reused dialyser (aldehyde, Renalin®)		Discontinue dialyser reuse
		Anaphylactoid (bradykinin)	AN69 dialyser or Renalin®-reused dialyser + ACEI		Avoid AN69 dialyser with ACE inhibitor Discontinue dialyser reuse with Renalin®
Mild reaction	20–40 minutes	Complement activation	Cellulose dialyser	Continue dialysis (symptoms abate within 1 hour)	Use non-cellulose dialysers
Pyrogenic reaction	Anytime	Bacterial contamination	Transmembrane passage of soluble bacterial products	Stop dialysis (in presence of hypotension) Blood cultures Antibiotics Antipyretics	See Table 259.3

negatively charged cysteine sulphonate moieties, and contact activation of factor XII.

Drug-induced reactions

Anaphylactoid reactions to parenteral iron dextran occur in 0.6–1% of dialysis patients. It is believed that dextran produces a dose-dependent basophil histamine release. Significantly higher rates of anaphylactoid reactions have been observed among users of high-molecular-weight compared with low-molecular-weight iron dextran (Chertow et al., 2004). Alternative iron preparations such as sodium ferric gluconate complex and iron sucrose have rapidly replaced use of iron dextran, and hypersensitivity reactions appear to be more less frequent among patients receiving these agents compared to iron dextran (Michael et al., 2002; Aronoff et al., 2004; KDOQI Work Group, 2006). The newest intravenous iron formulation, ferumoxytol (Singh et al., 2008), has not been directly compared to the other three agents, and safety studies are needed to compare these agents (Coppol et al., 2011). It is recommended that the dialysis staff be trained and resuscitative medications be available to evaluate and treat hypersensitivity reactions should they occur following administration of iron preparations (KDOQI Work Group, 2006).

Hypersensitivity to heparin formulations is rare, and usually responds to the substitution of beef with pork heparin, or vice versa. A recent nationwide outbreak in the United States of severe adverse reactions in haemodialysis patients was attributed to heparin vials that were contaminated with over-sulphated chondroitin sulphate (Blossom et al., 2008).

Treatment and prevention

Treatment of an anaphylactic/anaphylactoid reaction requires the immediate cessation of haemodialysis without returning the extracorporeal blood to the patient. Epinephrine, antihistamines, corticosteroids, and respiratory support should be provided, if needed. Specific preventive measures include rinsing the dialyser immediately before first use, substituting ETO- with gamma ray-, steam-, or electron beam-sterilized dialysers, avoiding unmodified AN69 membranes in patients on ACEIs, and discontinuing dialyser reprocessing in selected cases.

Mild reactions

Mild reactions have traditionally been described in patients dialysing with an unsubstituted cellulose membrane. These reactions develop 20–40 minutes after initiating dialysis and consist of back and chest pain. Dialysis can be continued as symptoms usually abate after the first hour, suggesting a relation to the degree of complement activation. These reactions decrease with the use of substituted and reprocessed unsubstituted cellulose membranes. Oxygen therapy and analgesics are usually sufficient. Preventive measures include automated cleansing of new dialysers or using non-cellulose dialysers.

Pyrogenic reactions

Pyrogenic reactions (with or without bacteraemia) are the result of an infection or bacterial contamination of the haemodialysis apparatus. Several factors that are operative during dialysis can expose patients to bacterial products including, contaminated water/bicarbonate dialysate, improperly sterilized dialysers, central venous catheters, and cannulation of infected grafts or fistulas (Jaber and Pereira, 1997). Soluble bacterial products can diffuse across the dialyser into the blood, resulting in cytokine production and, consequently, pyrogenic reactions. Preventive strategies against pyrogenic reactions are summarized in Table 259.3 (Association for the Advancement of Medical Instrumentation, 2009).

When fever develops during haemodialysis, the first step is to address haemodynamic stability. If the patient is hypotensive, administration of fluids, cessation of ultrafiltration, and discontinuation of dialysis should occur in this order as necessary. The presence of severe sepsis should trigger hospitalization. The next step is to determine if there is a source of infection. Careful examination of the dialysis access is warranted. If it is clear that the fever is caused by an infection that is not related to the vascular access, specific therapy should be instituted depending on the diagnosis. Tunnelled central venous catheters should always be suspected as a likely cause of infection, even in the absence of redness or purulent drainage along the tunnel or at the exit site, respectively. Non-tunnelled catheters with evident signs of infection at the exit site should be removed and the tip cultured. Antipyretics should be administered. Blood cultures should be drawn before the initiation of antibiotic therapy. In the presence of a catheter, paired blood cultures should be drawn from both a peripheral vein and the catheter lumen. In the case of *Staphylococcus aureus* bacteraemia, the patient should be investigated for endocarditis.

The initial choice of antibiotics should include vancomycin plus empirical Gram-negative rod coverage, and should be adjusted after the culture results (Mermel et al., 2009).

Although the use of antibiotic catheter lock solutions has been advocated as an adjunct treatment for tunnelled catheter-related infections (Jaffer et al., 2008; Mermel et al., 2009), in patients with *Staphylococcus aureus* infections, the cure rate is < 55% (Allon, 2009). Therefore, infected catheters should ideally be removed, and the patient should receive at least 21 days of antibiotic therapy (Mermel et al., 2009). Alternatively, if the catheter cannot be removed due to vascular access failure, guidewire exchange might be a better option than antibiotic lock solution in the case of infections due to *Staphylococcus aureus* (Aslam et al., 2014). Candidaemia should prompt catheter removal.

An outbreak of bacteraemia among several patients involving a similar organism should prompt a thorough search for bacterial contaminants in the dialysis equipment (Jaber and Pereira, 1997). Attention should also be paid to single-use vials that are punctured several times, such as erythropoietin, which has been linked to an outbreak of bloodstream infections (Grohskopf et al., 2001).

Other complications

Post-dialysis fatigue

Post-dialysis fatigue is a common ill-defined 'washed-out' feeling or malaise experienced during or after haemodialysis (Parfrey et al., 1988). Reduced cardiac output, intradialytic cardiac ischaemia, peripheral vascular disease, depression, poor conditioning, post-dialysis hypotension, hypokalaemia or hypoglycaemia, uraemic encephalopathy, myopathy due to carnitine deficiency, and membrane bioincompatibility have all been incriminated in the pathogenesis of this vexing symptom. The use of glucose and bicarbonate-containing dialysate and L-carnitine supplementation (20 mg/kg/day) has been shown to improve post-dialysis fatigue, although there is insufficient data to support the latter approach (KDOQI Work Group, 2006). More frequent haemodialysis has

Table 259.3 Strategies to prevent bacterial contamination

Strict adherence to the AAMI standards		
Type of fluid	**Microbial count**	**Endotoxin**
Water products	< 200 CFU/mL	< 2 EU
Dialysate	< 2000 CFU/mL	No standard
Reprocessed dialysers	No growth	–
Using appropriate germicide:		
◆ 4% formaldehyde[a]		
◆ 1% formaldehyde heated to 40°C[a,b]		
◆ Glutaraldehyde[b]		
◆ Hydrogen peroxide/peracetic acid mixture (Renalin®)[a,b]		
◆ Heat sterilization (105°C for 20 hours) for reprocessing of polysulphone membranes[b]		
Washing and rinsing of arteriovenous fistula/graft arm with soap and water		
Inspection of arteriovenous fistula/graft arm for signs of inflammation prior to cannulation		
Scrubbing of skin with povidone iodine or chlorhexidine, and allowing to dry out for 5 minutes prior to cannulation		
Recording temperature prior pre and post dialysis		
Central delivery system:		
◆ Cleaning and disinfecting regularly connecting pipes		
◆ Removing residual bacteria or endotoxin by additional filtration		
Single-patient proportioning dialysis machine		
◆ Freshly preparing bicarbonate dialysate on a daily basis		
◆ Discarding unused solutions at the end of each day		
◆ Rinsing and disinfecting containers with fluids that meet AAMI standards		
◆ Air-drying containers prior to dialysate preparation		
Following manufacturer's guidelines for use of preservative-free medications		

AAMI = Association for the Advancement of Medical Instrumentation; CFU = colony forming unit; EU = endotoxin unit.

[a]A minimum 11-hour exposure is required for peracetic acid, and/or 24-hour exposure for formaldehyde.

[b]These germicides are all equivalent or superior to 4% formaldehyde.

been shown to markedly shorten the time it takes for patients to recover from a dialysis session and resume their daily activities (Lindsay et al., 2006; Jaber et al., 2010).

Pruritus

Itching is common in dialysis patients. Causes include dry skin, hyperphosphataemia, hyperparathyroidism, and inadequate dialysis. In some instance, pruritus is more severe during or after dialysis and may be an allergic manifestation to heparin, the dialyser membrane, sterilant (e.g. ETO), or germicides (e.g. formaldehyde). In such patients, the use of gamma ray-, steam-, or electron beam-sterilized dialysers, the discontinuation of reuse, and use of low dialysate calcium and magnesium might result in cessation of itching. Eczematous reactions to antiseptic solutions, rubber glove or puncture needle components, puncture needles, or cellophane used to secure dialysis needles should also be considered (Weber and Schmutz, 1988).

Therapies include the use of emollients and antihistamines, activated charcoal, ultraviolet therapy, sunbathing, ketotifen (a mast cell stabilizer), topical capsaicin, or topical tacrolimus ointment. Dialysis adequacy should also be assessed.

Priapism

Priapism, a prolonged penile erection that is not associated with sexual stimulation, occurs in < 0.5% of men while on dialysis. The patient is usually awakened from sleep by a painful erection. Although the majority of cases are idiopathic, secondary causes include sickle cell disease, haemoglobinopathies, anticoagulants (heparin and warfarin), psychotropic medications (trazodone), alpha blockers (prazosin), sildenafil citrate (Viagra®), high haematocrit from erythropoietin or androgen therapy, and dialysis-induced hypoxaemia and hypovolaemia due to excessive ultrafiltration.

Urological referral is mandatory. Acute treatment consists of corporal aspiration and irrigation. Although shunt surgery provides venous egress from the corpora cavernosa, erectile dysfunction is a common complication.

Hearing and visual loss

Intradialytic hearing loss is a rare occurrence and may be secondary to bleeding in the inner ear from anticoagulation therapy, or cochlear hair cell injury from oedema. Intradialytic visual loss is also rare and can be caused by central retinal vein occlusion, precipitation of acute glaucoma, ischaemic optic neuropathy secondary to hypotension, and Purtscher-like retinopathy secondary to leucoembolization. Finally, concomitant ocular and hearing impairment can occur following the use of outdated cellulose acetate dialyser membranes (Hutter et al., 2000).

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CHAPTER 260

Haemofiltration and haemodiafiltration

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Introduction

Uraemia is a pathological condition caused by the retention of solutes that are normally excreted by the kidneys. The aim of haemodialysis (HD) is to control fluid overload, correct electrolyte unbalance and metabolic acidosis, and remove these solutes. However, standard low-flux HD is not very efficacious and patient morbidity and mortality rates are still very high (15–25% per year).

More than 20 years ago, the hypothesis that the extremely high morbidity and mortality rates of low-flux HD were associated with inadequate removal of middle molecules solutes (MMs) led to the proposal of high-flux haemodialysis (hf-HD) as an alternative efficient dialysis technique (Von Albertini et al., 1984).

The hf- HD characteristic is in the use of membranes of high permeability that increase the *in vitro* clearance of vitamin B_{12} (molecular weight 1355 Da), considered as a marker of middle molecules. Moreover, these membranes remove solutes of higher molecular weight such as β_2-microglobulin (11.8 kDa). Another important characteristic of high-flux membranes is the high biocompatibility. During conventional HD with so-called bioincompatible membranes, several cellular mechanisms and biological systems are activated. Chronic inflammation and oxidative stress (Del Vecchio et al., 2011) are common features among dialysis patients and a strong relation between malnutrition, chronic inflammation, and atherosclerosis (MIA syndrome) has been documented in this population. In uraemia, chronic inflammation is associated as an independent factor together with malnutrition and anaemia (Ridker et al., 1997; Ross, 1999; Carrero and Stenvinkel, 2010) to accelerated atherosclerosis, cardiovascular complications, and death (Arici and Walls, 2001; Honda et al., 2006; Panichi et al., 2008). There are several reasons why chronic inflammation affects uraemic patients, and the type of the dialysis membrane and the microbial dialysate contamination could add to the pro-inflammatory state (Himmelfarb, 2009).

Convective treatment

Theoretical advantages of convective treatments (haemofiltration (HF), haemodiafiltration (HDF)) in chronic kidney disease stage 5 on dialysis (CKD5D) patients when compared with standard low-flux HD, may include higher toxins removal (especially 'middle molecules') and better biocompatibility of the treatment, including membrane and water quality.

High-flux dialysis

Leypoldt et al. (1999) on a data subset from the United States Renal Data System showed a clear correlation between the death rate and the *in vitro* vitamin B_{12} dialyser clearance, thus supporting the importance of MMs in uraemic toxicity. More recently, experimental data gathered by the EUTox group has revived the interest for middle molecules toxicity (Vanholder et al., 2008). With the advent of hf-HD many observational studies have consistently shown that high-flux treatments have positive effects on the morbidity and survival of dialysed patients. However, the 2002 results of the HEMO study (Eknoyan et al., 2002), an United States prospective, randomized study aimed at verifying the advantages of hf-HD over low-flux HD, were disappointing as they showed at primary analysis that hf-HD was associated with a non-significant mortality relative risk (RR) reduction of 8%, although a secondary analysis on patients who were on renal replacement therapy for > 3.7 years, showed a significant better survival in the high-flux group, with a 32% reduction of the mortality RR (Cheung et al., 2003).

The impact of hf-HD on mortality was addressed in another prospective, randomized study, the Membrane Permeability Outcome (MPO) study (Locatelli et al., 2009), a European study specifically designed to include a sicker patient population that could take more advantage from hf-HD, in order to provide sufficient statistical power to possibly demonstrate differences in patient survival. Serum albumin ≤ 4g/dL was considered an indicator for increased morbidity and mortality risk. Besides, whereas the HEMO study included incident and prevalent patients, the MPO study enrolled only incident patients, to avoid early mortality bias (so-called selection of survivors) and a carryover effect of the previous treatment to the actual intervention phase and the reuse of the dialyser was not allowed. Seven hundred and thirty-eight CKD5D patients were enrolled in 59 European centres (567 of them had serum albumin < 4 g/dL and 171 had serum albumin > 4 g/dL) and were separately randomized in order to not jeopardize the original study design. No significant effect of membrane permeability on survival was found in the population as a whole. However, according to the initial study design, hf-HD showed a significant 37% RR reduction of mortality, after adjustment for confounding factors, in patients

with serum albumin < 4g/dL. A secondary analysis found a higher survival rate in the diabetic population as a whole treated with high-flux, with an adjusted RR reduction of 38%. These results of a post hoc analysis from the German Diabetes and Dialysis (4D) Study (Krane et al., 2007) are in line with the MPO study results in diabetic patients.

During the course of the MPO study, the impact of hf-HD on mortality was further addressed in a number of epidemiologic studies. In an analysis of a sample of the United States Renal Data System registry, including nearly 14,000 HD patients, the effect of reuse practice and type of dialyser membranes were evaluated. The RR for mortality was 24% higher in patients treated with low-flux than in those treated with high-flux membranes (Port et al., 2001). Similarly, a reduction of the RR for mortality by 38% in the patients on hf-HD versus those on low-flux dialysis was found in a European observational cohort of 650 patients (Chauveau et al., 2005), further supporting the positive effect of convective treatments in CKD5D patient survival.

The causal relation between treatment with hf-HD and survival could lie in the removal capacity of high-flux membranes for β_2-microglobulin (an acknowledged surrogate of the middle molecules) positively affecting serum levels in the long term, which in turn are related to mortality (Cheung et al., 2006). Of course the interpretation of these findings could be related to many factors including a better volume control, which is easier with this dialysis technique.

The European Best Practice Guidelines (EBPG) on dialysis strategies published in 2007 contain the following recommendation: 'Guideline 2.1: The use of synthetic high-flux membranes should be considered to delay long-term complications of haemodialysis therapy.' Specific indications include to reduce dialysis-related amyloidosis (evidence level III); to improve control of hyperphosphataemia (level II); to reduce the increased cardiovascular risk (level II); and to improve control of anaemia (level III) (Tattersall et al., 2007). The European Renal Best Practice (ERBP) Advisory Board, in the light of the MPO results, published a position statement to change existing guideline 2.1. The board considers that the MPO study provides sufficient evidence to upgrade the strength of the guidance to a level 1A (strong recommendation, based on high-quality evidence) that hf-HD should be used in the case of high-risk patients (comparable to the low-albumin group of the MPO study). Because the substantial improvement in an intermediate marker (β_2-microglobulin) in the high-flux group of the MPO study, the ERBP Advisory Board considers that synthetic high-flux membranes should be recommended even in low-risk patients (level 2b: weak recommendation, low-quality evidence) (Tattersal et al., 2010).

On-line convective treatments

A further improvement in convective treatments is represented by the on-line modality. On-line preparation from fresh dialysate by a cold-sterilizing filtration process is a cost-effective method of providing large volumes of infusion solution. By making fluid volume no longer a limiting factor, blood-cleansing techniques are permitted, characterized by the removal of solutes by high convective transfer: on-line HF and on-line HDF. On-line HDF is considered the most efficient technique of using high-flux membranes. Clearances of small solutes like urea are higher than in HF and clearances of middle solutes like β_2-microglobulin are higher than in hf-HD. Thus HDF, as a strategy based on simultaneous diffusive and convective transport, may combine the beneficial effects of diffusive standard HD with the possible advantages of convective HF.

Haemofiltration

As far as the HF is concerned, controlled, randomized, large-size trials with long follow-up are unfortunately lacking, possibly suggesting the difficulties in performing these trials, mainly in providing the same urea Kt/V considered adequate in HD (Table 260.1). However, it is still matter of discussion if HF, a pure convective treatment, should provide the same urea Kt/V foreseen for low-flux diffusive HD.

A randomized, prospective, multicentre, 3-year follow-up, controlled trial has been performed in 64 patients enrolled in 20 Italian dialysis centres designed to evaluate the comparative long-term effects of on-line pre-dilution HF versus ultrapure low-flux HD

Table 260.1 Randomized and observational clinical studies evaluating the role of haemofiltration on dialysis tolerance and patient mortality

Reference	Design	Treatments	Patients	Sample size	Relative risk reduction %	P-value
Altieri et al., 1997	Prospective crossover	HF High-flux HD	23	23	66	0.003
Altieri et al., 2001	Prospective crossover	HF High-flux HD	24	24	70	0.04
Altieri et al., 2004	Prospective crossover	HF HDF	39	39	54.5	0.017
Locatelli et al., 2010	Randomized, prospective	Low-flux HD On-line HF On-line HDF	70 36 40	146		NS
Santoro et al., 2008	Randomized, prospective	HF Low-flux HD	32 32	64	55	0.05

in 64 CKD5D patients (Santoro et al., 2008). Twenty-two patients completed the follow-up, 11 in each group. The odds ratio of all-cause death was 0.45 for HF compared with HD (P = 0.05). The number of hospitalization events per patient was not significantly different across the two trial arms. Because of the small sample size of this trial, a larger randomized controlled trial is needed to get clearer confirmation about the improved survival observed with HF in this study. However, as underlined above, the implementation and the conduction of such a trial is very difficult.

Haemodiafiltration

The experience in using HDF is larger than the data available for HF. In a prospective, randomized, multicentric trial, Locatelli et al. (1996) compared biocompatible and non-biocompatible membranes, convective and diffusive treatment modalities (cuprophane HD, low-flux polysulphone HD, high-flux polysulphone HD, high-flux polysulphone HDF) in 380 patients followed for 24 months. No significant differences in treatment tolerance and cardiovascular stability were shown between the four treatment groups. It is likely that significant differences in cardiovascular stability were not seen because the incidence of intradialytic hypotension in the population as a whole was much lower than expected. Moreover, no difference of mortality between low-flux and high-flux groups was found; however, it is important to underline that the study was not designed for this endpoint.

HDF is also the most effective method of removing advanced glycation end products (AGEs; molecular weight 15,000 Da). A study by Lin et al. (2003) analysed long-term changes in serum levels among different dialysis modalities (low-flux HD, high-flux HD, and on-line HDF). In a 6-month study period, pre-dialysis serum AGE levels were significantly lower in patients treated with on-line HDF. Gerdemann et al. (2002), in agreement with Lin et al.'s data, found that the pre-dialysis AGE levels of patients on HDF were significantly lower than those of patients on hf-HD using standard dialysis fluid. However, the difference between the levels of patients on HDF was not significant in comparison with the levels of patients on hf- HD using ultrapure dialysis fluid.

Some studies have reported specific advantages of on-line HDF on anaemia control, better haemodynamic stability, phosphate reduction, improvement of dyslipidaemia, and well-being in general. Importantly, on-line HDF has been shown to reduce the effects of underlying conditions of uraemic toxicity, inflammation, oxidative stress, and endothelial dysfunction which are all known to contribute to cardiovascular complications and mortality of CKD patients.

Hyperphosphataemia has been associated with increased risk of all-cause mortality, including cardiovascular mortality (Block et al., 2004). By promoting passive and active vascular calcification, hyperphosphataemia is a well-recognized factor implicated in the cardiovascular risk of CKD patients. Adequate control of hyperphosphataemia is rarely achieved even when, according to urea Kt/V values suggested by the present guidelines, dialysis seems adequate. In the Dialysis Outcomes and Practice Pattern Study (DOPPS), 52% of CKD5D patients were above Kidney Disease Outcomes Quality Initiative (KDOQI) phosphate recommendation despite the extensive use of phosphate binders (Young et al., 2005). Enhancing phosphate removal by dialysis requires increasing phosphate clearance including enhanced duration (or frequency) of treatment. In a study in 16 patients, Zehnder et al. (1999) compared the clearance of phosphate during hf-HD and on-line HDF, during two 1-week periods. The results provide evidence that HDF increases the clearance of phosphate. It should be underlined that because of its short length, this study cannot give any information about the possible difference of pre-dialysis plasma phosphate levels in the long term in the two treatments.

Recently a 6% decrease in pre-dialysis phosphate levels after 6 months of on-line HDF (P < 0.001) compared with low-flux HD has been reported by Penne et al. (2010). However, in this study, the mean dialyser surface as well as the mean blood flow were higher in the HDF group as reflected by the single pool Kt/V values equal to 1.6 in HDF and 1.4 in HD. Locatelli et al. (2014) did not find differences in plasma phosphate levels between patients treated with predilution on-line HDF and patients treated with low-flux haemodialysis.

Anaemia is well recognized, together with hypertension, as the main cause of ventricular hypertrophy in dialysis patients. The difference between conventional HDF (mean replacement fluid 4 L/session), roughly comparable in convection entity to hf-HD, and on-line HDF (mean replacement fluid 22.5 L/session) was evaluated by Maduell et al. (1999) in 37 patients over a period of 1 year. On-line HDF provided a better correction of anaemia with lower dosages of erythropoietin. However, patients also experienced an improvement in dialysis dose (15% increase in Kt/V) possibly contributing to anaemia improvement. Lin et al. (2002) shifted a larger number of patients from conventional HD to on-line HDF and found a significant decrease of the median recombinant human erythropoietin (rHuEPO)/haematocrit ratio (from 504.6 ± 310.1 to 307.6 ± 334.4). However, the study is also limited by the fact that switching to on-line HDF went together with a significant increase of Kt/V values (from 1.28 ± 0.99 to 1.63 ± 0.26). Differing from the previous two studies (Maduell et al., 1999; Lin et al., 2002), Bonforte et al. (2002) studied 32 patients treated by on-line HDF for at least 9 months in whom Kt/V was kept constant; they found a significant increase in haemoglobin levels or a non-significant reduction in rHuEPO doses.

The suggested explanations for these results was a greater elimination of middle sized molecules reducing erythropoietin response and (or) a better biocompatibility of the system, secondary to a better quality of dialysate due to on-line treatment. This last possibility is supported by a paper (Schiffl et al., 1999) pointing out that the use of ultrapure (filtered, pyrogen-free, and sterile) dialysate, reduces the rHuEPO doses required to maintain haemoglobin levels via a reduction in systemic inflammatory processes. Recently Locatelli et al. (2012) did not find differences in haemoglobin levels between patients treated with predilution on-line HDF and patients treated with low-flux haemodialysis. However, Panichi et al. (2015) in a single cross-over, randomized multicentre study reported that high-volume on-line HDF improves erythropoiesis-stimulating agent resistance in comparison with low-flux bicarbonate dialysis.

Until recently, β_2-microglobulin toxicity was mainly associated with the risk of developing β_2-microglobulin amyloidosis in long-term dialysis patients. Serum β_2-microglobulin concentration is now strongly associated with mortality risk in dialysis patients. Post-hoc analysis of the HEMO study has shown that increased β_2-microglobulin concentrations above a threshold value of 27 mg/L are predictive of an increased risk of death in HD patient. For this reason, β_2-microglobulin concentrations should be considered as a quite interesting marker of dialysis efficacy. In a study

of 58 patients who converted from hf-HD to HDF for 8 months, pre- and post-treatment serum β_2-microglobulin levels markedly declined compared to hf-HD (Lin et al., 2001b). On the other hand Ward et al. (2000) performed a prospective clinical trial in 44 patients randomized to on-line post-dilution HDF or hf-HD for a 12-month study period. There was a similar decrease of pre-treatment plasma β_2-microglobulin concentrations, despite an apparent difference in removal of β_2-microglobulin as indicated by a significantly higher pre- to post-treatment reduction in plasma β_2-microglobulin concentration in HDF. Regarding this last point, it should be remembered that a change in plasma concentration of a solute is a good indicator of removal only for solutes distributed in a single pool including plasma. A substantial rebound in post-treatment plasma β_2-microglobulin concentrations has been reported, suggesting that a single-pool model is not adequate to describe β_2-microglobulin kinetics (Locatelli et al., 2000).

In a large observational study comparing convective with diffusive treatments, a 10% non-significant better survival was associated with convective treatments (Locatelli et al., 1999). Of note, a 42% lower RR for surgical intervention for carpal tunnel syndrome was reported in patients in convective treatments.

p-Cresol (PC) and indoxyl sulphate (IS) are the two leading compounds that are implicated in the endothelial dysfunction. Thus increasing removal of these compounds appears highly desirable. Recent studies on HDF have confirmed that low PC concentrations were associated with a significant reduction of dialysis patient mortality (Bammens et al., 2006).

A randomized crossover study on 14 patients compared the influence of hf-HD, pre-dilution low-volume (20 L) HDF, and post-dilution low-volume (20 L) as well as high-volume (60 L) HDF on removal of the protein-bound solute PC (Bammens et al., 2004). Elimination of PC was best during HDF and increased with greater filtration volumes.

Wizemann et al. (2000) conducted a 24-month controlled prospective study in which 44 chronic dialysis patients were randomized to low-flux HD or on-line HDF. There were no differences in morbidity, blood pressure, dialysis-associated hypotensive episodes, haematocrit, or erythropoietin dose between the groups, nor any differences in body weight and nutrition parameters. As expected, plasma β_2-microglobulin concentrations did not change in the HD group throughout the 2 years but decreased from similar values to 18 mg/L before dialysis ($P < 0.01$) during the first 6 months of HDF treatment, and then remained constant until the end of the study. However, it is possible that the clinical reversal of the situation by convective methods takes a long time, including the effects of a reduction in β_2-microglobulin levels.

A prospective, multicentre, randomized cross-over study evaluated the effects of long-term on-line HDF on the levels of solutes of different molecular weights (Pedrini et al., 2011). Sixty-nine patients from eight Italian centres were randomly assigned to two 6-month treatment sequences: A–B and B–A (A = low-flux HD and B = on-line HDF). Comparative evaluation of basal levels of different solutes at the end of the two treatment periods was performed. On-line HDF resulted in enhanced removal and lower basal levels of small (including phosphate), medium-sized, and protein-bound solutes, which are markers or causative agents of uraemic pathologies (mainly inflammation, secondary hyperparathyroidism, and dyslipidaemia). This may contribute to reducing uraemic complications and possibly to improving patient survival. These data have been confirmed by Movilli et al. (2011).

Although HDF offers the advantage of increased convective clearance for middle molecules, there is still controversy as to whether reinfusion should occur pre or post filter. Pre-dilution limitations include dilution of blood side solute concentration and reduced small solute clearance; post-dilution limitations are haemoconcentration, increased fibre clotting, and protein denaturation.

Mid-dilution HDF is a technique that uses a haemodiafilter, OLpUr MD 190 (Nephros, Inc, New York, USA), which allows both pre- and post-reinfusion and a reinfusion rates of 10–12 L/hour. In a prospective crossover study of 10 patients, mid-dilution HDF was compared to on-line post-dilution HDF (Krieter et al., 2005). While urea and creatinine clearances were significantly lower, middle molecule removal was higher in mid-dilution HDF over the whole range of investigated solutes including β_2-microglobulin (mean of 202 vs 166 mL/minute).

Cardiovascular instability is the most frequent clinical problem on dialysis. The importance of preventing intradialytic hypotension is mainly related to the need of achieving the patient dry body weight, thus better controlling hypertension that in CKD5D patients is mainly dependent on fluid overload. A better cardiovascular stability on HDF in comparison to haemodialysis has been reported. A retrospective study by Pizzarelli et al. (1998) compared the results during on-line HDF (4284 on-line treatments on 13 patients) with those during standard bicarbonate haemodialysis. On-line HDF was associated with better cardiovascular tolerance to fluid removal, with a significantly lower incidence of episodes of symptomatic hypotension. The better haemodynamic stability of on-line HDF was also reported in a prospective, randomized trial by Lin et al. (2001a). One hundred and eleven patients were randomly divided into four groups receiving different frequencies of on-line HDF and hf-HD (group 1: HDF three times a week; group 2: HDF twice and hf-HD once a week; group 3: HDF once and hf-HD twice a week; group 4: hf-HD three times a week). Episodes of symptomatic hypotension and mean saline infusion volumes during treatments were significantly reduced when frequencies of on-line HDF were increased. Of interest, the authors reported an higher pre-dialysis plasma sodium concentration (2.3 mEq/L) in patients with higher frequency of on-line HDF, thus suggesting reduced sodium removal, possibly at least partially responsible for the better cardiovascular stability. The same holds true for the results of Maduell et al. (1999).

According to the original observation by Maggiore et al. (1982) that dialysate temperature set at about 35°C affords a better haemodynamic stability than the standard dialysate temperature of 37–38°C, an alternative hypothesis to explain the reduction of hypotension episodes during on-line HDF is suggested by Donauer et al. (2003) who identify blood cooling as the main blood pressure stabilizing factor in on-line HDF. During on-line HDF, an enhanced energy loss within the extracorporeal system occurred, despite identical temperature settings for dialysate and substitution fluids. As a result, the blood returning to the patient was cooler during on-line HDF than during HD. Moreover, the mean blood temperature was lower in on-line HDF, even in the patient's circulation, and blood volume was significantly more reduced. The incidence of symptomatic hypotension was similar to that of on-line HDF by using cooler temperature-controlled HD.

It is matter of fact that survival, together with quality of life, are the most important outcomes. In 2006, characteristics and outcomes of patients receiving HDF versus HD in five European countries in the DOPPS Study (Canaud et al., 2006) were published. The study analysed 2165 patients from 1998 to 2001, stratified into four groups: low- and hf-HD (respectively 63.1% and 25.2% of all patients), and low- and high-efficiency HDF (respectively 7.2% and 4.5% of all patients). High-efficiency HDF patients were associated with a significant 35% lower mortality RR (RR = 0.65; P = 0.01) than those receiving low-flux HD, while patients receiving low-efficiency HDF were associated with a non-significant 7% lower mortality RR (RR = 0.93; P = 0.68) compared to those receiving low-flux HD. It must be observed that the number of patients treated by HDF was quite small and while these results are apparently very impressive, in any case they show only an association and not a demonstration. A selection bias by indication could not be ruled out. As the study authors themselves acknowledged, the benefits of HDF must be tested by randomized controlled clinical trials before recommendations can be made for clinical practice. These data have been confirmed by Jirka et al. (2006).

The RISCAVID study (Panichi et al., 2008), an observational and prospective trial aimed to elucidate the relevance of traditional and non-traditional risk factors of mortality and morbidity in HD patients as well as the impact of different HD modalities, showed that HDF was associated with a significantly improved cumulative survival compared to standard HD.

A systematic review of randomized controlled trials comparing HD, HF, HDF, and acetate-free biofiltration to assess their clinical effectiveness has been performed (Rabindranath et al., 2005) but because the trials assessed were not adequately powered and had suboptimal method quality a conclusive definition about the better replacement therapy modality cannot be derived as clearly underlined. However, this systematic review was heavily criticized for its imprecision (Locatelli, 2005).

In an Italian prospective multicentre study (Locatelli et al., 2010), 146 long-term dialysis patients from 27 Italian dialysis centres were randomly assigned to standard low-flux HD (N = 70), on-line pre-dilution HF (N = 36) or on-line pre-dilution HDF (N = 40) and followed up for a median of 1.5 years. The primary endpoint was the frequency of intradialytic symptomatic hypotension (ISH). Compared with a run-in period, the frequency of sessions with ISH during the evaluation period increased for HD (7.1% to 7.9%) and decreased for both HF (9.8% to 8.0%) and HDF (10.6% to 5.2%; P < 0.001). The main finding of this study is the demonstration of a lower frequency of ISH in patients treated with pure (HF) or mixed (HDF) convection in comparison with patients treated with a diffusive technique (low-flux HD). The beneficial effect of a 54% reduction of ISH in HDF should be balanced with a mean increase in pre-dialysis systolic blood pressure of 4.2 mmHg. The interpretation of these findings is an open question. The ESHOL trial (Maduell et al., 2013) confirmed the results of the Italian trial.

The Convective Transport Study (CONTRAST), a prospective, randomized, international study designed to investigate the effect of increased convective transport by on-line HDF on all-cause mortality and cardiovascular morbidity and mortality, has been published (Penne et al., 2005; Grooteman et al., 2012). Seven hundred and fourteen prevalent HD patients were randomly assigned to undergo either on-line HDF (post-dilution, target convection volume 6 L/hour; N = 358) or low-flux HD (N = 356). The primary outcome was all-cause mortality. The main secondary endpoint was the composite of fatal and non-fatal major cardiovascular events. After a mean follow-up of 3.03 years the incidence of all-cause mortality was not affected by treatment assignment. However, subgroup analysis suggests benefit among patients treated with high convection volumes (> 20 L/treatment) on all-cause mortality (HR 0.57; P < 0.016). Unfortunately this study was not comparing hf-HD with on-line HDF, thus leaving still open the key question if on-line HDF is superior using hard outcomes (like survival) in comparison with hf-HD.

Another prospective randomized, controlled trial, the TURKISH HDF Study (Ok et al., 2013), compared post-dilution on-line HDF and hf-HD regarding morbidity and mortality. Seven hundred and eighty-two haemodialysis patients were enrolled and randomly assigned in a 1:1 ratio to either post-dilution on-line HDF or hf-HD. The follow-up period was 2 years. Primary outcome was composite of death from any cause and non-fatal cardiovascular events. The major secondary outcomes were cardiovascular and overall mortality, intradialytic complications, hospitalization rate, changes in laboratory parameters, and medications. Composite endpoint of death from any cause and non-fatal cardiovascular events is not different between post-dilution on-line HDF and hf-HD. However, HDF treatment with substitution volume > 17.4 L was associated with a 46% RR reduction for overall mortality (RR = 0.54; P = 0.02) and a 71% RR reduction for cardiovascular mortality (RR = 0.29; P = 0.003) compared to HD (Ok et al., 2013).

Interestingly, in these two studies the volume of substitution delivered (17–20 L/session) during the entire HDF session was identified as an independent risk factor associated with improved survival. In other words, the volume of substitution, a surrogate of the convective dialysis dose, should be considered as a critical factor for patient survival thus supporting the findings of the DOPPS study (Canaud et al., 2006).

ESHOL is the first randomized study showing a significant advantage for on-line HDF in all-cause mortality, stroke mortality, and infection-related mortality (Maduell et al., 2013). Interestingly enough the ESHOL trial was the trial with the highest achieved convection volumes (22.9–23.9 L/HD session). However, the solidity of the data depends on the quality of randomization; unfortunately the patients randomized to the on-line HDF in the ESHOL trial were younger, more male, with less diabetes, using in a higher percentage a fistula and less catheters, and had a lower comorbidity index (Locatelli and Hoerl, 2013).

It is, however, intriguing that post hoc analyses of three studies showed that patients in on-line HDF who received the highest convection volumes were associated with a lower mortality and cardiovascular events than those randomized to hf-HD (Grooteman et al., 2012; Maduell et al., 2013; Ok et al., 2013).

Unfortunately the majority of patients on these trials (Grooteman et al., 2012; Maduell et al., 2013; Ok et al., 2013) did not reach the target exchange volume. It is very likely that the exchange volume was related to the flow of vascular access, likely related to better vessels, thus possibly affecting also patient survival. Moreover, in the ESHOL, post hoc exclusion occurred if the pre-set 18 L were not reached.

Thus a selection bias could be a possible explanation for the results of the secondary analyses of these trials, since the possibility that larger reinfusion volumes could be easier in patients with

Table 260.2 Randomized and observational clinical studies evaluating the role of haemodiafiltration on patient mortality

Reference	Design	Treatments	Patients	Sample size	Relative risk reduction %	P-value
Locatelli et al., 1996	Randomized, prospective	Cuprophan HD Low-flux HD High-flux HD HDF	132 147 51 50	380		NS
Locatelli et al., 1999	Historical, prospective	HDF High-flux HD	188 6256	6444	10	NS
Wizemann et al., 2000	Randomized, prospective	HDF Low-flux HD	23 21	44		NS
Bosch et al., 2006	Observational, prospective	High-efficiency HD High-flux HD HDF		183	59	0.05
Canaud et al., 2006	Historical, prospective	Low-flux HD High-flux HD Low-efficiency HDF High-efficiency HDF	1366 546 156 97	2165	35 (high-efficiency HDF vs low-flux HD)	0.01
Jirka et al., 2006	Observational, prospective	HD HDF	2170 394	2564	35	
Schiffl, 2007	Randomized, crossover, prospective	High-flux HD HDF	76			NS
Panichi et al., 2008	Observational, prospective	Bicarbonate-HD HDF On-line HDF	424 204 129	757	22 (HDF and on-line HDF vs bicarbonate-HD)	0.01
Vilar et al., 2009	Observational, retrospective	High-flux HD HDF	636 232	858	34	0.014
Locatelli et al., 2010	Randomized, prospective	Low-flux HD On-line HF On-line HDF	70 36 40	146		NS
CONTRAST, 2012	Randomized, prospective	Low-flux HD On-line HDF		714	9%	NS
CONTRAST, 2012	Adjusted Cox-regression analysis	Low-flux HD On-line HDF (substitution volume > 20 L)		714	34%	0.03
TURKISH HDF Study, Ok et al., 2013	Randomized, prospective	High-flux HD On-line HDF	391 391	782		NS
TURKISH HDF Study, Ok et al., 2013	Adjusted Cox-regression analysis	High-flux HD On-line HDF (substitution volume > 17.4 L)	391 391	782	46%	0.02
Maduel et al., 2013	Randomized, prospective	High-flux HD On-line HDF	450 456	906	30%	0.01

better vascular access and intradialytic cardiovascular stability cannot be ruled out

The main points of concerns of on-line HDF during the last years were safety and extra costs in relation to HD and also to HF-HD. Since on-line HDF is characterized by infusion of large volumes of replacement fluid into the blood, the question arises whether on-line HDF does not increase risk of infection. The three studies (Grooteman et al., 2012; Maduell et al., 2013; Ok et al., 2013) were not specifically designed to study safety. However, apparently on-line HDF was very safe dialysis technique and the ESHOL trial demonstrated that infection-related mortality declined by 55% (Maduell et al., 2013). The additional costs of on-line HDF could

Table 260.3 Randomized and observational clinical studies evaluating the role of haemodiafiltration on dialysis tolerance

Reference	Design	Treatments	Patients	Sample size	Relative risk reduction%	P-value
Locatelli et al., 1996	Randomized, prospective	Cuprophan HD Low-flux HD High-flux HD HDF	132 147 51 50	380		NS
Pizzarelli et al., 1998	Observational, retrospective	Bicarbonate HD On-line HDF		13	35.7	0.03
Donauer et al., 2003	Observational, prospective	On-line HDF Polysulphone HD	11	11	90	0.001
Altieri et al. 2004	Randomized, crossover, prospective	HF HDF		39	54.5	0.017
Schiffl, 2007	Randomized, crossover, prospective	High-flux HD HDF	76			
Vilar et al., 2009	Observational, retrospective	High-flux HD HDF	636 232	858		0.001
Tiranathanagul et al., 2009	Observational, prospective	High-flux HD HDF		22	41.4	
Locatelli et al., 2010	Randomized. prospective	Low-flux HD On-line HF On-line HDF	70 36 40	146	50	0.001
Maduel et al., 2013	Randomized, prospective	High-flux HD On-line HDF	450 456	906	28	< 0.001

mainly be attributed to disposables and a more frequent control for dialysis water purity. However, the costs of disposables should decrease with their larger use, thus making on-line HDF economically competitive to hf-HD and also to standard HD.

Tables 260.2 and 260.3 report the main studies evaluating the role of HDF on mortality and dialysis tolerance.

Another randomized controlled trial, the 'French Multicenter Trial' comparing the effects of high-efficiency on-line HDF with hf-HD on dialytic tolerance (primary endpoint) and mortality in dialysis patients aged 65 years or more in a 2-year follow-up period was just completed with no difference between the two groups (B. Canaud, personal communication).

To try to better clarify these aspects, recently three meta-analyses have been published (Susantitaphong et al., 2013; Nistor et al., 2014; Wang et al., 2014). The meta-analysis of Wang et al. (2014) included 16 studies, two of which were crossover (3220 patients in total). There was no significant difference in the overall mortality and cardiovascular events, as defined by the authors, between patients treated with HF and HDF and low-flux and hf-HD, although a numeric relative risk reduction of 15% and of 17% respectively was found. Of note, a significant reduction of 51% of intradialytic symptomatic hypotension was found in patients treated with convective techniques, associated with a significant reduction of β_2-microglobulin pre-dialytic mean plasma levels of 5.96 mg/L, without a significant difference of the clearances of small molecules evaluated as KT/V of urea. In their meta-analysis, Nistor et al. (2014) included 35 randomized trials, of which 17 were crossover (4039 patients overall). No significant advantages of convective techniques in comparison to the prevalent diffusive techniques were shown, although a numerical reduction of 13% was seen. Of note, a 25% significant reduction of cardiovascular mortality and a significant reduction of 28% of intradialytic symptomatic hypotension were found in patients treated with convective techniques. No significant advantages for non-fatal cardiovascular events and hospital admission were found. Susantitaphong et al. (2013) in their meta-analysis included 65 studies, of which 29 were crossover (12,182 patients overall), and found a significant reduction of 16% and of 45% of intradialytic symptomatic hypotension in patients treated with convective techniques in comparison with the patients treated with prevalent diffusive ones, associated with a significant increased removal of several low-molecular-weight molecules (urea, creatinine, and phosphorous), middle-sized molecules (β_2-microglobulin and leptine), and protein-bound molecules (homocysteine, advanced glycation end-products, and pentosidine) and a reduction of the markers of inflammation (interleukin 6). Moreover a significant reduction of albumin, triglycerides, and HDL cholesterol was found.

Conclusions

At present, considering the results of the HEMO and MPO studies, there are evidence-based data favouring high-flux treatments. Moreover, even if the number of randomized prospective trials comparing HDF and hf-HD is still limited and no conclusive,

randomized data are available concerning the effect of increased convection of on-line HDF, including the use of ultrapure dialysate, on survival and morbidity in CKD5D patients, there is considerable evidence available based on post hoc analyses, observational, epidemiological, or data from small prospective randomized cross-over trials indicating better patient outcomes with on-line HDF.

Convective treatments are also able to facilitate the removal of sodium and water overload, including via a better intradialytic vascular stability (Locatelli et al., 2011). We believe that the possible positive effects of convective treatments in survival of haemodialysis patients are mainly related to better fluid control. This could be an explanation of why it is so difficult to demonstrate the positive effects of convective treatments in randomized controlled trials, where there is a selection bias of motivated participating centres including doctors, nurses, and patients. The positive trial effect in the control group is well known.

The discrepancies between the results of HDF observational studies and the results of large randomized controlled trials must be underlined and are reminiscent of the results regarding hf-HD.

In conclusion, the three meta-analyses (Susantitaphong et al., 2013; Nistor et al., 2014; Wang et al., 2014) have underlined the methodological limitations of the included trials. Thus their conclusions should be carefully evaluated, although a favourable effect of convective treatments on overall mortality, frequency of hospital admission, cardiac structure and function, arterial hypertension, and anaemia was seen. However, using the 'random effect' model, all three meta-analyses have shown a significant reduction of the intradialytic symptomatic hypotension in patients treated with convective techniques in comparison with the patients treated with prevalent diffusive ones, although the interpretation of these findings is matter of discussion.

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CHAPTER 261

Dialysis withdrawal and palliative care

Arkadiy Pinkhasov, Michael J. Germain, and Lewis M. Cohen

Introduction

Following passage of the 1973 end-stage renal disease (ESRD) amendment to the Social Security Act, American nephrologists were no longer confronted by the ethically difficult decision as to whether or not to offer renal replacement therapy. With the cost of treatment covered by the government, dialysis facilities multiplied throughout the country and the demographics of the chronic kidney disease (CKD) patient population changed dramatically.

In the United States and most developed countries, the dialysis population has become increasingly elderly with more co-morbid illnesses (Robinson and Port, 2010; United States Renal Data System, 2010; Canaud et al., 2011) (Fig. 261.1). This is associated with a high early (3–6-month) mortality in incident dialysis patients, particularly those patients > 75 years of age (Figs 261.2 and 261.3). In patients who reside in long-term care facilities, initiation of dialysis is associated with poor quality of life (QOL) and its outcomes (Kurella Tamura et al., 2009). While the mortality rate of prevalent dialysis patients has modestly decreased in the past decade, the rate of incident patients has not decreased. Death preceded by withdrawal from dialysis has increased over this time period. The Dialysis Outcomes and Practice Patterns Study (DOPPS) found that this same pattern occurred in other developed countries which have loosened treatment criteria. When DOPPS surveyed medical directors in their international database, they found that the countries where medical directors were more likely to accept poor prognosis patients (United States, Australia) had a higher rate of withdrawal from dialysis (Fig. 261.4).

Adjusted all-cause mortality in the ESRD and general populations, by age, 2008

Loosened treatment criteria also translated to starting early dialysis in geriatric patients which probably also contributes to higher withdrawal rates. Over the past decade, the average glomerular filtration rate (GFR) of patients who have started dialysis has been steadily increasing. It has been suggested that elderly people who start dialysis at a higher GFR may lose their GFR more quickly with the initiation of dialysis, and they are more liable to have the burdensome complications associated with renal replacement therapy. Many elderly patients with severe and multiple co-morbidities might have otherwise survived with their low GFR and a better QOL if they had not received dialysis (Rosansky et al., 2011). In fact, O'Hare et al. showed that elderly patients may have slower progression to ESRD and are more likely to die of other causes than progress to ESRD (O'Hare et al., 2007).

During the past decade, medicine has accepted the underlying philosophy of palliative medicine and come to realize that many patients are uninterested in undergoing onerous treatments that do not allow them a reasonable QOL. Put differently, patients often will reject treatments that prolong dying rather than meaningfully prolong life. The emphasis on autonomy, increased communication, advance care planning, and shared decision-making between the dialysis team, patients, and family members have all resulted in lowering the threshold for terminating dialysis. Conservative measures and palliative care will be discussed elsewhere in this book.

Guidelines

Anticipating the burgeoning of the population, in 1973, Medicare called for the creation of a medical review board to reduce the acceptance of patients for whom dialysis would not offer, 'a reasonable expectation of benefit without acceptable harm'. It was not until 1997 that the Renal Physicians Association (RPA) and the American Society of Nephrology began to develop a guideline, and in 2000, *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis* was finally published (Renal Physicians Association and American Society of Nephrology, 2000). Ten years later, the RPA was instrumental in developing and issuing revised guidelines regarding shared decision-making (Renal Physicians Association, 2010), and guidelines with a more limited scope have been published in Europe and Australia.

The Gold Standard Framework from the United Kingdom provides prognostic indicator guidance in order to identify patients who have < 1 year to live. The goal in these cases is to help them remain as comfortable as possible. The general mantra of the UK guidelines is not to identify 'how long' but to answer a question of 'what can we do?' for patients who have a limited time frame (The Gold Standards Framework, 2011). The Renal Association of the United Kingdom has also developed specific guidelines on planning, initiating, and withdrawing dialysis (The Renal Association, 2014). Particular attention is paid to the 'conservative' management of patients with advanced CKD who chose not to initiate dialysis or for those patients who are failing dialysis (The Renal Association, 2014). The Kidney Health Australia – Caring for Australians with Renal Impairment

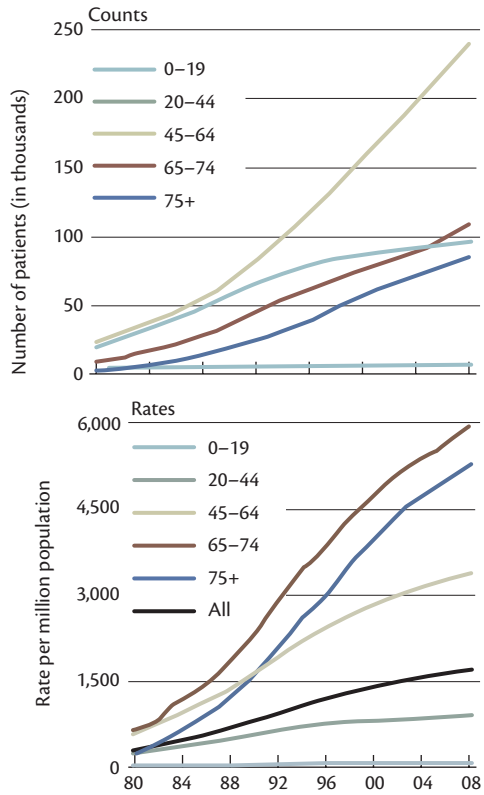

Fig. 261.1 Incident counts and adjusted rates, by age.
The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

(KHA-CARI) guidelines similarly rely on determining QOL data in order to assist in decisions about initiating dialysis. The guidelines suggest that discussion of the effect of dialysis on QOL should be included in the decision-making process and it cites the effects of dialysis maintenance on a patient's physical function, burden of treatment, and family and social life (KHA-CARI, n.d.). Another subset of the CARI guidelines addresses ethical considerations of dialysis. Much like the American guidelines, they suggest that there may be value when uncertain in attempting time limited treatment trials (KHA-CARI, n.d.). There have not been any empirical studies of time-limited trials, but they are described in Recommendation No. 7 of the RPA guidelines (Renal Physicians Association, 2010). With more countries beginning to offer dialysis, there is a growing need for Kidney Disease: Improving Global Outcomes (KDIGO) or a similar group to develop international guidelines to address palliative care and ethical issues of CKD patients.

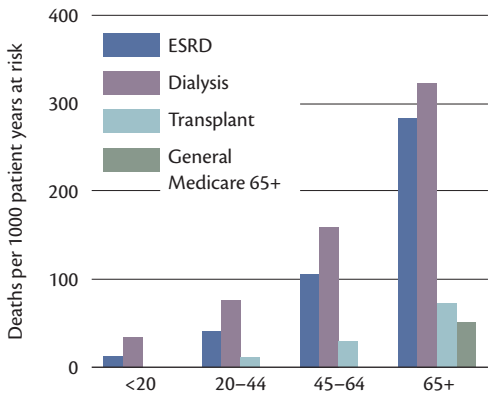

Fig. 261.2 Prevalent ESRD patients and general Medicare patients, 2008. Adjusted for gender and race. Incident dialysis patients, 2008, used as reference cohort.
The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

Dialysis withdrawal

Discontinuation of dialysis has received considerable attention since the publication of the seminal article by Neu and Kjellstrand (1986). Previously, many nephrologists had considered stopping dialysis to be the equivalent of assisting suicide, and they were reluctant to consider this even when patients were demented or permanently unconscious. At the same time, other practitioners had quietly been withdrawing renal replacement therapy under those same circumstances and when patients were obviously dying or insisting that they had enough. Neu and Kjellstrand's report that 22% of all patient deaths in their Minnesota clinic were preceded by dialysis termination propelled this hitherto secret practice out into the open.

By 2000, the rate of dialysis discontinuation prior to death in New England was 31%, and it has steadily risen over the succeeding years and was 39% in 2010 (End-Stage Renal Disease Network of New England, 2010). The national discontinuation rate is somewhat lower (25% in 2006), but it has also been increasing. There has been growing societal awareness of end-of-life issues, and many religions, American jurisprudence, and mainstream medicine have become more accepting of clinical practices that accelerate dying among the terminally ill, including withholding and withdrawal of life-prolonging treatments (Cohen, 2010). Prior to 2004, the Centers for Medicare and Medicaid Services (CMS) ESRD Death Notification form in the United States asked whether dialysis discontinuation was the 'cause' of the patient's death, this prompted objections by a number of nephrologists, and the question was subsequently altered to enquire whether dialysis had been stopped prior to death.

Especially if they are not transplant candidates, dialysis patients often suffer with progressive functional disability and significant discomfort which may or may not be balanced by prolongation of life. It is understandable that the problems and limitations attendant to long-term dialysis may eventually outweigh the perceived benefits. Under such circumstances, withdrawal from dialysis is appropriate and permits the facilitation of a good death characterized by comfort, dignity, and brevity (Levy and Mirot, 2007).

Withdrawal from dialysis allows patients who are terminally ill to shorten the duration of their suffering. Following cessation of dialysis, death may occur on the following day or up to a couple of months later depending on other co-morbid problems and the presence of residual kidney function; in one research sample the average was 8.2 days, and the median was 6 days (Cohen et al., 2000). Approximately 90% of patients die within a month of their last dialysis session (Murray et al., 2006).

Discontinuation itself does not usually result in any pain or discomfort. Potentially, fluid gains and respiratory distress could

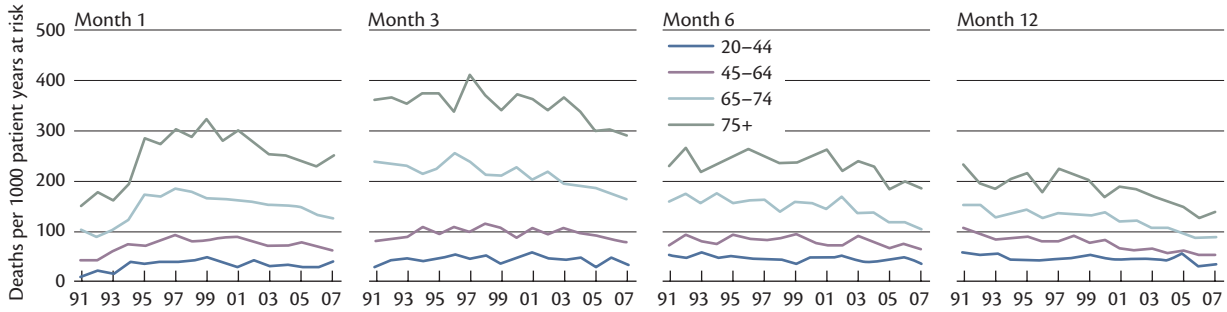

Fig. 261.3 Adjusted rates of cause-specific mortality in the first months of therapy: mortality due to cardiovascular disease, by age.
The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

result from pulmonary oedema, but this occurs infrequently and isolated ultrafiltration can be performed to treat these symptoms. Narcotics and sedatives can also be administered to manage respiratory distress (Cohen et al., 2007). Several Quality of Dying instruments have been created to assess such dimensions as symptom management, psychosocial/existential well-being, and duration of the terminal phase (Cohen and Germain, 2004). In a prospective multicentre sample, 85% of deaths following withdrawal of dialysis were judged according to one such tool to be either 'good' or 'exceedingly good' (Cohen et al., 1995).

It is likely that quality of dying can be improved if dialysis patients are provided with better access to hospice services (Bhargava et al., 2008). CMS policy is confusing in the case of dialysis patients who continue dialysis but need hospice care, but it will pay both the hospice and dialysis benefits providing that the patient is dying from a non-renal related diagnosis (Murray et al., 2006). Hospices are often reluctant to take on the expense of CKD patients who have not stopped dialysis when it is unclear that the diagnosis is not renal related. Cancer is a clear example of a non-renal-related diagnosis; by contrast, there is no clarity when it comes to diabetes and its complications (Fig. 261.5). In all cases of dialysis discontinuation, hospice should be actively pursued and offered.

In order to better understand and define the types of death observed in CKD, an algorithm has been proposed (Table 261.1) that examines psychosocial influences (Bostwick and Cohen, 2009). In this model, categorization is based on the patient's acknowledgment of death, intent to die, and collaboration with loved ones and staff throughout the decision-making process. Deaths following planned withdrawal from treatment are found in the first quadrant on the top and left of the table; they reflect both a positive intent to die and collaboration with the social network. In the upper right quadrant, patients are aware of the consequences of their actions but are likely to have isolated themselves from their social network throughout the decision-making process. In the lower-right quadrant, parasuicide refers to the suicidal gestures associated with character disorders especially borderline personality disorder. Also in this quadrant are deaths resulting from poor adherence to treatment, as is often seen among substance abusers. At the lower left of

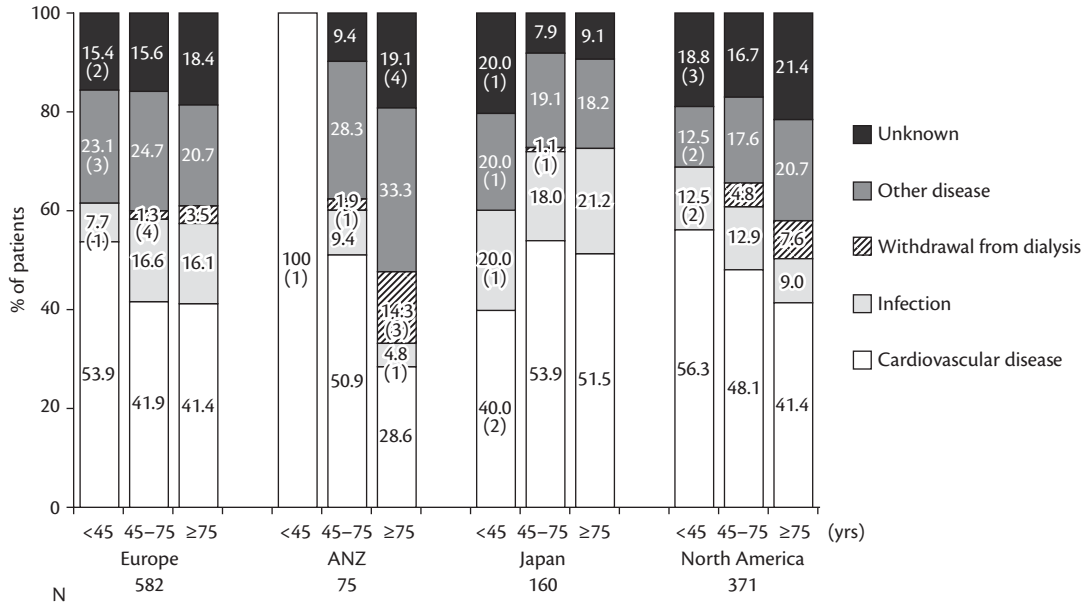

Fig. 261.4 Distribution of cause of death by age at study entry across DOPPS regions.
From Canaud et al. (2011).

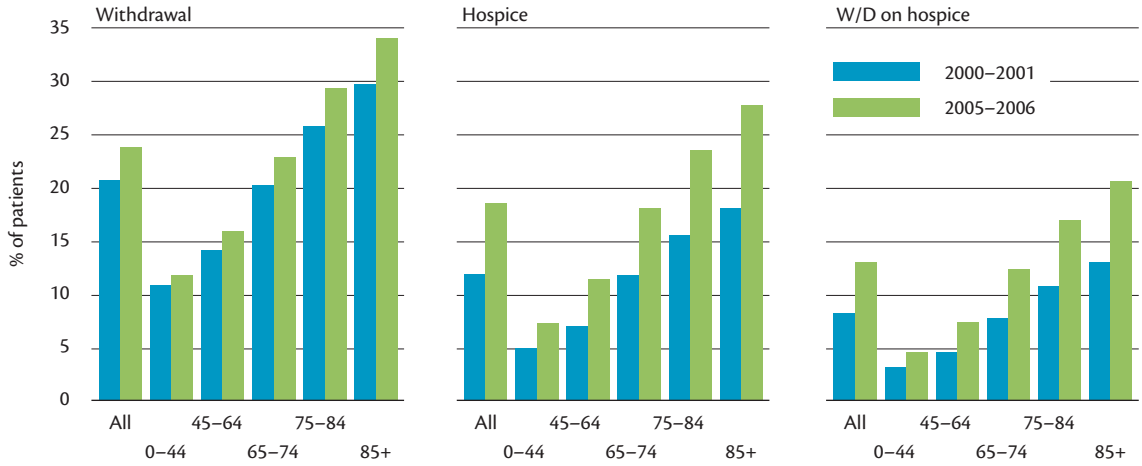

Fig. 261.5 Incident dialysis patients; adjusted for age, gender, race, and primary diagnosis. Incident dialysis patients, 2005, used as reference cohort.
The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

the grid are unexpected deaths. Though unanticipated, these deaths may occur as the result of predictable outcomes, such as co-morbid disorders (e.g. myocardial infarction).

Dialysis discontinuation rates vary substantially by age and ethnicity. When compared to individuals aged 45–69, patients over the age of 75 are three times more likely to withdraw from dialysis. Additionally, black patients are found to be half as likely to withdraw from dialysis compared to their white or Asian counterparts (Kurella et al., 2005). This may be due in part to African Americans' distrust of the medical community based on past inequities in care and violations of research ethics (e.g. the Tuskegee Studies) (Leggat et al., 1997).

Another variable of interest is physician training, and a survey of 360 Canadian and American nephrologists has reported that 60% of respondents did not feel well prepared to make end-of-life decisions about stopping dialysis (Davison et al., 2006). There is now a substantial body of knowledge that has addressed ways to improve end-of-life communication (Table 261.2), and nephrology fellowship training is in the process of being actively improved (Holley et al., 2003; Moss et al., 2004).

Perhaps the most important tool to assist in arriving at dialysis withdrawal decisions is the RPA guidelines on 'Shared Decision-Making'. The guidelines were developed by the nephrology community, and they emphasize that the stage of illness at which any particular patient experiences a conscious tolerance threshold in continuing or discontinuing dialysis is highly individualized and influenced by culture, religion, spiritual beliefs, and family. The guidelines deem it appropriate to refrain from starting or terminating dialysis at the direct request of patients who have decision-making capacity. The guidelines also extend this right to incapacitated patients who previously refused dialysis in oral or written directives, or whose legal agents and proxies refuse dialysis on their behalf. While the guidelines emphasize the autonomous right of patients to terminate treatment and the right of surrogates to arrive at similar decisions, they are also careful to underscore the possibility that psychopathologic factors can on rare occasions play a role in these life-and-death decisions and these factors need to be recognized and managed accordingly (Renal Physicians Association, 2010).

The guidelines highly recommend the use of a shared decision model that provides a collaborative approach and leads whenever possible to a consensus (Germain et al., 2011). The collaboration includes the patient, family, nephrologist, and ideally the primary care physician. When faced with disagreements on plans of care (Recommendation No. 8), attempts are made to reach consensus through listening and respecting the concerns of both sides (Box 261.1) (Renal Physicians Association, 2010). Despite improvements in the management of CKD patients, the annual mortality rate remains high, and dialysis discontinuation is increasingly being considered an option (De Francisco and Pinera, 2006). Each year, older, sicker, and frailer patients are undergoing dialysis. Paternalism is no longer an acceptable way to practise medicine; physicians are increasingly involving patients and families in formulating treatment plans and encouraging them to share in arriving at decisions about living and dying (Cohen et al., 2003). The approach described in the guidelines is distinct from what often occurs; a series of options are presented to the patient/family and they are asked to arbitrarily make a choice rather than share the decision with the clinician and other involved parties. When shared decision-making is not possible, informed assent is an option. Here

Table 261.1 Classifying end-stage renal disease deaths

Intent to die or acknowledgement of death	Collaboration with social network	
	+	–
+	Dialysis-withdrawal Natural death (expected) Dialysis-withholding Physician-assisted suicide (legal) Euthanasia (extralegal)	Suicide Dialysis-refusal
–	Natural death	Non-compliance Parasuicide

From Bostwick and Cohen (2009).

Table 261.2 Communication tools (Baile et al., 2000; Pollak et al., 2007; Renal Physicians Association, 2010)

Recommended skill	Example
I. Identifying concerns	
Eliciting concerns	
Open-ended questions Active listening	'What concerns you about your kidney disease?' Allowing patient to speak without interruption; Allowing pauses to encourage patient to speak
Recognizing concerns	
Informational concerns	Patient: 'I'm not sure about the treatment options'
Emotional concerns	Patient: 'I'm worried about that'
II. Responding to informational concerns	
'Ask–Tell–Ask'	Topic: communicating information about kidney disease
Ask	'What have others told you about what is going on with your illness?'
Tell	After learning what the patient knows, the physician can better tell the information in a way that addresses that patients concerns and needs.
Ask	'What questions do have about what I just said?'
III. Responding to emotional concerns	
Verbal empathy: N–U–R–S–E	
N	NAME the emotion: 'You seem worried'
U	UNDERSTAND the emotion: 'I see why you are concerned about this'
R	RESPECT the emotion: 'You have shown a lot of strength'
S	SUPPORT the patient: 'I want you to know that I will still be your doctor no matter what treatment plans'
E	EXPLORE the emotion: 'Tell me more about what is worrying you'
IV. Delivering bad news	
The six steps of SPIKES	
S	SETTING UP the interview
P	Assessing the patient's PERCEPTION
I	Obtaining the patient's INVITATION
K	Giving KNOWLEDGE and information to the patient
E	Addressing the patient's EMOTIONS with empathic responses
S	STRATEGY and SUMMARY

Box 261.1 Suggested steps for implementing Recommendation No. 8

Engage in extended conversation for either request for dialysis when not recommended or refusal of dialysis when recommended:

- Why does the patient or legal agent desire dialysis when it is not recommended by the renal care team?
- Does the nephrologist misunderstand the patient's or legal agent's reasons for requesting dialysis?
- Does the patient or legal agent misunderstand the diagnosis, prognosis, and treatment alternatives and why dialysis is not recommended?
- Why does the patient or legal agent refuse dialysis when it is recommended by the renal care team?
- Is the patient's refusal of recommended dialysis based on an accurate understanding of the likely benefits of dialysis?
- Is the patient's refusal of recommended dialysis consistent with the patient's values and goals?
- Does the nephrologist understand the psychosocial, cultural, or spiritual concerns and values the patient or legal agent has?
- Has the nephrologist consulted a psychologist, social worker, or chaplain for assistance in fully understanding the concerns of the patient or legal agent/family? Have strategies in the Decreasing Provider Patient Conflict project been used as appropriate?

(<http://www.esrdnetworks.org/special-projects/copy_of_DPPCProviderManual.pdf>)

For circumstances in which the patient/legal agent requests dialysis when it is not recommended, the following process may be helpful to resolve the conflict:

- Consult with other physicians.
- Do other physicians agree or disagree with the attending physician's recommendation to withhold or withdraw dialysis?
- Is the request for dialysis by the patient or legal agent medically appropriate?

Reproduced from Renal Physicians Association (2010). *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis* (2nd ed.). Rockville, MD: Renal Physicians Association.

the clinician makes the decision and the patient/family is asked to accept the decision even if they do not agree. It is understood that if they cannot accept the treatment choice they can ask for a different clinician to assume care of the patient.

Estimating prognosis

Once the conversation concerning end-of-life issues has been initiated, accurate estimation of prognosis is important to strengthen the discussion of goals of care with the patient and their family.

Accurate estimation of prognosis remains difficult but more sensitive instruments have recently been reported. Both the RPA guidelines, in particular Recommendation No. 3, and the UK Gold

Standard Framework recommend estimating prognosis through the use of the simple 'surprise question'. The clinician asks him/herself, 'Would you be surprised if the patient died in the next year (or 6 months)?' If the answer is no, then that patient should be considered for palliative care options (withholding or withdrawing of dialysis, time limited trial, palliative care, hospice) (Moss et al., 2008). A sensitive prognostic tool to estimate a 6-month survival in haemodialysis patients has been validated by Cohen et al. (2010). This instrument is easily accessible on the Internet or in mobile calculator applications for smart phones. Patients seem to want to be informed about prognosis and survival data (Schell et al., 2010).

Additional prognostic scoring approaches have been published and several administrative database studies are underway. Couchoud et al. used data from the French Renal Epidemiology and Information (REIN) registry to develop and validate a clinical score to assess risk of mortality within 6 months of initiation of dialysis in elderly patients with ESRD. They identified nine risk factors and assigned points to them with increase in mortality correlating with increased number of points. One of the limitations of their score was that the population did not account for elderly patients not yet on dialysis and the authors suggested that this score be used to evaluate patients with no obvious contraindications for dialysis (Couchoud et al., 2009). Mauri et al. also identified risk factors that were associated with death in the first year of starting dialysis which seemed to have a good predictive capacity as was seen in the validation study (Mauri et al., 2008). Using the USRD database, Cheung and Kurella Tamura also identified characteristics that were associated with mortality in elderly patients on dialysis. A point score was assigned to these characteristics and increased in the point system correlated with mortality (Cheung and Kurella Tamura, 2011). Other studies using large administrative databases like the United Kingdom Renal Registry database and the United States Renal Data System database have looked at predicting mortality using co-morbidities and they have showed similar findings (Liu et al., 2010; Wagner et al., 2011).

Use of survival prediction instruments for all CKD stage 5 patients should become routine in the future and can serve as the gateway to initiate end-of-life discussions.

Document the plan and goals of care

Discussions should be immediately followed by documentation of decisions. Currently this is done with advance care planning documents completed by the patient. The completion of these documents and their fidelity to the decisions has generally been poor (Perkins, 2007). This has led to development of tools, such as POLST or MOLST (<http://www.polst.org>) which are now legally binding in many states. With POLST the plans of care are discussed with the patient and family, documented by the clinician, and become physician orders that are accepted across sites of care (hospital, nursing home, dialysis unit, etc.). Specific issues based on the patient's current and potential future medical condition, include cardiopulmonary resuscitation, use of the ventilator, surgery, dialysis, and other medical interventions. The POLST relies on crisp and clear language, unlike what is commonly found in other advance directives (Hickman et al., 2010).

Conclusion

Most of the recommendations in this chapter are based on observational studies and small prospective trials; the empiric evidence foundation is not strong. It is our hope that larger multicentre randomized control trials can be performed to provide a more solid basis for recommendations and to generate new hypothesises for improving care.

Acknowledgements

With thanks to Sarah Cairo and Kiran M. Goli.

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CHAPTER 262

Frequent haemodialysis

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Introduction

Haemodialysis is a renal replacement treatment, an 'artificial kidney' that performs some of the functions of the normal kidney. It is an inelegant device, providing only a fraction of native kidney's ability to filter toxins from the blood, but with none of the responsiveness to volume, fine feedback control to regulate solute concentrations, or endocrine functions of the healthy organ. Conventional haemodialysis performed three times a week for 4 hours per treatment filters the blood for only 12 of 168 hours each week, and removes < 10% of small solutes like urea than does the normal kidney. It is therefore not surprising that haemodialysis patients suffer high morbidity and mortality. A dialysis patient's expected remaining lifetime is substantially shorter than a comparable person with normal kidney function. For example, a woman aged 40–44 years old in the general population can expect on average 40 more years of life, but if she is on dialysis her life expectancy is only 8.1 years (United States Renal Data System, 2008; Kliger, 2009). She is also more likely to have co-morbid disease, including hypertension, cardiovascular disease, metabolic bone disease, anaemia, sepsis, depression, malnutrition and inflammation, and physical and cognitive impairment.

Dialysis dose

Several studies have examined whether increasing the 'dose' of dialysis can improve the poor outcomes of patients on haemodialysis. These studies have focused on the hours of dialysis and the efficiency of solute removal. The National Cooperative Dialysis Study, a randomized trial published in 1981, showed that increased urea removal improved morbidity. There also was a trend to decreased morbidity with increased dialysis session time, but this result did not attain statistical significance (Lowrie et al., 1981). The next landmark randomized trial of dialysis dose was the Hemodialysis (HEMO) trial (Eknoyan et al., 2002). In this study, patients were randomized in a 2 by 2 factorial design to high versus standard dose (as measured by urea clearance) and to high- or low-flux dialysers. In this trial, the high doses were achieved primarily by slightly increasing dialysis time. Despite adequate statistical power, patients receiving the higher dose did not have any improvement in mortality compared to the standard dose group. However, there was a statistically significant interaction between dose and sex. Women randomized to the lower-dose group had a higher mortality than women treated with the higher dose (Depner et al., 2004), whereas the opposite was observed in men. A subsequent post hoc analysis demonstrated that if the dose was normalized to body surface area rather than volume, the dose of dialysis delivered to women in the HEMO trial was substantially lower than in men, possibly explaining this sex-specific effect (Daugirdas et al., 2010). This analysis also showed that if the dose of dialysis was expressed as a weekly standard Kt/V_{urea} (urea generation/mean peak pre-dialysis [urea] × time/volume), the high dose group in HEMO received only 16–17% more weekly urea removal than did the lower-dose group. Given this small separation in dose, it is not surprising that the HEMO trial failed to show overall improved survival in the higher-dose group.

Session length

In addition to urea removal, session length itself may be a measure of dialysis dose. The HEMO trial showed that modest lengthening of session time for conventional haemodialysis does not improve outcomes (Eknoyan et al., 2002). A more recent observational study of thrice-weekly haemodialysis demonstrated an inverse association between haemodialysis session length and mortality independent of the effects of session duration on the urea clearance. Brunelli and colleagues analysed data from a national cohort of 8552 incident patients on thrice-weekly haemodialysis using marginal structural analysis to adjust for time-dependent confounding (Brunelli et al., 2010). They found that shorter haemodialysis sessions were associated with higher mortality and there was a dose-dependent relationship between session duration and mortality.

Session frequency

For more than 40 years, conventional chronic haemodialysis has been delivered three times a week. Patients receive treatments Monday, Wednesday, and Friday, or Tuesday, Thursday, and Saturday. This model of dialysis provides a 2-day interval between dialysis treatments once a week—Friday to Monday, or Saturday to Tuesday. Several studies have suggested that intermittent dialysis, unlike the continuous filtering of the normal kidney, may be an 'unphysiologic' renal replacement treatment and leads to increased morbidity. Kjellstrand and colleagues proposed an 'unphysiology hypothesis' of intermittent, short haemodialysis, proposing that the fluctuations of solute concentrations caused by non-continuous artificial kidney treatments contributed to uraemic symptoms, poor quality of life, and poor outcomes (Kjellstrand et al., 1978, 2004). They proposed that more frequent dialysis, to more closely approximate the normal physiology of the intact kidney, would improve this 'unphysiology' and improve patient outcomes. Several studies suggest that the long 2-day dialysis-free interval each week for conventional thrice-weekly haemodialysis is particularly dangerous. Cardiac arrests occur more frequently on Mondays and Tuesdays, after the long interdialytic interval (Bleyer et al., 1999;

Karnik et al., 2001; Foley and Collins, 2010). Foley and colleagues examined retrospectively a US national cohort of haemodialysis patients that received thrice-weekly treatments (Foley et al., 2011). Mortality and hospitalization rates for these 32,065 patients were analysed in relation to the interval between treatments. Mortality and hospitalization rates were significantly higher on the day after the long dialysis-free interval. All-cause mortality, and mortality from cardiac causes, infection, cardiac arrest, and myocardial infarction all were significantly higher on the day after the long interval, as were hospital admissions for myocardial infarction, congestive heart failure, stroke, dysrhythmia, and any cardiac event. On weekends, adverse event rates were lowest on the day following the last dialysis, intermediate on the next day, and highest on the day of the first weekly dialysis. Of particular interest, a subgroup analysis of incident patients, those on dialysis for < 1 year, showed that these patients did not have increased mortality after the long interval. While this retrospective, observational study cannot assess the cause of these findings, it raises the question that dialysis frequency may have a significant effect on morbidity and mortality, particularly in prevalent patients once endogenous kidney function declines or disappears.

It has been hypothesized that more frequent or longer haemodialysis sessions could deliver a substantially higher dose of dialysis and improve outcomes. Several clinical teams and their patients have tried various dialysis regimens to increase the intensity of dialysis, by increasing either the frequency or the length of dialysis treatments, or both. We have published a review of these studies (Suri and Kliger, 2010). In the 1960s, Shaldon first treated his patients with long overnight haemodialysis 2–3 nights per week (Shaldon, 1968). In 1967, DePalma et al. published experience using daily haemodialysis five times a week for 4–5 hours each day (DePalma et al., 1967, 2004). Starting in the 1970s, Charra and his group from Tassin, France, treated patients with longer treatments, lasting 8 hours three times a week (Charra et al., 1992; Laurent and Charra, 1998). Combined with low-salt diets, these patients achieved better volume control. Initial and follow-up studies (Charra et al., 1983, 2003) over many years showed impressive volume control, blood pressure (BP) control, and survival.

Currently, programmes are offering long and more frequent haemodialysis therapies both in-centre and at home. Home haemodialysis offers patients more flexibility than in-centre treatments, allowing for longer treatments and daytime or night-time schedules. Initial enthusiasm for home haemodialysis programmes waned in the United States in the late twentieth century. In the 1970s, 40% of US dialysis patients received their treatments at home (Blagg, 1996). As the model for in-centre care accommodated an ever-increasing dialysis population through the 1990s, patients interested in home treatments largely chose home peritoneal dialysis, and home haemodialysis almost disappeared. In the late 1990s, through the beginning of the twenty-first century, home haemodialysis again grew, particularly in high-income countries like Canada, New Zealand, Australia, and several European countries (Macgregor et al., 2006; Perl and Chan, 2009). Haemodiafiltration has shown promising results in Europe (Ronco and Cruz, 2007).

Short daily haemodialysis

Short daily haemodialysis is typically done for 2–3 hours, 5–6 days per week. Some centres offer this programme in-centre, while others offer it at home. Following on from the original work done by DePalma (1967), showing improved urea removal for patients treated 5 days a week for 4–5 hours per treatment, several observational studies reported favourable outcomes when patients were treated with long-term frequent (5 or more days a week) short haemodialysis (Bonomini et al., 1972, 1983; Louis et al., 1975; Snyder et al., 1975; Twardowski, 1975; Manohar et al., 1981). Several groups, including those of Buoncristiani (Buoncristiani et al., 1988, 1998) and Ting (Ting et al., 2003) changed patients to these 'daily' protocols when they were failing the traditional thrice-weekly treatments. Ting et al. reported observations of 31 patients who were switched from conventional thrice-weekly to short daily haemodialysis because of possible inadequate dialysis, and followed for 1–6 years. Hospitalization rate was reduced by about 35%. However, the retrospective design and its survivor bias make these results difficult to interpret. Several other observational studies (Yuen et al., 2005; Fagugli et al., 2006; Vos et al., 2006; Kumar et al., 2007) and one prospective controlled trial (Ayus et al., 2005) report improvements in left ventricular hypertrophy (LVH) and inflammatory markers, phosphorus control, BP, cognitive function, and quality of life.

In 2006, Suri and colleagues performed a systematic review of the literature reporting experiences with short daily haemodialysis (Suri et al., 2006). Reports published in the 'modern' era, between 1998 and 2005 were systematically reviewed. Studies describing five or more adults who were receiving daily haemodialysis (defined as a 1.5–3-hour session, 5–7 days/week), reporting a follow-up time of > 3 months were included. Of > 800 citations screened, 233 full-text articles were reviewed in detail. Twenty-nine articles met the inclusion criteria, 25 of which were published in 1998 or later. These 25 described 14 cohorts of at least 268 unique patients. Most were observational studies, and one (Fagugli et al., 2001) was a small randomized trial. Decreases in systolic or mean arterial BP were reported in 10 of 11 studies, only two of eight found a statistically significant change in phosphate or phosphate binder dose with daily haemodialysis. No consistent improvements in anaemia measures, albumin level, or health-related quality of life measures were seen. The randomized crossover trial (Fagugli et al., 2001) showed significant decrease in left ventricular mass (LVM) index. A later (2008) review by Punal et al. described similar findings (Punal et al., 2008).

There are few studies that examine mortality in short daily haemodialysis. A relatively small, long-term observational trial from Brazil showed good outcomes when patients were switched from conventional to short daily haemodialysis (Martins Castro et al., 2006). Mortality and morbidity in these 26 patients were reportedly low following conversion to daily dialysis, and vascular access survival was high after up to 48 months of treatment. Blagg and colleagues compared survival in 117 US patients treated by short daily haemodialysis with patients reported in a contemporaneous national database, the United States Renal Data System (USRDS) (Blagg et al., 2006). Using the standardized mortality ratio, adjusting for differences in patient age, sex, race and cause of renal failure, these authors reported an SMR for short daily haemodialysis patients of 0.39, a statistically significant 61% better survival than comparable patients treated with conventional thrice-weekly haemodialysis. In a subsequent report from this same group, Kjellstrand et al. examined survival in 415 patients treated for 1006 patient-years with short daily haemodialysis performed five,

six, or seven times a week (Kjellstrand et al., 2008). Daily dialysis patients were from Europe and the United States, and were treated at home (415 patients) or in-centre (150 patients). The reported 5-year cumulative survival was 68% and 10-year survival 42%, much better than USRDS-reported survival for matched patients treated with conventional thrice-weekly dialysis, and comparable to survival for deceased donor kidney transplant recipients. Interpretation of these findings is difficult, given that neither study adjusted adequately for potential confounding factors. Specifically, Blagg et al. did not adjust for duration of end-stage renal disease (ESRD); the conventional group was drawn from incident patients starting dialysis while the short-daily patients had been on dialysis for many years—potentially suggesting a survivor effect. Similarly, Kjellstrand et al. compared a predominantly European daily dialysis study sample to patients receiving conventional dialysis in the United States—where mortality rates are known to be substantially higher than in Europe. Finally, nearly two-thirds of daily dialysis patients were treated at home, while USRDS comparison patients were treated in-centre.

Kjellstrand and colleagues went on to examine the association of survival with time on dialysis, dialysis site, and dose of dialysis (Kjellstrand et al., 2010). While no association between Kt/V_{urea} and survival was found, four factors were independently associated with survival: age, weekly dialysis hours, home dialysis, and secondary renal disease. Of particular interest, daily haemodialysis patients did not show a pattern of excessive death early in the week, unlike the sudden and cardiac deaths on Mondays and Tuesdays after the long weekend interval between dialyses observed with conventional haemodialysis (Bleyer et al., 1999; Foley and Collins, 2010; Foley et al., 2011).

Virtually all studies of short daily haemodialysis are examinations of observational cohorts. Particularly in the area of chronic and end-stage kidney disease, there are very few randomized controlled studies (Himmelfarb et al., 2007). For studies of dialysis patients, who frequently come to end-stage kidney disease with many co-morbidities, selection bias is particularly difficult to control. Despite attempts to limit selection bias with risk stratification and other manoeuvres, bias may still remain. For example, Quinn and colleagues showed that selection bias explains the apparent differential mortality between dialysis modalities, haemo- and peritoneal dialysis (Quinn et al., 2011). Recruitment into randomized controlled studies of frequent haemodialysis has proven to be both difficult and costly. Prospective observational studies with adequate matching of controls and study subjects may be the next best study design, but such studies have not yet been done. The retrospective observational studies that have been published must be viewed in the context of their intrinsic methodological limitations, and should be interpreted with care.

Randomized trials of daily dialysis

Frequent Haemodialysis Network Daily Trial

The Frequent Haemodialysis Network (FHN) Trial Group reported findings from the first modest-sized randomized controlled trial of in-centre 'daily' (six times a week) haemodialysis compared to conventional (three times a week) treatments (Suri et al., 2007; FHN Trial Group et al., 2010; Rocco et al., 2011a). This multicentre trial enrolled 245 dialysis patients from 65 centres in the United States and Canada. Randomization was stratified according to clinical centre and diabetes status, and between-group comparisons were concealed from the investigators throughout the trial. Patients assigned to thrice-week dialysis (120 subjects) continued their usual dialysis prescriptions (minimum target equilibrated Kt/V_{urea} 1.1 and session length 2.5–4.0 hours). Patients assigned to frequent dialysis (125 subjects) were prescribed six times per week treatments, and target equilibrated Kt/V_{urea} (with V normalized to $3.271 \times V^{2/3}$) 0.9 for each dialysis, provided that the dialysis session length was 1.5–2.75 hours. Patients were treated on this protocol for 12 months.

The study was not powered to assess individual endpoints of death or hospitalization, since this would have required randomization of several thousand subjects (Kliger, 2007). Therefore two co-primary outcomes were examined: (1) death, and for those surviving, the change in LVM as assessed by cardiac cine-magnetic resonance imaging, and (2) death, and for those surviving, change in the physical-health composite score from the RAND 36-item health survey (RAND-36). Many secondary outcomes were also examined, including the domains of cardiovascular structure and function, hypertension, physical health, mental health, cognitive function, nutrition, mineral metabolism, anaemia, death, and hospitalization.

The baseline characteristics of the two groups were similar. Intention-to-treat analyses were performed. Results showed good adherence to prescribed protocol: weekly number of treatments delivered averaged 2.88 for the conventional (three times per week) group and 5.17 for the frequent (six times per week) group. Total dialysis time per week: 10.4 hours for conventional, and 12.7 hours for the frequent haemodialysis group. Weekly standard Kt/V_{urea}: 2.57 for the conventional and 3.60 for frequent haemodialysis. This 40% increase in weekly standard (std) Kt/V_{urea} was substantially greater than the 16% increase of the HEMO study (Daugirdas et al., 2010). Both co-primary outcomes showed significant improvements in the short daily haemodialysis group. Death or change in LVM showed mean reduction of 12.3 g in left ventricular (LV) size (excluding the papillary muscles) in the frequent haemodialysis group, compared with a 2.2 g reduction in the conventional group, with hazard ratio (HR) of 0.61 (95% confidence interval (CI) 0.46–0.82). Death or change in physical health component of the RAND-36 showed mean increase of 2 points in the frequent dialysis group, compared with no change in the conventional dialysis subjects, with a HR of 0.70 (95% CI 0.53–0.92). Of the main secondary outcomes, pre-dialysis phosphorus (mineral metabolism domain) and pre-dialysis systolic BP showed significant differences, with frequent haemodialysis showing better outcomes. No other main secondary outcomes showed significant differences between the groups. However, time to first vascular access intervention was significantly shorter in the daily haemodialysis group, and the total number of vascular access interventions was also higher. Vascular access failure rate was not different between the groups.

Nocturnal haemodialysis

Nocturnal haemodialysis is typically done for 6–8 hours while patients sleep, for 5–7 nights per week. Given the intensity of this schedule, most patients receiving this therapy dialyse at home. In the 1960s, Shaldon demonstrated the feasibility of over-night unattended haemodialysis in the home (Shaldon, 1964, 1968). Charra

and colleagues began long (8-hour, three times per week) treatments in the 1970s, some done overnight (Charra, 2005), believing that overnight dialysis produces 'the lowest possible hindrance on a patient's life'. In 1994, Uldall started a nocturnal haemodialysis programme in Toronto, Canada (Uldall et al., 1996), which grew to become one of the largest programmes of its kind. Pierratos and colleagues reported improved BP control, anaemia, phosphate levels, and quality of life in this cohort (Pierratos et al., 1998).

In 2005, Walsh and colleagues published a systematic review of nocturnal haemodialysis (Walsh et al., 2005). Ten full-text articles were included in the review, all observational studies. Study sample size ranged from 5 to 63 patients, followed for 6 weeks to 3.4 years. They found improved control of hypertension in all seven studies that examined BP. All five studies examining phosphate control showed reduced serum phosphorus levels or reduced need for phosphate binders with nocturnal haemodialysis.

Since 2005, several interesting studies of nocturnal haemodialysis were published. In 2008, Bergman and colleagues retrospectively compared 32 patients on nocturnal haemodialysis to 42 matched conventional haemodialysis patients (Bergman et al., 2008). After a mean follow-up of 26 ± 3 months, the cardiovascular hospitalization rate was reduced by 43% in the nocturnal haemodialysis patients. Pauly et al. performed a matched cohort study comparing survival of 177 nocturnal haemodialysis patients from two regional nocturnal haemodialysis programmes in Canada, and 1062 kidney transplant recipients in the USRDS database (Pauly et al., 2009). Subjects were followed for up to 12.4 years. There was no difference in the adjusted survival between nocturnal haemodialysis patients and deceased donor kidney transplant recipients, while living donor kidney transplant recipient survival was better than both. Since survival for conventional thrice-weekly haemodialysis patients is inferior to deceased donor transplant recipients, a survival advantage for nocturnal haemodialysis over conventional dialysis is implied. One limitation of this study was that the analysis censored for switches back to conventional haemodialysis. As the number of patients who were censored in each group was not reported, the possibility of bias exists. A retrospective review of the USRDS database estimated survival and hospitalization among 94 nocturnal haemodialysis patients compared with 10 propensity score-matched control patients for each nocturnal dialysis patient. Nocturnal haemodialysis was found to be associated with significant reductions in mortality risk and risk for mortality or major morbid event when compared to conventional haemodialysis (Johansen et al., 2009). This study may have been affected by immortal time bias.

Several other observations in nocturnal haemodialysis patients deserve mention. While the effects of nocturnal dialysis on erythropoietin-stimulating agent dose and anaemia have been inconsistent, Chen and colleagues demonstrated improvement in haematopoietic progenitor cell growth and a coordinated increase in expression of genes affecting red blood cell production (Chan et al., 2009a). A case report suggesting improvement in open-angle glaucoma after conversion to nocturnal haemodialysis was published (Kocak et al., 2006).

Randomized trials of nocturnal haemodialysis

Alberta Trial

The first randomized controlled trial of nocturnal haemodialysis compared with conventional dialysis was performed in Alberta, Canada, and reported by Culleton and colleagues in 2007 (Culleton et al., 2007). Patients were recruited from 10 haemodialysis units at two universities between August 2004 and December 2006. Subjects were randomized to frequent home nocturnal haemodialysis or conventional thrice-weekly treatments. Nocturnal haemodialysis patients were trained to have dialysis at home without remote monitoring, and dialysed 5–6 nights a week for a minimum of 6 hours per night. Conventional dialysis patients continued their pre-randomization thrice-weekly dialysis, with targeted single pool $Kt/V_{urea} \geq 1.2$. All were studied for 6 months. The primary outcome was change in LVM measured by cardiovascular magnetic resonance. Readers were blinded to any clinical or group-specific information. Secondary outcomes included change in health-related quality of life, pre-dialysis systolic BP, change in the erythropoietin:Hb ratio and change in the calcium × phosphate product. Fifty-two patients were randomized, 44 completed the baseline magnetic resonance imaging and were included in the analysis using an intention-to-treat approach. LVM (including the papillary muscles) decreased by an average of 17.8 g in the nocturnal group, and increased by 1.8 g in conventional dialysis patients (CI 1.9–37.4 g; P = 0.03). Of the secondary outcomes, BP and calcium × phosphate product were significantly reduced. No differences in anaemia control were seen, and quality of life measures will be discussed below.

Frequent Hemodialysis Network Nocturnal Trial

In 2011, the FHN Trial Group published results of a modestly larger randomized controlled trial of frequent nocturnal haemodialysis compared to conventional thrice-weekly treatments (Rocco et al., 2011a, 2011b). Patients were recruited from eight regional centres comprising 14 dialysis units in the United States and Canada between March 2006 and May 2009. Patients were studied for 12 months on their assigned treatments, and the trial concluded in May 2010. Eighty seven patients were randomized in a 1:1 ratio to either home nocturnal haemodialysis performed six times per week for ≥ 6 hours per session, or conventional thrice-weekly dialysis. A protocol change was made after an initial 'vanguard' phase of the study. For the first 15 subjects randomized, conventional dialysis was delivered in-centre. Thereafter, for the remaining 72 patients randomized, conventional thrice-weekly treatments were performed at home. The same primary and secondary outcomes as described in the FHN Daily Hemodialysis Trial (see 'Short daily haemodialysis') were measured.

The baseline characteristics of the two groups were similar. Eighty-six per cent of patients in the frequent nocturnal arm had a delivered mean weekly std Kt/V_{urea} of ≥ 4.0, and 100% of patients in the conventional arm had a delivered mean std Kt/V_{urea} of ≥ 2.0. Adherence to treat modality was defined as a patient attending at least 80% of dialysis treatments in a given month. Nocturnal dialysis patients adhered to the dialysis prescription 72.7% of the time, while conventional dialysis adherence was 97.6%. Frequent nocturnal dialysis patients had an average reduction in LVM of −10.9 g, but with a wide confidence interval (−23.7 to +1.8). The HR for the co-primary outcome of death or change in LVM was 0.68, and did not reach statistical significance (CI 0.44–1.07). The physical health composite (PHC) of the RAND-36 increased in all subjects, and there was no significant difference between the study groups. For the co-primary outcome of death or change in the PHC, the HR was 0.91, with 95% CI 0.44–1.07. Among the secondary outcomes, pre-dialysis phosphorus and pre-dialysis systolic BP were

each significantly lower in the nocturnal dialysis patients when compared to conventional dialysis, and none of the other secondary outcomes were significantly different. No clinically important effect on anaemia management was seen (Ornt et al., 2013). One important finding was the effect of frequent haemodialysis on residual kidney function (Daugirdas et al., 2013). Among the 63 participants with non-zero residual kidney function at baseline, those assigned to frequent dialysis showed significantly accelerated decline in urine volume, creatinine, and urea clearance when compared to patients on conventional haemodialysis.

Frequent haemodialysis, whether performed at home or in-centre, requires using the vascular access more often than with conventional haemodialysis. In the FHN daily in-centre haemodialysis trial, the risk for a first access event was 76% higher with daily haemodialysis than with conventional haemodialysis (Suri et al., 2013). Among patients with an arteriovenous access at randomization, the risk was 90% higher with daily haemodialysis. In addition, daily haemodialysis patients had significantly more arteriovenous access repairs than conventional haemodialysis patients. Losses of arteriovenous access did not differ between the groups. In the FHN nocturnal trial, there was a trend toward an increased rate of vascular access complications in the frequent nocturnal arm, with more access procedures, slightly more access failures, and sooner time to first vascular access event. These differences did not reach statistical significance.

The different results from the two FHN trials may seem surprising; the pre-determined criteria for demonstrating a positive effect of frequent dialysis were achieved in the Daily Hemodialysis trial, and not in the Nocturnal trial. It should be noted that the mean change in LVM for frequent dialysis versus standard thrice-weekly subjects in both trials was similar (12.3 g reduction in the daily trial and 10.9 g in the nocturnal trial), and this was in the same range as the reduction in the LVM seen in the Alberta trial. The patients enrolled in the two FHN trials had some important differences: patients in the daily study were largely 'prevalent' haemodialysis patients, with a mean (SD) time on dialysis of 5.71 (6.05) years before randomization, while most patients in the nocturnal trial were 'incident' to dialysis, starting dialysis for the first time. Endogenous kidney function and urine volume were higher among nocturnal trial patients than daily trial subjects. Finally, the nocturnal trial had inadequate statistical power to show a difference between groups: post hoc analysis shows that a sample size of 275 patients would have been needed to obtain 80% power to detect a mean effect on LVM of 10 g, and 125 patients to detect a mean change of 15 g. In terms of the quality of life, the Daily Trial PHC scores for subjects receiving frequent haemodialysis were significantly better than those of thrice-weekly dialysis subjects. In the Nocturnal Trial, the PHC scores were no different between frequent haemodialysis and thrice-weekly groups: scores for both groups increased modestly. Since most patients in the Nocturnal Trial switched from in-centre to home dialysis, we speculate that the positive effect of moving dialysis to the home setting was the dominant force in improving the PHC score to a similar extent in both groups in this trial.

Home setting versus frequency of dialysis

One difficulty in interpreting the results of frequent home haemodialysis is the confounding of dialysis frequency and the home location for treatments. As described above, improvements in physical health as perceived by patients in the FHN nocturnal home trial may be related to the home setting and not the frequency of dialysis. An observational cohort analysis of 26,016 patients in the Australia and New Zealand Dialysis and Transplant registry examined mortality (Marshall et al., 2011). Marginal structural modelling was used to adjust for time-varying medical co-morbidity. They found a survival advantage of home haemodialysis without a difference between conventional and frequent or extended modalities. The confounding between the home setting and frequency or length of treatments can only be sorted out definitively with prospective clinical trials, difficult to perform given the relatively small numbers of home haemodialysis patients and the reluctance of patients and their physicians to enter such randomized clinical trials.

The International Quotidian Dialysis Registry

In April 2001, the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) and the Health Care Financing Administration (HCFA) sponsored a meeting with key leaders in the field to explore the role of frequent dialysis as a treatment option for ESRD. At that meeting, the significant knowledge gaps regarding frequent haemodialysis were highlighted, and several recommendations were made to address this deficiency. The first recommendation was that two randomized trials of daily and nocturnal dialysis should be conducted—it is from this recommendation that the FHN trials were sponsored and carried out (Suri et al., 2007; FHN Trial Group et al., 2010; Rocco et al., 2011b). However, it was recognized that these initial randomized trials would likely be pilot trials, without adequate statistical power to examine the effect of frequent haemodialysis on hard outcomes such as hospitalizations, vascular access complications, and mortality. Moreover, as randomized trials usually enrol a selected population and implement a single, specific intervention, other studies would be required to assess how frequent haemodialysis therapies were currently being used in practice. Thus, the second recommendation was to establish a North American Registry of Daily Dialysis. It was based on this recommendation that the International Quotidian Dialysis Registry (IQDR) was established.

The IQDR is a collaborative, multinational, cooperative effort that involves multiple investigators. In 2004, an International Registry Steering Committee (IRSC) was assembled, including representatives from the International Society for Hemodialysis, the USRDS, and NIH/NIDDK (Nesrallah et al., 2004). The project is funded mainly through unrestricted grants from industry sponsors, whose representatives are included as non-voting members. The IRSC provides oversight of data collection and quality control, maintains patient confidentiality, and raises funds. The Coordinating Center for the Registry was designated to be Lawson Research Institute, University of Western Ontario, London, Canada, where the local Operations Committee is responsible for day-to-day management. The Coordinating Center obtained local Research Ethics Board approval, and established Scientific and Operational Committees.

The IQDR collects data on patients who are receiving 'intensive' haemodialysis: all patients who are receiving either long (>5.5 hours) or frequent (more than five treatments per week) haemodialysis are eligible to participate. Treatment may be in a haemodialysis unit or at home. The goals of the IQDR are to (a) describe

national and centre-specific trends in frequent haemodialysis prescription, delivery, and adherence; (b) to assess overall rates of specific outcomes in patients receiving frequent haemodialysis; such as mortality, hospitalizations, and vascular access complications; (c) to compare patient characteristics and outcomes of patients receiving various frequent haemodialysis regimens; and (d) to compare hard outcomes (such as mortality, hospitalizations, vascular access complications, and modality survival) of patients undergoing frequent haemodialysis with those undergoing conventional thrice-weekly haemodialysis using a matched cohort design.

Participation is completely voluntary, although participating centres are provided with a minimal stipend for each patient they enrol. After obtaining patient consent, coordinators from each centre enter data on demographics, comorbidities, laboratory parameters, medication use, physical parameters such as BP and target weight, and events such as death, hospitalizations, vascular access complications, change of dialysis therapy, and transplantation. In 2006, a second means of data collection was added. The secondary data collection consists of merging databases from other organizations already collecting data on patients undergoing intensive dialysis with the IQDR. Such organizations to date have included industry databases, such as Fresenius Medical Care North America, and national registries, such as the French Renal Epidemiology and Information Network (REIN) Registry and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).

To date, the IQDR has collected data on > 4000 patients from five countries, and enrolment continues (Nesrallah et al., 2005). Participating countries are Canada, the United States, France, New Zealand, and Australia and plans are underway to include the United Kingdom during the next phase. International trends in frequent and intensive haemodialysis therapy have been described in successive annual reports of the IQDR since 2005 (Nesrallah et al., 2005, 2006, 2007, 2008, 2009; Lindsay et al., 2011; 70-75). Three matched cohort studies have been completed and presented at the 2011 World Congress of Nephrology and the 2011 American Society of Nephrology. These results are awaiting publication.

Will patients choose short daily and home nocturnal haemodialysis?

Both short daily and nocturnal haemodialysis require changes to the daily routine and to the dialysis facility structure to provide these more frequent therapies. In-centre dialysis programmes are structured around thrice-weekly treatments, accommodating one set of patients on Monday/Wednesday/Friday, and another on Tuesday/Thursday/Saturday. Daily dialysis restricts availability of the dialysis machine to one set of patients 6 days a week. Even though the treatments are shorter, scheduling daily dialysis patients in facilities structured to care for conventional thrice-weekly treatments is difficult. Daily dialysis also requires that patients agree to and tolerate the frequent schedule, which can have significant impact on patients' lives. One of the challenges to recruit patients to participate in the FHN Daily Trial was the requirement for daily treatments, travel to and from the dialysis facility twice as often as for conventional dialysis, and twice the frequency of venepuncture for vascular access.

For nocturnal dialysis, patients must be willing and able to do their own dialysis treatments in the home, and centres must have the resources and infrastructure to support them. Several systematic barriers to the effective delivery of home dialysis in the United States have recently been reviewed (Golper et al., 2011). These include inadequate education about home therapies for patients, and inadequate education, training, and experience with home therapies among physicians and dialysis staff. Other barriers to home dialysis include governmental and regulatory barriers, and barriers related to the business practices of dialysis providers. Lack of support for a home care partner is also discussed. The likelihood that patients and their doctors will choose home dialysis rather than in-centre treatments varies widely across the globe. The use of home haemodialysis ranges from 1% of all haemodialysis patients in the United States, to 4.6% in Denmark, 9.4% in Australia, 15.6% in New Zealand, and 41% in Hong Kong (United States Renal Data System, 2010). These differences are related in part to local custom, familiarity with home therapies, and patient preferences. Financial pressures may also influence choice of dialysis modality. In the United States, payment for dialysis care by the largest payer, the federal government through the Medicare system, has not been directly related to the cost of providing that care. Home dialysis therapies generally cost less than in-centre dialysis, in large part because nurses or technicians do not perform dialysis at home. Nonetheless, home treatments have been reimbursed at the same rate as in-centre dialysis. Recent changes to the law, expanding bundled payments to dialysis facilities, and promoting payment for quality outcomes instead of payment for episodes of care, may change this. In this new payment environment, dialysis facilities no longer receive most of their payment for episodes of care or for individual dialysis-related medications, but instead receive a fixed sum covering all dialysis sessions and medications associated with those treatments. Many believe that this change incentivizes facility owners to encourage more home-based dialysis.

What are patients' views regarding choice of dialysis modality? Lee and colleagues described focus group interviews with 24 dialysis patients, three pre-dialysis patients, and 18 relatives in Denmark (Lee et al., 2008). Key factors in determining modality choice were flexibility, independence, and feelings of security. Other factors included physical space and noise, and maintenance of a normal life. Of note, none of the patients treated with conventional in-centre haemodialysis had been given a choice of dialysis modality, and only 25% of patients had attended a pre-dialysis educational programme. Patients' families thought it important that they were involved in the modality decision-making. The authors conclude that a move towards more patients on home dialysis requires professional support, timely education, and closer consideration of patients' preferences and current lifestyle.

Several dialysis machine manufacturers developed dialysis devices specifically for home use to ease burden on patients. The machine that has gained the most popularity is the NxStage System One. This portable machine differs from other dialysers, delivering slow dialysate flow, typically 15–30 L per dialysis. This simplifies its design, making the dialysis machine easy to install and use at home, but limits per-treatment clearance of small molecular size solutes. It is well suited to deliver daily dialysis, producing weekly standard Kt/V_{urea} 2.5 + 0.3 when used 6 days a week for an average 17.5 hours weekly (Kohn et al., 2010). Currently, a prospective cohort study of daily home haemodialysis with matched control group is underway, using this device (Jaber et al., 2010). This study seeks to enrol up to 500 participants at 70 clinical sites, and to study hospitalization, medical expenditures and other outcomes following 1 year of treatment.

Although patients do not perceive nocturnal home haemodialysis as a more intrusive treatment than home peritoneal dialysis (Fong et al., 2007), patient-perceived barriers to the adoption of nocturnal home haemodialysis include fears of self-cannulation, a catastrophic event, and the burden on family (Cafazzo et al., 2009). In the FHN trial, most home dialysis patients perceived substantial burden on their unpaid caregiver. This self-perceived burden was associated with worse depression and quality of life (Suri et al., 2011). In-centre daily haemodialysis did not result in higher perceptions of caregiver burden (Suri et al., 2014). This finding contrasts with an earlier study showing caregiver burden with daily haemodialysis (Rutkowski and Rychlik, 2011).

In-centre nocturnal haemodialysis

Several centres around the world have reported experience delivering long hours dialysis, in-centre overnight, three times a week (Troidle et al., 2007; Bugeja et al., 2009; Powell et al., 2009; Lacson et al., 2010; Ok et al., 2011). This is in contrast to home nocturnal haemodialysis that is typically done 5–6 nights per week. Charra and colleagues from Tassin, France, have for 30 years been treating patients with a low-salt diet, long, slow dialysis with careful efforts to return total body volume to normal (Charra et al., 1983, 2003). Most of these treatments were delivered during the day. In recent years, this basic technique has been used to create in-centre nocturnal haemodialysis (ICNH), delivering thrice-weekly overnight treatments lasting 6–8 hours with reduced blood pump speeds of about 300 mL/min (Kliger, 2009). Prolonged dialysis time allows the ultrafiltration rate to be lower than standard time dialysis, a feature of ICNH that might be expected to improve patient survival (Kliger, 2009). Centres in the United States, United Kingdom, Germany, Italy, Canada, and Turkey have reported observational studies of ICNH, and described reduced phosphorus and beta-2-microglobulin, lower ultrafiltration rates and enhanced clearances of urea. Improved BP control with fewer antihypertensive medications, reduced erythropoietin-stimulating agent use, and improved quality of life were also described.

In one large retrospective case control study from a US national dialysis company, 655 patients from 56 haemodialysis units were treated with ICNH for 55 ± 73 days, and compared with concurrent information from all other (15,334) prevalent conventional haemodialysis patients treated in 244 dialysis units within the surrounding geographic area of the 56 ICNH facilities (Lacson et al., 2010). Primary outcomes were mortality (composite of death plus withdrawal from dialysis therapy) and hospitalization. Patients on ICNH were younger, were less likely to have diabetes, had larger surface area, were more likely to be black and used proportionately more fistulas for vascular access. After adjustment for case mix and vascular access, the HR for 1-year survival was 0.90, not significantly different than control subjects. The adjusted HR for hospitalization risk was 0.88 (95% CI 0.78–0.98; $P < 0.02$). In a subsequent analysis, this group analysed 746 patients initiating nocturnal in-centre haemodialysis in 2006–2007, and compared mortality risk to a propensity score-matched cohort of 2062 control patients on conventional haemodialysis from the same geographic area (Lacson et al., 2012). Two-year mortality was 19% versus 27%, favouring nocturnal haemodialysis patients. HR for death was 0.75 (95% CI 0.61–0.91; $P = 0.004$) after adjustment for baseline characteristics of the groups. Another large prospective case–controlled study compared 247 ICND patients to 247 4-hour conventional dialysis patients matched for age, sex, diabetes status, and haemodialysis duration (Ok et al., 2011). The primary outcome was 1-year mortality. Results showed mortality rates were 1.77 for ICNH and 6.23 for controls per 100 patient-years ($P = 0.01$), a 72% risk reduction (HR 0.28, 95% CI 0.09–0.85, $P = 0.02$). The patients in the ICNH group had fewer hospitalizations. In addition, patients in the ICNH group showed increasing serum albumin levels, declining doses of antihypertensive and erythropoietin-stimulating medications, and declining LVM index and left atrial and LV end-diastolic diameters. Use of phosphate binders and serum phosphate levels fell in the ICNH group and cognitive function improved.

The limitations of these non-randomized studies, where patients and their physicians self-selected for ICNH treatment, and adjustment for co-morbid conditions and other differences between the compared groups was incomplete, must be considered when assessing the results that are reported. Nonetheless, when taken together with the randomized controlled trials of more frequent haemodialysis (Culleton et al., 2007; FHN Trial Group et al., 2010; Rocco et al., 2011b), these reports suggest that there may be several advantages to ICNH. Patients and nephrologists have been choosing this alternative form of dialysis with some enthusiasm: the two largest dialysis providers in the United States reported treating > 1600 patients with ICNH in March, 2009 (Kliger, 2009). Dialysis providers may find ICNH a particularly attractive dialysis modality from a financial standpoint, since dialysis units are usually closed at night, with unused dialysis machines in empty facilities. The marginal cost to establish an ICNH programme is less than the cost of a *de novo* facility. Bujega et al. report several barriers to ICNH, including nurse recruitment, nocturnal physician visits, and the challenges to provide comfortable sleep for patients (Bugeja et al., 2009).

Specific effects of more frequent or intense haemodialysis

Cardiovascular effects

The leading causes of death among patients with kidney failure treated with dialysis are cardiovascular events. Patients with ESRD are usually volume expanded and pressure overloaded from salt and water retention, increased peripheral vascular resistance and arterial stiffness (London, 2003; Pauly and Chan, 2007). More frequent haemodialysis may reduce the usually expanded volume of patients and reduce the wide swings of intravascular volume between dialysis treatments. To the extent that these volume-induced abnormalities cause hypertension, LVH and congestive heart failure, more frequent or intense haemodialysis could ameliorate these changes and ultimately avoid left ventricular remodelling, LVH, CHF and uraemic cardiomyopathy (Pauly and Chan, 2007). In addition to its effect on volume, more frequent haemodialysis may have other cardiovascular effects that prove to be beneficial. We will review evidence that frequent haemodialysis reduces BP and baroreflex effectiveness, myocardial stunning, LVH, and dysfunction, ventricular volumes, uraemia-associated inflammation, and improves vascular smooth muscle biology. ICNH may even improve myocardial fibrosis.

Hypertension

More than 80% of patients with ESRD have hypertension (Chan et al., 2002, 2003). The systematic reviews of more frequent haemodialysis (Walsh et al., 2005; Suri et al., 2006; Punal et al., 2008) and

the randomized controlled trials (Culleton et al., 2007; FHN Trial Group et al., 2010; Rocco et al., 2011b; Kotanko et al., 2015) show that reduced BP is one of the most consistent effects of more intensive haemodialysis. While this may in part be a function of better volume control, other effects of more intensive haemodialysis may also be important. Renal failure may increase reflex neurogenic vasoconstriction without volume expansion (Converse et al., 1992). Increasing dialysis treatment time may lower BP without changes in extracellular fluid volume or weight (Luik et al., 2001; McGregor et al., 2001), perhaps by increasing clearance of vasoconstrictors (Katzarski et al., 1999). Chan and colleagues reported that nocturnal haemodialysis significantly reduced total peripheral resistance, while stroke volume and pre-dialysis and post-dialysis weights remained unchanged (Chan et al., 2003). The observed improvement in BP was thus attributed to a decrease in the elevated afterload of ESRD rather than to a fall in cardiac filling pressure or intravascular volume. These investigators demonstrated a sustained reduction in plasma norepinephrine with nocturnal haemodialysis, despite withdrawal of angiotensin-converting enzyme inhibitor medication in more than half of their subjects. They found that endothelium-dependent, flow-mediated vasodilation can be restored by the augmented dose of nocturnal haemodialysis, resulting in gradual reduction in vascular smooth muscle tone with progressive fall in total peripheral resistance over time. Nocturnal home haemodialysis also improves the baroreflex effectiveness index. Chan and colleagues studied 20 consecutive patients who were changed from conventional thrice-weekly to nocturnal haemodialysis (Chan et al., 2008). Antihypertensive medications were withdrawn, because systolic BP fell, and the baroreflex effectiveness index and baroreflex sensitivity both increased. The authors speculated the improved baroreflex regulation of heart rate reduces heart rate variability and contributes to greater haemodynamic stability.

Punal et al. systematically reviewed studies of hypertension in short daily haemodialysis (Punal et al., 2008). Patient treated with daily dialysis, compared to thrice-weekly treatments, have greater reductions in both systolic and diastolic BPs (Buoncristiani et al., 1996; Pinciaroli, 1999; Koshikawa et al., 2003; Reynolds et al., 2004; Traeger et al., 2004; Goldfarb-Rumyantzev et al., 2006). When patients are switched from conventional to daily dialysis, they frequently can reduce or discontinue antihypertensive medications (Buoncristiani et al., 1996; Galland et al., 2001; Koshikawa et al., 2003; Ting et al., 2003; Traeger et al., 2004; Williams et al., 2004). Short daily haemodialysis may reduce intradialytic BP variability. In a small retrospective cohort study, Murashima et al. examined 12 hypertensive patients converted from conventional to short daily haemodialysis (Murashima et al., 2010). A significant reduction in intradialytic BP variability was seen, and less hypotension was observed during treatment with short daily haemodialysis. Reduced BP has also been reported in patients on continuous ambulatory peritoneal dialysis (Leenen et al., 1985). Reduced intravascular volume, reduced swings in volume with continuous or more frequent treatments, or non-volume related factors could all contribute to the observed improvements in BP.

Myocardial stunning

Myocardial stunning is one possible non-traditional risk factor for sudden death that haemodialysis patients may experience. Coronary artery disease in the non-uraemic population may induce recurrent myocardial stunning, causing heart injury and heart failure (Homans et al., 1989; Bolli, 1992). Haemodialysis patients may also suffer from recurrent dialysis-induced ischaemic injury, which may be modified by reduction of ultrafiltration rate and episodes of intradialytic hypotension (Burton et al., 2009). In a study of 46 patients comparing conventional thrice-weekly haemodialysis, daily dialysis, and nocturnal dialysis, more frequent dialysis regimens were associated with lower ultrafiltration volumes and rates compared with conventional treatments, and experienced fewer episodes of intradialytic hypotension (Jefferies et al., 2011). Echocardiograms were performed on all subjects. While there were no differences in resting cardiac ejection fraction among the groups, the proportion of patients with myocardial stunning was strongly related to the intensity of dialysis: all 12 patients on conventional thrice-weekly haemodialysis exhibited myocardial stunning; 92% of patients receiving short daily haemodialysis, 75% of those on home dialysis, and 50% on nocturnal haemodialysis showed this finding. There was also a strong correlation between the number of regional wall motion abnormalities and ultrafiltration rate. Lower ultrafiltration rates, fewer episodes of hypotension, fewer cases of regional wall motion abnormalities, and myocardial stunning all are factors that have been shown to influence survival.

Left ventricular hypertrophy

LVH and dysfunction are common in ESRD dialysis patients, and have been associated with survival (London et al., 2001; Foley, 2003; London, 2003; Zoccali et al., 2004). Expanded extracellular fluid volume, hypertension, and uraemic toxins are possible risk factors in these patients (Zoccali et al., 2003). Many observational trials showed less LVH in patients treated with daily or nocturnal haemodialysis (Chan et al., 2002; Lockridge et al., 2004; Ayus et al., 2005; Fagugli et al., 2006; Weinreich et al., 2006). The first randomized controlled trial of nocturnal haemodialysis, reported from Alberta, Canada, showed a significant decline in LVM for patients dialysed 5–6 nights a week compared with those on conventional thrice-weekly treatments (Culleton et al., 2007). The FHN Nocturnal Trial showed a statistically insignificant decline in LVH of the same magnitude as was seen in the Alberta study (Rocco et al., 2011b). The FHN Daily Trial showed significant decline in LVH for patients dialysed frequently in-centre compared with conventional treatments (FHN Trial Group et al., 2010). Some patients experienced a decline of > 60 g in LVM after 12 months of daily dialysis. A more pronounced effect of frequent haemodialysis on LVM was evident among patients with LVH at baseline, and changes in LVM were associated with changes in blood pressure (Chan et al., 2012). Taken together, these studies provide convincing evidence that more frequent dialysis reduces LVH. The observation that reduction in LVH correlates with survival in haemodialysis patients makes this a compelling finding for patients and their physicians as they make decisions regarding renal replacement therapies. Frequent haemodialysis also reduces left and right ventricular end systolic and diastolic ventricular volumes, but does not appear to affect left ventricular remodelling (Chan et al., 2013). A meta-analysis examining the effect of frequent or extended haemodialysis on cardiovascular parameters brought together single-arm cohort studies and randomized controlled trials examining the effect of frequent or extended haemodialysis on cardiac morphology and function. This analysis included 38 single-arm studies, five crossover trials and three randomized controlled trials. The analysis showed that frequent or extended haemodialysis

significantly reduced left ventricular mass index and improved left ventricular ejection fraction (Susantitaphong et al., 2012). Daily dialysis decreases plasma levels of brain natriuretic peptide (BNP), a biomarker that is stimulated in LV failure (Odar-Cederlof et al., 2006). ICNH may reduce myocardial fibrosis and improve cardiac performance. Jin et al. measured myocardial calibrated integrated backscatter, an ultrasonic technique that assesses myocardial fibrosis and contractile performance, in 32 ICNH patients and 58 matched conventional haemodialysis patients (Jin et al., 2011). After 12 months of follow-up, there was a significant decrease in the measured backscatter in the ICNH patients, and no change in conventional haemodialysis patients.

Impaired vascular function

ESRD patients demonstrate endothelial dysfunction (Verbeke et al., 2011). Shear stress-mediated increase of brachial artery diameter in response to hand-warming is impaired in patients with ESRD and particularly in those with both ESRD and cardiovascular disease. Impaired vascular smooth muscle responsiveness in ESRD dialysis patients may be a factor in their high cardiovascular mortality rate. Endothelial cell dysfunction is associated with intradialytic hypertension, and may partially explain the higher event rates observed in these patients (Inrig et al., 2011). Blunted vasodilator response to nitroglycerine (in coronary arteries) or nitric oxide donor (in the brachial artery) predicts cardiovascular events (Heitzer et al., 2001). Chan and colleagues studied flow-mediated and endothelium-independent vasodilatation in the brachial arteries of patients treated with nocturnal haemodialysis (Chan et al., 2003). Responses to post-ischaemic reactive hyperaemia and sublingual nitroglycerine were measured during conventional dialysis treatment, and then for 2 months after conversion to nocturnal dialysis. Flow-mediated vasodilatation was absent during conventional haemodialysis, and became evident and significantly different from baseline values after 1 month of nocturnal haemodialysis, and increased further after the second month. Nocturnal haemodialysis also increased the vasodilator response to nitroglycerine progressively over the 2 months of study. Thus the reflex neurogenic vasoconstriction commonly found in ESRD patients, which persists in conventional haemodialysis, may be ameliorated by more frequent dialysis. Improving this inappropriate increase in peripheral vascular resistance, the predominant haemodynamic abnormality in this population, may improve cardiovascular mortality. The same group examined vascular smooth muscle cells proliferation, a factor in the pathogenesis of atherosclerosis and medial calcification (Chan et al., 2009b). Chronic vascular smooth muscle cell apoptosis is associated with plaque rupture and vascular calcification in patients with normal and impaired kidney function (Clark et al., 2008). They demonstrated that nocturnal haemodialysis is associated with restoration of abnormal vascular smooth muscle cell biology. Another vascular abnormality induced by uraemia is impaired ischaemia-induced angiogenesis. Yuen et al. examined angiogenic activity of early-outgrowth endothelial progenitor-like cells, known promoters of angiogenesis in the setting of normal renal function. These cells were cultured from conventional haemodialysis patients, nocturnal haemodialysis patients and age- and gender-matched controls and then injected into the ischaemic hind limb of rats (Yuen et al., 2011). Although conventional dialysis cell injection had no effect, nocturnal haemodialysis and control cells significantly improved ischaemic hind limb perfusion and capillary density. Nocturnal haemodialysis is associated with normalization of endothelial progenitor cell number and their migratory function (Chan et al., 2005).

Inflammation

Frequent dialysis may reduce the inflammatory process that uraemia induces, and thus reduce atherosclerosis and cardiovascular mortality. Yuen and Chan reviewed the evidence that nocturnal haemodialysis may reduce uraemia-associated inflammation (Yuen and Chan, 2005). They described a preliminary observation of low rates of coronary artery calcification in a nocturnal haemodialysis cohort, where coronary artery calcium scores were low and may even decline after 1 year of nocturnal haemodialysis. Nocturnal haemodialysis patients have significantly lower levels of pro-inflammatory interleukin 6 (IL-6) compared to matched patients on conventional haemodialysis (Yuen et al., 2005, 2006). Biomarkers of inflammation have been correlated with myocardial stunning. Patients with myocardial stunning have higher levels of IL-6 (Jefferies et al., 2008) and pre-dialysis levels of cardiac troponin T (cTnT) predict the risk of stunning. Trends toward lower level of high-sensitivity C-reactive protein and cTnT in home-based frequent dialysis patients raise the interesting hypothesis that frequent dialysis may reduce pro-inflammatory biomarkers and thereby reduce myocardial injury (Jefferies et al., 2011).

Cardiovascular-related hospitalization rate

Cardiovascular-related hospitalization rate may be reduced in patients on nocturnal haemodialysis. Bergman and colleagues published a controlled cohort study, examining 32 nocturnal haemodialysis patients 1 year before and 2 years after conversion to nocturnal haemodialysis, and 42 matched conventional haemodialysis in the same period (Bergman et al., 2008). During the study period, dialysis or cardiovascular-related hospitalization rate was stable for the conventional haemodialysis cohort. Conversion to nocturnal haemodialysis was associated with a significant decrease in dialysis or cardiovascular-related admissions. The FHN Nocturnal trial did not confirm this finding. The rates of cardiovascular hospitalization, non-access hospitalizations, and all hospitalizations did not differ significantly between conventional and nocturnal haemodialysis groups (Rocco et al., 2011b). Similarly, the FHN daily dialysis trial showed that death or hospitalization rates were no different between daily dialysis and conventional dialysis groups (FHN Trial Group et al., 2010).

Mineral metabolism

Hyperphosphataemia, elevated calcium × phosphate product, hyperparathyroidism, and bone disease are common in ESRD and dialysis patients (Hruska and Teitelbaum, 1995; Block et al., 2004). Poor control of mineral metabolism is independently associated with mortality in these patients (Ayus et al., 2007). Phosphorus removal by conventional thrice-weekly haemodialysis is generally less than ingested phosphorus, and oral phosphate binders have been used to minimize hyperphosphataemia and bone disease. More frequent and longer dialysis regimens may increase phosphate removal and improve mineral metabolism. Pre-dialysis serum phosphorus was studied in a cohort of patients converted from conventional to daily haemodialysis (Yuen et al., 2005). Phosphorus fell significantly after conversion, with no change in serum calcium or phosphate binder use. Ayus and co-workers

performed a 12-month prospective, non-randomized controlled study of daily haemodialysis patients compared to conventional haemodialysis patients (Ayus et al., 2007). Phosphate control was superior in the daily haemodialysis group, and the percentage of patients using phosphate binders decreased from 77% to 40% in the daily haemodialysis group, while these values did not change in the conventional haemodialysis group. These investigators also described the effects of daily haemodialysis on five patients with severe secondary hyperparathyroidism (Achinger et al., 2010). After 1 year of daily haemodialysis, there was a 70% reduction in median parathyroid hormone (PTH) level, a 39% reduction in the calcium × phosphorus product and a 17.6% increase in the serum calcium. These changes permitted administration of high-dose paricalcitol, and improved control of severe secondary hyperparathyroidism. Nocturnal haemodialysis permits substantially more removal of phosphorus and often permits complete discontinuation of oral phosphate binders (Musci et al., 1998; Walsh et al., 2010). Kooienga reported that total weekly removal of phosphorus with nocturnal haemodialysis is more than twice that removed by conventional haemodialysis (Kooienga, 2007), and is associated with significantly lower serum phosphorus levels. Alternate nightly home haemodialysis is likewise effective. Van Eps et al. (2007) prospectively studies 26 patients converted from home dialysis performed 3.5–4 sessions per week for 3–5 hours, to alternate-night home treatments, 6–9 hours, 3.5–4 sessions per week. Most patients stopped their phosphate binders; serum phosphate and PTH levels fell significantly. Bone mineral density remained stable and ectopic calcifications (vascular and ectopic) improved or stabilized in 87.5% of patients. Bone histomorphometry showed persistence of abnormal bone turnover and mineralization in most patients. The effects of daily and nocturnal haemodialysis on mineral and bone disorder were examined in the randomized controlled FHN trials (Daugirdas et al., 2012). In the daily dialysis trial, assignment to frequent haemodialysis was associated with a significant 0.53 mg/dL decrease in mean serum phosphorus compared to the conventional arm, with a reduced oral phosphate binder intake. In the FHN Nocturnal Trial, there was a 1.34 mg/dL decrease in mean serum phosphorus, and phosphate binders were discontinued in 73% of the nocturnal haemodialysis group. At the 12-month end of the trial, 57% of nocturnal haemodialysis patients added phosphorus to the dialysate to prevent hypophosphataemia. Frequent haemodialysis did not exert major effects on calcium or PTH levels in either trial.

Sleep-disordered breathing and sleep apnoea

Perhaps the most common of all symptoms among ESRD patients are fatigue and tiredness, present in 12–97% of patients, and sleep disturbance, in 20–83% (Murtagh et al., 2007). Physiologic abnormalities of sleep may account for a substantial part of these symptoms. Sleep-disordered breathing is common in the general population, affecting as many as 60% of the elderly (Ancoli-Israel et al., 1991). This condition is associated with all-cause and coronary artery-related mortality (Punjabi et al., 2009), and an increased risk of developing cognitive impairment (Yaffe et al., 2011). Sleep-disordered breathing and excessive daytime sleepiness are also common among patients with chronic kidney disease and those on haemodialysis (Roumelioti et al., 2011). Obstructive sleep apnoea is the most common form of this disorder. It causes poor sleep, and has been associated with increased cardiovascular risk (Zoccali et al., 2002). Higher pre-dialysis serum phosphorus and depression are independently associated with decrements in sleep quality (Unruh et al., 2011). In one study, nocturnal hypoxaemia was significantly higher in haemodialysis patients than pre-dialysis chronic kidney disease patients (Roumelioti et al., 2011). The severity of sleep-disordered breathing did not vary between dialysis and off-dialysis evenings or morning and afternoon/evening dialysis shifts. In another cross-sectional study comparing sleep/wake behaviour in chronic kidney disease stages 4 and 5 and haemodialysis patients, all groups were shown to have short and fragmented sleep. Of particular interest, an early morning haemodialysis shift was associated with shorter total sleep time, and greater variation in nightly total sleep time (Barmar et al., 2009). The authors speculated that more frequent haemodialysis treatments might reduce the effect of the haemodialysis treatment itself on sleep, and help with a more balanced sleep time. Many dialysis patients would be willing to undertake intense haemodialysis for symptomatic benefits, with a majority of surveyed patients saying that improvement in sleep is a potential benefit of daily haemodialysis (Ramkumar et al., 2005). Observational studies have suggested that sleep apnoea improves when patients undergo nocturnal haemodialysis (Hanly and Pierratos, 2001; Hanley et al., 2003), perhaps related in part to physiologic changes in the upper airway or improvements in the melatonin-induced rhythms of sleep. Conversion from conventional to nocturnal haemodialysis was associated with an increase in pharyngeal cross-sectional area (Beecroft et al., 2008). In another study, 13 patients converted from conventional to nocturnal haemodialysis had significant improvements in subjective and objective measures of sleep, with partially restored nocturnal melatonin rhythm (Kock et al., 2009).

Quality of life

Patients' own assessment of the quality of their lives is an important outcome measure for any life-long treatment like haemodialysis, which has a profound effect on the rhythm and flow of everyday life. However, comparing the quality of life on daily or nocturnal dialysis compared to conventional dialysis is difficult. Patients and their physicians are never blinded to the treatment modality, and most patients studied have been switched from conventional to frequent dialysis regimens, likely with the expectation for improvement. In addition, investigators have used multiple instruments to measure quality of life, so comparing one study to another can be difficult. In the systematic reviews, most observational studies showed improvements in uraemic symptoms, and many described improvements in quality of life measures (Walsh et al., 2005; Suri et al., 2006; Punal et al., 2008). However the results were inconsistent. One study showed no clear effect of short daily haemodialysis on cognitive function or electroencephalogram tracings (Vos et al., 2006). Publications after these reviews have continued to suggest quality of life benefits for frequent haemodialysis (Punal Rioboo et al., 2009; Van Eps et al., 2010; Visaya, 2010). Participants in the FHN daily in-centre and home nocturnal haemodialysis trials did not show improvement in cognitive function (Kurella Tamura et al., 2013). Neither executive function nor global cognition improved following conversion from conventional thrice weekly haemodialysis to in-centre daily or home nocturnal haemodialysis. To eliminate the home setting as a confounder for comparing quality of life, Fong and associates used the Kidney Disease Quality of Life—Short Form (KDQoL) to compare all home dialysis patients,

treated with either peritoneal- or haemodialysis in one university health network (Fong et al., 2007). There were no differences in physical health summary, mental health summary, or kidney disease component summary between these groups. Thus, the home setting may be a key component of patient-perceived quality of life improvements. In another study, daily dialysis also was associated with long-term improvement of restless legs syndrome and sleep disturbances (Jaber et al., 2011).

The FREEDOM study examined the long-term impact of daily haemodialysis on depressive symptoms and post-dialysis recovery time (Jaber et al., 2010). Daily haemodialysis was provided using the System One NxStage dialyser. In this prospective observational study, the percentage of patients with depressive symptoms decreased significantly from 41% to 27% ($P = 0.03$) over the 12-month course of treatment. There was also a significant decrease in post-dialysis recovery time from 476 to 63 minutes ($P < 0.001$).

Two prospective randomized controlled trials of nocturnal haemodialysis and one of daily dialysis describe quality of life outcomes. Manns et al. described the quality of life measures in the Alberta study comparing nocturnal to conventional haemodialysis (Manns et al., 2009). The primary quality of life outcome, change in the EuroQoL-5D index score, showed a trend toward improvement that did not reach statistical significance. Nocturnal haemodialysis was associated with statistically significant and clinically important changes in pre-specified kidney-disease-specific measures, including symptoms/problems, effects of kidney disease, and burden of kidney disease. Following completion of the 6-month study, these investigators examined quality of life measures over a more extended period. Quality of life was relatively stable in the small number of patients who remained on nocturnal or conventional dialysis, and no significant association between dialysis modality and EuroQol-5D index was found. The FHN Nocturnal Dialysis Trial examined death or 12-month change in the patient self-reported RAND Short Form 36 (SF36) physical health composite as one of its co-primary outcomes (Rocco et al., 2011b). There was no significant difference in this measure between patients treated with nocturnal haemodialysis and those randomized to conventional thrice-weekly treatments. When this same measure was used to examine the effect of daily haemodialysis on the quality of care, a significant improvement was found in patients treated with daily in-centre dialysis compared with conventional treatments (FHN Trial Group et al., 2010). Other measures of quality of life did not show these improvements with daily dialysis: patients randomized to six times a week in-centre dialysis compared to three times a week treatment showed no significant change in the short physical performance battery, or the physical functioning subscale of the SF-36 (Hall et al., 2012). Thus, frequent in-centre haemodialysis improved self-reported physical health and functioning, but had no significant effect on objective physical performance.

Summary

More frequent haemodialysis has clearly been shown in randomized controlled trials to reduce LVH, pre-dialysis systolic BP, and pre-dialysis serum phosphorus, and to improve some aspects of patient-perceived quality of life. Evidence from observational trials suggest possible benefits of reduced inflammation, less myocardial stunning, improved vascular function, improved sleep-disordered breathing, possibly fewer hospitalizations, and improved mortality. It is possible that patient survival on frequent haemodialysis regimens may be comparable to deceased-donor kidney transplant recipient survival. Chronic kidney disease patients and their doctors should take these findings into consideration as they consider renal replacement therapies. The financial and lifestyle challenges of these therapies, along with the threats posed by more frequent vascular access, must be part of the discussion for choice of renal replacement modality. Home treatments are becoming easier and more popular, and the home setting itself may enhance quality of life. The IQDR will give us more information about the thousands of patients worldwide using frequent and home dialysis therapies.

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CHAPTER 263

Peritoneal dialysis: overview

Rajnish Mehrotra and Jonathan Himmelfarb

Introduction

Peritoneal dialysis (PD) requires the periodic instillation of dialysate into the peritoneal cavity and induces the movement of solutes and fluid across the semipermeable peritoneal membrane that allows for the successful management of the uraemic syndrome. Even though this was recognized as far back as 1923 (Ganter, 1923), technical limitations precluded the large-scale use of PD for the long-term treatment of end-stage renal disease (ESRD) for 50 years. This changed with the development of an indwelling catheter for PD by Henry Tenckhoff (Tenckhoff and Schechter, 1968), the description of the technique of continuous ambulatory peritoneal dialysis by Popovich and colleagues (Popovich et al., 1976), and the introduction of plastic bags in lieu of glass bottles (Oreopoulos et al., 1978). It is estimated that > 200,000 patients are undergoing treatment with PD worldwide, accounting for about 15% of the international dialysis population.

Types of peritoneal dialysis

Treatment with PD entails the sequential performance of 'exchanges'; an exchange refers to a single cycle of instillation of dialysate (1.5–3.0 L) followed by drainage after varying lengths of time. The possibility of varying the pattern of exchanges over the course of the day makes the therapy versatile and readily adaptable to the medical and lifestyle needs of individual patients. The exchanges can be performed either manually by a patient or with the assistance of a cycler (automated PD). The different ways to perform PD can be grouped as follows:

Continuous regimens

The overwhelming majority of patients are treated with such regimens in which a patient has intraperitoneal dialysate 24 hours a day, 7 days a week. This is achieved with one of the following approaches:

- *Continuous ambulatory peritoneal dialysis* (CAPD) is an approach in which a patient performs three to four exchanges over a 24-hour period and the dwell times for each exchange range from 3 to 8 hours.
- *Continuous cyclic peritoneal dialysis* (CCPD) is a form of automated peritoneal dialysis in which the patient performs three to five exchanges over generally a 9-hour period overnight. The intraperitoneal dialysate may or may not be exchanged by the patient manually during the remainder of the 15-hour period.
- *Tidal peritoneal dialysis* (TPD) is a modified form of automated PD in which the peritoneal cavity is not drained completely at the end of each exchange in order to maintain an intraperitoneal reservoir of fluid at all times. While the initial premise of using TPD to enhance peritoneal solute clearances has not been borne out in subsequent clinical trials, its use is now limited to patients with infusion pain.

Intermittent regimens

On occasion, PD can be performed without instillation of intraperitoneal dialysate for the entire 24-hour period:

- *Nocturnal intermittent peritoneal dialysis* (NIPD) is a regimen in which the patient undergoes cycler-assisted PD overnight only. NIPD is used either to reduce the burden of therapy or to minimize fluid reabsorption and hence, volume overload with the long-day dwell. However, this approach should be used only in individuals who have significant residual kidney function.
- *Diurnal ambulatory peritoneal dialysis* (DAPD) is a form of CAPD in which the patient performs two to four exchanges during the course of the day but does not have intraperitoneal dialysate overnight. This regimen should be limited to individuals with significant residual kidney function who reabsorb significant amounts of fluid with the long overnight dwell of CAPD.
- *Intermittent PD* is a therapy that should be used sparingly for the long-term treatment of ESRD, if at all. With this, patients are treated with frequent exchanges over 8–36-hour periods several times a week. This can be used as a bridge therapy, for example, in a new patient before training can begin.

Key advances in the delivery of peritoneal dialysis

The PD therapy delivered in 2012 differs considerably from the first attempts to fashion a CAPD regimen in 1978. Three key developments have had a substantial impact on the delivery of care of patients undergoing PD. First, there have been significant reductions in risk for PD-related peritonitis (Piraino, 1998). The average peritonitis rates in the 1980s were one episode per 6–12 patient-months. Since then, technical advances in how patients make connections and disconnections with each exchange, the prophylactic application of antibiotics either at the exit site or nares, and continuous quality improvement programmes have led to substantial reduction in risk for peritonitis such that some facilities have been able to achieve rates as low as one episode in 60 patient-months. Second, the cycler technology has evolved such that the machines used for APD are volumetric, considerably smaller, and hence, more portable. This

has driven an increase in use of cycler-assisted PD in many countries, primarily to reduce the burden of therapy on patients (United States Renal Data System, 2012). Finally, the recognition of the limitations of conventional PD solutions has led to the development of numerous alternatives that use an osmotic agent other than glucose (icodextrin or amino acids), glucose-based solutions with a buffer other than lactate (bicarbonate- or bicarbonate lacate-based solutions), or glucose and lactate-based solutions with very low concentrations of glucose degradation products (Mehrotra and Agarwal, 2008). The development of these alternative solutions has allowed for greater flexibility in designing PD prescriptions.

Utilization of peritoneal dialysis

PD can be successfully used for the treatment of ESRD as long as the patient or the caregiver is motivated to perform self-care dialysis, contingent upon the availability of a home and a functional peritoneal cavity. Consistent with this observation, over three-quarters of patients with ESRD have no medical or psychosocial contraindications for treatment with PD (Mendelssohn et al., 2009). Yet, the proportional utilization of PD varies considerably from one clinical practice, region, or country to the other, driven primarily by non-medical considerations such as physician education or enthusiasm, structure or availability of patient education, investments in infrastructure, and reimbursement patterns (Mehrotra, 2007). Furthermore, there is considerable evidence to support the thesis that secular decline observed in the use of PD in countries like the United States, Canada, and United Kingdom was driven primarily by non-medical considerations (Mehrotra, 2007).

The total societal costs of PD are lower in developed economies than in-centre haemodialysis and countries with predominantly public funding of healthcare have higher utilization of the therapy than countries with either a mixed model or those with primarily private payers. In order to promote a greater use of PD, several developed countries such as the United States have offered reimbursement incentives to dialysis providers to promote a greater use of the therapy (Sedor et al., 2010). While there seems to be an immediate increase in use of PD for treatment of ESRD in the United States, the long-term impact of such policy changes remains to be seen. The lower societal costs have driven two jurisdictions—Hong Kong and Thailand—to adopt a 'PD first' policy whereby in the absence of contraindications, the government will pay for renal replacement therapy only if the patient with ESRD is treated with PD. Consequently, > 80% of ESRD patients are treated with PD in these two jurisdictions. In contrast, the cost of PD is considerably higher in developing countries where the cost of importing PD solutions and disposables is significantly higher than the manpower costs for delivering in-centre haemodialysis (Li and Chow, 2001). In such countries, utilization of PD remains low. In addition to the overall utilization of PD, economic considerations also drive the use of different PD modalities. Thus, while substantial proportions of patients in the United States, Canada, and Western Europe are treated with automated PD, continuous ambulatory peritoneal dialysis is used almost exclusively in many developing countries.

Trends in outcomes with peritoneal dialysis

Randomized, controlled clinical trials remain the gold standard to compare the safety and efficacy of different therapies for the treatment of any clinical condition. However, the disparate effects of in-centre haemodialysis and PD on patients' lifestyles have precluded the successful completion of a clinical trial comparing the two therapies for the treatment of ESRD (Korevaar et al., 2003); one such clinical trial is currently underway in China (Clinicaltrials.gov identifier: NCT01413074). In the absence of adequately powered clinical trials, a large number of observational studies have compared outcomes with the two therapies (Chiu et al., 2011). Recent studies have been better able to adjust for bias inherent in such studies where the treatment assignment is non-random and allow for a few key observations. First, better control for confounding demonstrates a similar risk of death for patients treated with haemodialysis and PD early during the course of the disease (Quinn et al., 2011). Second, starting from the mid 1990s, there have been greater reductions in death risk for patients treated with PD than for patients undergoing maintenance haemodialysis in many different parts of the world (Grenêche et al., 2005; Mehrotra et al., 2007; McDonald et al., 2009; Chang et al., 2012). Third, the 4-, 5-, and 10-year survival of patients starting treatment with haemodialysis and PD with varying levels of use of the two therapies are remarkably similar. Finally, there have been significant reductions in risk for patients treated with PD to transfer to maintenance haemodialysis (Mehrotra et al., 2009). These data suggest that patient choice, rather than consideration of clinical outcomes, should drive the selection of PD for the treatment of ESRD.

Future directions

Despite these improved outcomes, significant challenges remain. Many ESRD patients are unaware of the choice of performing dialysis at home and given the equivalency of short- and long-term survival of patients treated with PD or maintenance haemodialysis, it is imperative to focus on empowering patients to select a dialysis modality that best fits into their lifestyle and meets their expectations. The life expectancy of dialysis-dependent patients remains between 3 and 5 years and it is important to identify potentially modifiable risk factors specific to PD to enhance patient longevity. Many PD patients still need to transfer to haemodialysis from therapy-related complications and it is crucial to identify practice patterns to maximize time on PD therapy. With longer time on therapy, more patients will be at risk for encapsulating peritoneal sclerosis—a rare, devastating but poorly-understood complication of PD; there is a need to better understand the pathobiology of peritoneal membrane changes with PD. Finally, it is important to determine whether the newer formulations of PD solutions have any tangible effect on clinically relevant patient outcomes. Nevertheless, PD is a viable long-term therapy for the treatment of uraemia.

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CHAPTER 264

Peritoneal dialysis: principles and peritoneal physiology

Joanna Stachowska-Pietka, Jacek Waniewski, and Bengt Lindholm

Overview

The efficiency of peritoneal dialysis (PD), the leading form of home-based dialysis therapy, is determined by the fluid and solute transport processes in the microvasculature and other parts of the subperitoneal tissue, and how these processes can be modified by dialysis prescription. Osmotically driven ultrafiltration to the peritoneal cavity (PC), hydrostatic pressure-driven fluid absorption from the PC, and diffusional and convective exchange of solutes depend on their respective driving forces and the structure of the tissue, all of which are influenced by the dialysis exchange and undergo changes with time on dialysis. In the short term, increased hydrostatic and osmotic pressures of interstitial fluid modify the physiological equilibrium in the relatively thin peritoneal tissue layer and induce water exchange between the PC and the peritoneal capillary bed. Increased interstitial concentration of the osmotic agent and decreased concentration of solutes that are removed to dialysis fluid induce a rapid exchange of solutes. In the long term, these disturbances of tissue homeostasis together with the repeated exposure to unphysiological components of dialysis fluid may lead to denudation of mesothelium, epithelial-to-mesenchymal transition, fibrosis, neoangiogenesis, and thickening of the peritoneum, contributing to functional changes in the peritoneal transport system (PTS). During long-term PD, loss of ultrafiltration capacity due to multifactorial causes including increased small solute transport rate and decreased osmotic conductance is a frequent complication. Clinical monitoring of peritoneal transport and treatment effectiveness, based on the evaluation of peritoneal transport rates, includes basic methods such as 24-hour collection of drained dialysis fluid and the peritoneal equilibration test (PET, in different versions). For more detailed understanding of transport processes and the causes of ultrafiltration failure, other tests may be useful, such as peritoneal dwell studies with volume marker, mini-PET, and double mini-PET. Whereas our knowledge of peritoneal transport physiology, especially processes inside the tissue, comes mostly from animal experiments, clinical studies are needed to ensure that this knowledge can be translated into clinical benefits for the individual patient.

Introduction

The PC is a potential space contained within the tissue layer called the *peritoneum*, which covers the abdominal wall as well as the internal organs. In the normal physiological state, the PC contains only a small amount of fluid that lubricates the surfaces and helps to protect organs and reduce the friction during their movements. In PD, the repeated infusion and drainage of a large volume of hypertonic dialysis fluid alters this steady state condition, invoking exchange of fluid and solutes between the PC and the tissues surrounding it.

Although the fundamental physiological principles for the treatment—diffusion, osmosis, fluid flow, and the underlying forces that that drive these processes—are well established, the dialytic properties of the dialysis system depend on complex, variable, and multiple interrelations between these system components. The repeated exposure to high hydrostatic and osmotic pressures of dialysis fluid in the PC makes PD unique among medical procedures and result in short- and long-term changes in the structure and function of the PTS. Different clinical methods have been developed to assess various aspects of peritoneal transport by studying kinetics of intraperitoneal fluid volume and solute concentration by frequent sampling of dialysis fluid. However, more detailed studies on transport processes within the tissue are possible only in animal models of PD. The combination of these two types of studies with anatomical data (biopsies in patients, and studies of the anatomy of the tissue under different stimuli in animals) and mathematical modelling have advanced our knowledge of peritoneal physiology and the theory and principles of PD.

Principles of peritoneal dialysis

In PD, dialysis fluid is infused through a *catheter* into the PC, where the *dialysate* participates in a bi-directional exchange of fluid and solutes with the adjacent *tissue layers* perfused by *blood* and *lymph* vessels; these components constitute the *peritoneal transport system* (PTS). The removal of excess water from the body to the dialysate is provided by the process of *osmosis* whereby a high concentration of an osmotic agent—usually glucose—in the dialysate induces *ultrafiltration* that extracts water from the circulation via the PTS into the PC. On the other hand, fluid infusion into the PC increases intraperitoneal volume and hydrostatic pressure, and induces *fluid absorption* from the PC into the PTS. The exchange of solutes between the PTS and PC occurs by *diffusion* due to concentration differences, and by *convective transport* of solutes—the major transport mechanism for macromolecules—with the osmotically

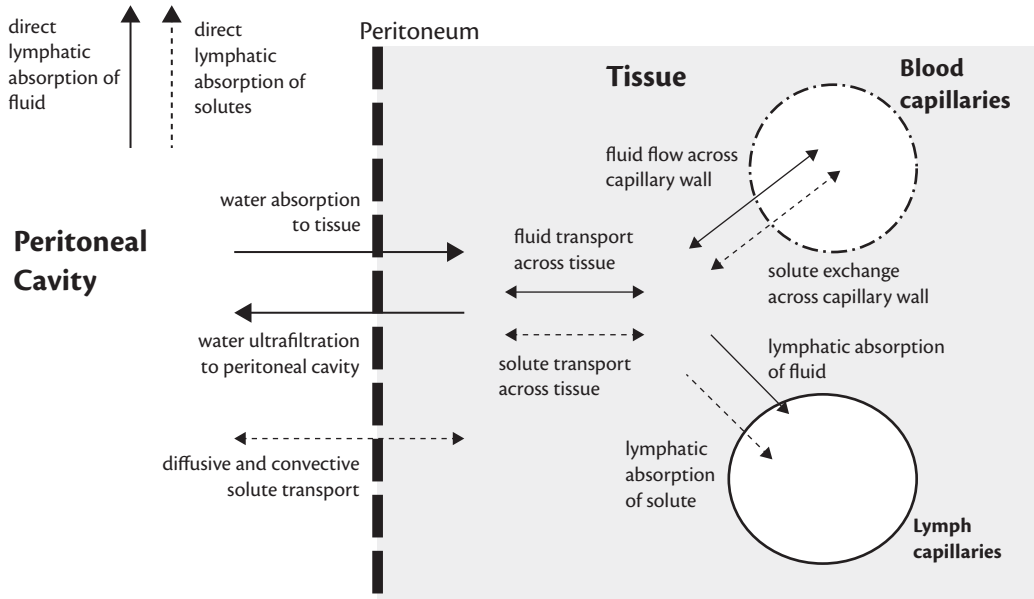

Fig. 264.1 Fluid and solute transport pathways during peritoneal dialysis.

induced water flow. As a result, numerous metabolic waste products such as urea and creatinine, and water, are removed from the body, whereas other solutes with higher concentration in the dialysate, such as the osmotic agent, are absorbed into the body. These fluid and solute transport pathways are schematically presented in Fig. 264.1. In principle, both fluid and solute transport pathways are bi-directional and transport thus can occur in both directions. Finally, after some time of the exchange (often called 'dwell'), the remaining dialysate is drained from the PC, and depending on the prescription, fresh dialysis fluid is again instilled or the PC is left empty.

Peritoneal fluid transport

The transport of water between the PC and blood circulation via the PTS occurs in two directions: osmotic-pressure driven ultrafiltration to the PC and hydrostatic-pressure driven fluid absorption from the PC (cf. Fig. 264.1). The *net ultrafiltration* rate (or the net fluid removal rate) is equal to the difference between the volume of ultrafiltered fluid (capillary ultrafiltration) and the volume of fluid absorbed (previously called 'lymphatic absorption') divided by the duration of the dwell. It can be estimated in individual patients by measuring the difference in volume between drained dialysate and infused fluid, divided by the dwell time (and, if such data are available, corrected for the residual volume remaining in the PC after drainage). The driving forces (osmotic-pressure driven ultrafiltration and hydrostatic-pressure driven fluid absorption), depend on patient characteristics, position during the treatment, dialysis fluid (volume and concentration of the osmotic agent), dialysis regimen (frequency and duration of dwell), and vary during the dwell time. During a typical 6-hour dwell in a continuous ambulatory peritoneal dialysis (CAPD) patient with normal peritoneal transport characteristics, using dialysis fluid with 3.86% glucose, the intraperitoneal volume (IPV) increases from about 2.4 L (including the residual dialysate volume and a slight overfill of the 2 L bag) to a maximum value of about 3.5 L within 2–4 hours, and then decreases gradually (Fig. 264.2) (Heimbürger et al., 1992). The initial high ultrafiltration rate decreases during the dwell time, due to absorption of the osmotic agent from the dialysate and the constant fluid reabsorption from the PC (Fig. 264.2). Whereas it is, in principle, possible to remove as much as 0.9 L of fluid per hour by rapidly exchanging 3.86% glucose solution, during standard PD treatment such as CAPD, net ultrafiltration rate becomes negative after 3–4 hours and, at the end of 6-hour dwell time, this negative rate does not differ much between the different solutions (Waniewski et al., 1996a, 1996b; Smit et al., 2004b, 2004c). Using a crystalloid osmotic agent such as glucose, the negative net ultrafiltration rate limits net fluid removal already after 4–8 hours, and during the long (8–12-hour) dwell, the substantial fluid absorption may contribute to fluid overload. Note that the alternative oncotic agent icodextrin is much more slowly absorbed; therefore, icodextrin-based solutions improve fluid and sodium removal during the long (8–12-hour) dialysis exchange, particularly in patients with increased peritoneal solute transport rate (Garcia-Lopez et al., 2012).

Fluid absorption

The infusion of dialysis fluid into the PC leads to elevation of the intraperitoneal hydrostatic pressure (IPP), inducing hydrostatic pressure-driven *fluid absorption* from the PC (Fig. 264.1). The fluid absorption is directly proportional to IPP (Zink and Greenway, 1977; Imholz et al., 1993; Zakaria and Rippe, 1995), but independent of fluid hypertonicity, and therefore not influenced by ultrafiltration to the PC (Flessner et al., 1983; Nolph et al., 1987; Heimbürger et al., 1992; Flessner and Schwab, 1996). Fluid absorption, occurring at a rate of 0.5–3 mL/min (typical values of 1–2 mL/min correspond to as much as 1440–2880 mL/day), markedly reduces fluid removal from the patient. A negative correlation between *net* ultrafiltration (capillary ultrafiltration minus fluid absorption) and IPP was found in CAPD patients (Durand et al., 1992).

The level of IPP depends on the amount of dialysis fluid infused, the patient's position and physical activity, and the reference

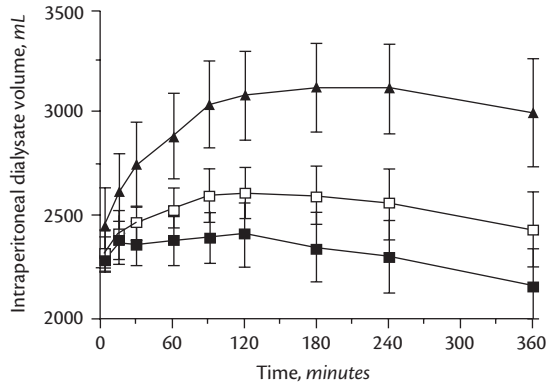

Fig. 264.2 The average values (± SD) of intraperitoneal volume, V_D, as a function of dwell time, estimated using radiolabelled serum albumin (RISA) as a volume marker, in CAPD patients during 6-hour single dwell study with an exchange of 2 L of three different glucose-based dialysis solutions (1.36%—■, 2.27%—□, and 3.86%—▲).

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point used for this measurement. IPP is proportional to the IPV (Twardowski et al., 1983), and increases by compression of the abdomen (Imholz et al., 1993). Typical values of IPP, measured in CAPD patients, are 6.7 ± 0.8 mmHg (3.9–10.8 mmHg) in the supine position and 12.6 ± 0.8 mmHg in the upright position (Gotloib et al., 1981; Imholz et al., 1998). IPP may transiently increase, even above 100 mmHg, due to patient's activity such as speaking, coughing, walking, jogging, and so on (Twardowski et al., 1986).

Fluid absorption from the PC involves two different pathways: direct lymphatic absorption, mainly by diaphragmatic lymphatics (10–20%), and fluid absorption into the adjacent tissue and from there to blood and the lymphatic system (Flessner, 1992; Heimbürger et al., 1995). Typical values of peritoneal fluid absorption rate, that is, the amount of fluid absorbed from the PC divided by the time interval, are in the range 0.5–3 mL/min (Imholz et al., 1993; Heimbürger et al., 1995; Pannekeet et al., 1995; Waniewski et al., 1996b; Olszowska et al., 2007).

Transcapillary ultrafiltration

The infusion of hypertonic dialysis fluid creates an osmotic force between the PC and surrounding tissue layers that removes water from the tissue and blood to the PC in a process called *ultrafiltration* (Fig. 264.1). The ultrafiltration rate, calculated as ultrafiltered volume divided by duration of a dwell, is called *transcapillary ultrafiltration* rate. Note that whereas this flow cannot be directly measured, it can be estimated by adding the (estimated) fluid absorption to the measured drainage volume.

Ultrafiltration flow varies with the *tonicity of dialysis fluid, peritoneal transport characteristics* of the individual patient (such as *peritoneal small solute transport rate* and *osmotic conductance*, see below), and *dwell time* (cf. Fig. 264.2). As shown in Fig. 264.2, the initial high ultrafiltration rate of about 6, 8, and 15 mL/min for 1.36%, 2.27%, and 3.86% glucose solutions, respectively, decreases during the dwell time, due to the rapid absorption (by diffusion as for glucose) of the osmotic agent from the dialysate and the constant fluid reabsorption. *Osmotic conductance* measures the amount of fluid ultrafiltration to the PC induced by unit gradient of unit osmolality or osmotic agent concentration and varies between 0.063 and 0.133 mL/min (mmol/L) (Stelin and Rippe, 1990; Waniewski et al., 1996a; Parikova et al., 2006; La Milia et al., 2007).

Peritoneal solute transport

The concentration of the osmotic agent is substantially higher in the fresh dialysis fluid (before infusion into the PC), than its concentration in the surrounding tissue and blood (Fig. 264.3). This creates a concentration gradient that results in diffusion of the osmotic agent from PC into the adjacent tissue. The absence of endogenous small solutes, such as urea and creatinine, in fresh dialysis fluid creates a concentration gradient, which induces their diffusive transport to PC. This leads to a gradual increase of their concentration in dialysate that tends to equilibrate with plasma and tissue concentrations after a few hours (Fig. 264.3). For other solutes, for which the concentration in dialysate is almost in equilibrium with their plasma concentration (such as sodium), diffusive transport is minimal, and therefore convective transport prevails. Large molecules, such as albumin and immunoglobulin G, are not present in fresh dialysis fluid and therefore their concentration in dialysate increases during the dwell time. However, since their transport is slow due to high molecular weight (MW), the final concentration remains much lower (about 10 times or more) than the corresponding concentration in blood.

Diffusion and convection of solutes

During PD, solutes can be transported by *diffusion* and/or *convection* in both directions, that is, to and from PC (Fig. 264.1). The passive, diffusive transport is driven by the diffusive force created by the difference in solute concentration between dialysate in the PC and the surrounding tissue. The convective transport is possible due to high water flow that occurs during PD. Transport of low-MW solutes, that is, with MWs < 600 Da, such as urea, creatinine, or glucose occurs mainly due to diffusion, whereas convection is less important. However, for solutes such as sodium which have a similar concentration in dialysate and plasma, the convection is the dominant transport mechanism. Furthermore, all small solutes are sieved by the water-only-pathway, that is, the aquaporin channel, there is a typical 'sodium dip' reflecting dilution of dialysate with sodium-free water (see Fig. 264.3). For larger molecules, such as proteins, with MW > 30,000 Da, convection is the dominant mechanism of transport, although diffusive transport is also of some importance (Leypoldt and Blindauer, 1992; Flessner et al., 1997). For solutes with MWs in the range from 600 to 30,000 Da, both transport components, diffusive and convective, play important roles. In the convective transport, water is used as a vehicle to transport large molecules such as serum albumin and other proteins. In PD, convective transport to PC typically occurs by ultrafiltration, which brings water and solutes to dialysate. Finally, independently of the size, solutes are also directly absorbed from PC by direct lymphatic uptake of dialysate and by fluid absorption to the tissue; in both these processes solute absorption occurs without so-called sieving.

Methods of assessment

The most common way of estimating the peritoneal transport of solutes is to analyse the ratio between dialysate and plasma (D/P) concentrations for small MW solutes such as urea, creatinine, and

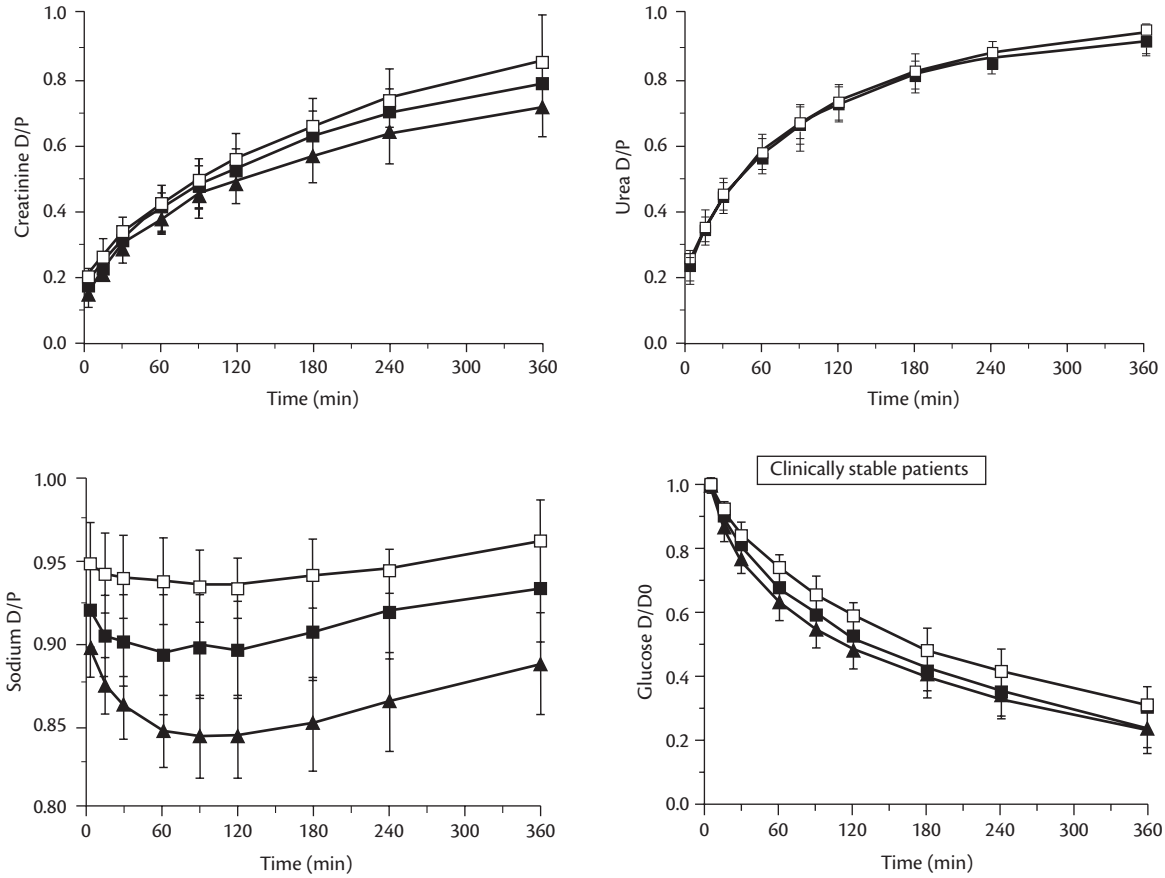

Fig. 264.3 The average value of the dialysate to plasma concentrations (D/P) ratio for urea, creatinine, sodium, and dialysate to initial dialysate concentration (D/D_0) ratio for glucose, as a function of dwell time for clinical 6-hour dwell studies of CAPD patients with glucose 1.36% (□), 2.27% (■), and 3.86% (Δ) dialysis fluids.
Reprinted by permission from Heimbürger, O., Waniewski, J., Werynski, A., *et al.* (1994). Dialysate to plasma solute concentration (D/P) versus peritoneal transport parameters in CAPD. *Nephrol Dial Transplant*, 9, 47–59.

sodium. In the case of glucose, its concentration in dialysate is usually compared with the initial glucose concentration in dialysate (D/D_0). These ratios, which reflect the process of solute concentration equilibration between dialysate and blood, depend on the type of dialysis fluid and duration of PD as well as on patient specific peritoneal transport characteristics (cf. Fig. 264.3). The total and peritoneal solute removal from the patient is often presented as *clearance* defined as the amount of solute removed from body per unit time over its concentration in plasma (or dialysate). It can be calculated from the final D/P (or D/D_0) value after multiplying by the net ultrafiltration. The diffusive and convective solute transport can be separated using mathematical modelling. As a result, the diffusive mass transport parameter (signed often as K_{BD}, MTC, MTAC, or PS) and sieving coefficient (S) can be estimated. The interpretation of these parameters can be based on the three-pore model of the PD (cf. Fig. 264.4).

Physiology of the peritoneal transport system

Water and solutes that enter the peritoneal tissue have to cross several transport barriers with different properties before getting to blood or dialysate. These complex, non-homogenous barriers together with the underlying transport processes are sometimes considered in compartmental models as a single membrane. This simplified description of PTS, applied in mathematical models and called the *peritoneal membrane*, is used in analogy to the membrane of the haemodialyser. In this case, the term 'peritoneal membrane' has a functional meaning and is used to describe the whole complex structure that separates plasma and PC.

In reality, the PTS is a three-dimensional structure made up of the peritoneum, the underlying tissue layers with interstitial matrix, parenchymal cells, and blood and lymph capillaries that cross this tissue. The thickness of tissue layer that is penetrated by the solute (penetration depth) depends on many factors, such as the solute size, hydrostatic and osmotic pressure gradients, ultrafiltration, type of dialysis, and so on. The penetration depth values may be 200–300 μm for small and middle MW solutes, such as creatinine or inulin, and a few millimetres for water ((Waniewski, 2001; Waniewski et al., 2009b; Stachowska-Pietka et al., 2012). Water and solutes, which enter the tissue from the PC and local capillaries, are transported across the interstitium, changing its local homeostasis. The inflow of water increases interstitial hydrostatic pressure and tissue hydration. The increase of local glucose concentration in the tissue creates a local osmotic force between tissue and blood. The differences in solute concentration and oncotic pressure between plasma and interstitium have an impact on the local exchange in the tissue. The local lymphatic vessels absorb fluid and solutes

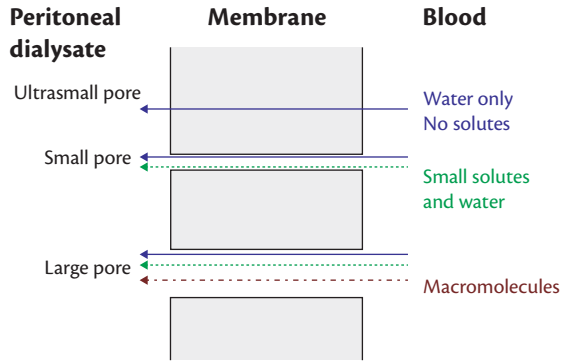

Fig. 264.4 Schematic presentation of the three-pore model of peritoneal dialysis that describes transport of water (blue arrow), small solutes (green arrow), and large molecules (brown arrow) through the porous membrane that separates blood from peritoneal dialysate with three type of pores: ultra-small pores that are available only for water transport and not permeable for solute transport, small pores that are the main route of small and middle molecules transport, and large pores that allows for transport of macromolecules (of the size of albumin and larger) mainly by convective flow.

without sieving, and the rate of this lymphatic absorption depends on local hydrostatic pressure and tissue hydration.

The anatomical structures most important for the exchange of fluid and solutes between dialysis fluid and blood (interstitium, capillary wall, lymphatics) are spatially intertwined and therefore mathematical models are necessary to describe how the overall transport parameters result from the specific parameters of these structures (Waniewski et al., 2009b; Stachowska-Pietka et al., 2006, 2012).

Peritoneum

The peritoneum lines the PC, covering most of the internal organs, such as the intestines, part of stomach, liver, spleen, and pelvic organs (visceral peritoneum), and the anterior abdominal wall, diaphragm, retroperitoneal structures of the kidneys, and the muscles of the back (parietal peritoneum) (diZerega and Rodgers, 1992; Flessner, 1999; de Vriese et al., 2009). It consists of a single layer of mesothelial cells and four to five layers of connective tissue. The mesothelial cells form a continuous layer, whereas the connective tissue layers are rather loose, and arranged in bundles parallel to the surface (diZerega and Rodgers, 1992). Under normal physiological conditions, the layer of the mesothelial cells is covered with a thin (5 μm) film of a stagnant peritoneal fluid layer containing glycosaminoglycans such as hyaluronan. This layer prevents adhesion and allows for displacement of abdominal visceral organs during body movements, such as respiration, peristalsis and physical activity (diZerega and Rodgers, 1992; Flessner, 1999; Heimbürger, 2005). Typically, PC contains up to 100 mL of peritoneal fluid but this volume can be even 20-fold increased without causing patient discomfort (de Vriese et al., 2009). In general, the peritoneal surface area is proportional to the body surface area and was estimated to be in humans on average 0.8–1.3 m^2 (Stachowska-Pietka et al., 2006). The actual area of the peritoneum (effective surface area) that is in contact with dialysis fluid was estimated in CAPD patients by computed tomography scanning to be 0.55 m^2, that is, about one-third of the body surface area (Chagnac et al., 1999).

The anatomical peritoneum does not appear to be a substantial barrier for peritoneal solute and water exchange; in fact, the removal of the peritoneum had no impact on the ultrafiltration rate and small solute transport in animal studies and in patients undergoing partial or total peritonectomy (de Lima Vazquez et al., 2003; Flessner, 2005). However, the changes in the structure and size of the peritoneum after a long time on PD may increase its resistance to fluid and solute transport (Flessner et al., 2003).

Interstitium

The interstitium fills the extracellular space and forms connective and supporting tissues located between the blood and lymphatic vessels and parenchymal cells, and constitutes the 'physical and biochemical environment of the cells in the body' (Aukland and Reed, 1993; Wiig et al., 2008). The interstitium consists of interstitial fluid and structural molecules that compose the three-dimensional structure of the interstitial (extracellular) matrix. The structure of extracellular matrix has been shown to be highly ordered and made up mainly by collagen, glycosaminoglycans (hyaluronan and proteoglycans), and elastic fibres.

In a healthy adult man, every day about 2–4 L of plasma water is effectively ultrafiltered to the interstitium and drained by the local lymphatic system. The interstitial fluid volume (IFV) which accounts for 10–20% of the wet weight of skeletal muscle (Aukland and Nicolaysen, 1981; Aukland and Reed, 1993) is strongly influenced by interstitial fluid hydrostatic pressure (IFP) (Guyton, 1965; Reed and Wiig, 1981; Wiig and Reed, 1981; Reed and Wiig, 1984; Zakaria et al., 2000). In particular, fluid infusion into the PC increases IFP and IFV irrespectively of fluid osmolality, and the IFV fraction (per wet tissue volume) may increase from 0.18 at 0 mmHg to 0.36 at 6 mmHg (Zakaria et al., 1999, 2000).

The interstitial matrix affects both the diffusive and convective transport of solutes in the tissue. The movement of the low-MW solutes across interstitium is only slightly retarded, whereas the macromolecular diffusive transport through the interstitium may be slower by 30–100 times compared to the transport through water (Flessner, 1997).

Microvascular exchange

The capillaries play the main role in the microvascular exchange of fluid and solute between blood and tissue. The average diameter of the mammalian capillary varies between 5 and 8 μm (de Vriese et al., 2009). The blood capillary wall is composed from the endothelium and basal lamina (de Vriese et al., 2009). The endothelium in the peritoneal blood capillaries belongs mostly to the continuous type, that is, endothelial cells form a continuous layer. The luminal side of endothelium is covered by the negatively charged glycoprotein layer called glycocalyx (Heimbürger, 2005; de Vriese et al., 2009).

The solute transport pathways across the capillary wall are still speculative although several different routes have been suggested on the basis of experimental studies, such as interendothelial (intercellular) junctions (clefts, gaps), fenestrates, and transcellular channels. It has been established, on the basis of numerous experiments, that blood capillaries behave functionally as having a heteroporous structure, which restrict solute transport. According to the pore theory, which was developed to model microvascular transport, there are three types of pores: the rather rare *large pores* (typically assumed radius 200–400 Å), and much more frequent *small pores* (usually modelled with radius 39–67 Å) and *ultrasmall pores* (also termed water-only channels, transcellular pores or

aquaporin channels) (Wolf, 1994). The interendothelial junction has been identified using electron microscopy as a long slit-like pore (Landis and Pappenheimer, 1963; Intaglietta and Zweifach, 1971). Moreover, current evidence suggests that large macromolecules are transported mainly by convective bulk flow through the rare large pores (Taylor and Granger, 1984; Rippe and Haraldsson, 1994). The water transport across the capillary wall may occur not only through the interendothelial gaps, but also through the endothelial transcellular channels formed by aquaporin 1 (Agre et al., 1993). This water exclusive pathway plays a very important role in the osmotic transport across the blood capillary wall. The elimination or blocking of aquaporin 1 results in substantial (> 50%) reduction of total ultrafiltration as revealed by animal studies of PD (Carlsson et al., 1996; Ni et al., 2006).

According to Starling's hypothesis, the microvascular exchange occurs due to hydrostatic and oncotic pressure differences between plasma and interstitium, and can be quantitatively expressed as:

$$q_V^{cap} = L_p a(\Delta P - \sigma_S^{cap} \cdot \Delta \Pi)$$

where q_V^{cap} is the flux of water from blood to interstitium, and $L_p a$ is the hydraulic conductivity of the blood capillary wall times surface area per unit tissue volume, ΔP and $\Delta \Pi$ are the hydrostatic and oncotic pressure difference between plasma and interstitium, respectively, and σ_S^{cap} is the reflection coefficient of the blood capillary wall of proteins (Michel, 1984). Under normal conditions, the hydrostatic pressure difference drives filtration from the plasma into the interstitium, whereas the oncotic pressure difference works in the opposite direction, resulting in local absorption of interstitial fluid back into the circulation. Solute transport across blood capillary wall is driven by the diffusion (due to the concentration difference between plasma and interstitial fluid) and convection (by water flow), which can be expressed for each pore type as:

$$q_S^{cap} = p_S a \Delta C_S + \left(1 - \sigma_S^{cap}\right) \cdot q_V^{cap} a v C_S$$

where q_V^{cap} is the solute flux from blood to interstitium, $p_S a$ is the permeability of capillary wall to diffusive solute transport, ΔC_S is solute concentration difference between plasma and interstitium, and avC_S is the mean value of solute concentration across the capillary wall.

The exposure to the high concentration of glucose, application of vasoactive drugs, and changes occurring during long-term PD treatment may result in changes of the microvascular exchange process of the blood capillary wall, leading to changes in the peritoneal transport characteristics.

Lymphatic absorption from tissue

The lymphatics form a closed vascular system composed of endothelial-lined channels that are parallel to the arterial-venous system (Gnepp, 1984). The most distal part of the lymphatic system is composed of *lymphatic capillaries*, also called the initial lymphatics or terminal lymphatics, which cross and drain the interstitial space.

The major role of lymphatic capillaries is to return plasma proteins from the extracellular space to the circulation and to help maintaining the IFV balance. The increase of interstitial volume and hydrostatic pressure results in a concomitant increase in lymph flow. In this way, the excess water is drained from the tissue, thereby preventing formation of local tissue oedema and returning tissue to the normal physiological state (Gnepp, 1984; Granger et al., 1984).

The regulatory role by lymphatics is not only limited to the fluid volume self-regulation. The lymphatic capillaries take part in the local processes of the interstitial protein regulation. The plasma proteins, that enter the interstitium through the blood capillary wall, are taken back to the circulation by the lymphatic capillaries. This effect is important, since every day around 50% of the total amount of circulating plasma proteins leaves the blood capillaries (Gnepp, 1984).

Peritoneal blood flow

The typical capillary network that participates in the exchange of fluid and solutes during PD consists of many elements, such as arterioles, capillaries, post-capillary venules, and venules. Blood flow through a capillary network is not constant but oscillates for the single capillary, starting and stopping, and sometimes even reversing its direction (de Vriese et al., 2009). Under normal conditions, only 20–50% of muscle capillaries are perfused. The fraction of perfused capillaries is influenced by vasoactive drugs, exposure to peritoneal dialysate solutions, local metabolic demands, and physical exercise (de Vriese et al., 2009).

The peritoneal transport of water and solutes is strongly related to the effective peritoneal blood flow, that is, blood flow rate in capillaries involved in peritoneal transport. It can be defined as the blood flow in a tissue layer of the depth equal to the solute penetration depth. Therefore, effective peritoneal blood flow is solute specific as the solute penetration depth is much different for different solutes and varies from about 50 mL/min for glucose, urea, and creatinine, to 130 mL/min for hydrophobic gases, such as CO_2 (Waniewski et al., 1999).

Quantitative assessment of peritoneal transport

The efficiency of PD depends on the water and solute transport. Because one cannot observe these processes directly, clinical and mathematical methods have been developed to monitor the status of 'peritoneal membrane'. The current knowledge of mechanisms and processes that occur during PD would not have been achieved without using animal experiments and mathematical models. Animal studies have played an important role not only for the understanding of physiological mechanism of fluid solute transport, but also as an initial source of information about the effects of new components, additives, and other modifications of dialysis fluid (Lameire et al., 1998; Zakaria el et al., 2008b). The mathematical models can be used for the evaluation of peritoneal fluid and solute transport especially when combined with clinical data. They also may provide new information about physiological processes and factors, which cannot be monitored clinically, such as the assessment of tissue profiles of interstitial hydrostatic pressure, tissue hydration, and solute concentration profiles.

Clinical studies and measurements are needed to assess the actual patient status and efficiency of the treatment. The available information is usually limited to concentrations of some solutes in blood, dialysate, and urine, the volume of drained dialysate, and hydrostatic pressure in the PC. There are several tests available for clinical assessment and evaluation of peritoneal transport status of

Table 264.1 Comparison of clinical methods developed for the assessment of fluid and solute peritoneal transport.

Parameter	Net UF	Peritoneal absorption	Free water fraction	Osmotic conductance	Daily clearances	D/P and D/D_0	Daily glucose absorption	Daily protein intake	Daily sodium removal	Kt/V
Daily collections of urea and dialysate	+				+		+	+	+	+
Threefold peritoneal test	+	+		+	+		+	+	+	+
PDC	+	+	+	+	+	+	+	+	+	+
PET						+				
Mini-PET	+		+			+				
Double mini-PET	+		+	+		+				
sPET	+	+	+	+		+				
Dwell study/SPA	+	+	+	+		+				

the patient. The complexity of these tests varies from simple methods that provide only limited information to very complex ones that allow for a more detailed description of peritoneal transport. Peritoneal clearances, typically assessed for creatinine and urea, the evaluation of sodium removal, protein losses, and residual glomerular filtration rate (GFR, the measure of residual renal function) may be available for the monitoring of the patient status depending on the test (cf. Table 264.1) (Blake and Daugirdas, 2006).

Three types of models have been developed so far for the evaluation of fluid and solute transport during PD. In the classical *membrane model*, the PTS is treated as a homogenous membrane between the PC and blood. It allows for the estimation of peritoneal fluid absorption and ultrafiltration from dwell studies, and for the evaluation of diffusive and convective solute parameters, that is, K_{BD} and S, respectively. In the *three-pore model*, one assumes that the PTS can be represented by a membrane with three types of pores. The three-pore model explains the discrepancy between sieving coefficient and reflection coefficient for small solutes and allows for the separation of the reflection coefficient from the osmotic conductance of the 'peritoneal membrane'. The *distributed model* has been derived based on the local structure and physiology of the PTS, and allows for estimation of the contribution of each of the PTS components to the overall peritoneal transport. Two commercial programs, PD Adequest® and personal dialysis capacity (PDC®) test, apply the membrane and three-pore models for the evaluation of many transport parameters using different clinical procedures.

Twenty-four-hour collections

This relatively simple method gives information on the 24-hour drained dialysate volume and dialysate and renal clearances, including markers of PD efficiency, such as urea, creatinine, glucose, and others. The patients are asked to collect all dialysate bags and urine during 24 hours. In addition, a blood sample is taken at the end of the24-hour collection. This procedure allows also for the calculation of Kt/V for urea, which is defined as total urea mass removed divided by total mass of urea in the body (cf. Table 264.1).

The threefold peritoneal test is based on the 24-hour dialysate collections with three different schedules of glucose-based dialysis fluids (Waniewski et al., 2013). It allows for a more detailed description of fluid transport. The additional estimation of peritoneal absorption, osmotic conductance, and ultrafiltration efficiency of glucose can be derived based on the pure data without any additional assumptions or complex modelling such as in the three-pore or distributed models (Table 264.1) (Waniewski et al., 2013).

Peritoneal equilibration test

The PET is the most widely used method for the evaluation of peritoneal transport characteristics of PD patients (Twardowski et al., 1987). Peritoneal transport is assessed based on the dialysate-to-plasma concentration ratio (D/P) for small solutes such as creatinine and sodium, and the ratio of concentration of glucose in the dialysate to the initial glucose concentration in dialysis fluid (D/D_0), and drainage volume. Comparing the obtained values of D/P and D/D_0 with the standard ones, allows for classification of patient transport status and therefore helps in the optimization of PD treatment by altering the duration and frequency of exchanges and type of dialysis fluid.

Conventionally, in standard PET, drainage volume, and glucose and creatinine concentrations are measured. Typically, 2 L of dialysis fluid glucose 2.27% are infused and three dialysate samples are collected: initial (taken after fluid infusion), after 2, and after 4 hours of fluid dwell (Heimbürger, 2005; Blake and Daugirdas, 2006). A blood sample is drawn once at 2 hours of dwell time, and the drainage volume is recorded at the end of the fluid exchange. The measured drainage volume, D/P for creatinine and D/D_0 for glucose are compared with the respective references values. The dialysate drainage volume is used for the estimation of the net ultrafiltration (cf. Table 264.1).

Patients are categorized into four groups on the basis of the mean and standard deviation (SD) values of D/P for creatinine or D/D_0 for glucose. However, this classification may be confusing, since the obtained equilibration ratios for glucose and creatinine may classify patient to different categories. Therefore, typically patients are usually classified on the basis of their D/P ratio for creatinine at 4 hours to one of the four transport groups: high, high average, low average, and low transport group (Twardowski et al., 1987). An alternative nomenclature has recently been proposed with fast, fast average, slow average, and slow transport, respectively (Krediet, 2009). Patients with fast transport, which is reflected in

rapid equilibration of creatinine and fast glucose absorption from PC, are classified to high (D/P for creatinine 0.81) and high average (D/P for creatinine between 0.65 and 0.81) transport group, respectively. These patients tend to have poor net ultrafiltration. Patients from low average (D/P for creatinine 0.5–0.65) and low (D/P for creatinine below 0.5) transport groups have slow solute transport resulting in slower creatinine equilibration, low glucose absorption and have higher net ultrafiltration (Heimbürger, 2005; Krediet, 2009).

Personal dialysis capacity test

The PDC® is a combination of the PET and daily collections. Namely, blood, dialysate, and sample are collected during five exchanges: two short (2–4 hours), two long (4–6 hours), and one long overnight (Haraldsson, 1995), and a mathematical model based on the three-pore concept of the peritoneal transport barrier is applied to calculate various transport parameters (Table 264.1).

Mini-PET

Another test called mini-PET allows for the evaluation of water transport pathways (La Milia et al., 2005). A 1-hour fluid exchange with glucose 3.86% solution is performed and dialysate and blood samples are taken at the beginning and at the end of dwell. The mini-PET is one of the methods that can be used for the assessment of the free water fraction (FWF), that is, the fraction of ultrafiltered water that is solute free and comes through the ultrasmall pores (cf. Table 264.1). Briefly, the net ultrafiltration is separated into small pore and free water fractions assuming, based on the three-pore structure of the 'peritoneal membrane', a high free water transport rate during the initial hour. This method utilizes estimation of sodium removal, which during the initial dwell period occurs mainly by convection with ultrafiltered water. Sodium removal therefore can be used as an indicator of peritoneal water transport through the small and large pores while water transported through ultra-small pores is deprived of sodium. This results in the sodium dip shown in Fig. 264.3. The 'double mini-PET' is composed of two mini-PETs using glucose 1.36% and 3.86% solutions, respectively. It allows additionally for the estimation of osmotic conductance for glucose (cf. Table 264.1).

The sequential peritoneal equilibration test (sPET) is another method that can be used for the monitoring of peritoneal transport (Galach et al., 2013). It is composed of the PET followed by the mini-PET combining the advantages of both methods (Table 264.1). In addition to the double mini-PET, sPET allows for the estimation of the peritoneal absorption based on the three-pore approach (Galach et al., 2013).

Dwell studies

Kinetics of intraperitoneal fluid volume can be measured by fast draining of dialysis fluid, weighing it, and infusing it back to the PC repeatedly at consecutive time-points of the peritoneal dwell (Freida et al., 2007; Zhe et al., 2007). An alternative method is based on use of a *volume marker*. Two types of volume markers were proposed and applied so far: radioisotopically labelled serum albumin (RISA) and dextran 70 (standard peritoneal permeability test, SPA) (Krediet et al., 1992; Waniewski et al., 1994). The volume marker is added to the fresh dialysis fluid before this is infused to the PC. Several blood and dialysate samples are taken during the dwell time (Heimbürger et al., 1992; Pannekeet et al., 1995). Finally, dialysate is drained, and PC is rinsed for a few minutes using fresh dialysis fluid for the estimation of residual volume at the end of dwell. This procedure allows for the estimation of peritoneal absorption rate, diffusive mass transport coefficient (K_{BD}), sieving coefficient (S), and osmotic conductance for glucose. It also brings information on the temporal pattern of changes in net ultrafiltration during the dwell time (cf. Table 264.1).

Clinical aspects of peritoneal transport physiology

Infusion of hyperosmotic dialysis fluid into the PC immediately induces changes in the tissues surrounding the cavity: (1) high intraperitoneal hydrostatic pressure yields increases in interstitial fluid, hydrostatic pressure, and overhydration in the tissue layer close to the peritoneum, and absorption of fluid from the cavity; (2) high concentration of the osmotic agent (typically glucose) results in its diffusive transport to the tissue and blood, and increased concentration in interstitial fluid in tissue layers close to the peritoneum; (3) increased osmotic pressure of interstitial fluid results in high ultrafiltration flow from capillaries to the tissue and the PC; and (4) diffusion and convective transport of solutes in interstitial fluid from tissue to the PC results in low concentrations of these solutes in interstitium and induces their inflow from blood. All these immediate alterations in the local environment in the peritoneum and subperitoneal tissue covered by it, occur after each infusion of dialysis fluid and will induce adaptive changes in the tissue that in turn have an impact on peritoneal transport and effectiveness of PD (Struijk and Khanna, 2009). Note, however, that newer PD solutions with alternative buffers, a higher pH, and reduced content of glucose degradation products, or ones that contain icodextrin or amino acids as osmotic agents, have been introduced in many countries and have been shown to improve peritoneal membrane health and viability compared with conventional glucose-based solutions (Garcia-Lopez et al., 2012).

Alteration in the peritoneal transport system with time on PD

The source of the changes in peritoneal transport may be patient specific, related to the changes in the PTS, and/or to the treatment. The high concentration of osmotic agent, unphysiological low pH, and formation of glucose degradation products (GDPs) make dialysis solutions not fully biocompatible with physiological fluids in the body. The high concentration of glucose has vasoactive properties (Heimbürger, 2005; Zakaria el et al., 2008a) and increases expression of aquaporin 1 in mesothelial and endothelial cells (Lai et al., 2001). The accumulation of GDPs in long-term PD patients has an impact on the structural changes in the PTS (Heimbürger, 2005). The high concentration of glucose as the osmotic agent may stimulate a local inflammatory response (Flessner, 2005). Drugs and hormones can also influence the peritoneal transport rates and tissue perfusion (Heimbürger, 2005; Flessner et al., 2006). A substantial change in water flux and in the diffusive mass transfer parameter of mannitol was found after application of a vasoactive drug in animal experiments (Flessner et al., 2006).

The exposure to dialysis solutions results in a series of structural and functional changes of the PTS. These changes seem to begin already with the first exposure to the dialysis solution, although their clinical impact can be detected only after some time on PD

(Flessner, 2005). Denudations of mesothelial cells and their transition from the epithelial to mesenchymal phenotype due to PD were recently reported (Flessner, 2005; Heimbürger, 2005). The progressing thickening of the submesothelial zone with angiogenesis and fibrosis of this layer was positively correlated with the number of years on PD (Flessner, 2005; Heimbürger, 2005). The vascular changes, such as progressive subendothelial hyalinization and luminal narrowing or obliteration, tend to increase during PD (Heimbürger, 2005). New microvessels that appear by neoangiogenesis have less glycocalyx and are more permeable (Flessner, 2008). The development of encapsulating peritoneal sclerosis was reported in PD patients (Heimbürger, 2005). Although the reasons for this rare but serious complication are not clear, it is typically related to the fibrotic thickening of the submesothelial layers, formation of adhesions, and, in last phase, fibrous encapsulation of the intestinal loops (Heimbürger, 2005).

The changes in the morphology and functioning of the PTS have a significant impact on the peritoneal fluid and solute transport. In some patients, the progressing ineffectiveness in the removal of fluid and solutes results in therapy failure. The changes in the PTS and the corresponding changes in the peritoneal transport characteristics are initiated by the start of PD and a significant increase of D/P for creatinine after 6 months of CAPD was reported (Heimbürger, 2005). On the other hand, there is a decrease of solute transport in some patients who initially were classified as high transporters (Heimbürger, 2005). No changes in the amount of ultrafiltered water during short-term PD were found (Heimbürger, 2005). However, in long-term PD, the progressive changes in the PTS may cause ineffectiveness of fluid removal and lead to permanent loss of ultrafiltration capacity (ultrafiltration failure). A tendency towards decreased ultrafiltration as well as increase of small solute transport can be seen in some patients treated with PD for 4 or more years (Heimbürger, 2005). On the contrary, protein clearances and transport of macromolecules remain stable or decrease with time on dialysis (Davies et al., 2005; Heimbürger, 2005).

The changes in the physiology of the PTS due to the peritoneal therapy are very complex. They influence the efficiency of the treatment, and in some cases may result in termination of the therapy. The use of more biocompatible solutions, which decrease structural changes in the PTS, may decrease but do not seem to entirely cancel the changes in the PTS during long-term PD treatment (Garcia-Lopez et al., 2012).

Mechanisms of ultrafiltration failure

Permanent loss of ultrafiltration capacity (ultrafiltration failure (UFF)) is a frequent complication of long-term PD patients that consists of an inability to efficiently remove water by PD even if hypertonic fluids are used and results in oedema and other symptoms of overhydration (Heimbürger et al., 1990). Technically it is defined as obtaining < 400 mL of net ultrafiltration after 4 hours of peritoneal dwell with glucose 3.86% (Garcia-Lopez et al., 2012). There are several different causes for UFF that may occur individually or in combinations (Smit et al., 2004a; Waniewski et al., 2009a). The most frequent cause is a very fast absorption of glucose from dialysis fluid and therefore fast dissipation of osmotic pressure and a short period of ultrafiltration to the PC. The fast diffusion of glucose is accompanied by fast diffusion of other small solutes, as urea and creatinine, and their concentrations in dialysis fluid therefore quickly equilibrate with blood. However, the short period of ultrafiltration and the continuous fluid absorption process result in a low volume of drained dialysate thereby reducing the amount of removed uraemic toxins. The patients who have UFF due to fast diffusion of small solutes may be treated by increased frequency of short dwells which can be facilitated by using automated PD, and by using icodextrin-based fluid during the long dwell. Frequently, these patients have also impaired osmotic conductance, that is, decreased effectiveness of the osmotic pressure of dialysis fluid in inducing ultrafiltration (Smit et al., 2004a; Waniewski et al., 2005). One of the reasons for this decrease in osmotic conductance may be fewer or damaged ultra-small pores and this may be reflected by decreased sodium dip (Smit et al., 2004a; Waniewski et al., 2009a). A rare cause for UFF is high absorption of fluid from the PC despite relatively normal transport of small solutes and osmotic conductance (Heimbürger et al., 1990; Smit et al., 2004a; Waniewski et al., 1996a, 2005).

Summary

The physiological principles that govern the efficiency of PD aim at restoring homeostasis by eliminating the unphysiological conditions introduced by the treatment. Thus, the temporal patterns (shown in Figs 264.2 and 264.3) of the shifts of volume and solutes between PC and blood demonstrate the effectiveness of the main physiological driving forces, diffusion and osmosis, and feedback mechanisms in restoring steady state levels. This makes PD an inherently safe and robust therapy as these processes do not 'run out of control' (which can happen in an artificial renal replacement therapy such as haemodialysis). These control mechanisms together with the ability of PD to provide fluid and solute removal that are sufficient for patient survival similar to that provided by haemodialysis, and the ease of use and specific medical advantages, explain why PD remains the leading form of home-based dialysis therapy.

On the other hand, the unphysiological conditions introduced by the treatment, may harm the PTS, causing structural and functional changes that limit the fluid and solute removal capacity especially during long-term treatment. These changes can be better understood and monitored using different kinetic methods which are all based on assessment of the rate of fluid and solute removal.

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CHAPTER 265

Peritoneal dialysis: adequacy and prescription management

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Introduction

Dialysis adequacy is a term used to describe how well any dialysis therapy effectively mitigates some of the uraemic complications of end-stage renal disease (ESRD). In the simplest terms, dialysis adequacy measures the dose of dialysis and judges it to be sufficient (adequate) or insufficient (inadequate). In peritoneal dialysis (PD), adequacy refers to the ability of dialysis to perform any or all of myriad tasks including (1) removing metabolic waste products, (2) maintaining proper fluid balance and blood pressure control, (3) removing excess electrolytes, (4) correcting acid–base imbalances, (5) maintaining healthy bone mineral metabolism, and (6) promoting the maintenance of a proper nutritional status. In practice, PD adequacy is most often measured mono-dimensionally, in terms of small solute (i.e. urea) clearances; however, it is most useful to incorporate a wider view of dialysis adequacy when caring for patients with ESRD.

Standardized targets for small solute clearance in PD were not developed *de novo* but rather were created as amendments to pre-existing haemodialysis (HD) adequacy guidelines. No studies have been able to define the absolute minimum required Kt/V_{urea} (the amount of urea removed divided by the volume of distribution) for PD patients but interventional trials over the past two decades have allowed a consensus to recommend a minimum total (peritoneal plus residual kidney) Kt/V_{urea} of 1.7. Peritoneal membrane transport characteristics should be used to individualize PD prescriptions and adjust regimens when necessary. Residual renal function lowers the risk of death in PD patients, even when glomerular filtration rate (GFR) is as little as 0.5 mL/min/1.73 m^2, therefore care must be taken to preserve residual renal function however possible in PD patients.

Solute clearance: small, water-soluble solutes

One of the major functions of dialysis is removal of metabolic waste products, specifically, removal of accumulated solutes that would normally be eliminated from the body via the kidneys. Although many potential uraemic toxins have been identified, and thousands more proposed, urea is the prototype of uraemic solutes (Vanholder et al., 2003; Neirynck et al., 2013). It is easy to understand why urea remains the most widely measured molecule in clinical dialysis practice; it is easy to measure with currently available laboratory equipment, it is fairly rapidly generated in the body and therefore changes in its blood concentration can be seen within hours to days, and finally, due to its small size, urea is relatively easy to remove with dialysis (either PD or HD). Interestingly, despite its ubiquitous presence in dialysis patients, there is a lack of evidence regarding the adverse biological effects of urea per se (except when present in extremely supra-physiologic levels) (Johnson et al., 1972; Vanholder et al., 2003; Neirynck et al., 2013). Nevertheless, because of the reasons previously listed, urea clearance measurement is a useful tool one can use, in addition to others, when determination of dialysis adequacy is required.

Urea is a small molecule (60 Da) and easily traverses the peritoneal membrane during PD. Since the concentration of urea in peritoneal dialysate is zero, it can easily diffuse down its concentration gradient, from the blood into the peritoneal cavity, until equilibrium is reached between the two spaces; on average, 90% urea equilibration is attained 4 hours after the start of a PD dwell; thereafter, additional urea clearance is minimal (Twardowski et al., 1987). Thus, peritoneal urea clearance during a set time period is highly dependent upon the drained volume of dialysate and less influenced by dwell time, once the equilibration point has passed (approximately 4 hours' dwell time on average). It should be noted that a minor quantity of urea is removed via convection during the PD dwell.

In chronic kidney disease (CKD) patients, creatinine is used to measure renal clearance but it plays a less prominent role in PD. With a size of 113 Da, creatinine does not traverse through the peritoneal membrane pores as rapidly as do smaller molecules such as urea; on average, creatinine is 70% equilibrated between blood and dialysate after a 4-hour dwell period (Twardowski et al., 1987). In some ways creatinine may be a more useful uraemic solute than urea because it is not as readily affected by daily changes in dietary intake; in other words, over a period of hours to days, the serum creatinine concentration is more likely to remain at constant levels than serum urea (or, blood urea nitrogen (BUN)) concentrations. On the other hand, since creatinine is derived directly from body muscle, underweight individuals with little muscle and therefore low rates of creatinine generation are at higher risk for overestimation of true solute clearance when adequacy is measured solely using dialysis creatinine clearance rather than with urea or combined urea and creatinine clearances.

Potassium is a small molecule (39.1 Da) that is rapidly and effectively cleared in PD; on average, potassium is 85% equilibrated between the blood and peritoneal fluid after a 4-hour dwell (Twardowski et al., 1987). Peritoneal dialysate contains no

potassium therefore in PD, potassium behaves similarly to urea in the sense that it diffuses across the peritoneum down its concentration gradient. Theoretically, potassium clearance could be used as a measure of PD adequacy but in practice its use in this regard is limited because serum potassium concentrations can vary rapidly with dietary changes in potassium intake; intra-patient 'potassium clearance test' results would be difficult to validate even when separate measurements were taken within the same week. Nevertheless, serum potassium levels per se can be helpful in the assessment of PD adequacy. Since PD is a continuous therapy that removes potassium from the body, non-oliguric PD patients rarely become hyperkalaemic (Zanger, 2010), and any newly hyperkalaemic patient who does not have an obvious source of rapid potassium influx (e.g. gastrointestinal bleeding, haematoma, recent large dietary intake of potassium, rhabdomyolysis, tumour lysis, diabetic ketoacidosis, etc.) should undergo evaluation regarding the quantity and quality of their dialysis.

Despite its small size, phosphorus (96 Da) has been described as a middle molecule in its biochemical behaviour (Bammens et al., 2003; Kuhlmann, 2010). It is hydrophilic in nature, has a negative charge, and is kept mostly intracellularly and therefore does not diffuse as rapidly as urea across the peritoneal membrane. In clinical scenarios, phosphorus clearance is strongly correlated to creatinine clearance but not urea clearance (Sedlacek et al., 2000; Badve et al., 2008). Both phosphorus and creatinine clearances appear to increase when dwell times are longer, but only in patients with either high-average, low-average, or low peritoneal membrane transport type; in rapid (high) transporters, longer dwell times do not increase phosphorus clearances (Badve et al., 2008). Since hyperphosphataemia is associated with poor cardiovascular outcomes in CKD, PD phosphorus clearance (or its surrogate, creatinine clearance) should be measured alongside the ubiquitous Kt/V_{urea} when determining any patient's dialysis adequacy (Eddington et al., 2010).

Box 265.1 Signs and symptoms of inadequate dialysis

- Persistent nausea and/or vomiting
- Fatigue
- Sleep disturbances
- Pruritus
- Restless leg syndrome
- Worsened anaemia and/or ESA resistance
- Hyperkalaemia
- Hyperphosphataemia
- Worsened hyperparathyroidism and/or resistance to vitamin D or vitamin D analogues
- Pericarditis
- Neuropathy
- Unexplained weight loss
- Worsened metabolic acidosis
- Volume overload.

Solute clearance: middle-molecular-weight and protein-bound solutes

Middle molecules are small peptides that have an atomic size > 500 Da; because of their size, middle molecules do not diffuse as readily across the peritoneal membrane as smaller solutes do (Neirynck et al., 2013). The quintessential middle molecule measured in dialysis patients is beta-2 (β_2) microglobulin (12,000 Da). Excess β_2 microglobulin accumulation in ESRD is a well-known contributor to the development of dialysis-related amyloidosis. In contrast to urea or creatinine clearance, in PD β_2 microglobulin clearance is strongly dwell-time dependent. In one study that evaluated the effect of PD schedule on solute clearance, β_2 microglobulin clearance nearly doubled when two 6-hour exchanges were increased to two 12-hour exchanges; β_2 microglobulin clearance did not change in the continuous ambulatory peritoneal dialysis (CAPD) patients when the number of exchanges per day was increased (Kim et al., 2001).

Other middle molecules that have been shown to accumulate in ESRD include molecules related to nutrition (leptin, ghrelin, adiponectin), bone mineral metabolism (fibroblast growth factor 23, parathyroid hormone, calcitonin), and inflammation (tumour necrosis factor alpha, vascular endothelial growth factor, interleukin 6) (Neirynck et al., 2013). Some of these larger molecules are protein bound and, along with other protein-bound solutes such as *p*-cresyl sulphate, indoxyl sulphate, and advanced glycosylation end-products (AGEs), represent a distinct group of uraemic solutes that has not been extensively studied in PD patients. From the available data it appears that peritoneal transport of protein-bound solutes is restricted only by solute size and whether it is unbound or not, that is, solutes are available for transperitoneal transport only when present in the serum in the unbound state; furthermore, only a small fraction of protein-bound solutes are thought to be removed from the blood via peritoneal albumin loss (Bammens et al., 2005; Pham et al., 2008). Since only a small fraction of protein-bound solutes circulate freely in the serum, their removal is dependent upon the functioning kidney.

Peritoneal dialysis adequacy: background

An adequate dose of PD is that which is associated with an overall sense of well-being, absence of malnutrition, no uraemic symptoms, biochemical balance, euvolaemia, bone-mineral metabolism balance, and erythropoiesis-stimulating agent (ESA) responsiveness (Box 265.1). Adequate dialysis should be assessed clinically and not only by measurement of solute clearance. Nevertheless, in clinical practice, the concept of dialysis adequacy has become synonymous with the achieved solute clearance, particularly urea clearance which is most commonly measured as Kt/V_{urea}.

The evolution of PD adequacy guidelines is an interesting story that begins nearly four decades ago. In 1981, the National Cooperative Dialysis Study (NCDS) was published; the NCDS was the first randomized control trial (RCT) to examine the effect of dialysis dose on outcome in HD. Patients were randomized to two different time averaged urea concentrations (TAC_{urea} of 50 mg/dL vs 100 mg/dL) and two different HD treatment times. TAC_{urea} was found to inversely correlate with the likelihood of poor outcomes. In 1985, Gotch and Sargent reanalysed the data and introduced single pool (sp) Kt/V as a measure of dialysis adequacy (Gotch and

Sargent, 1985). In their report, HD outcomes were found to be superior when spKt/V was 1.0 or higher. Based on these data, an achieved spKt/V of 1.2 developed as a clinical target in HD patients (the additional 0.2 provided a buffer so that spKt/V remained > 1.0 at all times).

At this time there were no significant studies examining the effect of dialysis dose on PD outcome, but the generalization that more dialysis provides better outcomes (as per the NCDS study) was generally extrapolated to the practice of PD. In 1996, the Canada-USA (CANUSA) study was presented as the first study to examine the effect of dialysis dose on survival specifically in PD patients. This collaborative effort between researchers in Canada and the United States studied a prospective observational cohort of 680 patients in whom the majority (98%) received CAPD rather than automated peritoneal dialysis (APD). In the CANUSA study, renal and peritoneal clearances were assumed to be equivalent and were added together. The relative risk of mortality decreased by 6% for each 0.1 U/week increase in weekly Kt/V_{urea}, and decreased by 7% for each 5 L/week/1.73 m^2 increase in creatinine clearance.

It was assumed in this study that (a) Kt/V_{urea} remained constant over time, and (b) renal Kt/V_{urea} and peritoneal Kt/V_{urea} were equivalent, such that any loss in renal Kt/V_{urea} was made up for by an equal increase in peritoneal Kt/V_{urea} (Canada-USA (CANUSA) Peritoneal Dialysis Study Group, 1996). Five years later, in 2001, a reanalysis of the original CANUSA data was presented wherein renal Kt/V_{urea} and peritoneal Kt/V_{urea} data were first separated and then examined. Important findings included the following: (1) PD outcome was predicted by renal Kt/V_{urea} but not peritoneal Kt/V_{urea}, (2) changes in survival over time were due to changes in residual renal function, and (3) each 5 L/week renal GFR was associated with a 12% survival benefit (Bargman et al., 2001).

Two subsequent studies confirmed that PD survival does not improve with higher urea clearance rates. The first, ADEMEX, was a randomized trial of 965 CAPD patients in Mexico; patients were randomized to receive either a conventional PD prescription of four daily exchanges with 2 L inflow, or additional PD to achieve peritoneal creatinine clearance (pCrCl) of > 60 L/week/1.73 m^2. Both groups had similar baseline residual kidney function, and outcome was measured based only upon peritoneal clearance differences. The study achieved a good separation between the two groups (pCrCl of 46 vs 57 L/week/1.73 m^2). There was no difference in survival at the end of 2 years. Interestingly, the overall mortality rates in this study were similar to the 2-year survival rates seen in the HEMO trial, which evaluated the effect of dialysis dose on outcomes in HD (Paniagua et al., 2002). The second, known as the Hong Kong Trial, was published 1 year later. It randomized 325 PD patients to three target peritoneal Kt/V_{urea} goals (1.5–1.7, 1.7–2.0, and > 2.0). This study also achieved good separation between the groups, and residual renal function was the same in all groups. There was no difference in survival between the three groups; however, the lowest Kt/V group (pKt/V_{urea} 1.5–1.7) exhibited greater drop-out due to inadequate dialysis, and also required higher doses of ESA to achieve haemoglobin targets (Lo et al., 2003).

In summary, the clinical trials described above have all shown that survival in PD is not improved by increasing peritoneal Kt/V_{urea} from 1.7 to 2.0 (or higher). No prospective study has established a lower limit of peritoneal Kt/V_{urea} but the Hong Kong trial found that patients with Kt/V_{urea} < 1.7 experienced more clinical complications than those with Kt/V_{urea} 1.7 or above. One retrospective trial, also from Hong Kong, showed poorer survival in anuric PD patients with Kt/V_{urea} < 1.67 (Lo et al., 2005). It should be noted that all of the above studies calculated V using the Watson formula for estimation of total body water, and actual body weight was in the calculations (Watson et al., 1980). Finally, residual renal function was found to confer survival benefits in PD patients even when renal clearances were as low as 5 L/week, equivalent to a GFR of 0.5 mL/min/1.73 m^2.

Peritoneal dialysis adequacy: current guidelines

In clinical practice, the concept of dialysis adequacy has become synonymous with the achieved solute clearance, particularly urea clearance which is most commonly measured as Kt/V_{urea}, however, adequate dialysis should be assessed clinically and not only by measurement of small solute clearances. Current guidelines from the International Society for Peritoneal Dialysis (ISPD) clearly emphasize this point by stating:

> In order to emphasize that there is more to adequate dialysis than a focus on small solute kinetics and ultrafiltration targets, the Committee decided to name this guideline, *Guideline on Targets for Solute and Fluid Removal in Adult Patients on Chronic Peritoneal Dialysis* instead of *Guideline on Adequacy of Peritoneal Dialysis.* (Lo et al., 2006)

Clinical and laboratory parameters should all be taken together to assess the patients overall well-being and health. In the absence of any singly useful marker of dialysis adequacy, small solute clearance remains the focus of current guidelines for PD adequacy. A number of regional nephrology professional organizations have published guidelines for PD solute clearance targets; for the most part all of these are similar to guidelines set forth by the ISPD, who commissioned a task group with representation from Asia, Australia, Europe, and North America. A summary of common main points from all of these references can be found in Box 265.2.

A few points deserve special mention. First, for patients using APD, a target creatinine clearance of 45 L/week/1.73 m^2 is recommended by some groups (in addition to a minimum total Kt/V_{urea} of 1.7), due to a more variable relationship between urea clearance and creatinine clearance in APD, as compared to CAPD. Second, solute clearance recommendations cannot necessarily be made for patients who are at the extremes of body size; traditional anthropometric formulae estimate body water based upon actual body weight and do not account for the decreased presence of water in adipose tissue versus muscle. Therefore, obese patients (with more fat) may have less water than expected based on V calculations, and therefore may actually be receiving more dialysis than calculated by Kt/V_{urea}. The reverse situation may be present in malnourished individuals who lack body fat therefore causing them to be functionally underdialysed with respect to measured Kt/V_{urea} (Dumler and Cruz, 1995). Finally, whenever the target Kt/V_{urea} or creatinine clearance cannot be attained with dialysis alone (i.e. when residual renal clearance is required in order to reach the target) it is imperative to measure renal function regularly so that any loss in renal clearance can be promptly attenuated by increased dialysis dose, remembering always that one unit of peritoneal clearance is not fully equivalent to one unit of renal clearance and that a full complement of clinical criteria should be met before declaring dialysis to be 'adequate'.

Box 265.2 Common guidelines for PD solute and fluid removal

- Minimum total (renal + peritoneal) $Kt/V_{urea} \geq 1.7$.
- Dialysis dose should be increased in patients with uraemic symptoms (even if Kt/V_{urea} exceeds targets).
- Twenty-four hours per day of peritoneal dialysis is preferred.
- Creatinine clearance should be ≥ 45–50 L/week for APD patients.
- Residual renal function should be measured no less than every 6 months, and more often (e.g. every 3 months) if target Kt/V_{urea} does not reach 1.7 without renal clearance.
- Peritoneal urea and creatinine clearance should be measured every 3–6 months.
- Measures should be taken to preserve residual renal function whenever possible; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used; hypovolaemia and hypotension should be avoided.
- Daily ultrafiltration should be > 750 mL for most patients; those with lower ultrafiltration volumes should be carefully monitored and a dialysis prescription (or modality) change considered.
- Use the lowest concentration of glucose necessary to achieve desired ultrafiltration volumes.
- Consider icodextrin for the long dwell, particularly in patients with high or high average peritoneal transport status.

Reference: CARI (Australia); Renal Association (UK); ISPD; Canadian Society of Nephrology.

Measurement of peritoneal solute clearance: Kt/V_{urea}

In PD, urea clearance is simply determined by measuring the amount of urea removed in the effluent, per unit time. Kt/V_{urea} in HD is dimensionless; in PD it is dimensionless by convention only. Traditionally, PD urea clearance is reported as weekly Kt/V_{urea} whereas for in-centre HD it is typically reported as a per-session Kt/V_{urea}, which partly explains why targets are different for the two modalities. Creatinine clearance in PD is reported as litres per week rather than millilitres per day, which is used for reporting renal clearance.

Methods for calculating peritoneal Kt/V_{urea} are described in detail in Boxes 265.3 and 265.4. Renal Kt/V_{urea} can be determined by drawing blood for BUN measurement, performing a 24-hour urine collection and measuring its total urea nitrogen (UN) concentration, then applying the formula:

$$\left(\text{Dialysate UN} / \text{BUN}\right) \times \left(24 - \text{hour drain volume} / 1440\right) = \text{renal Kt}\ \left(\text{mL} / \text{min}\right)$$

Converting it to L/week:

$$\text{Renal Kt}\ \left(\text{mL} / \text{min}\right) \times 10.08 = \text{renal Kt}\ \left(\text{L} / \text{week}\right)$$

and dividing by V (Box 265.5) to finally obtain renal Kt/V_{urea}. Simple addition of renal and peritoneal Kt/V_{urea} yields 'total Kt/V_{urea}'.

Box 265.3 How to collect samples for peritoneal Kt/V_{urea} in PD

CAPD collections

1. At time zero of a 24-hour collection period, the patient drains the peritoneum and discards this effluent; the patient immediately instils a fresh bag of dialysate (exchange 1).
2. Later, when the patient drains exchange 1, the patient weighs the drain bag using the spring scale, records the weight, and removes an aliquot into a collection cup marked 'exchange 1'.
3. The patient repeats step 2 for all of the following exchanges in the 24-hour period, then immediately brings the following to the dialysis unit:
   - Recorded drain volumes for each of the exchanges in the 24-hour aliquots—one from each exchange; these are pooled into one container which is sent to lab for measurement of dialysate urea nitrogen (DUN).
4. Venepuncture is performed (during the 24-hour collection or as soon as possible afterwards) and sent to lab for measurement of blood urea nitrogen (BUN).

CCPD collections

1. The 24-hour collection begins in the morning, when the cycler instils the 'last fill'.
2. For each daytime manual exchange, the patient weighs the drain bag(s) using the spring scale, and records the weight(s).
3. Later, when the patient connects to the cycler, the initial drain (I-drain) volume is recorded. The cycler exchanges proceed as usual. The cycler should be set up to drain into a 15 L drain bag for collection.
4. The next morning, the patient records the total ultrafiltration volume (UF) from the cycler.
5. The patient records the total instilled volume from the cycler (i.e. the cycler prescription, for example, 4 exchanges of 2 L each = 8 L total)
6. An aliquot of dialysate is taken from the large 15 L drain bag and one each from any daytime manual drain bags. These are pooled into one container and sent to lab as for CAPD, above.

Prescribing peritoneal dialysis: principles

There are several initial factors to consider when planning a PD prescription (incident or prevalent patient). First, it is important to take into account the patient's lifestyle and how different PD modalities could affect it. For example, a patient who works full-time might be best suited to APD because it allows for an uninterrupted workday. A patient whose spouse is a light sleeper might prefer to forego the cycler and choose CAPD so that his or her spouse is not disturbed by the low sounds of a cycler. Second, body size should always be taken into account when a PD prescription is made. Body size affects the amount or dose of PD needed, that is, how many litres of dialysate per inflow and how many exchanges per day. Third, the presence or absence of residual kidney function

Box 265.4 How to calculate peritoneal Kt/V_{urea} in PD

Calculations

1. Calculate total 24-hour drain volume:

   For CAPD = sum of drain volumes from each exchange in the 24-hour collection

   For CCPD = (sum of drain volumes from all daytime manual exchanges) + (I-drain volume) + (cycler instilled volume) + (total cycler UF)

2. Calculation of peritoneal Kt, mL/min:

   DUN (mmol/L) 24-hour drain volume (mL/day)
   BUN (mmol/L) 1440 minutes/day

3. Convert pKt/V into L/week:

   pKt (mL/min) × 10.08 = L / week

4. Calculate V (see step 1).

5. Calculate weekly pKt/V (using V from step 4).

affects the amount/dose of PD needed. For example, a patient with a residual kidney GFR of 7 mL/min/1.73 m^2 might initiate nightly intermittent peritoneal dialysis (NIPD), with its 'dry day', or alternatively may be adequately dialysed with two to three exchanges per day as long as his or her GFR remains stable. In general, most PD guidelines recommend that patients do not have a 'dry day' because middle molecule clearance is largely dwell time dependent (night-time cycler exchanges provide only short dwell times).

Peritoneal membrane transport characteristic should be kept in mind whenever a clinician prescribes, or adjusts, the PD prescription. Prevalent PD patients should have data regarding peritoneal membrane transport characteristics (PET data). Incident patients do not have PET data available at the time of PD initiation (since the initial PET should not be performed before 4 weeks of continuous PD), and one should assume average membrane transport characteristics in these patients.

Box 265.5 Anthropometric equations used to estimate total body water

Watson

(*Males*) TBW = 2.447 – (0.09516 × A) + (0.1074 × H) + (0.3362 × W)
(*Females*) TBW = –2.097 + (0.1069 × H) + (0.2466 × W)

Hume

(*Males*) TBW = (0.194786 × H) + (0.296785 × W) – 14.012934
(*Females*) TBW = (0.34454 × H) + (0.183809 × W) – 35.270121

Chertow

TBW = H × (0.0186104 × wt + 0.12703384) + W × (0.11262857 × male + 0.00104135 × A – 0.00067247 × W – 0.04012056) – A × (0.03486146 × male + 0.07493713) – male × 1.01767992 + diabetes × 0.57894981

TBW = total body water in litres
A = age in years
H = height in cm
W = weight in kg

References: Watson et al. (1980), Hume and Weyers (1971), and Chertow et al. (1997).

Writing the peritoneal dialysis prescription

The most common initial CAPD prescription (Table 265.1) is the 4 × 2 L prescription, meaning four exchanges per day with 2 L inflow volume for each exchange. The most common variations on this standard prescription take into consideration patient size and residual kidney function. Some considerations when writing the initial CAPD prescription include the following:

- Smaller patients can usually meet solute clearance targets with smaller inflow volumes of 1500–2000 mL, whereas large patients typically require inflow volumes of 2500 mL or more.
- Inflow volumes that are too large for a particular patient can be associated with discomfort (abdominal distension, back pain, decreased appetite from bloated sensation); however, some patients may grow accustomed to the inflow volume with time.
- Large inflow volumes increase intraperitoneal pressure, and therefore increase the risk of developing a new hernia or peritoneal leak. To decrease intraperitoneal pressure, larger inflow volumes should be preferentially used at night, while supine; if the patient has large inflow volumes during the day, the patient should avoid any activity or situation which could further increase intraperitoneal pressure (e.g. constipation, Valsalva manoeuvre, squatting, chronic coughing, heavy lifting, etc.)
- If significant residual kidney function is present, fewer exchanges per day may be sufficient (as long as the total peritoneal + renal Kt/V_{urea} meets targets); in these cases NIPD (nocturnal dialysis only) can also be considered. Patients must have residual kidney function must be measured frequently (i.e. every 3–4 months) to detect any decrement in GFR that would necessitate a change in the PD prescription in order to meet solute clearance targets.

APD refers to the PD procedure that utilizes an automated cycling machine to perform the PD dialysate exchanges. APD is further classified as either (1) NIPD, or nightly intermittent PD, which uses the cycler at night followed by a 'dry day' without dialysate in the

Table 265.1 Typical CAPD prescription based upon body size

BMI	Inflow volume	Exchanges/day	Comments
< 25	1500–2000 mL	3–4	If needed, larger fill volumes should be used at night (supine)
25–30	2000 mL	4	
>30	2500–3000 mL	4–5	Larger fill volumes should be used at night (supine)

Additional comments:

(1) If significant residual kidney function is present, can consider NIPD (dry day), fewer cycles, or smaller inflow volumes.

(2) The prescribed dialysate tonicity will vary depending upon volume status and membrane transport status. See text for details.

peritoneum; (2) CCPD, or continuous cyclic PD, where the cycler is used nightly, followed by a day dwell; dialysate dwells throughout the day until the time of reconnection to the cycler at night; (3) high-dose APD (also called PD plus) where nightly PD with the cycler and a daytime dwell is combined with one or more manual daytime exchanges, before reconnecting to the cycler at night; or (4) tidal PD which is nightly APD where each cycle drains a percentage of the infused volume (incomplete draining) before refilling the peritoneum, therefore allowing a constant amount of dialysate to remain in the peritoneum. Tidal PD is most often used to reduce drain pain due to PD catheter abutment against the viscera (see Chapter 266).

The typical APD prescription requires consideration of several factors. First, inflow volume should be determined. A typical starting volume is 1500–2000 mL but larger patients or those needing additional solute clearance may require 2500–3000 mL. Cycler inflow volumes need not be in increments of 500 mL (i.e. 1500, 2000, 2500, etc.), which is helpful when inflow volumes must be increased but the patient cannot immediately tolerate and additional 500 mL of dialysate. Second, total cycler therapy time must be chosen. Therapy time should depend upon the patient's lifestyle characteristics and needs, and the amount of solute clearance needed. Third, one decides the number of cycles per night which is typically three to five cycles; care should be taken to avoid more than five cycles per night if possible because each additional cycle causes a greater proportion of total cycler time to be spent draining and filling, rather than in the dwell phase when solute and fluid removal occur. Additionally, the use of many short overnight dwells creates a sodium sieving effect, the result of which is morning thirst and increased fluid intake. The tonicity of dialysate in APD, much like in CAPD, is a dynamic factor because changes will be made on a daily or weekly basis according to the patient's extracellular fluid status.

Special mention should be made regarding NIPD. This modality should be used only in patients who have significant residual kidney function, because the short nocturnal cycler PD exchanges provide poor middle molecule clearance. Residual kidney function, or a long dwell in the daytime, provides middle molecular solute clearance that NIPD cannot provide. Occasionally, NIPD is used temporarily after abdominal surgery; intraperitoneal pressures are much lower in the supine than upright position, and NIPD allows surgical to heal without added stress of high intraperitoneal pressure. Patients using NIPD should have frequent and regular measurement of residual renal function so that any decline in GFR can be matched with an appropriate increase in dialysis dose.

NIPD is one form of incremental PD, which is defined as PD using an initial dose of PD that is small but enough to bring total (dialysis + urine) clearances at or above target vales. It is prescribed with the understanding that PD doses will be increased as residual kidney function is lost. Incremental PD is used in up to 33% of incident PD patients and provides certain benefits over waiting to start dialysis until frank uraemia appears; incremental PD allows for the ability to learn PD before uraemic symptoms develop, prevents deterioration in nutritional status, and provides patients with a break-in period when they can gradually accommodate to the dialysis lifestyle rather than having an abrupt dialysis start (Nolph, 1998; Tzamaloukas, 1999). There are risks to incremental dialysis, however, including peritonitis, hernias, and catheter-related complications (Burkart and Satko, 2000). Further studies will hopefully be conducted to examine and better define the proper role of incremental PD in ESRD.

Adjusting the peritoneal dialysis prescription

Routine monitoring of PD adequacy is recommended for all maintenance PD patients. Over time many patients require modifications to their PD prescriptions, for example, when GFR is lost or when peritoneal membrane transport type changes. If patients develop signs or symptoms of uraemia, or if they grossly fail to meet solute clearance targets, prompt adjustments should be made to the PD prescription. A summary of manoeuvres than can increase dialysis solute clearance is provided in Box 265.6.

Knowledge of the peritoneal membrane transport type can be helpful when adjusting a PD regimen in an attempt to increase small solute clearance. Slower transporters tend to have a greater gain in urea clearance than faster transporters when a daytime exchange is added to the long dwell (in CCPD) (Page and Smith, 1999). On the other hand, high transporters benefit more from an additional hour of cycler therapy than low transporters; the former often have a choice between additional cycles or increased fill volumes when additional small solute clearance is required while the latter do not. In general, when attempting to increase solute clearances, one should keep in mind the biochemical behaviour of the solute in question in order to understand how best to increase clearances in different membrane transport types. Nevertheless, it

Box 265.6 Methods to increase solute clearance in PD patients

CAPD

1. Increase inflow volume per exchange (most effective, especially in low, low-average, and high-average transporters).
2. Increase the number of day exchanges (typically less effective than increasing the inflow volume).
3. Increase the ultrafiltration volume (ultrafiltration causes solvent drag, which leads to additional solute clearance) either by using hypertonic fluid or icodextrin for the long overnight dwell (icodextrin should not be used for dwell times < 8–9 hours).
4. Consider changing to APD (particularly in high/rapid transporters).

CCPD

1. Increase the inflow volume per exchange (most effective).
2. Increase the number of cycles (caution: too many cycles create ineffective dialysis, since more time is spent draining and filling dialysate than dwelling dialysate; additionally, frequent short cycles leads to sodium sieving which can create morning thirst due to hypernatremia).
3. Add daytime manual exchanges ('high-dose PD').
4. Increase ultrafiltration (see above).
5. Consider changing to CAPD (in low transporters).

is rarely the case that a patient cannot be prescribed CAPD or APD because of their transport type per se. The most difficult patient to dialyse with PD is an anuric, large-sized, slow transporter and fortunately this type of patient is infrequently encountered in clinical practice. A number of computer-based PD prescription modelling programmes are available to help optimize PD treatment regimens using known clinical data; these can prove quite helpful when trying to optimally configure a PD prescription to meet clearance, ultrafiltration, transport type, and lifestyle specifications.

Summary and conclusions

PD adequacy generally should be assessed globally and not only by measurement of small solute clearance. A sufficient dose of PD is that which is associated with an overall sense of well-being, absence of malnutrition, no uraemic symptoms, biochemical balance, euvolaemia, ESA responsiveness, and other clinical parameters. In clinical practice, the concept of dialysis adequacy has often become synonymous with the achieved solute clearance, particularly urea clearance which is most commonly measured as Kt/V_{urea}. The currently recommended minimum standard total Kt/V_{urea} of 1.7 in PD was established based upon the results of several interventional trials, although none of them defined the absolute minimum threshold for Kt/V_{urea} in PD. Residual renal function appears to play a major role in predicting outcome in PD such that more residual renal function is associated with better survival. All measures should be taken to preserve GFR as long as possible in PD patients. The PD prescription should be written after consideration of several factors including residual renal function, body size, patient preferences, and peritoneal transport type. PD patients should be monitored regularly for any signs of inadequate dialysis, and their PD regimens must be quickly modified to effect timely improvement.

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CHAPTER 266

Peritoneal dialysis: non-infectious complications

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Hernias and leaks

Dialysate dwelling in the abdomen during peritoneal dialysis (PD) results in increased intra-abdominal pressure. The empty peritoneal cavity has a pressure of 0.5–2.2 cmH_2O and with dialysate present this pressure can increase to 2–10 cmH_2O. The pressure can increase further with activities such as coughing or straining with bowel movements. The increased pressure associated with PD can result in complications including hernias and dialysate leaks.

Most series report a prevalence of hernias in PD patients of 9–25%, with an incidence of 0.06 hernias per dialysis-year. Many potential risk factors for hernia formation have been identified, although none have been identified consistently in the literature. Some possible risk factors include polycystic kidney disease, older age, multiparity, continuous ambulatory peritoneal dialysis (CAPD) (vs automated PD), higher body mass index, and larger dialysate fill volumes. Many hernia locations have been reported and are listed in Box 266.1. Umbilical and inguinal hernias are the most commonly reported sites for hernia formation. See Figs 266.1 and 266.2.

A careful abdominal exam prior to placement of the PD catheter is important. One group found that two-thirds of the hernias diagnosed at their centre were found prior to the initiation of PD. If diagnosed before the start of dialysis, hernia repair can be performed at the time of catheter placement. Sometimes clinically undetectable hernias are found incidentally during laparoscopic placement of the PD catheter. As they can be repaired during the same procedure as catheter implantation it is important to add this to the preoperative consent. This reduces the number of surgeries that need to be performed and therefore decreases the associated anaesthetic risk. Hernias are often clinically apparent and are easier to appreciate with the patient standing and bearing down or coughing. If needed, ultrasound or computed tomography (CT) imaging can be used to differentiate between a hernia and other masses.

Once diagnosed, hernias should be repaired. This is especially true for small hernias, such as those in the umbilical region, which are more likely to incarcerate. Furthermore, the perioperative management of dialysis is easier early in the course of end-stage renal disease (ESRD) when the patient has more residual kidney function. Aside from the risk of bowel incarceration and strangulation, hernias constitute a disruption in the boundary of the peritoneal cavity and are therefore a source of leak of dialysate out of that cavity into the surrounding soft tissues (see later discussion on dialysate leaks). Patients with a hernia should be advised about the signs and symptoms of incarceration, and should seek medical attention if they are unable to reduce their hernia. While waiting for repair, the intra-abdominal pressure should be lowered. This may involve decreasing or eliminating daytime fluid dwells if adequacy concerns allow. Surgical repair using a mesh will reduce the risk of reoccurrence of the hernia. Many centres have reported good results without having patients switch to interim haemodialysis. PD can safely be continued until the morning of the surgery at which time they should be drained of dialysate. Intermittent peritoneal dialysis (IPD) (night cycling with day dry) with 750–1000 mL volumes can be restarted within 24–48 hours of surgery and volumes gradually increased within the first 2 weeks. There have been reports of patients successfully restarting PD the day of their surgery for those unable to go without dialysis. A brief transfer to haemodialysis and delay in restarting PD should be considered if a hernia is repaired in the setting of bowel incarceration or strangulation. Due to possible compromise in the integrity of the bowel wall due to ischaemia, there may be an increased risk of enteric peritonitis if PD is recommenced immediately.

A dialysis leak is considered any movement of dialysate out of the peritoneal cavity other than through the PD catheter. Dialysate can leak external to the catheter around the exit site of the catheter. It usually tracks along the course of the catheter from the peritoneal cavity to the exit site. It can also leak internally into other tissues or body cavities including the abdominal wall, genitalia, or pleural cavity. There has even been a report of a pericardial effusion confirmed as dialysate solution. Pericatheter leaks commonly occur within the first 30 days after catheter placement. Leaks into other body cavities are related to loss of integrity of the peritoneal membrane and more commonly occur after 30 days. Pleural leaks are an exception and can occur almost immediately after the commencement of PD if there are pre-existing defects in the hemidiaphragm.

The incidence of dialysate leakage is 5–10%. Risk factors have been identified that increase the risk. Midline surgical placement of the PD catheter has been shown to increase the rate of leaks when compared to paramedian placement. Earlier initiation of dialysis after the catheter has been placed has also been shown to increase the rate of leaks. It is important that the deep catheter cuff be placed firmly in the rectus muscle and secured with a purse-string suture to prevent dialysate from leaving the peritoneal cavity and tracking along the course of the catheter. Fig. 266.3 is a CT image of fluid that has leaked along the catheter into the abdominal wall. Conditions that result in abdominal wall weakness or poor healing

Box 266.1 Hernia sites reported in PD patients

- Umbilical
- Inguinal (direct and indirect)
- Catheter exit site
- Other incision site
- Femoral
- Ventral
- Epigastric
- Diaphragmatic
- Pelvic
- Spigelian.

can also increase the risk. These include use of steroids, mammalian target of rapamycin (mTor) inhibitors such as sirolimus, multiple abdominal surgeries, multiparity, obesity, or hernias.

Leak of dialysate into the soft tissues of the abdomen is usually caused by a defect in the abdominal wall, such as a hernia or previous surgery, or from improper securing of the deep catheter cuff in the rectus muscle (see above). The patient can present with protuberance of the abdomen, asymmetry of the abdominal wall, or subcutaneous oedema of the abdomen, giving a '*peau d'orange*' appearance. The pathophysiology of genital oedema is more complex. If the processus vaginalis, the tract connecting the fetal peritoneal cavity to the labia or scrotum, fails to obliterate normally, the patent tract can allow for the peritoneal fluid to track out of the cavity and into the tunica vaginalis, leading to hydrocele of the scrotum or labia. However, abdominal wall leaks, as alluded to above, can allow the leaking dialysate to transit caudally by gravity and cause oedema of the penis or mons pubis.

Dialysate leaks can present as decreased ultrafiltration, weight gain, or localized oedema. The leak is often more prominent while the patient is upright and often the oedema or swelling improves while the patient is supine at night. A leak into the pleural cavity causing a hydrothorax can present as shortness of breath. Physical examination and X-ray are consistent with a pleural effusion, almost always right-sided. If these symptoms are present in the absence of generalized oedema, a dialysate leak should be suspected. If the fluid is leaking from the catheter site or if a thoracentesis is performed, the fluid should be tested for glucose concentration. A high glucose concentration can help confirm the presence of dialysate. If the fluid has been dwelling for many hours, or if the dialysate is icodextrin, the glucose concentration may not necessarily be increased compared to a simultaneous blood glucose reading. Often imaging is required for definitive diagnosis. A CT scan is the most commonly used imaging modality. One to two litres of dialysate containing contrast material should be infused into the abdomen. The patient should be encouraged to mobilize prior to the imaging, to increase the intraperitoneal pressure and ensure that the contrast-containing fluid has the opportunity to leak from the peritoneal cavity.

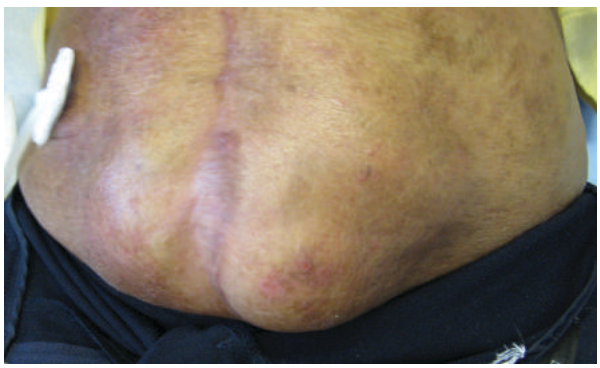

Fig. 266.1 The ventral hernia can be seen at the location of a previous surgery.

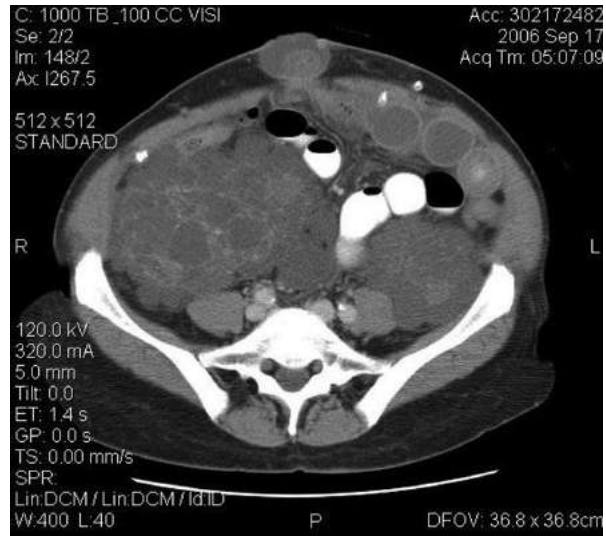

Fig. 266.2 An umbilical hernia in a patient with polycystic kidney disease.

The initial approach to a dialysate leak is to discontinue CAPD for 1–2 weeks. Transition to nocturnal intermittent peritoneal dialysis (NIPD) or haemodialysis is usually required in the interim. Many leaks will resolve spontaneously but if it recurs it will likely require surgical correction. For pleural leaks, PD should be discontinued and haemodialysis initiated for 2–6 weeks. If the leak recurs after a period of rest it will likely require pleurodesis or surgical repair if the patient wants to continue with PD. However, pleural leaks usually recur, and therefore pleurodesis could be attempted without waiting the extra few weeks. The rate of leaks related to the abdominal incision or laparoscopic port holes can be minimized by delaying the initiation of PD for at least 2 weeks after the insertion of the PD catheter. This wait time does not apply after exteriorization of buried PD catheters. If dialysis is required earlier, IPD should be performed with the patient in the supine position, and using small fill volumes. If the leak is the result of a hernia or patent processus vaginalis, these are easily repaired surgically and the patient can return to low-volume PD within a few days.

Catheter malfunction

Some PD patients report pain during either filling of an empty peritoneal cavity, or more commonly near the end of the emptying (or drain) phase. The pain is usually described as a pulling or tugging discomfort in the lower abdomen. The mechanism of this pain is unclear, but likely relates to the 'jet effect' during inflow (especially

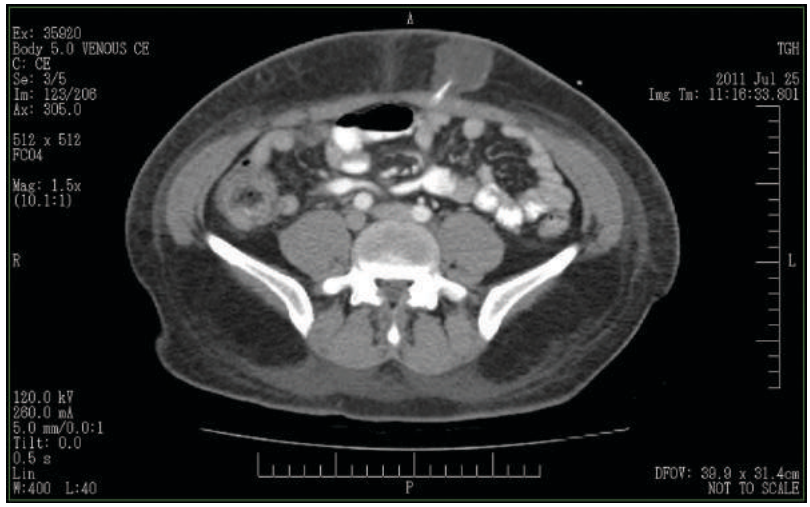

Fig. 266.3 The fluid can be seen tracking along the catheter into the abdominal wall.

with straight, as compared to coiled catheters), and the Bernoulli suction on local viscera during draining. Instituting tidal PD, wherein there is always a residual volume in the peritoneal cavity, relieves this discomfort in the majority of patients.

Mechanical obstruction of a PD catheter is a very common problem and occurs in 6–55% of all catheters. Mechanical problems, most of which are due to obstruction, account for 20% of transfer from PD to haemodialysis. The majority of catheter obstructions occur within the first month of catheter placement. The first step in troubleshooting obstruction is to determine if it occurs with both inflow and outflow or with outflow alone.

Obstruction to both inflow and outflow usually suggests an intraluminal obstruction with fibrin or blood clots. Less commonly it can represent a kink in the catheter. A kink in the catheter is usually related to poor placement technique. As part of catheter insertion good hydraulic inflow and outflow should be assured before and after tunnelling and exit site creation. Once the catheter is examined for kinks or bends, attempts should be made to aspirate and flush the catheter. This is often sufficient to dislodge a clot. If unsuccessful, the catheter can be filled and allowed to dwell with a heparin (1:1000) solution for 2–3 hours followed by further attempts at aspiration. If still unsuccessful, this can be repeated with tissue plasminogen activator.

Obstruction to outflow alone generally suggests extraluminal obstruction by bowel or omentum. The most common cause is constipation. This is believed to be caused by stool-filled loops of bowel that draw up against the catheter lumina during the drain phase and impede the dialysate outflow. Even without a compelling history or X-ray findings of constipation, aggressive treatment with laxatives should be attempted and is often successful in improving catheter flow. If laxatives do not relieve the obstruction, an X-ray should be performed to assess catheter position. Often catheter migration can result in obstruction due to its position against bowel or other intraperitoneal organs or through movement into the upper abdomen out of reach of the dialysate. It is important to note, however, that a malpositioned catheter may still function appropriately and a catheter can still be obstructed despite a good position within the pelvis. A catheter that has migrated to the left upper quadrant can often reposition itself with the descending peristalsis associated with treatment of constipation. A catheter in the right upper quadrant is less likely to return to the pelvis.

If obstruction persists despite treatment with the above minimally invasive techniques, the next step is manipulation with a guidewire under fluoroscopy. This should be attempted even if the catheter appears to be well positioned as the obstruction may be due to adhesions within the pelvis or omental wrapping. A guidewire can also disrupt intraluminal lesions which may be causing obstruction. Manipulation with a stiff guidewire has initial success rates between 64% and 86% but the result is often temporary and many patients require repeated manipulations. Furthermore, swan-neck and pre-sternal catheters are difficult to access with a stiff guidewire. The final and perhaps optimal procedure, when available, is laparoscopic correction. Under direct visualization, the catheter can be repositioned and sutured into place. Additionally, omentectomy or lysis of adhesions can be performed as needed.

Gastro-oesophageal reflux disease and back pain

Gastro-oesophageal reflux disease (GORD) has frequently been noted in the PD population. One study recorded a prevalence of 44.7% compared to only 18.9% in the haemodialysis population. The exact mechanism causing the increased prevalence is unknown, but several theories exist. It is possible that the increased intra-abdominal pressure results in increased transient relaxation of the lower oesophageal sphincter. In one study there was a tendency towards decreased lower oesophageal sphincter pressures with increasing dialysate fill volumes. In another study, however, there was no correlation between intra-abdominal pressure and the frequency of GORD. Another possible explanation is that the symptoms are related to delayed gastric emptying. Dialysate containing glucose has been shown to delay gastric emptying in PD patients which may increase reflux of gastric contents and symptoms of GORD.

GORD often presents with classic symptoms of heartburn and acid regurgitation. Another common presentation that has been well documented in PD patients is chronic cough. Management of GORD is the same as the general population. Elevation of the

head of the bed and avoiding the supine position after eating may help mild symptoms. Acid suppressive medications are usually effective. A patient should be considered for upper endoscopy if the symptoms are atypical or not resolving with traditional measures.

Another possible complication of PD related to increased intra-abdominal pressure is back pain. The abdominal fluid will affect the centre of gravity and pull the spine in a more lordotic position which results in mechanical back pain in some patients. Analgesics and gentle strength training exercises may help. If possible, reducing the day fill volumes or switching to continuous cyclic PD with higher volumes at night and lower (or no) volume during the day may also improve the pain.

Sleep apnoea

Sleep apnoea is a very common problem in patients with ESRD. Its prevalence within the PD population has been estimated at > 50%, compared to only 2–4% in the general population. Both central and obstructive forms of sleep apnoea occur with increased frequency, although the mechanism is not completely understood. Patients on CAPD have been found to have higher rates of sleep apnoea than patients on nocturnal cycler PD. During sleep, nocturnal PD is associated with a higher rate of solute clearance and volume removal when compared to CAPD. This supports the theory that uraemia and excess total body volume contribute to the increased frequency of disordered breathing during sleep. Also in support of this theory is the finding that sleep apnoea improves on nocturnal haemodialysis as well as after renal transplant. Decreased quality of sleep has been shown to negatively affect quality of life in PD patients. Additionally, as in the general population, sleep apnoea has been shown to be a risk factor for cardiac morbidity and death. There should be a low threshold for investigating sleep apnoea with polysomnography. If possible, conversion to nocturnal cycler PD may be helpful in patients diagnosed with sleep apnoea. Traditional methods of treating sleep apnoea include continuous positive airway pressure (CPAP). Unfortunately, many PD patients are hesitant to utilize both a CPAP machine in addition to PD cycler during the night and therefore go untreated.

Metabolic complications

Glucose remains the most common osmotic agent used in PD solutions. In many ways it is an ideal compound as it produces large ultrafiltration per unit mass, is non-toxic, and readily available. An unfortunate consequence is that a significant amount of glucose is absorbed by the patient. In a 6-hour dwell, 60–80% of the glucose instilled in the peritoneal cavity crosses the peritoneal membrane, resulting in 100–300 g of glucose (400–1200 kcal) absorbed per day in the average PD patient. These extra calories can be beneficial in malnourished patients, although the additional caloric load can also result in undesired weight gain. In diabetic patients, exposure to large glucose loads can lead to increased difficulty with control of blood glucose. The large daily glucose absorption may also contribute to the development of *de novo* diabetes or impaired glucose tolerance in previously non-diabetic patients. In addition to the direct effects, the glucose absorption can result in elevated insulin secretion and hyperinsulinaemia. High insulin levels are felt to contribute to increased atherogenesis in PD patients as in the general population. Recent studies have shown that the onset of impaired fasting glucose among patients on PD is associated with decreased survival. The patients who developed impaired fasting glucose tended to be older with more co-morbidities; however, impaired fasting glucose remained an independent risk factor despite controlling for these variables. A limitation to the diagnosis of impaired 'fasting' glucose is that patients on PD have continuous exposure to glucose via their dialysate and therefore reference ranges are not well defined. Recent evidence suggests dialysis with a low-glucose regimen leads to a decrease in glycosylated haemoglobin and improved lipid profile. Unfortunately it also resulted in increased complications from extracellular fluid volume expansion. This finding suggests that ultrafiltration and adequate volume control should not be sacrificed in the pursuit of minimizing peritoneal glucose exposure. The clinical benefit of low-glucose PD remains unclear.

In addition to the metabolic and cardiovascular risks associated with weight gain, obesity can result in increased intra-abdominal pressure. This may result in higher risk of hernias, leaks, and reduced catheter survival.

In addition to systemic effects, exposure to glucose and glucose degradation products may contribute to the long-term changes to the peritoneum that are seen after many years on PD. High glucose concentrations have been shown to have adverse effects on cellular function and contribute to an inflammatory and pro-fibrotic state. This can lead to fibrotic changes in the peritoneum, vasculopathy of the submesothelial venules, and changes in the permeability of the membrane.

Patients on CAPD lose an average of 5 g per day of protein through the peritoneal effluent, although this amount can increase substantially in patients with increased effective peritoneal surface area, or during supervening inflammation such as peritonitis. The majority of the protein lost is albumin; other proteins that are lost include immunoglobulins, transferrin, complement factors, and β_2-microglobulin. The loss of protein is usually balanced by an increase in protein synthesis, but this process can be suppressed if inflammation or illness is present. Initial small studies suggested a possible correlation between peritoneal albumin loss and mortality, however, a recent large study revealed no effect on survival.

Patients on PD have been found to have a much more atherogenic-type lipid profiles than patients on haemodialysis. They tend to have higher total and low-density lipoprotein (LDL) cholesterol values as well as increased concentrations of small dense LDL and apolipoprotein B. The exact mechanism is unclear, although it has been proposed that the increased protein loss in the dialysate promotes hepatic synthesis of albumin and other proteins including cholesterol. This is similar to what occurs with the nephrotic syndrome. PD patients are also more likely than patients on haemodialysis or with chronic kidney disease to have high levels of triglycerides. This has been attributed in the past to systemic glucose absorption. A recent study, however, illustrated that while triglyceride levels are higher in CAPD patients, there was no correlation with the concentration of glucose used in the dialysate. While it is well established that dyslipidaemia is an important risk factor for cardiovascular disease in the general population, the role it plays in the dialysis population is less clear. Traditional lipid-lowering medications such as statins have a less clear role in the dialysis population and there is a paucity of literature specifically pertaining to those on peritoneal dialysis.

Pancreatitis

Many studies show that patients on dialysis have a higher rate of pancreatitis than the general population. PD patients seem to be at an even increased risk compared to haemodialysis patients. One study found that PD patients were 15 times more likely than the general population to develop pancreatitis while haemodialysis patients were five times more likely. In autopsy studies, up to 60% of PD patients have abnormalities of the pancreas. The mechanism to explain the increased risk of pancreatitis remains unclear. Both hypercalcaemia and high triglycerides are more common in PD patients and these have both been shown to be risk factors for pancreatitis. Even removing these as causative factors, however, PD patients have an increased risk. Another possible explanation is anatomical: the lesser sac of the peritoneal cavity is contiguous with the anterior surface of the pancreas. The dialysate may irritate the pancreas resulting in inflammation. Alternatively, the higher concentration of calcium in the dialysate may result in localized high calcium concentrations at the pancreas despite normal serum calcium.

The most common presenting symptom of pancreatitis is abdominal pain, often associated with nausea and vomiting. It can easily be confused with peritonitis, a much more common presenting condition. Serum amylase and lipase are often elevated at baseline in the dialysis population; values greater than three times the upper limit of normal are often used as cut-off values in the diagnosis of pancreatitis. However, metabolites of the dialysis fluid icodextrin are absorbed systemically and can suppress the laboratory measurement of amylase. In PD patients using icodextrin suspected of having pancreatitis, a normal amylase level should prompt the measurement of serum lipase. Furthermore, even PD patients not on icodextrin have presented with a clinical picture of pancreatitis and normal amylase levels. Effluent can be cloudy which further confuses the picture with peritonitis.

Treatment of pancreatitis in a PD patient is similar to the general population with supportive management including pain control and volume resuscitation. Patients should initially receive nothing by mouth and will require nutritional support if the fasting is prolonged. The prognosis of acute pancreatitis in PD patients is unclear and the mortality in case series has been reported from 0% to 58%. Surgical management may be required for pancreatic necrosis or pseudocysts. Although automatic conversion to haemodialysis during an episode of pancreatitis is not required, it will be necessary following a laparotomy.

Hepatic subcapsular steatosis

Hepatic subcapsular steatosis (HSS) is a rare form of fatty liver that occurs almost exclusively in CAPD patients with diabetes who receive intraperitoneal insulin therapy. It was first described in an autopsy study in 11 diabetic patients on CAPD receiving intraperitoneal insulin. It is a focal fatty infiltration that occurs beneath the liver capsule. The intraperitoneal insulin diffuses directly across the hepatic capsule and promotes esterification of free fatty acids, which leads to an increased synthesis of triglycerides. The prevalence of HSS is uncertain and wide variations have been reported in the literature, from 18% to 88%. Risk factors for development include higher daily insulin doses, obesity, hypertriglyceridemia, and high peritoneal transport rates. The risk does not seem to be related to the concentration of glucose in the dialysate. HSS is most commonly diagnosed via CT scan although the lesion can also be seen on ultrasound and magnetic resonance imaging. CT imaging reveals subcapsular areas of low attenuation that can either be nodular and discrete, or thin confluent rinds. The lesions are more commonly seen on the cranial aspect of the liver. HSS is asymptomatic and there are no known clinical consequences. It is not associated with liver dysfunction or abnormal lab results. With the appropriate history of intraperitoneal insulin it is important to consider the diagnosis of HSS. This will avoid further unnecessary investigations and anxiety about more sinister causes of liver lesions. HSS has been shown to resolve after discontinuation of PD although it is not an indication for conversion to haemodialysis.

Encapsulating peritoneal sclerosis

Encapsulating peritoneal sclerosis (EPS), previously known as sclerosing encapsulating peritonitis, is one of the most serious complications of PD. The International Society of Peritoneal Dialysis has defined EPS as 'a clinical syndrome with persistent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications, and encapsulation confirmed by macroscopic inspection or radiologic findings'.

In EPS, peritoneal membrane inflammation progresses to extensive fibrosis of the visceral peritoneum. This results in progressive encapsulation or cocooning of the small intestine. Symptoms are initially non-specific and often gradual in onset. They include nausea, vomiting, anorexia, weight loss, and a sense of abdominal fullness. As encapsulation progresses, recurrent bowel obstructions, nutritional deficiency, and ascites can occur. There may be an inflammatory phase that precedes the encapsulation. This includes anorexia, serositis, and biomarkers of inflammation, such as elevated C-reactive protein (CRP), anaemia, and decreased serum albumin. In patients in whom EPS appears rather abruptly after discontinuation of PD, the inflammatory phase is not well recognized.

EPS remains a rare complication of PD. The reported incidence increases with time on PD and varies geographically. The most common incidence rates range from 0.7% to 2.5%. One study from Japan reported an incidence of 17.2% in patients who had undergone PD for > 15 years. Despite its low incidence, it is a devastating condition with > 50% mortality within the first year. A more recent report suggests that the mortality may be diminishing and that the mortality in EPS may be similar to the overall mortality in dialysis patients without this syndrome.

The pathogenesis of EPS remains incompletely understood. The most commonly accepted theory involves a 'two-hit' hypothesis. Chronic PD results in deterioration of the peritoneum. A superimposed inflammatory stimulus such as infectious peritonitis or stopping PD (transfer to haemodialysis or renal transplantation) acts as the 'second hit' and leads to the inflammatory and encapsulating syndrome.

Time on PD has been consistently been shown to be a risk factor for the development of EPS. However, there is currently no evidence for routine transfer to haemodialysis after a given time on PD. The overall incidence of EPS remains low and the risk must be balanced with the benefits and lifestyle advantages of PD. A modality change to haemodialysis might also necessitate a haemodialysis catheter that carries its own risks. In addition, EPS has presented

in patients after they have switched to haemodialysis or after renal transplant. Peritonitis has also been associated with a higher rate of EPS, but it is usually a very toxic, severe single episode of peritonitis that functions as the second hit. Overall rates of uncomplicated peritonitis poorly correlate with the development of EPS. More recently, increased use of icodextrin solution has been associated with higher risk of EPS although this may represent confounding by indication; late ultrafiltration failure is felt to be another possible risk for EPS and patients would be likely to receive icodextrin for this problem.

The histological changes seen in the peritoneum of patients with EPS are not specific. They can also be seen in the membranes of patients with infectious peritonitis and patients on long-term PD who develop ultrafiltration failure. The appropriate constellation of symptoms along with compatible imaging are generally considered sufficient for diagnosis. A high index of suspicion is required for the diagnosis since the initial symptoms are often vague and non-specific. If EPS is suspected, inflammatory markers including CRP and albumin should be measured. CT is the imaging tool of choice for diagnosis. CT findings consistent with EPS include peritoneal thickening and bowel encapsulation, intestinal obstruction, peritoneal enhancement, calcification, and loculated fluid. CT scans should be performed in all patients suspected of EPS; however, there is currently no role for surveillance imaging in asymptomatic patients.

Once the diagnosis of EPS is confirmed, PD should be discontinued and the patient converted to haemodialysis. Some centres advocate leaving a PD catheter *in situ* for regular lavage of the peritoneal cavity. The optimal medical therapy for EPS remains unclear. In the early inflammatory stages there may be a role for immunosuppressive agents. Prednisone is generally the agent of choice although case series have been described with azathioprine and mycophenolic acid. Non-randomized trials have shown a benefit with the use of tamoxifen. As an anti-oestrogen drug with antifibrotic effects, tamoxifen has a therapeutic role in the later, fibrotic stages. Surgical intervention with lysis of adhesions has had good outcomes in a few centres; the procedure is technically quite difficult and should only be performed by experienced surgeons. Supportive therapy is also crucial to management of a patient with EPS. Nutritional support is important and patients with recurrent ileus may require parenteral therapy to maintain adequate nutrition.

Haemoperitoneum

Haemoperitoneum is an infrequent complication of PD but can be quite concerning to the patient when it occurs. The incidence varies widely depending on patient demographics, and has been reported from 6.1% in a general PD population to 52% in younger women on PD. It can have a dramatic presentation as it takes as little as 2 mL of blood to cause 1 L of dialysate to appear bloody (Fig. 266.4).

The severity of haemoperitoneum in a PD patient can range from benign to life-threatening depending on the aetiology. Gynaecological causes remain the most common cause of haemoperitoneum and account for 33% of all causes. Retrograde menstruation is the most common cause but it can also occur with ovulation or with shedding of intraperitoneal ectopic endometrial tissue at the time of menses. An appropriate history can often clarify the timeline to correlate with menstruation or ovulation. Some women experience haemoperitoneum rarely while others can experience

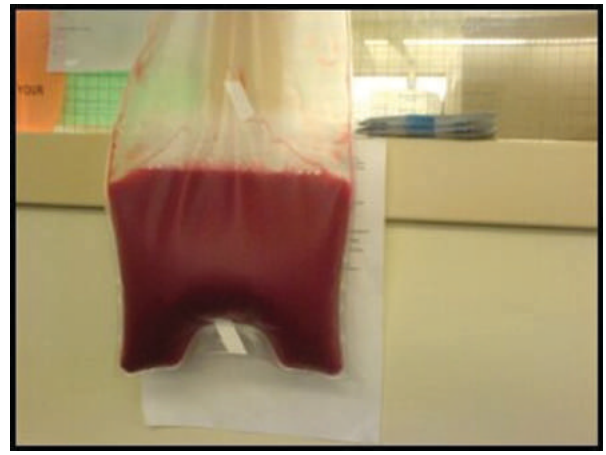

Fig. 266.4 Bloody dialysate.

it with every cycle. Haemoperitoneum has also been reported in pregnant women on PD. Post-procedural haemoperitoneum is also fairly common and can be seen with exchanges done shortly after a new catheter insertion. As catheters are often placed in patients not yet on dialysis, uraemic coagulopathy may play a role in haemoperitoneum after catheter insertion. Abnormalities with all intra-abdominal organs have also been associated with this complication. Although the kidneys are retroperitoneal, ruptured renal cysts can cause haemoperitoneum. A possible explanation is that the cyst and the peritoneal wall are in close proximity and the inflammation results in adhesion to the peritoneum with subsequent rupture of both structures. Vascular complications including aneurysm rupture are a rare cause of haemoperitoneum. Grossly bloody dialysate is rare with peritonitis, although red blood cells are often reported with fluid sent for cell count and differential. Gross blood in the setting of PD peritonitis should mandate a search for surgical causes of peritonitis.

When a patient presents with haemoperitoneum, several rapid exchanges should be performed. Dialysate that clears with this manoeuvre will help differentiate an acute bleed that has stopped from an ongoing source of bleeding. Room temperature dialysate will cause vasoconstriction and help reduce ongoing bleeding. Heparin 500 units/L should be added to the dialysate to help prevent clots in the catheter. This will not lead to systemic anticoagulation, as heparin does not cross the peritoneal membrane.

Further workup depends on the clinical picture of the patient. Unstable patients require prompt blood work including a complete blood count and coagulation factors. Transfusions may be required if the blood loss is severe and coagulation defects should be corrected. Urgent investigations should be performed to identify the source of the bleeding and can include imaging, angiography, or laparotomy. An abdominal ultrasound can also be performed to investigate intra-abdominal and gynaecological organs if there are concerning features. A patient who is well, however, and presents with haemoperitoneum coincident with menses needs no particular investigation. Recurrent haemoperitoneum related to gynaecological causes can be treated with surgical or hormonal therapy if intervention is warranted. Recurrent haemoperitoneum that occurs with ovulation has been shown to resolve with anovulants.

Haemoperitoneum does not appear to affect clinical outcomes. It rarely requires a catheter exchange or a switch to haemodialysis and it has not been shown to affect peritonitis rates or ultrafiltration.

Chyloperitoneum

Chyloperitoneum is a rare cause of turbid dialysate. It presents with a characteristic 'milky' appearance and is often initially mistaken for peritonitis. Although it can occasionally occur with abdominal pain, it usually is painless. Dietary fats are absorbed via the lymphatic channels and drain into the *cisterna chyli*. Any obstruction or leak in this system can result in chyloperitoneum. The most common aetiology is malignant obstruction, with lymphoma the most frequent cause. Chyloperitoneum can present soon after insertion of the PD catheter and the cause is presumed to be traumatic disruption of the lymph system. Other causes that have been reported include cirrhosis, heart failure, tuberculosis, pancreatitis, constrictive pericarditis, sarcoidosis, calcium channel blockers, nephrotic syndrome, systemic lupus erythematosus, and superior vena cava syndrome. In children, congenital anomalies of the lymph system can also result in chyloperitoneum. Fat loss through chyle can contribute to malnutrition, and the loss of lymphocytes can result in relative immunosuppression.

Chyloperitoneum is most commonly defined by a triglyceride concentration in the peritoneal fluid > 1.24 mmol/L (110 mg/dL). Abdominal imaging should be performed to rule out malignancy. Lymphangiography may provide more details about the leak. It is not a commonly used test, however, because it is not readily available, it carries significant risks including tissue necrosis and fat embolism, and it may prolong the duration of the leak. The optimal treatment is not well known. Patients are commonly started on a low-fat diet to reduce lymphatic flow and supplemented with medium-chain triglyceride oil to avoid deficiency of essential free fatty acids. Medium-chain triglycerides are absorbed directly into the portal venous system and bypass the thoracic duct. Some clinicians advocate complete bowel rest with no oral diet and initiation of total parenteral nutrition. This should be considered very carefully, as total parenteral nutrition has a considerable risk of infection. Octreotide, a somatostatin analogue, decreases intestinal fat absorption and therefore reduces lymphatic flow. It has been shown in a case report to treat chyloperitoneum effectively in combination with a low-fat diet. Most patients are continued on PD following a diagnosis of chyloperitoneum. Given the rarity of the condition, little is known about long-term outcomes or mortality.

Calciphylaxis

Calciphylaxis is a skin condition characterized by small vessel and subcutaneous calcification leading to ischaemic ulceration of the skin and subcutaneous tissue. It remains quite rare, although the prevalence may have increased in recent years. It is unclear, however, if this represents a true increase or simply greater recognition of the condition. It is found almost exclusively in patients on dialysis or with advanced kidney disease. PD has been identified as a risk factor for its development. Other risk factors include female sex, obesity, diabetes, white race, hyperphosphataemia, elevated calcium × phosphate product, and the use of calcium salts and vitamin D. More recently the use of warfarin, through its inhibition of matrix-GLA protein, may have superseded abnormalities of the calcium/phosphorus/parathyroid hormone axis as the principal cause of this disorder. Calciphylaxis presents as painful, violaceous subcutaneous plaques. These can progress to necrotizing, ulcerating lesions (Fig. 266.5). They are usually bilateral and commonly occur in quick succession on the calves, thighs, breasts, abdomen, or buttocks. This syndrome should not be confused with indolent distal ischaemic necrosis of the fingers and toes, typically seen in patients with diabetes and extensive calcific vascular disease. The diagnosis is usually clinical and based on physical examination of the lesions. Bone scan reveals abnormal subcutaneous uptake in 97% of all cases. Biopsy of the lesion can be supportive, revealing medial calcification of arterioles with adipose tissue necrosis. The presence of vascular calcification alone does not confirm the diagnosis. There is a risk, however, that biopsy of a plaque lesion can result in ulceration at the biopsy site. Biopsy should be avoided if the diagnosis is recognized on physical exam alone.

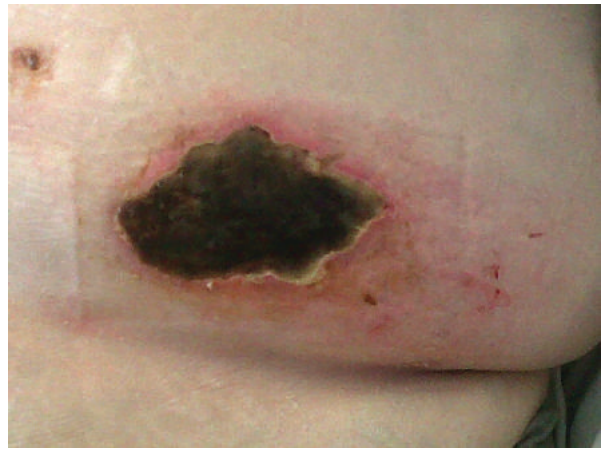

Fig. 266.5 Calciphylaxis on the breast of a PD patient.

Optimal treatment of calciphylaxis remains unclear. Careful wound care and aggressive pain management are important. If the patient is on warfarin, this should be discontinued. Given the potential causative role of hyperparathyroidism and hyperphosphataemia, dialysis should be intensified. A switch to haemodialysis may be required if the area of calciphylaxis threatens the PD catheter site. Parathyroidectomy can also be considered although is not always successful. For patients in whom surgical risk is considered prohibitive, there may be a role for calcimimetics. Some believe that inflammation plays a role in the formation of calciphylaxis and corticosteroids are occasionally used in treatment. Prednisone should be reserved for non-ulcerating lesions and in patients who are deemed at low risk of infection. Hyperbaric oxygen therapy has demonstrated some success in the treatment of calciphylaxis. Sodium thiosulphate has also been successfully used in treatment, possibly through increasing the solubility of soft tissue calcium deposits. Vitamin K and bisphosphonates can also be tried, although the evidence supporting their efficacy is weak. Furthermore, given isolated reports of iron therapy as a triggering factor, iron repletion therapy should be avoided. Despite aggressive therapy, the prognosis remains quite poor with mortality rates up to 80% for ulcerating disease. Most patients die of sepsis related to the skin wounds.

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CHAPTER 267

Overview of dialysis patient management and future directions

Allen R. Nissenson, John Moran, and Robert Provenzano

Introduction

Nearly 2 million patients worldwide have end-stage renal disease (ESRD) and require dialysis or kidney transplantation. The advent of clinical dialysis in the 1950s has had a huge impact on the way ESRD and acute kidney injury are managed, but several decades later, the morbidity and mortality in patients with ESRD remain unacceptably high (Kjellstrand et al., 1975; United States Renal Data System, <http://www.usrds.org>) and patients often have a poor quality of life. Many believe that we have focused attention on a few key treatment-related outcomes, and have done well with these (i.e. anaemia, adequacy of dialysis, and metabolic bone disease), but achieving great results in only these domains has clearly not been sufficient to drive improvements in survival or patient-reported outcomes. Recent experience with integrated care management, focusing on comorbidity management, offers promise. In addition, a number of investigators have been challenging the current thrice-weekly, diffusion-based treatment paradigm and have been developing approaches to emulate the function of natural kidneys. Thus an ideal care delivery model would focus on the holistic needs of the patient with kidney disease, while the ideal form of renal replacement therapy (RRT) would mimic native kidneys, operating continuously, removing solutes with a molecular-weight spectrum similar to that of native kidneys, removing water and solutes on the basis of individual patient needs, and would be biocompatible, wearable, and ideally implantable. It would also be low cost, reliable, and safe. A few years ago, these technical requirements would have seemed impossible to achieve, but with advances in the sciences of nanotechnology and microfluidics, renal replacement of the future may come closer to this ideal (Rastogi and Nissenson, 2007).

Changing demographics of end-stage renal disease patients worldwide

The aetiology of chronic diseases and therefore ESRD worldwide continues to evolve. Historically, infectious diseases were the major cause of global morbidity and mortality; chronic diseases have assumed equal importance. Diabetes followed by hypertension and obesity have become epidemic as countries become more financially successful: moving from Third to Second and Second to First World economies (Levy et al., 2007). This has led to a predictable increase in chronic kidney disease (CKD) and ultimately ESRD, resulting in increased economic pressure on fragile healthcare systems, particularly in developing countries.

Data from renal registries, albeit variable in quality, support the growing prevalence and incidence of ESRD across the globe. Reflected as the prevalence rate of RRT, there is a strong relationship between prevalence rate and per capita income and governmental infrastructure, influencing both the availability and the quality of RRT. It is now estimated that > 1.8 million patients are receiving RRT worldwide with > 80% living in Europe, North America, and Japan, but we are now seeing rapid increases in India and China as those economies continue to expand (World Health Organization, 2000). Interestingly, the rise of chronic disease may not be the only factor responsible for the growth of this population.

Caskey et al. have shown that macroeconomic and renal service factors are more often associated with RRT incident rates than measured demographics of general health status factors. Reviewing renal registries across 46 countries representing a total population of 1.8 billion, incident rates ranged from 12 to 455 per million population. Only gross domestic product (GDP), percentage of GDP spent on healthcare, and dialysis facility reimbursement rate relative to GDP were independently associated with RRT incidence (Caskey et al., 2011).

Are there are lessons learned in the delivery of ESRD care in the United States that can be applied worldwide? Maybe so! Since the inception of the ESRD Medicare benefit in 1972 there has been exponential growth in the ESRD programme. It is estimated that there will be > 600,000 ESRD patients 5 years from now, and despite a forecasted decreased incidence count the point prevalence of ESRD patients continues to have an exponential growth due to improved survival rates both for dialysis and transplant patients; death rates are lower and patients continue to accumulate at a rate exceeding the influx of new patients. This growth now accounts for the consumption of > 9% of all Medicare dollars by approximately 1% of the ESRD Medicare beneficiaries, a non-sustainable rate (United States Renal Data System, 2010).

Despite this rapid growth, there is no doubt that patients' quality of life as well as clinical outcomes have improved dramatically over the past 30 years. We have advanced from dialysing patients so they 'just don't die' to a status where an evolution of pharmacologic and dialysis equipment has provided a broad palette of therapies meeting individual patient needs, so allowing a functionally high-quality lifestyle. Unfortunately the provision of dialysis services has bumped up against an increasingly ageing incident population, well past the retirement age, with multiple other chronic disorders that impact their quality of life and clinical outcomes. Although past the scope of this chapter, cardiovascular disease and the complications of diabetes continue to take an increasingly large toll in both the morbidity and mortality of dialysis patients. Infectious complications also remain one of the highest causes of mortality in this population, but are much more actionable as the focus of elimination of catheters has made major improvements in this area.

Considering older, sicker patients now disproportionally on dialysis the financial/clinical value formula becomes more complex. Part of the answer lies with early identification of patients with CKD with focused intense management. Not only does this help forestall progression to ESRD but it facilitates a working relationship with patients so that the appropriate therapy can be selected as they transition to ESRD. A big part of this therapy includes appropriate education on conservative CKD management that may not include RRT, as well as pre-emptive transplantation. Several studies have shown that timely education results in beginning RRT in a controlled outpatient environment and by avoiding the use of temporary catheters has markedly improved mortality in the first 90 days—currently estimated to be 40% annualized. The continued value proposition of caring for ESRD patients should include reasonable quality goals, agreed upon by payers as well as clinicians with a functional risk payment model that places the patient at the centre of the care paradigm. Using the United States Renal Data System programme data as an example of this model, we have seen continued improvement in mortality in all quality measures since the 1980s, despite no significant increase in reimbursement. As mentioned earlier though, with the increased number of prevalent patients being dialysed who are older and sicker, total costs are rising (United States Renal Data System, 2010). One financial tool to address this is a bundled payment system encouraging a more appropriate application of pharmaceutical and technological advances into the care of this at-risk population.

Although much debate can be had about the nuances of this payment model, everyone agrees that dialysis providers and nephrologists are markedly advanced in their understanding of the relationship between clinical outcomes, financial incentives, and diminishing financial resources.

As the United States embarks on an ambitious next step of accountable care organizations tying the inpatient and outpatient cost to clinical outcome through a more integrated care model, there is hope that this represents the most efficient clinical/financial model of care to date.

We have seen in the United States that offering a lifesaving therapy such as ESRD results in increased demand for services with the resulting increased financial burden on the healthcare systems. We have had to play constant catch-up by balancing clinical care with diminishing financial resources all while improving clinical outcomes. Although challenging, we have done so successfully (Dor et al., 2007).

When looking at global provisions of RRT, one can only hope that governments will look to the United States and take advantage of the lessons we have learned by focusing on early identification and management, appropriate transition to RRT, and development of the appropriate incentive to see that the burden of care does not bankrupt fragile medical resources.

Evolving outcomes: morbidity, mortality, and quality of life

There has been considerable public attention during the last several years on the quality of care received by patients with ESRD. A number of social, economic, and even political factors have come together to sharpen this focus. During the history of the ESRD programme we have seen an evolution of provision of services, generally in the hospital, with the hope for recovery of acute kidney injury to the acceptance of chronic therapy for patients deemed to have non-recoverable kidney failure. Our expectations have predictably evolved from solely preventing the predictable death of a patient without dialytic therapy to providing dialysis with the expectation that the patient will live a high-quality, high-functioning life. Although there may be lingering impressions that there are poor survival rates on dialysis in the United States, there has been continued improvement with the focus on both process and outcome aspects of the care of these patients. Beginning in 2005 and continuing to the present time, the Centers for Medicare and Medicaid Services (CMS) has required through the ESRD network (<http://www.esrdnetworks.org>) a quality improvement programme initially focusing on anaemia, metabolic bone disease, adequacy of dialysis, and nutrition. It soon became apparent that although contributing to improved morbidity/mortality and patients' quality of life, these quality measures do not account for the entire picture of the complex clinical/physiologic world of our patients. Recently additional focus has been placed on the type of vascular access (Fistula First; CMS.gov, 2005) or more appropriately the avoidance of catheters, which has moved us forward with improved morbidity and mortality rates. Continued innovative focus on outcomes is a work in evolution. From our simple early measures to a broad integrated focus through integrated care models attempting to address ESRD patients as a whole, a broader focus has addressed cardiovascular, diabetic, hyperlipidaemia, and other co-morbidities known to impact patient outcomes (Lieberman et al., 2011). Simultaneously the National Quality Forum has moved the dialysis industry forward with a focus on infection and patient volume management.

We have seen year-on-year continued improvement in every quality measure accepted as a benchmark by providers, in addition we have seen continued improvement in mortality despite an adverse case mix. The intersection of quality outcomes and the financial responsibility of providers has in our opinion created an environment where it is the providers, specifically the large dialysis organizations, who are now spearheading innovative quality goals that will continue to drive improved outcomes. Allowing industry to innovate with various care models using the knowledge gained from these opportunities tied to financial incentives seems to be the right mix to drive us forward.

Dialysis modalities and the current treatment paradigm

Many of the problems faced by clinicians and patients in managing ESRD are related to the fact that the usual management includes haemodialysis only three times per week for a limited number of hours. It is manifestly more difficult to replace the functions of the kidney with a thrice-weekly regimen than it is with more frequent dialysis regimens. How did the current standard of care become thrice-weekly haemodialysis? This is in fact an historical accident, as described by Scribner et al. (2004). In the early days of dialysis, resources, especially hardware, were greatly limited, and three times per week dialysis was the minimum regimen found to rehabilitate patients while allowing the maximum number this life-saving therapy. For this reason the early investigators all settled on this regimen—however, it must also be remembered that most patients were being treated by long overnight dialysis in the home. This regimen was used for patient convenience—but may have had unrecognized advantages in allowing long, slow fluid removal, as will be discussed below.

When the National Cooperative Dialysis Study (NCDS) was published in 1981, the abstract stated: 'Dialysis treatment time had no significant effects' (Lowrie et al., 1981). This study was seriously underpowered by current standards (151 patients randomized to four treatment groups) and the length of follow-up was only 24 weeks. Despite these limitations the P value for the effect of dialysis time was 0.056, thus very narrowly missing statistical significance. One should also note that this was a preliminary report, and the final report (Laird et al., 1983) did find that dialysis time significantly predicted failure defined as death, withdrawal from the study for medical reasons, or hospitalization.

An unfortunate conclusion by the dialysis community, especially in the United States, was that time was not an important factor in improving dialysis outcomes. After the publication of the 'mechanistic' analysis of the NCDS results by Gotch and Sargent (1985) it was widely believed that a Kt/V of ≥ 1.0 per treatment provided adequate dialysis. The problem was compounded by the introduction of high-flux dialysers, when it was tacitly assumed by the community that a high Kt/V with a high K was equivalent to a high Kt/V obtained with a high t, thus allowing shortening of dialysis times. This was of course embraced by most patients.

Perhaps the most difficult aspect of current dialysis care is achieving fluid balance and normotension with a thrice-weekly haemodialysis schedule. Shortening of dialysis times makes this considerably more difficult. The increasing age and comorbidity of the dialysis population worldwide adds further complexity.

What is to be done?

Given the ageing population in most developed countries, together with an increasing incidence of diabetes and a falling birth rate, the pressures on healthcare expenditure will inexorably increase. It is therefore fiscally as well as logistically impossible to increase the number of in-centre haemodialysis treatments per week, even to four, in any significant number of patients. Furthermore, patients are generally unwilling to undergo more frequent in-centre treatments, even when told of the potential benefits.

Moving a significant fraction of the ESRD population to peritoneal dialysis would significantly reduce the costs of care, as in the Hong Kong model of 'PD First'. However, unless there is a major shift in public policy worldwide, we must accept that thrice-weekly in-centre haemodialysis will remain the management of the majority of patients, at least in developed countries.

Therefore we must work to optimize the therapy delivered in the current model. The 'Kt/V model' of providing haemodialysis has not led to a dramatic improvement in outcomes and may have been deleterious by encouraging short dialysis times with consequent excessively rapid ultrafiltration and poor control of blood pressure. High ultrafiltration rates are associated with increased mortality (Flythe and Brunelli, 2011) and likely cause cardiac damage through cardiac stunning (Burton et al., 2009). Salt intake, sodium level in the dialysate, and dialysate sodium modelling (the last introduced to decrease hypotension with high-flux short haemodialysis sessions) are areas of care which need to be addressed and optimized.

As well as attention to the above dialysis 'inputs', dialysis times need to be optimized for the individual patient to manage salt and water balance—as well as uraemia itself. Additional treatments may be necessary, at least in the short term, to accomplish this. Nocturnal haemodialysis, either in-centre or at home, has been demonstrated to be the optimal method for controlling blood pressure. As many patients as possible should be established on haemodialysis in the home, where more frequent and/or longer treatments are facilitated. Continued simplification of this therapy is required. Until this is achieved, the simplicity of peritoneal dialysis will make it the usual home dialysis modality.

Technology of the future

Nanotechnology, as defined by Drexler, refers to atomically precise functional machine systems developed on the scale of the nanometre (i.e. one-billionth of a metre) (Drexler, 1995). This technology is an area of intense research, with a national commitment by the United States government to promote research in this field. The precision provided by nanotechnology will make possible the design of tools that will operate at the molecular level. Nanomedicine is the application of nanotechnology for the advancements of biomedical research and is defined as the monitoring, repair, construction, and control of human biological systems at the molecular level by use of engineered nanodevices and nanostructures. The number of potential applications to RRT is many, and a few major ones are discussed below.

Human nephron filter

Nissenson and colleagues have proposed the human nephron filter (HNF) as a novel mode of RRT for ESRD patients, an initial application of atomically precise *nanotechnology* to RRT (Nissenson et al., 2005a, 2005b). The HNF consists of two membranes operating in series within one cartridge. The first membrane is called the G membrane and is analogous to the glomerular basement membrane in the nephron. It mimics the functions of the glomerulus by using convective transport to generate plasma ultrafiltrate that contains solutes approaching the molecular weight of albumin. The second membrane is called the T membrane and this mimics the functions of the tubule. It is molecularly engineered and selectively reclaims designated solutes through convective transport to maintain body homeostasis. No dialysate is used in the system.

With both membranes manufactured at approximately one molecule thick, blood flow of 100 mL/min across the G membrane is

obtained without the need for a blood pump. The entire thickness of the membrane is approximately 1 mm, with the total surface area needed just over one-tenth of a square metre which is sufficient to produce 30 mL/min of ultrafiltration at the designated blood flow rate. In the initial iteration, a commercial polycarbonate membrane will likely be used and because this membrane has considerable thickness, a blood pump will likely be required. The clearance obtained is expected to be about 30 mL/min when operated 12 hours a day, 7 days a week.

To compare conventional haemodialysis with RRT that utilizes the HNF, dialysis was modelled with a 4-hour treatment three times a week (Monday, Wednesday, Friday), no residual kidney function, and a dialyser with a urea clearance of 277 mL/min at a Qb = 300 mL/min and a Qd = 500 mL/min. For the HNF model, the assumption was no residual kidney function, a 12-hour treatment 7 days a week, with a blood flow of 100 mL/min, and a 100% rejection of urea by the T membrane as noted above. Simulating 30 mL/min of glomerular filtration rate would result in a time-averaged urea concentration (TAC) in the HNF-modelled patient of approximately 27 mg/dL, with minimal fluctuations of blood urea nitrogen (BUN) throughout a weekly cycle. By contrast, the thrice-weekly dialysis simulation yields a TAC of 67.3 mg/mL, with wide excursions of BUN reflecting the intermittent nature of the treatment. If the HNF were to run continuously, the TAC would fall to normal levels.

Similar simulations were performed for beta-2 (β_2) microglobulin, assuming free passage of β_2 microglobulin through the G membrane and 100% rejection by the T membrane. For the β_2 microglobulin studies, the rate of β_2 microglobulin production was assumed to be 0.17 mg/min, and the rate of clearance for the conventional dialyser was assumed to be 78 mL/min. The HNF system can reduce and sustain low levels of β_2 microglobulin compared with other dialytic approaches. With 12-hour, 7-days-a-week treatment, levels of β_2 microglobulin are predicted to approach normal.

Silicon nanopore membranes

The conventional membranes currently in use are characterized by variation in both pore size and distribution and are relatively thick. In addition, the pores at the end of the cylindrical fibres tend to be round. The pores in these membranes are formed by extrusion and solvent-casting techniques, and their geometry and surface chemistry are determined by the chemistry of the polymers used in the synthesis and the fluid dynamics of the casting process. However, this geometry and surface chemistry do not provide the optimal filtration function for several reasons. Large-molecular-weight molecules are retained because of the dispersion of pore size. Such dispersion can be corrected for, but at the cost of hydraulic permeability. The hydraulic permeability of a round pore will depend on the fourth power of the radius of that pore. However, if a pore is slit shaped rather than round, the hydraulic permeability will depend on the long dimension of the pore. At the same time, the steric hindrance will still be determined by the smallest dimension of the pore. The glomerular membrane provides electrostatic hindrance in addition to the steric hindrance. Many substrates have an anionic surface charge at physiologic pH. This net charge density on a microfluidic substrate in contact with an aqueous solution gives rise to an electric double layer called the Debye layer (Humes et al., 2006). This layer has thickness that can be on the same scale as the nanopore size and can contribute to the selective property of these membranes by rejecting charged solutes. Recently Fissell and colleagues described *in vitro* results with such a membrane (Fissell et al., 2009).

Studies have proposed membraneless dialysis by application of the principles of microfluidics. This approach is based on the principle that at low Reynolds number, two miscible liquids can flow in parallel in direct contact with each other without significant mixing. This property permits diffusive transport to take place as in conventional dialysis but without the presence of a dialysis membrane. Elimination of the dialysis membrane and its limiting features offers many potential advantages to solute removal. This theoretical construct holds promise for future dialysis devices. An initial application focused on ultrafiltration, packaged in a wearable device, has been proposed by these investigators.

Leonard and colleagues proposed a microfluidic fluid-to-fluid contact system (Leonard et al., 2004, 2005, 2009). In this system, blood comes into contact with another fluid, not with a membrane. This second fluid flows in direct, membraneless contact concurrent with the blood layer and comes quickly to equilibrium with all solutes in the bloodstream. During contact with the bloodstream the second fluid isolates flowing blood, preventing direct contact with any solid material. When the sheath fluid is separated from the bloodstream it is not allowed to carry any cells; it is a cell-free stream. The separated sheath fluid is not dialysate, but in fact closely resembles plasma. In a second step, the sheath is dialysed through a conventional membrane, but in the absence of cells. The dialysed sheath is returned to contact with the bloodstream, flowing, thus, in a continuous loop. This indirect dialysis system offers two advantages: (1) it obviates blood contact with an extensive artificial surface, thus enhancing biocompatibility, and putatively obviating the need for anticoagulation; and (2) it allows for more aggressive dialysis, which can thus be carried out in a smaller device. The dialyser acts like any other dialyser and removes permeable solutes and water according to the difference, respectively, in concentration or pressure between the sheath and dialysate sides of the membrane.

Confinement of cells to the centre of the blood-sheath contact channel is essential to the envisioned performance of this device. Actual working systems have been constructed, designed as a wearable device. The total device requires the blood-sheath contactor, the dialyser, and a two-headed pump, one head of which circulates blood, while the other circulates sheath. A battery to drive the pump along with monitoring and control systems is also required.

Living membranes and bioartificial kidney

A major limitation of current membranes is the tendency to occlude over time because of protein deposition and thrombus formation. This tendency limits the life of the cartridge and the efficiency of the process. A technique that utilizes endothelial cell-lined conduits with microelectromechanical systems (MEMS) has made advances in this field. Another limitation of current technology is the lack of the biological functions of the tubule, including metabolic, reclamation, and endocrine functions. Two studies have proposed living membranes that incorporate renal tubule cells to overcome this problem. This technique depends on the ability to isolate and grow adult tubular cells in culture. These cells are subsequently grown along the inner surface of the fibres of the standard haemofiltration cartridge. This tubule-cell cartridge is then placed in series with a conventional haemofilter, constituting a bioartificial kidney called a renal assist device (RAD) (Humes et al., 2002; Tiranathanagul et al., 2005; Fissell et al., 2006). *In vitro* and *ex vivo* tests of RADs have

been conducted in animals and critically ill patients, with promising results that include better cardiovascular and haemodynamic parameters and improved survival. Of particular interest is the potential differential beneficial effect in patients with acute kidney injury associated with sepsis (Fissell et al., 2002; Humes et al., 2003, 2004a, 2004b; Tiranathanagul et al., 2006; Ding and Humes, 2008).

Nanoelectronics

To create a fully automated, implantable dialysis system, accurate real-time assessment of fluid/electrolyte/acid–base status is needed. In addition, this detection system must be miniature in size. MEMS technology is a miniature component system that integrates sensors, actuators, and electronics and is proposed as a more accurate, reliable, and yet miniature method of assessing fluid status and other critical variables. Applying MEMS to dialysis systems might provide the analytical platform needed (Roy et al., 2001; Kotzar et al., 2002).

Automated wearable artificial kidney and wearable artificial kidney

Lee and Roberts (2008) have reported on a wearable system for 'continuous' peritoneal dialysis (automated wearable artificial kidney (AWAK)). This system utilizes a sorbent cartridge to regenerate dialysate and will soon be in clinical trials. Similarly, but utilizing a haemodialysis platform, Gura and colleagues have been developing a wearable artificial kidney (WAK), also utilizing a sorbent cartridge to regenerate dialysate (Gura et al., 2009). Both AWAK and WAK take advantage of advances in miniaturization of components including key pumps. Preliminary results suggest that adequate small solute and water removal can be accomplished with both devices, the latter of which has undergone limited clinical trials.

Redesign of the care delivery system

The focus on identifying key outcomes unrelated to the dialysis process per se but rather the associated co-morbid conditions, and the technological work designed to emulate the functioning of natural kidneys point out the inadequacies of the current care delivery paradigm. Enormous progress has been made over the past 5 years to test new models of care delivery that rely heavily on integrated care management. In 2006, a demonstration project in this area was initiated through the CMS and the two largest dialysis providers were awarded contracts in order to demonstrate whether this re-engineering of care could improve clinical outcomes while constraining the overall costs of care. The results from the first 3 years of this 5-year programme have been published (Nissenson et al., 2011; Sauer et al., 2011). Programme design for both participating companies included integrated care coordination between physicians and nurses; in-hospital care management and discharge planning; intense focus on vascular access; protocol-driven care for management of anaemia and bone and mineral disease; extensive patient engagement and education; use of advanced care directives; management of co-morbid conditions including diabetes, hypertension, and cardiovascular; and attention to preventative care including immunizations, and nutritional needs.

The study results were impressive. Decreases in hospitalizations, improvement in mortality, and constraint of cost were all achieved. These results could in part be directly attributed to the improvement in intermediate outcomes, particularly a dramatic reduction in the use of percutaneous catheters, meticulous management of fluid status, appropriate use of nutritional supplements, and relentless attention to flu and pneumococcal vaccination. The movement of the entire healthcare delivery system to medical homes, another form of care coordination, Accountable Care Organizations and recently ESRD Seamless Care Organizations (ESCOs) will enable the further expansion of this approach to the care of kidney patients, with resultant improved clinical outcomes and better stewardship of scarce healthcare resources.

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CHAPTER 268

Cardiovascular complications in end-stage renal disease patients: pathophysiological aspects

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Introduction

Cardiovascular complications are the predominant cause of death in patients with end-stage renal disease (ESRD) (Levey et al., 1998; United States Renal Data System, 2008). The high incidence of cardiovascular complications results from pathology present before ESRD (generalized atherosclerosis, diabetes, hypertension) and an additive effect of multiple factors including haemodynamic overload and metabolic and endocrine abnormalities more or less specific to uraemia or its treatment modalities (Ritz, 2009). These disorders are usually associated and can exacerbate each other. While ischaemic heart disease is a frequent cause of cardiac death, heart failure and sudden death are the most frequent causes of death in ESRD (United States Renal Data System, 2008). Cardiomyopathy of overload with development of left ventricular hypertrophy (LVH) and fibrosis are the most characteristic alterations and major determinants of prognosis (Katz, 1990; Foley et al., 1995; London et al., 1996; Mall et al., 1990). LVH may result in systolic and/or diastolic dysfunction and is a risk factor for arrhythmias, sudden death, heart failure, and myocardial ischaemia (Parfrey et al., 1996; Glassock et al., 2009; Pecoits-Filho et al., 2012). Arterial disease, whether due to atherosclerosis or arteriosclerosis (or both), represents a major contributory factor to the cardiovascular complications (London et al., 1990; London and Drüeke, 1997). Arterial disease may result in ischaemic complications (ischaemic heart disease, peripheral artery diseases) or arterial stiffening with direct consequences on left ventricular (LV) afterload, decreased coronary perfusion, and microvascular abnormalities (inward remodelling and microvessel rarefaction) (Blacher et al., 1999; O'Rourke, 2006).

Left ventricular hypertrophy: overview

The development of cardiac hypertrophy is a physiological process. Cardiac hypertrophy is the primary mechanism by which the myocardial mass increases during the normal growth from infancy to adulthood in response to a steady increase in blood volume, cardiac output, and metabolic demand. Normal cardiac growth thus is a form of 'volume overload' and is characterized by a proportional increase in the LV radius and wall thickness, and normal ratio between myocyte volume and extracellular matrix (Maron, 1986). The term 'physiological hypertrophy' also refers to increased LV mass after long-term conditioning in highly trained athletes (Morgan and Baker, 1991). In these conditions, LV dimensions are only slightly increased, and the hypertrophy is reversible and not associated with deleterious functional alterations such as diastolic dysfunction.

Cardiac hypertrophy is an adaptive response that follows an increase in cardiac work related to changes in afterload (pressure load) and/or preload (volume load). The work performed per ventricular beat (stroke work (SW)) is the product of LV pressure and stroke volume changes during the cardiac cycle. Increased SW results from increased stroke volume or pressure or both. Cardiac work (LV minute work) is the product of SW and heart frequency (Maron, 1986). The stroke volume depends on the strength of cardiomyocyte contraction (altered by myocyte stretch during diastole—Starling's law), the myocyte contractility, and forces opposing the ejection of blood, that is, the afterload. Afterload depends on peripheral resistances, arterial stiffness, reflecting properties of the arterial tree, and inertial forces of blood in the arteries (O'Rourke, 2006).

In the case of pressure or volume overload, the initiating signal includes myocardial stretch and cell deformation, increasing the parietal tensile stress. Myocardial oxygen consumption and energy expenditure increase with SW as the consequence of the LV wall stress changes (σ). According to Laplace's law, the tensile stress (σ) is directly proportional to intraventricular pressure (P) and radius (r) and inversely proportional to ventricular wall thickness (h) according to the formula: $\sigma = Pr/2h$ (Gaasch, 1979; Dzau, 1993). Increased tensile stress is the mechanical initiating signal activating stretch-sensitive membrane ion channels and enzymes that lead to alterations of intracellular cationic content and greater activity of second messengers and intracellular mediators triggering complex signalling cascade which include Ca^{2+}–calcineurin–nuclear factor of activated T-cells (NFAT) signalling, G-protein coupled receptor (GPCR) signalling, mitogen activating protein kinase (MAPK)

signalling, PI3 kinase signalling via receptor kinase, and mammalian target of rapamycin (mTor) activation (McMullen et al., 2004; Kohli et al., 2011; Sala et al., 2012). These changes enhance gene expression for contractile proteins, re-expression of a fetal gene programme, and expression of proto-oncogene-encoding growth factors and growth factor receptors. The consequence is increased wall thickness (cardiac hypertrophy or remodelling) which by increasing *h* reduces the tension that must be developed during systole by each individual cardiomyocyte (Gaasch, 1979; Dzau, 1993). Increased cardiac work and tensile stress are associated and the consequence of increased release of neurotransmitters and vasoactive substances (catecholamines, angiotensin II, aldosterone, thyroid hormone, endothelin 1, etc.) that may have a permissive or direct effect on cardiomyocyte growth and cardiac remodelling (Kudoh et al., 1998; Lijnen and Petrov, 1999).

LVH usually develops in a pattern specific to the initiating mechanical stress (Calderone et al., 1995). The morphological differences between pressure- and volume-induced hypertrophy are associated with distinct myocyte phenotypes and differential induction of peptide growth factor mRNAs (Calderone et al., 1995). Pressure overload results in a parallel addition of new sarcomeres with a disproportionate increase of the LV wall thickness and normal chamber radius (concentric hypertrophy). Volume overload results primarily in the addition of new sarcomeres in series and with secondary addition of sarcomeres in parallel, resulting in an enlargement of the LV chamber with an increased wall thickness sufficient to counterbalance the increased radius (eccentric hypertrophy).

LVH is both beneficial and detrimental. By distributing the tension among a greater number of sarcomeres, the hypertrophy reduces the load imposed on each individual muscle fibre and regulates cardiac efficiency and myocardial oxygen demand, thus sparing energy. This beneficial effect maintains normal systolic function during the phase of compensated 'adaptive' hypertrophy. The variety of growth factors that participate in gene response in the overloaded heart, promote and regulate cell proliferation and differentiation of myocytes and other cellular populations including fibroblasts. In the fibroblasts, the activation of growth factors stimulates their proliferation and activity, resulting in an increase in collagen synthesis (Weber et al., 1988). As a framework for myocytes the increased extracellular matrix maintains the mechanical efficiency of the contracting heart. While the beneficial effects of LVH dominate in the initial adaptation to mechanical overload, the sustained overload leads progressively to 'maladaptive' hypertrophic response, characterized by the dominance of deleterious effects and the development of cardiomyopathy of overload and heart failure (Katz, 1994; Mercadier, 2000). Development of cardiomyopathy is characterized by an imbalance between energy expenditure (high) and production resulting in energy deficit (Katz, 1994; Mercadier, 2000). The chronic energy deficit is multifactorial and also includes decreased coronary reserve related to (a) coronary atherosclerotic stenosis, (b) increased resistance to coronary flow caused by microvascular disease and diminished relative myocardial capillary density, (c) extravascular compressive forces exerted by hypertrophic myocardium, and (d) upward shift of the plateau of the coronary flow autoregulation (Brilla et al., 1991; Ganz and Braunwald, 1997).

The chronic energy deficit is associated with cardiomyocyte apoptosis and necrosis. Cardiomyocytes are replaced by fibrosis, adding overload on surviving myocytes with progressive cardiosclerosis and heart failure (Katz, 1994; Mercadier, 2000). Several lines of evidence indicate that inflammatory mediators play an important role in the pathogenesis of 'maladaptive' hypertrophy and cardiomyopathy. Increased levels of inflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 are involved in processes leading to hypertrophy, fibrosis, and cardiomyocyte apoptosis (Gullestad et al., 2012). Transforming growth factor (TGF)-β plays an important role in the cardiac remodelling and fibrosis (Dobaczewski et al., 2011). Myocardial TGF-β expression is upregulated in cardiac hypertrophy and in patients with dilated or hypertrophic cardiomyopathy. TGF-β overexpression is associated with fibrosis and hypertrophy in the pressure-overloaded heart (Speiser et al., 1991). The disproportionate increase in extracellular matrix maintains the mechanical efficiency of the contracting heart but is associated with impaired diastolic filling (Brilla et al., 1991). In the presence of LV stiffening, the diastolic filling is ensured by active left atrial contraction associated with left atrial hypertrophy and dilation as a consequence of active left atrial contribution to ventricular filling (Patel et al., 2010). Left atrial dilation and hypertrophy are favourable conditions for atrial fibrillation and arrhythmia (Levy et al., 1987; Patel et al., 2010; Goldstein et al., 2012). Impaired diastolic filling is also linked to lusitropic abnormalities, that is, delayed relaxation as a result of cytosolic Ca^{2+} increase and slower reuptake of Ca^{2+} by the sarcoplasmic reticulum (Mercadier, 2000). Sarcoplasmic reticulum/endoplasmic reticulum Ca^{2+} disequilibrium can increase cardiac hypertrophy by stimulation of the Ca^{2+}/calmodulin, calcineurin, NFAT3 pathway. The prolongation of cytosolic Ca^{2+} transients increases the duration of the action potential. Delayed afterdepolarization contributes to arrhythmias which are further favoured by conduction abnormalities linked to the fibrosis and enlargement of hypertrophied hearts (Speiser et al., 1991) (Fig. 268.1).

Left ventricular hypertrophy in end-stage renal disease patients

The prevalence of LVH is high among ESRD patients. The structural alterations occur early in the course of renal failure (Levin et al., 1999). LVH is an independent factor associated with poor survival in dialysis patients. In a prospective study in patients starting ESRD therapy, 74% of the patients had LVH and high LV mass index was an independent predictor of death after 2 years of treatment (Silberberg et al., 1989; Foley et al., 1995). The prognostic impact of LV mass depends in part on the indexation to the body dimensions. Zoccali et al. (2001b) have shown that indexing to body height provides more a powerful prediction of mortality and cardiovascular outcome than indexation to the body surface area (BSA). The classification of LVH in excentric or concentric types is sometimes difficult in patients on dialysis because of the cyclic variations in extracellular fluid volume. The dimensions of the LV diameter are influenced by volume status, and contraction of blood volume during haemodialysis session decreases the LV diameter. As a result of the 'weight' of the LV diameter in the formula used for calculation of LV mass, an increase in internal diameter of the LV that is frequently observed in ESRD patients tends to overestimate the LV mass, while a decrease in LV diameter tends to overestimate the regression of cardiac hypertrophy (London et al., 1991). The

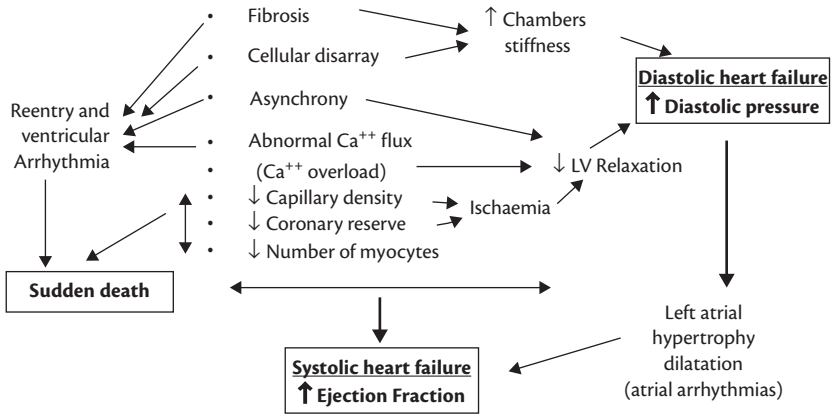

Fig. 268.1 Adverse effects associated with left ventricular hypertrophy.

influence of volume status on LV diameter has as a consequence an overestimation of LV mass by echocardiography relative to magnetic resonance imaging (Stewart et al., 1999). Although an increased haemodynamic load is the principal cause of LVH in uraemic patients, several experimental and clinical studies demonstrated that the cardiovascular structural changes are in part independent from haemodynamic factors (London et al., 1987; Amann et al., 1994; Zoccali et al., 2001a, 2002a; Gutiérrez et al., 2008).

The influence of loading conditions on systolic and diastolic function complicates the assessment of LV function because of changing volume status and variation in humoral parameters during a dialysis session. Decreased systolic function is frequently observed in ESRD patients who suffer from pre-existing cardiac disease or in patients with sustained and marked haemodynamic overload (Foley et al., 1995; London and Parfrey, 1997). In stable ESRD patients, the indices of systolic function are usually within the normal range (London et al., 1991; London and Parfrey, 1997). Diastolic filling is frequently altered in dialysis patients, characterized by steep pressure–volume relationship (London et al., 1991; London and Parfrey, 1997; Pecoits-Filho et al., 2012). A small increase in LV volume can thus cause pulmonary congestion, while volume depletion can induce a fall in filling pressure, systemic hypotension, and haemodynamic instability. Impaired diastolic filling is associated with left atrial hypertrophy and dilation associated with frequent atrial fibrillation and poor outcome (Patel et al., 2010; Goldstein et al., 2012).

Haemodynamic factors

Volume overload in ESRD

The principal causes of volume overload are (a) sodium and water retention, (b) arteriovenous shunts, and (c) anaemia (London et al., 1991).

Sodium and water retention

The sodium retention contributes to pathogenesis of LVH by influencing both preload and afterload. Overhydration with increased extracellular and blood volumes contributes to pathogenesis of LVH by increasing preload. The LV diameter, stroke volume, and end-diastolic pressure are significantly related to circulating blood volume (Chaignon et al., 1981). Body fluid volume contraction during a dialysis session decreases LV diameter and cardiac output with better blood pressure (BP) control (London et al., 1991). In dialysis patients, the regression of LV dimensions and cardiac hypertrophy can be achieved by ultrafiltration and reduced salt intake (Ozkahya et al., 1998; Fagugli et al., 2001). The control of extracellular fluid volume and sodium balance is also associated with better BP control. Sodium retention could directly increase the afterload by influencing sodium-related elevated concentrations of endogenous ouabain and marinobufagenin. These factors, by modulating intracellular calcium entry, could increase BP and stimulate the proliferation and differentiation of cardiomyocytes (Schroner and Schreiner-Bobis, 2007; Bagrov and Shapiro, 2008).

Arteriovenous shunts

The presence of an arteriovenous (AV) shunt lowers peripheral resistance, and BP is maintained through elevation of cardiac output, via increased heart rate and stroke volume (London et al., 1991). These changes induce an increase in LV diameter and mass which is significantly associated with the AV fistula flow. Acute compression of AV shunts induces an immediate decrease in stroke volume and heart rate (Branham–Nicoladoni sign). Long-term effects of high-flow AV shunts can adversely affect the cardiac function. Cardiomegaly with high-output cardiac insufficiency occurs as a complication of high-flow AV shunts (Ahearn and Maher, 1972). The creation of an AV shunt for haemodialysis access is in part responsible for LV dilation and high-output state (Ahearn and Maher, 1972; London et al., 1991). However, symptomatic cardiac failure due to AV shunts alone is uncommon, and occurs more frequently in patients with underlying cardiac disease.

Anaemia

Anaemia is associated with functional alterations whose ultimate goal is to maintain an optimal oxygen delivery to tissues and organs. The most typical haemodynamic change observed is increased cardiac output and cardiac work due to lower peripheral resistance, high stroke volume, and increased heart rate (Rosenthal and Braunwald, 1992). Several mechanisms are responsible, such as reduction in arterial resistance due to arteriolar dilatation and decreased blood viscosity; increased preload due to increased venous return; and increased LV contractility attributed to sympathetic activity and cardiotonic steroids (Schroner and Schreiner-Bobis, 2007). Haemodynamic adaptation occurs when the non-haemodynamic factors are not sufficient to compensate for

a decrease in haemoglobin concentration. This occurs at different levels according to age, physical activity, and gender, but is principally observed with pronounced anaemia and haemoglobin concentration < 90 g/L. The prospective, multicentre, Canadian cohort study in chronic renal failure has identified a decline in haemoglobin level (and an increase in systolic BP) as the principal predictors of LVH and progression (Foley et al., 1996). Several studies in ESRD have shown that partial or complete anaemia correction with erythropoietin decreases the cardiac output and heart rate, and induces a partial regression of the LVH. These studies concerned patients with very low haemoglobin at the start of erythropoietin treatment (Cannella et al., 1991; Portoles et al., 1997; Hayashi et al., 2000). The effects of anaemia correction on LVH were challenged by Foley et al. (2000), who showed that normalization of haemoglobin in haemodialysed patients with asymptomatic cardiomyopathy prevented the development of further LV dilation with a limited effect on LV mass as such.

Pressure overload in ESRD: role of arteriosclerosis

In chronic kidney disease (CKD), Levin et al. (1999) showed that high systolic BP is an independent predictor of LV growth. In ESRD patients, LVH is closely related to systolic or pulse pressure (London et al., 1992; Marchais et al., 1993). Pulse pressure is an independent cardiovascular risk factor in the general population and in patients undergoing haemodialysis (Benetos et al., 1997; Franklin et al., 1999; Klassen et al., 2002; Tozawa et al., 2002). Recognizing that increased systolic pressure is the most challenging form of hypertension today, and that pulse pressure acts as an independent cardiovascular risk factor, has focused attention on arterial stiffness and wave reflections as the most important factors determining these pressures (London et al., 1992; Marchais et al., 1993). In recent years, many studies emphasized the role of arterial rigidity in the development of cardiovascular diseases, and it was shown that stiffening of arteries is associated with increased cardiovascular mortality and morbidity in ESRD (Blacher et al., 1998; Guerin et al., 2001) and general populations (Laurent et al., 2001; Shoji et al., 2001).

The forces opposing the ventricular ejection are largely determined by the properties of the arterial tree, mainly stiffness and dimensions of the aorta (aortic input impedance); stiffness and geometry of peripheral arteries; peripheral resistance (arteriolar tone and remodelling, blood viscosity, and microvascular density); intensity and timing of wave reflections; and the inertial forces (inertance) represented by the mass of the blood in the aorta and LV (Nichols and O'Rourke, 2005; O'Rourke, 2006). Peripheral resistance and mean and diastolic BP are frequently increased in early renal disease and chronic renal failure. With the progression of anaemia, decrease in blood viscosity, and creation of AV shunts the peripheral resistances are most frequently normal in uncomplicated ESRD (London et al., 1991, 1996).

Aortic stiffness is the major determinant of the 'cushioning'/'windkessel' function whose role is the transformation of cyclic blood flow and pressure in the aorta into a continuous capillary flow; and dampening of arterial pressure oscillations, thereby limiting their transmission to the microcirculation (O'Rourke and Safar, 2005; Mitchell, 2008; Briet et al., 2012). Rigid arteries are resistant to distension by blood volume during LV ejection. When rigidity is mild, the arterial wall opposes low resistance to distension and the pressure effect is minimized. When the arterial system is rigid and cannot be stretched the systolic pressure developed by stroke volume is high. In addition to influencing the 'resistance to distension', arterial stiffness determines the propagation velocity (pulse wave velocity (PWV)) of the pressure wave from the proximal aorta (forward wave) towards peripheral vessels, and of partial reflections of forward pressure waves travelling back to the central aorta (reflected waves) (Nichols and O'Rourke, 2005; O'Rourke, 2006; Briet et al., 2012). In subjects with low stiffness and low PWV, reflected waves impact on central arteries during end-systole and diastole, increasing the aortic pressure in early-diastole but not during systole. This situation is physiologically advantageous, since the higher diastolic pressure boosts coronary perfusion, without increasing the LV pressure load (O'Rourke, 2006; Briet et al., 2012). Arterial stiffening disrupts the desirable timing. With increased PWV, the reflected waves return earlier, impacting on the central arteries during systole rather than diastole, amplifying aortic and ventricular pressures during systole, and reducing aortic pressure during diastole. By favouring early wave reflections, arterial rigidity increases peak- and end-systolic pressures in the ascending aorta, thereby raising myocardial pressure load, LVH (Nitta et al., 2004; Zoungas et al., 2007), and oxygen consumption, and decreasing diastolic BP and subendocardial blood flow (London et al., 1996; O'Rourke, 2006). With ageing, the rigidity is more pronounced in the aorta than peripheral conduit arteries (Avolio et al., 1983), leading to the disappearance or inversion of the arterial stiffness gradient and less protection of the microcirculation from high-pressure transmission (O'Rourke and Safar, 2005; Mitchell, 2008; Briet et al., 2012).

Premature vascular ageing and arterial stiffening are observed with progression of CKD and in ESRD (Shinohara et al., 2004; Wang et al., 2005; Briet et al., 2006, 2011, 2012; Sigrist et al., 2007; Taal et al., 2007). The arterial stiffening in ESRD patients is associated with remodelling of the arterial tree characterized by dilatation and, to a lesser degree, arterial intima-media hypertrophy of central, elastic-type, arteries such as the aorta or the common carotid artery (London et al., 1996; Briet et al., 2006, 2011). In ESRD patients, this remodelling is associated with alterations of the intrinsic properties of arterial wall materials characterized by increased incremental elastic modulus (Young's modulus) which provides information on the intrinsic elastic properties of the biomaterials constituting the arterial wall independent of vessel geometry (London et al., 1996; Mourad et al., 1997). In CKD and ESRD, hardening is associated with fibroelastic intimal thickening, calcification of elastic lamellae, elastinolysis and inflammation, increased collagen content and collagen cross-linking, apoptosis, and rarefied numbers of vascular smooth-muscle cells (Amann et al., 1995a, 1995b; Shroff et al., 2008) accompanied with extensive arterial calcifications (Ibels et al., 1979; Braun et al., 1996; Goodman et al., 2000; Guérin et al., 2000; London et al., 2003; Ng et al., 2011). These alterations are of multifactorial origin implicating endothelial dysfunction, mineral and bone disorders, inflammation, oxidative stress, accumulation of advanced glycation end products, vitamin D deficiency, DNA damage, and loss of calcification inhibitors (Giachelli, 2004; Mori et al., 2007; Moe and Chen, 2008; Shao et al., 2010; Hu et al., 2011; Neven et al., 2011; Liu et al., 2013), Remodelling and calcifications of aortic valves are frequently observed in ESRD patients, and may rapidly progress to calcific aortic stenosis contributing to the pressure overload and LVH and cardiomyopathy (Wang et al., 2003).

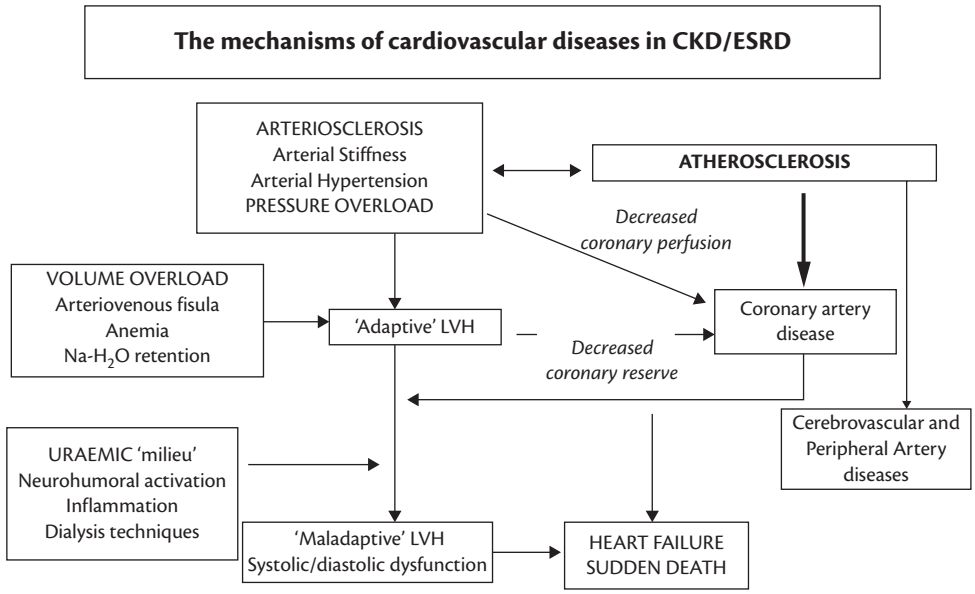

Fig. 268.2 The mechanisms of cardiovascular disease in chronic kidney disease/end-stage renal disease.

While arteriosclerosis refers to arterial stiffening/sclerosis and alters primarily the 'windkessel' function of arteries, atherosclerosis is characterized by the presence of eccentric intimal-medial plaques with calcification, fibrosis, and cholesterol-laden lipoprotein deposition. Atherosclerosis is primarily an intimal disease, focal and patchy in its distribution, occurring preferentially in medium-sized conduit arteries. Atherosclerosis is associated with long-term narrowing or occlusion of arteries with restriction of blood flow and resulting ischaemia or infarction of downstream tissues. The high incidence of atherosclerosis-related complications led Lindner and colleagues (Lindner et al., 1974) to hypothesize that atherogenesis is accelerated in chronic haemodialysis patients. However, it remains a matter of debate whether or not the atherogenesis of dialysis patients is accelerated and whether or not the nature of atherosclerotic plaques is similar in haemodialysis patients and the general population. Indeed, ultrasonographic studies have shown a much higher prevalence of heavily calcified plaques in ESRD patients than in age-matched controls. While ESRD produces atherogenic factors, including dyslipidaemia, calcium-phosphate alterations, malnutrition and activation of inflammatory cytokines (Stenvinkel et al., 1999; Zimmermann et al., 1999; Wanner et al., 2005), accumulation of asymmetric dimethylarginine (ADMA) (Zoccali et al., 2002a), poor endothelial function (Verbeke et al., 2011), and low vitamin D status (Li et al., 2002; London et al., 2007), these are additive to the number of risk factors observed in subjects with preserved renal function, such as age, hypertension, smoking, diabetes, male gender, obesity, insulin resistance, and endothelial dysfunction. Moreover, many haemodialysis patients already have significant vascular lesions before initiating dialysis and, in many patients, especially older patients, the generalized atherosclerosis can be the primary cause of renal failure (ischaemic renal disease, cholesterol embolization). While atherosclerotic complications are frequent in ESRD, the principal causes of death in this populations are sudden death and heart failure (Wanner et al., 2005; United States Renal Data System, 2008), and non-atherosclerotic arterial complications play an important role in accounting for the increased cardiovascular events in these patients (Fig. 268.2).

Non-haemodynamic factors and LVH in ESRD

Cardiac hypertrophy is frequently associated with release of neurotransmitters and vasoactive substances (catecholamines, angiotensin II, aldosterone, thyroid hormone, endothelin 1, ADMA, marinobufagenin, brain natriuretic peptide, etc.) that may have a permissive or direct effect on cardiomyocyte growth, apoptosis, or autophagy (Dzau, 1993; Vlahakos et al., 1997; Lijnen, and Petrov, 1999; Sato et al., 1999; Li et al., 2002; Zoccali et al., 2002a, 2002b; London et al., 2007; Dobaczewski et al., 2011; Gullestad et al., 2012).

Mineral and bone disorders associated with calcium and phosphate abnormalities, secondary hyperparathyroidism, decreased Klotho expression, and elevated fibroblast growth factor 23 (FGF23) serum levels are typical complications in ESRD (Isakova et al., 2011; Pavik et al., 2013). Loss of FGF23 function in CKD and ESRD is related to Klotho deficiency and decreased nephron number (the effectors of phosphaturia), and is associated with increased serum levels of FGF23. Several studies showed an association between FGF23 levels and progression of CKD, LVH (Gutierrez et al., 2009), and cardiovascular morbidity/mortality (Gutiérrez et al., 2008). Experimental study has shown that FGF23 has a direct effect on cardiomyocyte hypertrophy (Faul et al., 2011). Increased FGF23 is also associated with overt hyperphosphataemia, decreased vitamin D, and secondary hyperparathyroidism, all complications that could have their own and independent impact on cardiac and vascular alterations.

Therapeutic consequences/suggestions

The ESRD patients are characterized by advanced cardiovascular end-organ damage whose regression is difficult. Therefore the best therapeutic approach should be prevention and starting treatments at earlier stages of CKD. Randomized controlled trials are scarce in ESRD patients, and as far as cardiovascular mortality is concerned, almost all are negatives or non-conclusives. Besides the fact that many of these studies were underpowered, they usually focused on the correction of one single risk factor such as anaemia (Besarab et al., 1998), lipid disorders (Wanner et al., 2005),

vitamin D deficiency (Thadhani et al., 2012), divalent ions metabolism (Fellström et al., 2009), or secondary hyperparathyroidism (Suki et al., 2007). Regarding the number of risk factors involved in cardiovascular complications in ESRD, only multifactorial intervention strategies can be successful. The new strategies should intervene in parallel on several factors including haemodynamic and non-haemodynamic risk factors. In the absence of such trials, the 'recommendations/suggestions' would focus on the control of those factors which play a role in the pathophysiology of cardiac disorders including:

- Volume overload: control of overhydration (NaCl/fluid restriction; ultrafiltration/dry weight; daily or long dialysis). Control of anaemia (maintain haemoglobin between 10–12 g/dL). Avoid AV fistula flow > 0.8–1.0 L/min.
- Pressure overload: 24-hour systolic BP < 140 mmHg (control of overhydration; antihypertensive drugs with preference for renin–angiotensin–aldosterone system (RAAS) inhibitors). Controlling or improving arterial stiffness (BP reduction and RAAS inhibition; treatment of mineral and bone disorders to prevent or stabilize vascular calcifications (phosphate binders; cinacalcet)); avoid vitamin D deficiency (London et al., 1994, 2001; Cannella et al., 1997; EVOLVE Trial Investigators, 2012).
- Non-haemodynamic factors: as randomized controlled trials are not available, the new strategies should focus on non-traditional cardiovascular risk factors such as malnutrition/inflammation; dyslipidaemia (defective high-density lipoprotein/high oxidized low-density lipoprotein); uraemic toxins (haemodiafiltration, ultrapure water, biocompatible membranes); but also on the control of traditional risk factors (obesity and weight management, smoking cessation, glycaemic control).

Only future randomized controlled trials can provide concrete therapeutic recommendations.

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CHAPTER 269

Bacterial and fungal infections in patients on haemodialysis

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Introduction

Sepsis ranks only second, after cardiovascular disease, as a cause of mortality in haemodialysis (HD) patients, accounting for about 25% of all deaths (United States Renal Data Systems, 2010). Moreover, the mortality rate from sepsis is 100–300-fold higher in dialysed patients than in the general population (Laupland et al., 2004). Vascular access (VA) type is a major risk factor for infection, being highest in patients using a central venous catheter (Tokars et al., 2002; Taylor et al., 2004). Thus, catheter-related bloodstream infections (CRBSI) are costly and associated with high morbidity, hospitalization rates, and mortality (Lok and Mokrzycki, 2010). More than two-thirds of CRBSI in HD are caused by Gram-positive cocci, predominantly *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS), and can result in severe complications, including fulminant sepsis, endocarditis, and metastatic abscesses (Allon, 2004). The management and prevention of VA-related infections is thus a major challenge for HD staff.

Epidemiology

Infections are an important cause of hospitalization in dialysis patients, and have been progressively increasing: in 2008 they peaked 45.8% above their 1993 level (United States Renal Data Systems, 2010). Admissions for bacteraemia in HD represent 112 episodes per 1000 patient-years (United States Renal Data Systems, 2010). Forty-eight to 89% of bacteraemia in HD patients are related to VA infection (Vandecasteele et al., 2009). Taylor et al. reported a lower risk of bloodstream infections in patients with an AVF in comparison to an AVG (relative risk (RR) 1.47), and definitely lower than that of tunnelled (RR 8.49) and non-tunnelled (RR 9.87) catheters (Taylor et al., 2004). In a series of 445 chronic HD patients, more than half of *S. aureus* bacteraemia occurred in patients dialysed through a catheter (Marr et al., 1998). For temporary catheters, the site of insertion has an impact on the risk of CRBSI, its incidence is highest for femoral catheters, followed by internal jugular and subclavian catheters (7.6, 5.6, and 0.7 CRBSI per 1000 catheter-days, respectively) (Weijmer et al., 2004). Globally, incidence rates of bacteraemia are reported to be 0.04–0.55/1000 patient-days for AVF and AVG (Lafrance et al., 2008) and 0.6–6.5 episodes/1000 catheter-days for CRBSI (Lok and Mokrzycki, 2010). Most studies report four to six CRBSI episodes/1000 catheter-days. An incidence below two episodes/1000 catheter-days is considered as relatively low (Beathard and Urbanes, 2008).

Although infection rates with native AVF are low (Hoen et al., 1998; Rayner and Pisoni 2010), a significant increase in the incidence of infectious events, including metastatic complications and death, has recently been reported after shifting to buttonhole cannulation (Nesrallah et al., 2010; Labriola et al., 2011).

Much of the morbidity and mortality related to VA-related infections is due to serious metastatic infectious complications (Katneni and Hedayati, 2007; Lok and Mokrzycki, 2010). Metastatic complications, which may affect up to 44% of patients in case of *S. aureus* bacteraemia (Marr et al., 1998; Mokrzycki et al., 2006), include endocarditis (12% in the series of Marr et al. (1998)), septic arthritis, osteomyelitis, epidural abscess, pulmonary and peripheral septic emboli, atrial thrombi, and infection of intravascular devices, such as pacemakers. More than half of endocarditis cases are caused by *S. aureus*, with in-hospital mortality approaching 50% (Spies et al., 2004). Importantly, the risk of metastatic complications and treatment failure is higher when catheter salvage is attempted (Marr et al., 1997; Mokrzycki et al., 2006).

Aetiology and pathogenesis

Gram-positive bacteria cause more than two-thirds of CRBSI. In a large Canadian surveillance study, staphylococcal infections, both CoNS and *S. aureus*, each accounted for about one-third of cases of VA-related bacteraemia CRBSI (Taylor et al., 2004). In the US dialysis surveillance system, *S. aureus* caused 32% of CRBSI, 53% of VA-related bacteraemia in patients with an AVF or AVG, and 26.7% of bacteraemia unrelated to VA (Tokars et al., 2002). Other causative microorganisms are enterococci (2–18%) and Gram-negative rods (20–28%) (Katneni and Hedayati, 2007), predominantly *Enterobacter* and *Pseudomonas* spp. (Beathard and Urbanes, 2008). Polymicrobial infections may also occur, particularly in HIV-positive patients (Beathard and Urbanes, 2008).

MRSA has become increasingly frequent (12–38%), although its incidence strongly varies between HD units and countries (Lok and Mokrzycki, 2010). Surveillance data from the Emerging Infections Program of the Centers for Disease Control (CDC) in the United States shows that the risk of MRSA bacteraemia in HD patients is 100-fold higher than in the general population (45.2 vs 0.4 episodes per 1000 patient-years) (CDC, 2007). *S. aureus* bacteraemia is associated with greater morbidity, recurrence rates, mortality and cost than other bacteria (Mokrzycki et al., 2006; Lafrance et al., 2008; Vandecasteele et al., 2009; Fitzgibbons et al., 2011), with significantly higher mortality for MRSA than methicillin-sensitive

S. aureus (MSSA) in some (Selvey et al., 2000), but not all (Soriano et al., 2000) reports.

CoNS bacteraemia has increased in recent years, and is particularly associated with the presence of an intravascular catheter. Although CoNS bacteraemia is associated with lower mortality than *S. aureus*, metastatic complications, such as endocarditis, osteomyelitis, and device infection, may occur (Nassar and Ayus, 2001; Fitzgibbons et al., 2011).

Patients with uraemia have an impaired immune response, both humoral and cellular. Additional risk factors in chronic HD patients include VA type (see above), a history of CRBSI, site of catheter insertion, poor patient hygiene, inadequate dialysis, iron overload, hypoalbuminaemia, *S. aureus* nasal carriage, diabetes, and immunosuppressive therapy (Allon, 2004; Lok and Mokrzycki, 2010; Patel et al., 2010).

The exit site and subcutaneous track of a tunnelled cuffed catheter can be colonized by skin bacteria, particularly during catheter placement and before the exit site and the tunnel have healed, with the inherent risk of subsequent haematogenous spread. Even more frequently bacteria are transferred by hands of the dialysis staff during manipulations of the catheter hubs, leading to colonization of the internal catheter lumen and subsequently CRBSI (Lok and Mokrzycki, 2010). Bacteria attach to the inner catheter surface and aggregate forming sessile communities in a glycomatrix of their own synthesis (the *biofilm*). Bacteria seeded in biofilm are less susceptible to antibiotics than their planktonic forms. The biofilm is thus a permanent source of bacteraemia as well as a key factor favouring bacterial resistance (Donlan, 2001). Currently, the prevention of biofilm formation and its elimination are two crucial steps for the successful management of CRBSI.

Clinical features

Systemic VA-related infection should be suspected in any HD patient presenting with fever or chills, haemodynamic instability, or any unusual symptom like diarrhoea, vomiting, or altered mental status, in the absence of alternative source of infection. In case of catheters, inspection of the exit site (before the cuff) and the tunnel (beyond the cuff) can show local erythema, pain, tenderness, or exudate. Local AVF and AVG infections can be characterized by erythema, warmth, pain or tenderness, necrotic scabs, or drainage from cannulation site(s). In case of local infections (exit site infection, tunnelitis or local AVF and AVG infections), a swab must be taken. Importantly, in case of fever, chills, or sepsis of unknown origin, the lack of such local signs does not exclude a systemic vascular-related infection (Nassar and Ayus, 2001; Lok and Mokrzycki, 2010; Labriola et al., 2011), making blood cultures mandatory in all cases.

Investigations

According to the section devoted to HD catheters in the recent guidelines of the Infectious Diseases Society of America (IDSA), the definite diagnosis of CRBSI requires concurrent positive blood cultures from the catheter and a peripheral vein (as recommended in general population), with a colony count from the catheter at least fivefold greater than that obtained from the peripheral vein, or with a differential time to positivity of at least 2 hours (Mermel et al., 2009). However, accessible peripheral veins are few in dialysis patients, or they must be preserved for future VA. In addition, if symptoms present during the HD session, when blood flows through the catheter, there may not be a meaningful difference between peripheral and catheter blood culture results. Therefore, the European Renal Best Practice (ERBP) group recommends, in a position statement, the intradialytic collection of blood cultures through the dialysis circuit linked to the catheter, instead of peripheral venepuncture (Vanholder et al., 2010b). Alternative sources of infection should always be considered (e.g. clinical evaluation, chest radiography, urine culture, etc.). If the catheter is removed (see below), the IDSA guidelines recommend culturing the catheter tip. Nevertheless, the yield of this strategy has been questioned (Vanholder et al., 2010a).

Transoesophageal echocardiography (TOE) should be performed in those patients with CRBSI and either a prosthetic heart valve or another intravascular device, or persistent fever and/or persistently positive blood cultures obtained 72 hours after initiation of appropriate antibiotic treatment, despite catheter removal. TOE should not be performed before 5–7 days after the onset of bacteraemia or fungaemia, but unfortunately transthoracic echography is a not an adequate substitute to TOE alone (Mermel et al., 2009).

Additionally, the EBRP strongly recommends the registration of causative microorganisms of bacteraemia, their sensitivity pattern to antibiotics, and the outcome after treatment, in each dialysis unit, to guide future empiric antibiotic therapy (Vanholder et al., 2010a).

Treatment and outcome

Catheters

Empiric antibiotic treatment

Empiric antibiotic therapy should always cover S. *aureus*. The IDSA recommends vancomycin and additional Gram-negative coverage (e.g. ceftazidime) as first choice empiric therapy (Mermel et al., 2009). According to the EBRP, empiric treatment should be guided by the local epidemiology of the HD unit. In high MRSA prevalence settings or in patients with a history of MRSA colonization or infection, vancomycin or teicoplanin are the first choice; however, cefazolin should be used as empiric therapy if the prevalence of MRSA is low (Vanholder et al., 2010b). In units where CRBSI are regularly caused by both Gram-positive and Gram-negative microorganisms, broad-spectrum coverage should be provided. Although aminoglycosides may be considered in some cases, a third-generation cephalosporin is preferred, because of the risk of irreversible ototoxicity in HD patients (Mermel et al., 2009; Vanholder et al., 2010b). Once the causative microorganism (and its sensitivity) has been identified, the antibiotic regime should be modified, especially in patients with MSSA bacteraemia, in whom empirical (bacteriostatic) vancomycin should be replaced by (bactericidal) cefazolin (Mermel et al., 2009; Vanholder et al., 2010b). Preferred antibiotics are those whose pharmacokinetics allows administration after each dialysis session only; recommended dosages are 20 mg/kg and 1 g after each HD session for cefazolin and ceftazidime, respectively, and 20 mg/kg loading dose, then 500 mg during the last 30 minutes of each subsequent HD session for vancomycin (Mermel et al., 2009).

Uncomplicated cases of CRBSI without indication of catheter removal (see below) should be treated for 3 weeks (Mermel et al.,

2009; Vanholder et al., 2010b), and for 4–6 weeks in the rare cases of *S. aureus* CRBSI and retained catheter (Mermel et al., 2009). A 6-week course is recommended if blood cultures obtained > 48–72 hours after catheter removal remain positive, or in case of endocarditis or suppurative thrombophlebitis (Mermel et al., 2009; Vanholder et al., 2010b).

If catheter salvage is considered (see below) (Fig. 269.1), an antibiotic lock should be added to systemic antibiotics (Mermel et al., 2009; Vanholder et al., 2010b), since catheter salvage with systemic antibiotics alone is successful in less than one-third of the cases (Allon, 2004). This lock solution contains a combination of heparin and a high concentration of antibiotic (100- to 1000-fold above therapeutic plasma concentrations), and is instilled into each catheter lumen at the end of each session for the duration of the systemic antibiotic therapy. The aim is to eradicate the biofilm *in vivo*, allowing thus catheter salvage. This approach has been successful in treating CRBSI and salvaging the catheter in about two-thirds of cases (Allon, 2004). However, success rates are only 40% for *S. aureus* (Maya et al., 2007). Therefore, in case of *S. aureus* CRBSI, this approach should be considered only in absence of alternative VA (Mermel et al., 2009; Vanholder et al., 2010b).

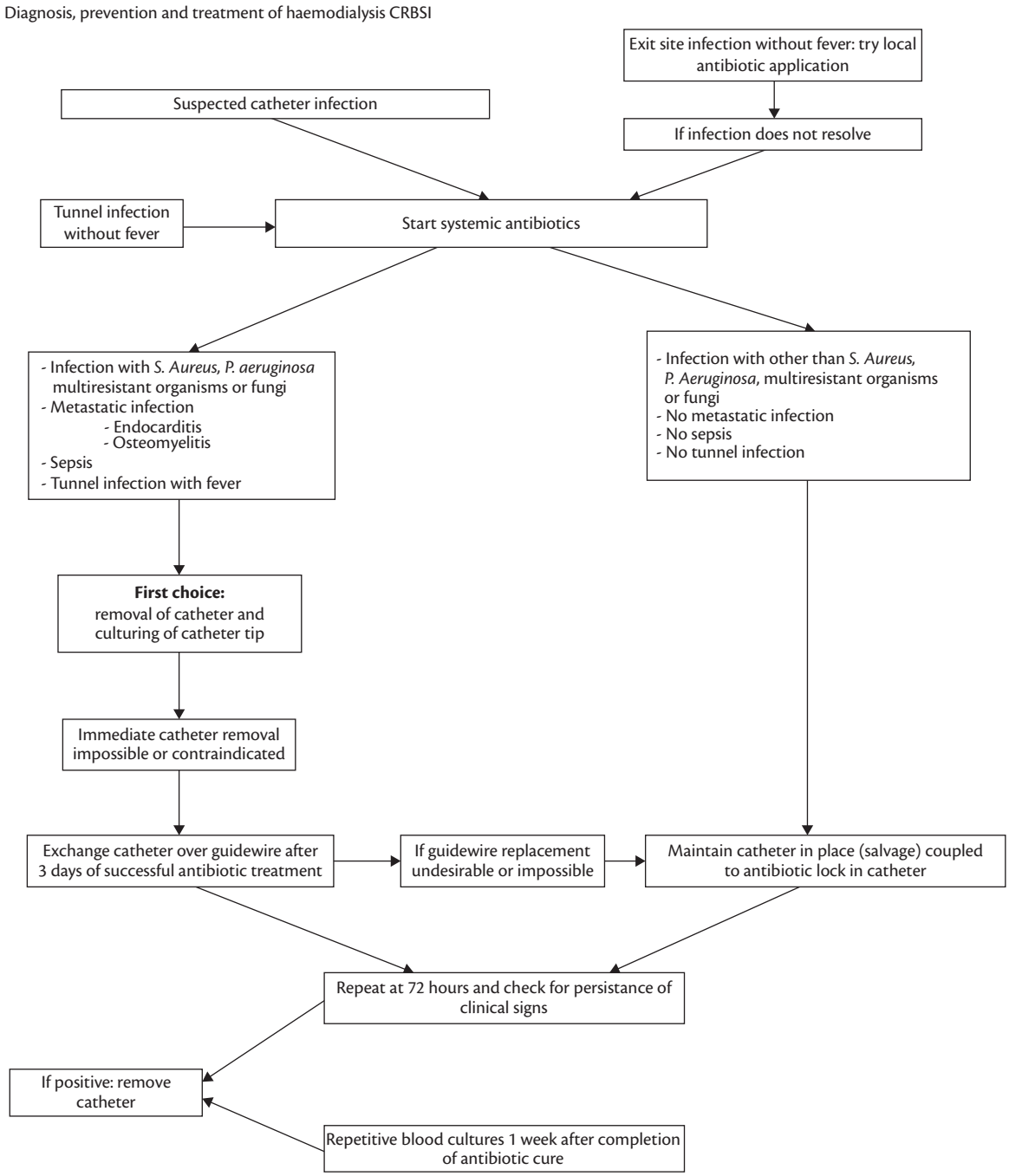

Fig. 269.1 Flow chart summarizing a stepwise approach in case of suspected or proven catheter-related infection, including strategies for catheter removal or preservation (salvage) of the catheter.

Uncomplicated exit site infections should be managed with topical antimicrobial agents. In case of non-response, systemic antibiotics should be administered (Mermel et al., 2009). For tunnelitis without systemic infection, and if the catheter has been removed, 7–10 days of intravenous antibiotics are sufficient (Vanholder et al., 2010b).

Catheter management

Prompt catheter removal should always be considered in the following circumstances (Mermel et al., 2009; Vanholder et al., 2010b) (Fig. 269.1):

- Severe sepsis, endocarditis, or other metastatic infections
- Persistence of infection symptoms or positive blood cultures despite 48–72 hours of appropriate antimicrobial treatment
- Concomitant tunnelitis
- CRBSI due to *S. aureus, Pseudomonas* spp., multiresistant microorganisms, or *Candida* spp.

A temporary catheter should be placed in another anatomical site. A new tunnelled catheter can be inserted once bacteraemia has resolved. If no alternative sites are available, the IDSA and ERBP recommend the exchange of the infected catheter over a guidewire after 48–72 hours of appropriate antibiotic therapy, if the patient is afebrile. In that case, it is not necessary to confirm that blood cultures are negative (Mermel et al., 2009). Surveillance blood cultures must be obtained 1 week after the completion of an antibiotic course for CRBSI if the catheter has been retained. If these cultures are positive, the catheter should be removed (Mermel et al., 2009; Vanholder et al., 2010b).

Arteriovenous fistulas and grafts

As for CRBSI, systemic antibiotic therapy should always cover Gram-positive cocci, especially *S. aureus* (Nassar and Ayus, 2001). MRSA and/or Gram-negative empiric coverage may be necessary in settings where these microorganisms are highly prevalent. For AVFs cannulated with the buttonhole technique presenting with necrotic scabs or drainage from the cannulation site(s), a new cannulation site must be chosen (Labriola et al., 2011). AVGs have a higher infection risk than AVFs (Taylor et al., 2004). Antibiotics alone are often inadequate, and surgical exploration and removal of the infected AVG, combined with systemic antibiotics, is frequently mandatory (Nassar and Ayus, 2001; National Kidney Foundation, 2006). The optimal duration of systemic antibiotic therapy has not been well studied and recommendations range from 3 to 6 weeks (Nassar and Ayus, 2001; National Kidney Foundation, 2006; Vandecasteele et al., 2009).

Prevention

Catheters

Reduction in catheter use

Permanent tunnelled catheters should be considered as the last resort option for VA, because of the risks of infection and central vein stenosis. Pre-dialysis nephrological care should include VA planning, in order to increase the proportion of patients initiating HD with an AVF (Patel et al., 2010).

Catheter care

Hygienic precautions using aseptic technique and sterile material should be applied at any occasion when a catheter is manipulated. Although initially recommended (National Kidney Foundation, 2006), the protective effect of masks is poorly demonstrated and thus not included in current recommendations for the prevention of CRBSI (Patel et al., 2010; Vanholder et al., 2010b). Chlorhexidine 2% seems to show superior antisepsis as an exit site solution, but alcohol 70% and povidone-iodine 10% remain effective alternatives (Lok and Mokrzycki, 2010; Patel et al., 2010).

Prophylaxis of exit site colonization

Catheters should be placed under strict aseptic conditions. The ERBP recommends mupirocin ointment on the exit site until it has healed (Vanholder et al., 2010b). Although the thrice-weekly application of topical antibiotic ointments (mupirocin and polysporin triple antibiotic ointment) at the exit site significantly decreased the incidence of CRBSI and exit site infection in some randomized studies and was recommended by the Kidney Disease Outcomes Quality Initiative (National Kidney Foundation, 2006), concerns exist regarding the development of resistance and, for mupirocin, selection of Gram-negative organisms and incompatibility with catheter material (Allon, 2004; Patel et al., 2010; Vanholder et al., 2010b). For these reasons, the CDC recommends against routine mupirocin ointment (CDC, 2002).

Nasal *S. aureus* carriage is associated with increased *S. aureus* CRBSI. The use of nasal mupirocin ointment in *S. aureus* nasal carriers resulted in the elimination of the nasal carriage in the majority of positive patients and a fourfold reduction of *S. aureus* CRBSI (Allon, 2004; Vandecasteele et al., 2009). However, concern again exists about the emergence of resistance and the rapid recurrence of nasal carriage (Vandecasteele et al., 2009).

Prophylaxis of biofilm formation

Interdialytic locking of the catheter with one or more highly concentrated antimicrobial agents has recently been shown to prevent biofilm formation. Antimicrobial lock solutions (ALS) containing citrate (at concentrations ranging from 4% to 46.7%), alcohol, EDTA, and various combinations of gentamycin, cefazolin, cefotaxime, and minocycline have been studied. Two meta-analyses showed that the use of ALS reduces by about two-thirds the risk of CRBSI in HD patients (Labriola et al., 2008; Yahav et al., 2008). Nevertheless, the limited follow-up does not exclude toxicity or bacterial resistance associated with longer use of ALS containing antibiotics, due to systemic spillage (Bleyer, 2007). Recently, prophylactic gentamycin-heparin ALS was associated with an increase of gentamycin-resistant bacteraemia (Landry et al., 2009). Trisodium citrate, with both antimicrobial and anticoagulant properties (by chelating calcium and magnesium) effectively eradicates biofilm *in vitro* and has been successfully used as prophylactic ALS in several trials. Nonetheless, caution is required: spillage into the systemic circulation, may lead to transient hypocalcaemia with metallic taste or perioral paraesthesiae (Bleyer, 2007). In 2000, the US Food and Drug Administration (FDA) issued a warning against highly concentrated citrate solutions (30% and 46.7%) following a fatal cardiac arrest attributed to abrupt hypocalcaemia caused by an excessive amount of 46.7% citrate into an HD catheter (FDA, 2000). However citrate 30% use has proved to be safe in Europe (Weijmer et al., 2005).

ALS should not replace universal hygienic protocols regarding catheter care and handling (Labriola et al., 2008; Vanholder et al., 2010b). Some randomized controlled trials with low CRBSI incidence in their control groups did not observe any significant effect

of ALS. Moreover, the incidence of CRBSI obtained with ALS is similar to that reported in observational trials with low incidence of CRBSI, with presumably stricter hygienic measures. On the other hand, a dramatic reduction in CRBSI can be obtained after reinforcing the basic hygiene precautions (Beathard, 2003). Hence ALS should be reserved to patients at high risk of infection (i.e. diabetics, carriers of femoral catheters, or cases of recurrent CRBSI) or subjects in whom a CRBSI would lead to dramatic consequences (i.e. patients with artificial heart valves, intravascular devices, etc.) (Bleyer 2007).

Arteriovenous fistulas and grafts

Hygiene precautions and aseptic technique should also be applied for any AVF or AVG cannulation and needle withdrawal. The hygiene protocol is particularly demanding for the buttonhole technique, and includes rigorous disinfection before and after scab removal, meticulous scab removal, and avoidance of over-use of sharp needles (Labriola et al., 2011). Recently, an observational study has shown the successful prevention of AVF-related infections with topical mupirocin on each buttonhole cannulation site, after haemostasis achievement (Nesrallah et al., 2010).

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CHAPTER 270

Bacterial and fungal infections in patients on peritoneal dialysis

Eric Goffin, Laura Labriola, and Michel Jadoul

Introduction

Infections related to peritoneal dialysis (PD) include peritonitis as well as catheter-related, for example, exit site and tunnel infections.

Peritonitis

Peritonitis remains the Achilles' heel of PD, accounting for both structural and functional alterations of the peritoneum, hospitalizations, and transfer to haemodialysis (HD) (Perl et al., 2012). Peritonitis is also associated with an increased risk of death. According to a recent study (Boudville et al., 2012), involving 1316 patients who died either on PD or within 30 days of transfer to HD (each patient serving as his own control), the risk of having peritonitis was significantly increased during the 120 days before death, the association being even stronger during the 30 days before death. The highest mortality is associated with specific organisms, particularly fungus, Enterobacteriaceae, and *S. aureus*. Mortality may also result from septicaemia, and non-infectious causes such as cardiovascular events due to persistent systemic inflammation and prothrombotic status (Boulware et al., 2006; Johnson et al., 2009; Boudville et al., 2012).

Several factors favour the occurrence of peritonitis. These include the presence of the indwelling catheter itself and repeated (dis)connections to the bags or cycler, as well as the relative non-physiologic nature of the dialysate impairing neutrophil and macrophage functions, and mesothelium integrity.

Incidence

The incidence of peritonitis is usually expressed for a PD population as either (1) the number of peritonitis episodes within a time period divided by dialysis years' time at risk, thus expressed as episodes/year or (2) the number of months between episodes (calculated as the number of PD months at risk divided by the total number of episodes). Alternatively, it may be expressed as the percentage of patients per period of time who are peritonitis free.

The incidence of peritonitis has dramatically decreased with the advent of technical improvements in PD systems and connectology. Studies comparing the use of the y-set system and double-bag showed an incidence of peritonitis ranging from one episode every 24.8 to one episode every 46.4 months with the latter system (Daly et al., 2001). Peritonitis rates of one episode every 12 months (Kavanagh et al., 2004) and every 14.7 months for continuous ambulatory peritoneal dialysis (CAPD) and 18.1 months for automated peritoneal dialysis (APD)/continuous cycling peritoneal dialysis (CCPD) (Davenport, 2009) have recently been reported. The most recent incidence rates from the French-speaking Registry for Peritoneal Dialysis (RDPLF) presented within Table 270.1, are even lower (C. Verger, personal communication, <http://www.RDPLF.org>). The International Society for Peritoneal Dialysis (ISPD) currently recommends that a PD unit should achieve an average peritonitis rate not exceeding one episode per 18 months or an incidence of 0.67% episode per year at risk (Li et al., 2010).

Clinical presentation and diagnosis

The typical clinical symptomatology of peritonitis associates a cloudy dialysate effluent with generalized moderate to severe abdominal pain associated with rebound. Other less common symptoms include nausea, vomiting, fever, and chills.

The diagnosis relies on the presence of two of the following three criteria, in combination: (1) cloudy dialysate effluent, (2) abdominal pain, and/or (3) dialysate white blood cell count > 100/μL (with > 50% of polymorphonuclear cells). Gram-staining and dialysate culture may identify the causative organism hereby confirming the diagnosis. Though the diagnosis yield of Gram-staining is low, it should always be performed as it may detect yeasts, allowing prompt antifungal therapy. Inoculation of a dialysate sample within blood culture bottles markedly enhances the yield of the dialysate culture and decreases the proportion of culture-negative peritonitis. The ISPD recommends that a PD unit should not have > 20% of culture-negative peritonitis (Li et al., 2010).

The identification of the causative organism is of major clinical and therapeutic importance to guide therapy. Awaiting the results of dialysate culture, a probabilistic approach, that is, to cover both Gram-positive cocci and Gram-negative bacilli, is recommended (see below).

Although a cloudy effluent usually points to an infectious peritonitis, it may infrequently be the consequence of other causes (Box 270.1).

Modes of contamination

The routes of entry for peritonitis are summarized in Box 270.2. The most common source of peritonitis is contamination at the time of exchange, leading to infection with skin flora organisms ('*intraluminal* infection', the organism invading the peritoneal cavity via the catheter lumen), such as coagulase-negative *Staphylococcus, Corynebacterium* spp., or Gram-negative organisms colonizing

Table 270.1 Trends in peritonitis incidence from the French-speaking PD registry (RDPLF) for adults > 16 years old in Belgium and Metropolitan France

	CAPD year: 1990	CAPD year: 2000	CAPD year: 2010	CAPD year: 2012
Patients number at risk	1387	2766	2442	2377
Total patient-months	10,904	20,608	16,911	15,955
Total peritonitis	642	746	551	394
Months between peritonitis	17.1	27.6	20.7	40,5
	APD year: 1990	**APD year: 2000**	**APD year: 2010**	**APD year: 2012**
Patients number at risk	62	887	1807	1759
Total patient-months	344	6620	13,165	12,682
Total peritonitis	26	176	438	356
Months between peritonitis	13.2	37.6	30.0	35.6
	All year: 1990	**All year: 2000**	**All year: 2010**	**All year: 2012**
Patients number at risk	1427	3453	3870	3795
Total patient-months	11,248	27,228	30,076	28,637
Total peritonitis	668	922	989	750
Months between peritonitis	16.8	29.5	30.4	38.2

Total number of APD and CAPD patients separately are greater than all (CAPD + APD) in the bottom part of the table because many patients change from CAPD to APD during the periods.

APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis.

the skin of some patients. The advent of the flush-before-fill technique and the use of APD have markedly decreased the incidence of 'touch contamination' peritonitis. Coagulase-negative *Staphylococcus* can also embed into a biofilm within the PD catheter, leading either to relapsing peritonitis (peritonitis with the same organism within 4 weeks of stopping antibiotics) or to persistent dialysate infection (Demoulin and Goffin, 2009), requiring catheter replacement. Recently a specific therapeutic approach with urokinase infusion (to dissolve the biofilm) and rifampicin (to eradicate the infecting organism hidden within the catheter silastic) has been reported (Demoulin and Goffin, 2009). Touch contamination also best explains peritonitis attributed to domestic animals such as *Pasteurella* spp. peritonitis occurring after pet bites to the tubing system (Broughton et al., 2010).

Box 270.1 Causes of cloudy dialysate effluent not due to peritonitis

- Intra-abdominal disease (cholecystitis, appendicitis, etc.)
- Retroperitoneal process (renal cell carcinoma, etc.)
- Dialysate contamination (peptidoglycans, aldehydes, etc.)
- Eosinophilic peritonitis (air within the peritoneal cavity, allergic reaction)
- Chylous peritonitis (lymphoma, breach within lymphatic vessels, drugs)
- Traces of blood within the effluent (trauma during placement of the catheter, ovulation, menstruations, etc.).

Box 270.2 Route of entry for peritonitis

- Intraluminal (touch contamination)
- Peri-luminal
- Enteric (transmural)
- Haematogenous spread
- Gynaecological

Catheter-related peritonitis can also be secondary to the migration of an infectious organism along the PD catheter (*periluminal* route of entry) in the context of exit site and/or tunnel infection. The most frequent causative organisms are *S. aureus, Pseudomonas* spp., and coagulase-negative *Staphylococcus*. Prolonged antibiotherapy together with local care is often necessary to cure the peritonitis episode. However, despite appropriate therapy, peritonitis associated with exit site or tunnel infection is often relapsing or refractory to therapy (failure of the effluent to clear after 5 days of appropriate antibiotics), requiring catheter removal. The technique of cuff(s) shaving may help in catheter salvage in cases with presumed subcutaneous cuff(s) infection (Scalamogna et al., 1995).

Enteric peritonitis (*transmural* route of entry) explains the majority of Gram-negative peritonitis through translocation of intestinal organisms across the bowel wall. Definite visceral perforations are rarely documented. Risk factors include constipation, large bowel diverticulosis (Mactier, 2009), and increased intraperitoneal pressure (Dejardin et al., 2007). The identification of multiple Gram-negative organisms together with anaerobes within the dialysate suggests intestinal micro-perforation.

Peritonitis due to *bacteraemia* (after invasive procedures or dental work) or resulting from an *ascending infection* from uterus and vagina (after gynaecological procedures) have occasionally been reported.

Risk factors and management

Several risk factors have been associated with peritonitis occurrence, such as frailty in elderly patients, under-dialysis, hypoalbuminaemia, diabetes, depression or changes in social circumstances, or *S. aureus* nasal carriage.

Given the high morbidity and mortality rates associated with peritonitis, antibiotic therapy has to be initiated without delay. The 2010 ISPD guidelines recommend empiric coverage of both Gram-positive and Gram-negative organisms: Vancomycin or a first-generation cephalosporin for the former, a third-generation cephalosporin or an aminoglycoside for the latter infections (Li et al., 2010). It is also recommended that each PD centre evaluates its own peritonitis records regarding organisms and resistance patterns, to adapt empiric coverage to local resistance rates.

Practicality must also be considered, in particular regarding 'in-patient' versus 'out-patient' therapy. Antibiotherapy has to be adjusted once culture results and sensitivities are available. Therapy duration should be 2 and 3 weeks for the milder and more severe infections, respectively.

The ISPD also recommends an intraperitoneal (IP) rather than intravenous administration of antibiotics given an increased local concentration with the former mode of administration. Still, vancomycin and aminoglycosides are absorbed and therefore requiring monitoring to facilitate appropriate dosing.

IP administration of antibiotics can be continuous (with each exchange) or intermittent (once daily). Appropriate dosing and mode of administration can be found at <http://www.ispd.org>. Increased dose for those drugs excreted through the kidneys is required in patients with significant renal residual function.

Antifungal therapy is indicated in patients at risk (diabetics, recent prolonged antibiotic administration) or if the Gram stain reveals yeast or fungus.

Because peritonitis is associated with structural and functional peritoneal membrane alterations and high mortality rates, catheter removal has to be considered in the following situations (Li et al., 2010):

- Relapsing peritonitis
- Refractory peritonitis
- Refractory exit site and tunnel infections
- Fungal peritonitis
- Fecal peritonitis (Li and Chow, 2012).

In a study of 565 consecutive episodes of peritonitis, a dialysate cell count above 1000/μL at day three after peritonitis diagnosis was associated (64% likelihood) with treatment failure, supporting the concept of early catheter removal to avoid untoward outcomes (Chow et al., 2006).

Simultaneous catheter removal and placement of a new catheter should not be encouraged except if the dialysate can be cleared in cases of relapsing peritonitis (Li et al., 2010) if the specific measures detailed above have failed. This situation is indeed suggestive of biofilm contamination.

Basic measures to prevent peritonitis include prophylactic antibiotic administration at catheter insertion, adequate patient education and training, avoidance of constipation, prevention of *S. aureus* infection with long-term use of gentamycin or mupirocin at the exit site, and fluconazole preventive administration in patients at risk of fungal infection.

The advantage of more biocompatible dialysate, versus standard PD solutions, on the incidence of peritonitis is still disputed. The recent open-label randomized controlled balANZ trial did not find any difference in the rates of culture-negative, Gram-positive, Gram-negative, and polymicrobial peritonitis, in the risk of peritonitis-related hospitalization or in the rates of peritonitis-related death and peritonitis-related technique failure. The use of biocompatible fluid was associated with a lower rate of non-pseudomonal Gram-negative peritonitis and a shorter median hospitalization duration. Peritonitis was more likely to be rated as mild (Johnson et al., 2012). Given conflicting results with other studies, further research is necessary to determine the potential benefit of biocompatible PD fluids on the incidence of peritonitis.

Tunnel and peritoneal exit site infections

Exit site infection is defined by the presence of a purulent discharge around the PD catheter, very often with accompanying skin erythema. Infecting organisms are mainly *S. aureus, S. epidermidis*, and *Pseudomonas aeruginosa*. Erythema around the catheter without purulent drainage rather indicates a simple skin reaction while a positive swab at the exit site without abnormal appearance around the catheter indicates exit site colonization rather than infection (Li et al., 2010).

Tunnel infection is defined by the presence of erythema, oedema, and tenderness around the subcutaneous pathway of the peritoneal catheter. It is usually associated with an exit site infection and infecting organisms are the same. Ultrasonography of the exit site and tunnel and white cell scans are useful additive tools for differential diagnosis. As exit site and tunnel infections often lead to peritonitis, therapeutic management is required with appropriate specific antibiotics, together with local dressing care with broad-spectrum antiseptic solutions (such as povidone iodine) or 10–20% saline. The latter should probably be preferred as it is less cytotoxic as compared to the former solution (Li et al., 2010).

Prevention of catheter infection includes appropriate daily or alternate-day care of the exit site with antibacterial soap or an antiseptic, avoidance of local trauma around the catheter by adequate catheter immobilization, and microbial prophylaxis with local mupirocin and gentamicin cream, in *S. aureus* carriers, a regular evaluation of the exit site appearance at the outpatient clinics, and the use of silver nitrate cauterization of exit site granulomas.

If the exit site remains infected despite adequate antibiotherapy, the external cuff is likely to be colonized by the infecting organism, therefore requiring its removal (cuff shaving).

Finally, catheter removal and its concomitant replacement should be considered in cases of resistant catheter infections and perioperative antibiotics should be given and pursued up to 2 weeks after catheter removal.

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CHAPTER 271

Viral infections in patients on dialysis

Michel Jadoul, Laura Labriola, and Eric Goffin

Introduction

Viral hepatitis has been recognized from the early days of haemodialysis (HD) as an extremely frequent complication. The manipulation of large quantities of blood during HD indeed favours dissemination in the HD environment and nosocomial transmission of blood-borne viruses. The most infective one is the hepatitis B virus (HBV), followed in descending order by the hepatitis C virus (HCV) and the human immunodeficiency virus (HIV), as illustrated by the risk of viral transmission after accidental needle-stick puncture with a contaminated needle: around 30% for HBV, 2% for HCV, and 0.3% for HIV. This gradient parallels the respective serum viral loads (Edey et al., 2010)

Hepatitis B

Epidemiology

Since the mid 1970s (when hygienic precautions started to improve) and the 1980s (when anti-HBV vaccination became available), the frequency of HBV infection in HD has decreased dramatically in most countries. Still, HBV infection remains more frequent in HD patients than in the general population worldwide, with prevalence figures of 0–6.6% in Western countries but up to 15% in some emerging countries (Edey et al., 2010) and incidence rates of 0.0078 events per patient-year in Western countries (Burdick et al., 2003).

Prevention

The infectivity of HBV is high. Thus, in addition to adequate screening of blood donors, the prevention of transmission of HBV within HD units requires the isolation of potentially infective HBV carriers in a separate ward, in addition to hygienic precautions (required for all blood-borne pathogens) and the vaccination of all susceptible patients.

Isolation

To be effective, isolation of infective patients should be prompt. Regular testing of non-immune HD patients is thus advised. The US Centers for Disease Control and Prevention currently still recommends monthly testing for the hepatitis B surface antigen (HBsAg); this should, however, probably be tailored to the local prevalence of HBV carriers, especially in (very) low-prevalence countries such as Northern European countries where frequent testing may detect more false positives than true positives. More importantly, patients should be tested when returning from a high-prevalence country (e.g. after a holiday) (Bhattacharya et al., 2009)

Hygienic precautions

These are discussed in the 'Prevention' section of HCV.

Vaccination

Ideally, CKD patients likely to ever reach end-stage renal disease should be vaccinated as soon as possible, prior to starting HD. In those referred late, a full vaccination course should be offered soon after the start of HD. This will provide immunity in 50–60% of patients only. More immunogenic vaccines are currently under investigation. Awaiting their availability, double-dose vaccination or additional intramuscular injections of a standard vaccine have been shown to somewhat increase the seroprotection rate. Finally the intradermal route modestly improves response rates in non-responders but the available vaccines are usually not licensed for intradermal administration (Edey et al., 2010; Labriola and Jadoul, 2010). In addition to lower response rates, HD patients also have lower peak titres of anti-HBs, declining with time, and thus shorter duration of protection. Booster doses are recommended in those whose titre falls below 10–100 IU/L.

Diagnosis

Unlike in the general population, acute HBV infection is frequently mildly symptomatic or asymptomatic in HD patients. Systematic screening for HBsAg and hepatitis B core antigen (anti-HBc) is thus required. In addition, the level of aminotransferases is markedly lower in HD patients than in the general population. Peak alanine aminotransferase (ALT) level may thus be as low as 50–100 IU/L in acute HBV infection. Such an ALT level, if unexplained, should prompt immediate serological testing for HBV (and HCV) in a HD patient. Chronic HBV infection is more frequent in HD patients than in the general population, most likely as a result of impaired immunity. Finally, occult HBV infection (negative HBsAg but positive anti-HBc and HBV-DNA) has recently been reported but has relatively little relevance in terms of nosocomial transmission. Most such patients indeed have very low HBV-DNA levels (< 50 copies/mL) (Aghakhani et al., 2010).

Treatment

Treating HBV infection is rarely required in HD patients, except in those with HBV replication (high titres of HBV DNA), either candidates for kidney transplantation or with little comorbidity and thus a long life expectancy. The available strategies should then be discussed with a consultant hepatologist, usually after a liver biopsy (Edey et al 2010).

Hepatitis C

Epidemiology

The incidence and prevalence of HCV infection in HD patients have decreased substantially since the identification of HCV in the late 1980s. Current prevalence rates are < 10% in most countries (Fissell et al., 2004; Jadoul et al., 2004; Johnson et al., 2009). Still, incidence rates remain high (> 1%), although improving, in several emerging countries (Johnson et al., 2009)

Prevention

The Kidney Disease: Improving Global Outcomes (KDIGO) workgroup (KDIGO, 2008) has reviewed the available evidence regarding the prevention of nosocomial transmission of HCV in HD. The cornerstone remains a careful, actual implementation of basic hygienic precautions. These are summarized in Box 271.1. The KDIGO workgroup further concluded that there was no evidence supporting either isolation by room or by machine of HCV carriers. These strategies should thus not be used as alternatives to the actual implementation of careful hygienic precautions. Admittedly, in many countries, the actual implementation of hygienic precautions remains suboptimal so that isolation has been used extensively. Units opting for isolation of HCV-positive patients in an attempt to reduce a persistently high incidence of HCV infection should, however, realize that this equals accepting the suboptimal implementation of hygienic precautions. Additional reasons against an isolation strategy include the need of four different wards for B+C−, B−C+, B−C−, and B+C+ patients and the diagnostic window between infection and positivity of serological tests, expected to limit the efficiency of an isolation strategy (Jadoul, 1995).

Diagnosis

Screening for HCV infection usually relies on third-generation immunoenzymatic assays. There is, however, a serological window (around 5 months) between contamination by HCV and the development of detectable anti-HCV antibodies in HD patients. In high-prevalence settings, the use of nucleic acid testing (polymerase chain reaction for the detection of HCV-RNA or similar tests) may thus be more appropriate, at least for initial testing. A recent systematic review (KDIGO, 2008) concluded that third-generation immunoenzymatic assays have a sensitivity of 75% and a specificity of 95% for the presence of HCV-RNA. In the absence of isolation policy, performing such serological tests at HD start and then twice a year, as well when patients return from another HD unit, is adequate. As for acute HBV infection, it should be realized that any increase in transaminase levels, even mild, may point to acute hepatitis and should prompt additional testing for HCV (and/or HBV as appropriate).

Box 271.1 Key points for the prevention of nosocomial transmission of blood-borne viruses

- Wear gloves, to be changed between patients/stations
- Hand hygiene (hydroalcoholic solution) before contact with patient and after gloves withdrawal
- Prepare injectable drugs in clean area
- Do not return unused material from contaminated to clean area
- Clean/disinfect surfaces of HD environment including surface of machine before next session
- Dedicate small items (tourniquet, tape, etc.) to a single patient (if not, disinfect between patients).

Treatment

The treatment of chronic HCV infection in the general population is changing rapidly with many new drugs available. In HD patients, the KDIGO guidelines (KDIGO, 2008) concluded that the treatment should not be started before 3 months after the diagnosis of infection as spontaneous remission is observed in up to 20% of cases. Beyond that delay, the current standard regimen in HD patients is pegylated interferon together with low-dose ribavirin, with weekly monitoring of haemoglobin level. This treatment should only be performed, usually after a liver biopsy, under careful supervision by clinicians with substantial experience in the field. Those likely to benefit among HD patients are, as for HBV treatment, potential candidates for kidney transplantation or with little comorbidity and thus a good life expectancy on HD. Tolerance is usually worse than in the general population but response rates tend to be good in those able to tolerate (KDIGO, 2008; Deltenre et al., 2011) and these responses are usually sustained after a kidney transplantation (Gordon et al., 2011).

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CHAPTER 272

Cognitive function, depression, and psychosocial adaptation

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Introduction

Psychiatric complications of end-stage renal disease (ESRD) are common, often debilitating, and potentially preventable. ESRD patients are at higher risk for psychiatric disorders compared to patients with other chronic health conditions, and those who suffer from psychiatric complications are at higher risk for death and dialysis withdrawal. Both dementia and depression also reduce quality of life and impair adherence to prescribed therapies. In addition, patients with ESRD are confronted with multiple stressors related to their illness and treatment. This chapter reviews the clinical approach to cognitive impairment, depression, and psychosocial adaptation among patients with ESRD.

Delirium

Definition and epidemiology

Delirium is a syndrome of acute decline in cognitive function characterized by inattention and altered consciousness attributable to a medical condition, medication side effect, or intoxication. A diagnostic algorithm based on *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria, the Confusion Assessment Method, has a sensitivity and specificity for delirium detection of > 90% among hospitalized patients (Inouye, 2006). Delirium occurs most often among hospitalized older patients, especially in the intensive care unit or postoperatively. In one study, the annual incidence of delirium among patients with ESRD was 3.4%, and an episode of delirium was associated with short-term mortality in excess of 50% (Fukunishi et al., 2002). Subacute delirium may also exist among ambulatory haemodialysis patients. For example, in two studies, cognitive function was noted to fluctuate according to the weekly haemodialysis schedule such that cognitive function was poorest over the long intradialytic interval (i.e. 72 hours after the last dialysis) and during a haemodialysis session (Williams et al., 2004; Murray et al., 2007).

Risk factors

Table 272.1 outlines the most common causes of delirium in patients with ESRD. Several syndromes of delirium specific to patients with ESRD deserve special mention:

Uraemic encephalopathy is a syndrome of delirium seen in untreated ESRD and attributed to retention of as yet unidentified uraemic solutes. It is characterized by lethargy and confusion in early stages, and may progress to seizures and/or coma. It may be accompanied by other neurologic signs, such as tremor, myoclonus, or asterixis. The syndrome is reversed with dialysis or kidney transplantation (Teschan et a., 1976). While markers of azotaemia and/or inadequate dialysis may be present, none are diagnostic. The electroencephalogram (EEG) has been studied as a diagnostic tool for uraemic encephalopathy, but its utility has not been confirmed in large studies (Teschan, 1975). Thus, the diagnosis of uraemic encephalopathy is usually one of exclusion

Dialysis disequilibrium is a syndrome of delirium seen during or after the first several dialysis treatments (Fukushige et al., 1971). It has been attributed to cerebral oedema, though the nature and cause of oedema remains uncertain. One hypothesis suggests this syndrome is caused by rapid removal of urea during dialysis leading to a urea gradient between the blood and brain, thus promoting the development of cerebral oedema (Chen et al., 2007). An alternative hypothesis is that the formation of idiogenic osmoles within the brain contributes to the development of cytotoxic oedema when an osmolar gradient is developed during dialysis (Arieff et al., 1973). Dialysis disequilibrium is most likely to occur in paediatric or older patients with severe azotaemia undergoing high-efficiency haemodialysis; however, it has also been reported in patients undergoing peritoneal dialysis and long-term haemodialysis (Miller and Tassistro, 1969). The syndrome is characterized by symptoms of headache, visual disturbance, nausea, or agitation, and in severe cases, delirium, lethargy, seizures, and even coma. The incidence and severity of this syndrome have not been studied among contemporary patients with ESRD, but may be declining due to earlier initiation of dialysis and institution of preventative measures in high-risk patients.

Evaluation

The initial evaluation of an ESRD patient with delirium should include history and physical examination to establish the acuity of change in mental status and provide clues about the underlying aetiology. A comprehensive medication review should be included as well, since medications are a common contributing factor for delirium. A metabolic panel, complete blood count, liver function studies, and drug screen can identify some of the most common causes for delirium. Infections are also a common cause of delirium, and should be ruled out with examination and appropriate

Table 272.1 Pharmacologic therapy for dementia

Drug class	Indication	Route of elimination	Usual starting dose	Dose modification in ESRD?	Common side effects
Cholinesterase inhibitors					
Tacrine	Mild to moderate dementia from Alzheimer disease *(used less commonly due to dosing frequency and need for lab monitoring)*	Extensive hepatic metabolism	10 mg every 6 hours	No data, but probably not required	Dizziness, nausea, diarrhoea, elevated transaminases, myalgia, neutropenia
Donepezil	Mild to severe dementia from Alzheimer disease	Partially excreted unchanged in urine and partially metabolized in liver	5 mg at bedtime	Very limited data suggests no dose modification is required	Dizziness, nausea, diarrhoea, myalgia, insomnia
Rivastigmine	Mild to moderate dementia from Alzheimer disease	Extensive hepatic metabolism, metabolites excreted in urine	1.5 mg twice a day	Very limited data suggests no dose modification is required	Dizziness, nausea, diarrhoea, anorexia
Galantamine	Mild to moderate dementia from Alzheimer disease	Partially excreted unchanged in urine and partially metabolized in liver	4 mg twice a day	Maximum dose 16mg daily in 'moderate' kidney disease. Use not recommended in ESRD	Dizziness, nausea, diarrhoea, anorexia
***N*-methyl D-aspartate (NMDA) receptor antagonists**					
Memantine	Moderate to severe dementia from Alzheimer disease	Partially excreted unchanged in urine and partially metabolized in liver	5 mg daily	Maximum dose 5 mg twice a day for patients with creatinine clearance < 30 mL/min or ESRD	Dizziness, hypertension, headache, constipation

ESRD = end-stage renal disease.

Adapted from Duarte et al. (2009), Mirotet al. (2008), Cohen et al. (2004), Ghaemi et al. (2004), and Goldberg and Truman (2003).

cultures. If an obvious cause for delirium is identified and there is no history of trauma or focal neurologic signs, neuroimaging may not be indicated during the initial evaluation, but can be considered subsequently if there is no improvement with appropriate medical treatment. Less commonly, the evaluation of delirium may include lumbar puncture to rule out central nervous system infection, or an EEG to rule out seizure activity.

Prevention and management

In hospitalized patients, preventative measures can reduce incidence and costs associated with delirium (Inouye, 2006). Specific measures to prevent dialysis disequilibrium include reducing the efficiency of dialysis, increasing the dialysate sodium concentration, and administering mannitol.

Once identified, management of delirium is aimed at identification and treatment of precipitating factors and management of behavioural symptoms. Pharmacologic therapy is indicated only when delirium threatens patient safety or interrupts essential therapy. In these cases, haloperidol is the agent of choice, with a usual starting dose of 0.25–0.5 mg twice daily. No dosage adjustment is needed in ESRD. Atypical antipsychotic medications, such as risperidone, olanzapine, and quetiapine have also been used for this purpose. Because of a possible risk of increased mortality when used in patients with dementia, short-term use is recommended (Schneider et al., 2005). Benzodiazepines, atypical antipsychotics, and some antidepressants have also been used for treatment of delirium, but these agents have side effects that make them less desirable as first-line agents except in the case of benzodiazepines for alcohol withdrawal. Supportive care to prevent aspiration, deep venous thrombosis, and pressure sores should also be provided in all patients.

Dementia

Definition and epidemiology

Dementia is a state of persistent and progressive cognitive dysfunction characterized by impairment in memory and at least one other domain of cognitive function, such as language, orientation, reasoning, attention, or executive functioning, the cognitive skill necessary for planning and sequencing tasks. The impairment in cognitive function must represent a decline from the patient's baseline level of cognitive function and must be severe enough to interfere with daily activities and independence. Mild cognitive impairment is the most common terminology used to describe cognitive impairment beyond that associated with normal ageing, but not crossing the threshold for dementia.

The estimated prevalence of cognitive impairment among patients with ESRD ranges from 16% to 38% in studies utilizing neuropsychiatric testing (Sehgal et al., 1997; Murray et al., 2006; Kurella Tamura et al., 2010), while the estimated prevalence of dementia based on diagnostic coding is 7–12% (Kurella et al., 2006; Rakowski et al., 2006). In one study of patients with ESRD, the annual incidence of dementia was 2.5%, with vascular dementia accounting for 90% of incident dementia cases, an incidence rate sevenfold higher than the general population (Fukunishi et al., 2002). *Dialysis dementia* is a term used to describe a rapidly progressive form of dementia associated with aluminium toxicity in ESRD patients (Rozas et al., 1978).

Risk factors

Advanced age is a major risk factor for dementia and cognitive impairment. An estimated 30–55% of ESRD patients over the age of 75 have cognitive impairment based on neuropsychiatric testing (Murray et al., 2006; Kurella Tamura et al., 2010). The prevalence of cognitive impairment is also elevated among middle-aged ESRD patients, ranging from 10-30% in several studies (Murray et al., 2006; Kurella Tamura et al., 2010). The neuropathology of dementia and cognitive impairment in ESRD is unknown, though several lines of evidence suggest cerebrovascular disease may play a prominent role. Stroke is a risk factor for dementia and cognitive decline among patients with ESRD (Kurella et al., 2006). Furthermore, vascular risk factors, such as diabetes, hypertension, and microalbuminuria are also risk factors for cognitive decline. In addition, neuroimaging studies have shown that patients with ESRD have a large burden of small vessel strokes and white matter hyperintensities (Martinez-Vea et al., 2006), lesions which correlate with cognitive decline.

Evaluation

The first step in the assessment of suspected dementia is an evaluation of cognitive function. A large number of brief cognitive assessment tools are available, such as the Mini-Mental State Exam, the Six-Item Screener, and the Montreal Cognitive Assessment, though it should be noted that none have been specifically validated among patients with ESRD (Kurella Tamura and Yaffe, 2011). History taking, ideally from the patient *and* caregiver, should focus on the onset, duration, and severity of cognitive and behavioural deficits and the presence of associated functional impairments. Examination should look for focal neurologic deficits suggestive of prior stroke and signs of parkinsonism (e.g. tremor, bradykinesia, and rigidity).

It is important to try to exclude delirium or depression as the sole cause of cognitive impairment before establishing a diagnosis of dementia, since these conditions are reversible, although in practice this may be difficult (screening for depression is discussed in the next section). Laboratory testing for vitamin B_{12} deficiency and hypothyroidism is recommended for all patients with suspected dementia. In ESRD patients, inadequate dialysis, severe anaemia, and aluminium toxicity should also be ruled out. AIDS dementia complex and neurosyphilis may be considered in patients with risk factors. The American Academy of Neurology supports the use of structural neuroimaging as part of the workup for dementia. However, functional neuroimaging and testing for genetic markers of dementia risk (e.g. apolipoprotein E variants) remains primarily for research.

Prevention and management

Two classes of medications are now available for treatment of Alzheimer disease, cholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists (Table 272.1). The clinical benefit of both classes of agents appears to be modest (roughly equivalent to a 4–6-month delay in cognitive decline). There is no published data on safety or efficacy of these agents in ESRD patients; thus therapy decisions should be individualized.

Behavioural symptoms should be treated with a stepped approach, beginning with removal of precipitating factors (e.g. pain and excessive noise), followed by psychosocial interventions and pharmacologic therapy as a last step, since many medications have not been shown to be efficacious or have significant adverse events (Schneider et al., 2006). For example, several atypical antipsychotics have been associated with an increased risk of stroke and death among elderly patients with dementia (Ballard and Waite, 2006). Key aspects of dementia management are the assessment of patient safety and ability to perform self-care functions, comply with medical regimens, participate in medical decision-making, and plan for future care needs. A multidisciplinary approach involving primary care, geriatrics, nursing, and social work is useful for addressing the complexity of medical and social issues in these patients.

The management of ESRD patients with mild cognitive impairment is uncertain. There is conflicting evidence regarding the role of vascular risk factor modification for prevention of dementia in the general population. For example, in a meta-analysis of hypertension trials, treatment of hypertension was associated with a 13% risk reduction for dementia (Peters et al., 2008). In contrast, a systematic review of hypertension trials excluding participants with pre-existing cerebrovascular disease suggested no benefit of hypertension treatment for preventing cognitive decline (McGuinness et al., 2009). In a pooled analysis of two clinical trials in patients with diabetes or cardiovascular disease, treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker reduced the incidence of cognitive decline among subjects with macroalbuminuria, but not among subjects without macroalbuminuria. In a large clinical trial of intensive versus standard glycaemic control in patients with type 2 diabetes that excluded individuals with chronic kidney disease (CKD), intensive glycaemic control was associated with larger brain volume but no difference in the rate of cognitive decline after 3.5 years (Launer et al., 2011). Homocysteine lowering with B vitamin supplementation does not reduce the risk of cognitive decline both in the general population and in the ESRD population (Brady et al., 2009). Physical activity and possibly cognitive activity have shown promise as effective interventions to slow cognitive decline in the general population (Lautenschlager et al., 2008). Given the other benefits of physical activity in particular, and the relatively low risk of harm, these interventions may be attractive options for patients with ESRD.

Treatment of severe anaemia with recombinant erythropoietin has been associated with improvement in neuropsychological test performance and EEG measures in uncontrolled studies of patients with ESRD (Grimm et al., 1990; Marsh et al., 1991). The lack of control arms in these studies impairs the interpretation of these results. It should be noted that pre-treatment haematocrit in these studies was substantially lower than current practice (mean ~ 23%), and that achieved post-treatment haematocrit was consistent with or slightly more aggressive than current clinical practice guidelines (30–36%). Large randomized trials of anaemia correction using erythropoietin in CKD or ESRD did not evaluate cognitive function, and one suggested that active treatment was associated with an increased risk for stroke (Pfeffer et al., 2009), which in turn is a major risk factor for dementia. Thus, there is currently insufficient evidence to justify changing current haemoglobin targets for the purposes of preventing dementia in patients with CKD or ESRD.

Similarly, while it is accepted that dialysis initiation reverses uraemic encephalopathy, there is no definitive evidence that more intensive dialysis improves cognitive function. Although an observational study suggested more frequent haemodialysis improves cognitive function (Jassal et al., 2006), this finding was not

confirmed in two clinical trials involving > 300 subjects (Chertow et al., 2010; Rocco et al., 2011). In short-term observational studies, kidney transplantation is associated with improvement in cognitive function (Griva et al., 2006); however, other studies suggest that significant residual impairment exists in some transplant recipients (Gelb et al., 2008).

Depression

Definition and epidemiology

Major depression is defined by depressed mood and/or loss of interest in nearly all activities for at least 2 weeks, accompanied by a minimum of three additional symptoms, for a total of at least five symptoms (Table 272.2) (American Psychiatric Association, 2013). A drawback to relying on the DSM-5 criteria for the diagnosis of major depression is that many of the core symptoms, for example, fatigue, are not caused by depression but are a direct result of kidney failure.

Depression is the most common psychiatric disorder affecting patients with ESRD, with up to 45% of incident dialysis patients and up to 20% of prevalent dialysis patients affected (Wang and Watnick, 2004). Despite its high prevalence, depression frequently is undiagnosed among patients with ESRD, and as a result, untreated. Consequences of depression include amplification of pain and disability, delayed recovery from other medical illness and surgery, worsening of drug side effects, frequent hospitalizations, cognitive impairment, malnutrition, and increased suicide and non-suicidal deaths (Cohen et al., 2007).

Evaluation of depression

Several standardized questionnaires have been validated in persons with ESRD and can be used to screen for depression. Beck Depression Inventory (BDI) scores of 16 or greater and Patient Health Questionnaire-9 (PHQ-9) scores of 10 or greater have a sensitivity and specificity for diagnosing clinical depression of approximately 90% among patients with ESRD (Watnick et al., 2005; Hedayati and Finkelstein, 2009). Positive screening results may be followed by structured interview, the gold standard for diagnosing clinical depression (American Psychiatric Association, 1994).

Among patients who screen positive for depression, evaluation should include an assessment of coexisting psychiatric disorders, suicide risk, and medications that may exacerbate symptoms. Major depression carries as much as a 20-fold increase in lifetime risk of suicide (Nutting et al., 2005). Patients with ESRD can commit suicide more easily than non-medically ill populations, by non-compliance with the dialysis regimen or by manipulation of their vascular access (Neu and Kjellstrand, 1986; Kurella et al., 2005). One study from the United States found the standardized incidence rate of suicide among patients with ESRD was almost twice as high as the general population (Kurella et al., 2005). Factors to consider include access to and lethality of suicide means, past history of suicidal behaviour, co-occurring substance abuse, the availability and adequacy of social supports, and recent medical illness.

Medication review should focus on identifying medications that may exacerbate depressive symptoms or interact with antidepressant medications, such as steroids, narcotics, sedative/hypnotics, benzodiazepines, beta blockers, alpha agonists, reserpine, H_2 antagonists, antipsychotics, and immunosuppressives.

Table 272.2 Diagnostic criteria for depression

	Criteria	Duration
Minor depression	2 to 4 depressive symptoms,[§] including depressed mood or anhedonia	≥ 2 weeks
Major depression:	≥ 5 depressive symptoms, including depressed mood or anhedonia	≥ 2 weeks
Mild	Few (if any) symptoms in excess of those required for the diagnosis; minimal impairment in functioning	
Moderate	Greater number and intensity of depressive symptoms; moderate impairment in functioning	
Severe	Marked intensity and pervasiveness of depressive symptoms; substantial impairment in functioning	
Depressive symptoms:		
Depressed mood	Depressed mood most of the day, nearly every day	
Anhedonia	Markedly diminished interest or pleasure in almost all activities	
Weight change	Substantial unintentional weight loss or gain	
Sleep disturbance	Insomnia or hypersomnia nearly every day	
Psychomotor problems	Psychomotor agitation or retardation nearly every day	
Lack of energy	Fatigue or loss of energy nearly every day	
Excessive guilt	Feelings of worthlessness or excessive guilt nearly every day	
Poor concentration	Diminished ability to think or concentrate nearly every day	
Suicidal ideation	Recurrent thoughts of death or suicide	

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (American Psychiatric Association, 2013).

Management of depression

General recommendations

Treatment options for depression include exercise therapy, psychosocial therapy, pharmacologic therapy, electroconvulsive therapy (ECT), or combinations of these modalities. For mild depression, exercise or psychosocial treatments are the first-line approach (American Psychiatric Association, 2000). Structured psychological interventions and antidepressants are effective in moderate to severe depression (American Psychiatric Association, 2000). Most treatment recommendations are extrapolated from studies in the general population, as there have been few clinical trials conducted in patients with ESRD.

Depression in the setting of ESRD should be comprehensively managed. Communication between the primary care provider and the psychiatrist is important in order to optimize resources, integrate the latest guidelines and evidence, and avoid overlap resulting in potentially dangerous medical outcomes and

increased costs. Because depression is often found among dialysis patients, it is important for the entire staff of a dialysis centre to have sufficient training with regards to its diagnosis and treatment. A team of providers, including the primary care physician or nephrologist, psychiatrist, nurse, and social worker can ensure that care is optimized by selecting appropriate medication, supporting medication adherence, managing side effects and efficacy issues, and incorporating behavioural and/or psychotherapeutic interventions into the treatment plan. A recent intervention involving nurses who provided guideline-based, patient-centred management of depression and chronic disease was shown to significantly improve control of medical disease and depression (Katon et al., 2010).

Consultation with a psychiatrist is necessary if a patient has coexisting psychiatric conditions (suicidal ideation, psychosis, mania, or substance abuse), if they have a labile or recurrent illness course, or if they fail to respond to an adequate trial of medication.

Exercise therapy

Combined aerobic exercise and resistance training during dialysis improves muscle strength, cardiac fitness, and mood (Painter et al., 2000; van Vilsteren et al., 2005). Kouidi et al. performed a randomized controlled trial in 20 haemodialysis patients to study the effect of aerobic exercise on depression. Depressive symptoms improved significantly in the exercise group but not in the control group in this pilot study. Interestingly, the most severely depressed patients had the greatest benefit from exercise training (Kouidi et al., 1997). Several studies have examined the effect of intradialytic exercise programmes on depressive symptoms and quality of life. In two studies, intradialytic exercise programmes effectively alleviated depressive symptoms (Levendoglu et al., 2004; Ouzouni et al., 2009). However another randomized trial (van Vilsteren et al., 2005) failed to show a significant improvement in self-reported depression scores in the short term from a moderate intensity intradialytic exercise intervention, though they did find that exercise improved measures of self-efficacy. Koudi et al. (2010) showed that improvement in cardiac autonomic disturbances paralleled improvements in depressive symptoms during a 1-year exercise intervention, suggesting the two conditions may be mechanistically linked.

In spite of the demonstrated benefits of exercise in patients with ESRD, there are currently no exercise guidelines for this population. In the absence of specific guidelines for the ESRD population, Johansen (2008) has suggested that the recommendations for older adults with clinically significant chronic conditions and/or functional limitations can be applied to patients with ESRD (Nelson et al., 2007).

Psychosocial therapy

Psychosocial therapy uses a combination of cognitive restructuring and behavioural assignments to promote the reorganization of negative thoughts, mood status, and adjustment of behaviours (Beck, 2005). Psychosocial therapy is as effective as medication for the initial treatment of moderate to severe depression (DeRubeis et al., 2005). In two short-term trials conducted in patients with ESRD, psychosocial therapy effectively reduced depressive symptoms and improved quality of life (Cukor, 2007; Duarte et al., 2009). The advantage of psychosocial therapy is that it avoids the adverse effects associated with pharmacotherapy. A drawback is that efficacy may be tied to the experience of the therapist.

Pharmacologic therapy

Very few studies have evaluated the safety and efficacy of antidepressants in patients with ESRD (Mirot et al., 2008). In addition to sparse efficacy data, concerns about adverse effects, drug interactions, polypharmacy, and non-compliance may also play a role in physician hesitance to prescribe these medications. Table 272.3 lists the dose range, route of elimination and side effect profile of commonly used antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are generally regarded as first-line pharmacologic treatment in patients with ESRD because of their more favourable side effect profiles compared to other antidepressant classes (Cohen et al., 2004). SSRIs are eliminated by hepatic metabolism and generally are not significantly removed by dialysis. SSRIs should be prescribed with caution in older patients who may have reduced hepatic metabolism, among those receiving drugs metabolized by the cytochrome P450 enzyme systems (e.g. calcineurin inhibitors and sildenafil) because SSRIs inhibit P450 enzymes, and among those with bipolar disorder because SSRIs may enhance the risk for mania (Goldberg and Truman, 2003; Ghaemi et al., 2004). There is also controversy regarding a reported link between SSRIs and increased suicide risk (Hall, 2006). Some observational studies have suggested an association between use of SSRIs and gastrointestinal bleeding (Dalton et al., 2003; Wessinger et al., 2006). This adverse effect may be particularly problematic in patients with ESRD and underlying qualitative platelet defects related to uraemia. However, in one case–control study, the risk of upper gastrointestinal bleeding was not increased by the use of SSRIs (Vidal et al., 2008).

Fluoxetine is the most used medication in this class, and it appears to be both safe and efficacious in patients with ESRD (Levy et al., 1996; Blumenfield et al., 1997). Sertraline, like fluoxetine, also undergoes hepatic metabolism, and pharmacokinetic studies in patients with advanced CKD suggest a favourable safety profile (Cohen et al., 2004). One beneficial effect of sertraline in patients with ESRD is that it may decrease orthostatic hypotension (Dheenan et al., 1998). Citalopram is known to have similar pharmacokinetics to both sertraline and fluoxetine, and dosage adjustments do not seem to be necessary in patients with ESRD (Spigset et al., 2000). In contrast, the recommended initial dose for paroxetine in patients with ESRD is half that for adults with normal kidney function (Doyle et al., 1989).

Tricyclic antidepressants (TCAs) are usually avoided in patients with ESRD due to orthostatic hypotension, slowed cardiac conduction, and proarrhythmic effects (Cohen et al., 2000). TCAs should not be prescribed for patients with a prolonged QT interval or other arrhythmias or those with ischaemic heart disease (Novotny et al., 2007). Other pharmacologic options for treatment of depression include monoamine oxidase inhibitors (MAOIs), reverse inhibitors of monoamine oxidase, and herbal supplements such as St John's wort (hypericum). However, these agents have increased risk for drug interactions, and special caution is advised in the ESRD population before prescribing herbal agents or MAOIs. St John's wort can reduce the serum levels of calcineurin inhibitors because it stimulates the CYP3A4 hepatic enzyme system, and thereby increases the risk for acute rejection in renal transplant recipients (Mai et al., 2003).

Patients need to undergo at least 4 weeks of treatment with an antidepressant medication before assessing the potential outcome of therapy. If no improvement occurs within that time period and the side effects are tolerable, the dose should be increased. If intolerable side effects occur or if there is little or no improvement

Table 272.3 Pharmacologic therapy for depression

Antidepressant	Daily dosage (mg/day)		Dialytic removal	Side effects
	Initial	Usual		
SSRIs				
Fluoxetine	10	20	Not removed by haemodialysis	Anxiety, agitation, nausea, diarrhoea, sexual dysfunction
Sertraline	25	25–150	Minimal removal by haemodialysis	Anxiety, agitation, nausea, diarrhoea, sexual dysfunction
Paroxetine	10	10–20	Minimal removal by haemodialysis	Anxiety, agitation, nausea, diarrhoea, sexual dysfunction
Citalopram	10	10–40	Not removed by haemodialysis	Anxiety, agitation, nausea, diarrhoea, sexual dysfunction
Tricyclic antidepressants				
Nortriptyline	10-25	50–100	Not removed by haemodialysis or by CAPD	Orthostasis, cardiac arrhythmia
Other drugs				
Bupropion	75	100–300	Minimal removal by haemodialysis	Seizures, agitation, insomnia, headaches, hallucination
Nefazodone	100	100–300	Minimal removal by haemodialysis	Agitation, nausea, orthostasis, sedation

CAPD = continuous ambulatory peritoneal dialysis; SSRIs = selective serotonin reuptake inhibitors.

after 3–4 weeks at the step-up dose, a trial of an alternative medication should be considered (Bostwick, 2010). Once symptoms are relieved, pharmacotherapy should be continued for at least 6–9 months to prevent relapse (Allart-van Dam et al., 2007). If symptoms recur, dosage adjustment, medication change, or psychiatric consultation is indicated (Whooley and Simon, 2000).

Other treatments

ECT is an effective treatment for patients with the diagnosis of major depression who are unresponsive to an antidepressant drug regimen, cannot take oral medications, have hypokinesia, or severe suicidal ideation (Frederikse et al., 2006). There are theoretical concerns that ECT may aggravate hyperkalaemia, metabolic acidosis, volume overload, and promote cardiotoxicity in ESRD; these concerns have not been confirmed in small case series (Williams and Ostroff, 2005; Wille, 2007).

A recent observational study reported that more frequent haemodialysis reduces depressive symptoms and improves quality of life (Vos et al., 2001; Heidenheim et al., 2003; Jaber et al., 2010). In a randomized controlled trial, short daily haemodialysis reduced depressive symptoms compared to conventional thrice-weekly haemodialysis, but this difference did not reach statistical significance (Chertow et al., 2010). While daily dialysis may be more effective in ameliorating depression compared to conventional haemodialysis schedules, this potential benefit needs to be weighed against the burden of increased treatment-related stress (Kurella et al., 2005).

Psychosocial adaptation

Patients with ESRD are confronted with multiple stressors, including lifestyle changes, social isolation, loss of employment, functional limitations, financial restraints, changes in family relationships, and fear of impending death. The ability to successfully adapt to the stress of chronic illness such as ESRD is dependent on psychopathology and behavioural characteristics, but also on social and environmental factors. Multiple studies have demonstrated an association between perceived social support and survival of patients with ESRD (McClellan et al., 1993; Kimmel et al., 1998). Several, though not all, have suggested an association between social support and compliance with dialysis and dietary regimens, and between social support and depressive symptoms (Cukor et al., 2007).

Marital and family supports are key determinants of psychosocial adaptation to ESRD; conversely, ESRD and other chronic illness may place significant strain on marital and family relationships. Sexual dysfunction and sleep disorders are common among patients with ESRD and infrequently assessed by healthcare providers, but may alter marital dynamics. Beyond family relationships, unit culture and neighbourhood characteristics also play important roles in helping patients adapt to ESRD. For example, in several studies, patients living in predominantly black neighbourhoods had poorer preparation for ESRD and lower access to transplantation (Rodriguez et al., 2007; Prakash et al., 2010).

In addition to treatment of psychiatric conditions such as depression and anxiety, several other interventions may enhance adaptation to ESRD. Patient and caregiver education improves knowledge and satisfaction with care. Caregiver support services reduce caregiver burden and improve quality of life in other chronic illnesses, though they haven't been extensively studied among caregivers of patients with ESRD. Peer support networks for patients with ESRD have also recently become available.

Summary

In sum, psychiatric conditions and psychosocial factors impair quality of life, reduce compliance, and contribute to poor survival among patients with ESRD. These factors may be amenable to intervention, and offer a unique though often overlooked target for improving the quality of ESRD care.

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CHAPTER 273

Volume assessment and management in dialysis

Rajiv Agarwal

The assessment of volume

There are seven ways that volume can be assessed in dialysis patients: history and examination, measurement of total body water, biochemical assessment of hypervolaemia, bioimpedance analysis (BIA), relative plasma volume (RPV) monitoring, blood pressure (BP) monitoring, and echocardiographic techniques including the emerging technique of lung ultrasound. Each of these seven tools will be discussed further.

History and examination

The physical examination may be quite benign in the setting of tremendous volume overload therefore it is not very reliable in excluding hypervolaemia. Some physical signs even when present may not indicate volume excess. For example, pedal oedema does not correlate with dry weight very well. In a case–control study, Agarwal et al. found that pedal oedema was not associated with simultaneously measured inferior vena cava (IVC) diameter, blood volume monitoring, and plasma volume markers such as B-type natriuretic peptide (Agarwal et al., 2008). On the other hand, pedal oedema correlated with cardiovascular risk factors such as age, obesity, and left ventricular mass. Thus, those who were older, more obese and who had more left ventricular mass were more likely to have pitting pedal oedema.

Whereas the isolated presence or absence of pedal oedema may not reveal the presence or absence of volume excess, it is quite possible that a constellation of signs and symptoms such as effort intolerance, shortness of breath, elevated jugular venous pressure, bibasilar rales, and pedal oedema may strongly suggest the presence of volume excess. Whether this is so should be evaluated in future studies.

One physical sign, BP, deserves special emphasis. Elevated BP confirmed by measurements at home suggests the presence of volume excess. This physical sign is discussed in 'Blood pressure monitoring'.

Measurements of total body water

Total body water can be directly assessed by dilution of markers that distribute in total body water. Two such markers are alcohol and deuteriated water and have been used to assess total body water among dialysis patients.

Alcohol space

Total body water was assessed in 19 stable patients on peritoneal dialysis (Dahl et al., 1999). Ethanol 0.3 g/kg was administered in a fasting state and breath alcohol concentrations were measured periodically over 4 hours (Dahl et al., 1999). The volume of distribution of ethanol correlated with volume of distribution of urea; measured on two separate occasions in the same patient, the volume of distribution of alcohol was reproducible. The technique is relatively straightforward, reproducible, and inexpensive. However, the 4-hour sampling time and repeated exposure to alcohol makes it somewhat less practical for routine implementation in the dialysis unit.

Deuteriated water space

Deuteriated water (non-radioactive, heavy water) after oral administration is absorbed and distributed in total body water and therefore serves as a probe for total body water. Mass spectrometers can distinguish heavy water from normal water and therefore can accurately estimate total body water. Absolute measurements of total body water have become more feasible with the use of portable mass spectrometers. In one such study, Chan et al. used a flowing afterglow mass spectrometer to measure total body water (Chan et al., 2008). Following ingestion of heavy water immediately after dialysis among 12 haemodialysis patients, measurements of total body water were made immediately after haemodialysis and immediately preceding the following dialysis. The two measurements showed excellent agreement after accounting for insensible losses and urine output; the coefficient of variation between the two measurements was 2.6%. Although this proof of principle study demonstrated that absolute total body water can be determined among haemodialysis patients, the diagnostic utility of this tool requires further refinement. Further work is required before this study can be used for day-to-day decision-making about volume management.

Biochemical assessment of hypervolaemia

Between 1989 and 2012, 13 studies were reported that related cardiac natriuretic peptides to assess volume in haemodialysis or peritoneal dialysis patients. Of these, four studies found no relationship with volume, whereas nine studies found a direct relationship between volume assessed using another technique such as IVC diameter or chest X-ray with the biomarker. Only two of these studies were longitudinal and none were interventional.

Between 2001 and 2008, five studies reported the relationship of either atrial natriuretic peptide, brain natriuretic peptide (BNP), or N-terminal pro-BNP (NT-proBNP) to left ventricular mass, left ventricular ejection fraction, cardiovascular outcomes, or all-cause mortality. Four of these five studies found a direct relationship of

these natriuretic peptides with left ventricular mass and function and cardiovascular outcomes. The smallest study that included only 30 patients was negative.

Only one interventional study has been reported to date that relates the change in BNP to probing dry weight. There was a cross-sectional association between BNP and interdialytic ambulatory BP. Since interdialytic ambulatory BP is related to left ventricular mass, the relationship of cardiac natriuretic peptides and BP is likely confounded by left ventricular mass and function. This study found no relationship between probing dry weight with change in BNP. Thus, reduction in volume was not related to reduction in BNP calling into question our ability to predict changes in BP based on baseline BNP concentrations.

Bioimpedance analysis

Principles of BIA

Bioimpedance is the opposite of electrical conductivity. It is a measure of the opposition to the flow of a weak imperceptible electric current through the tissues. In a copper wire, the opposition to the flow is directly proportional to its length and inversely proportional to the cross-sectional area of the wire ($R = L/A$). Stated another way, the resistance is proportional to the square of the length and inversely to the volume ($R = L \times L / A \times L$). Assuming that the length is proportional to the height of the person and volume to the total body water, this can then be used to calculate lean body mass; lean body mass is proportional to the total body water. The impedance to the flow of current is of two types: resistive and capacitative.

The cell membranes serve as an excellent storage compartment for current. In other words, they serve as a capacitor. When the frequency of the current tends to zero (a DC current), the current is not transmitted through the membranes and traverses through the extracellular fluid only. Thus, resistance at zero frequency is proportional to the extracellular fluid. On the other hand, the introduction of a high-frequency AC current through these cell membranes makes the cell membranes an excellent capacitor and the current flows through both the intracellular and extracellular water. Thus, resistance at infinite frequency is proportional to the intracellular and extracellular fluid. The impedance values at ideal measurement frequencies are predicted using a Cole-Cole plot. The capacitor changes the phase of the current that can be captured through modern electronics incorporated in most body impedance analysers. Knowledge of the capacitance (reactance) and resistance allows the measurement of body composition.

Total body water is distributed in the fat-free compartment of the body and the difference between fat-free body mass and body weight can be used to derive body fat. Accordingly, BIA is commonly used for estimating body composition, and in particular body fat. However, a National Institutes of Health technology assessment conference concluded that BIA does not measure fat mass, hence it has limited value (Ellis et al., 1999). Furthermore, fat-free mass estimates appear acceptable only when the fluid status is normal (Ellis et al., 1999).

Types of BIA devices

Single-frequency BIA, generally performed at 50 kHz is a weighted sum of extracellular water and intracellular water resistivities. On the other hand, multifrequency BIA uses different frequencies (0, 1, 5, 50, 100, 200, and 500 kHz) to evaluate distribution of water within and outside cells. Poor reproducibility has been noted at frequencies below 5 and above 200 kHz. Segmental BIA is performed by either placing two additional electrodes on wrist and foot on the opposite side, or by placing sensor electrodes on wrist and shoulder and upper iliac spine and ankle with sensor electrodes on the wrist and ankle. The placement and type of electrodes is an important consideration. It is proposed that the trunk of the body with its large cross-sectional area contributes 10% of the body impedance but represents half the body mass. Thus, even large changes in fluid volume within the abdominal cavity have minor influence on the measured resistance. On the other hand, change in impedance are closely related to changes in muscle mass of the limbs.

Interpretation of BIA

The bioimpedance vector analysis (BIVA) plots the reactance (Xc) standardized for height to the resistance (R) standardized for height to yield the RXC plot. Popularized by Piccoli, the impedance vector with a phase angle can be directly visualized on the RXC plot with confidence ellipses derived from gender and age-matched populations. It is proposed that displacement of the vector indicates the state of volume and nutrition.

Impedance through a tissue can be influenced by its state of electrolytes, hydration, and mass. Several other variables can influence the assessment of body composition including placement of electrodes, posture, volume depletion, moderate or high-intensity exercise, and consumption of a meal.

A survey of 1590 men and 1491 women undergoing haemodialysis for 3 months or more was performed to describe the BIA characteristics using a single-frequency BIA analyser (RJL systems) (Chertow et al., 1997). Among men, the median resistance was 458 ohms (interquartile range (IQR) 408–513, 5th percentile 344, 95th percentile 616); the median reactance was 39 ohms (IQR 32–48, 5th percentile 24, 95th percentile 65); the median phase angle was 5.16 degrees (IQR 4.01–5.73, 5th percentile 2.86, 95th percentile 8.02). Among women, the median resistance was 528 ohms (IQR 463–599, 5th percentile 380, 95th percentile 718); the median reactance was 38 ohms (IQR 31–48, 5th percentile 22, 95th percentile 67); the median phase angle was 4.01 degrees (IQR 3.44–5.16, 5th percentile 2.29, 95th percentile 7.45). Total body water decreased 0.92 kg/10-year increase and was greater in men compared to women. Likewise, body cell mass decreased 0.81 kg/10-year increase.

A cross-sectional study among 10 haemodialysis patients and five peritoneal dialysis patients evaluated the change in total body water assessed by BIA with the change in weight during dialysis (Kurtin et al., 1990). A poor relationship was found. Among 200 adult continuous ambulatory peritoneal dialysis patients studied cross-sectionally, BIVA plots revealed differences in R/H and Xc/H among oedematous and non-oedematous patients (Piccoli, 2004). Among 77 renal transplant patients, total body water was measured by deuterium and extracellular water by bromide space (van den Ham et al., 1999). Multifrequency BIA underestimated total body water by 0.7 L and extracellular water by 3.3 L. The standard deviation of the difference between methods for total body water was 2.1 L and for extracellular fluid volume was 1.8 L. Thus, large prediction errors are likely with individual estimations.

Wabel et al. measured body composition through body impedance analysis and pre-dialysis systolic BP among 500 patients from eight dialysis centres in Europe (Wabel et al., 2008). The

joint consideration of volume state and BP may provide a useful tool to classify patients in terms of volume-sensitive and volume-resistant hypertension. One-third of the patients had normal BP and normal fluid status by the definitions used by the authors. Hypertension and volume expansion was found in 15%, hypertension without volume expansion in 13% and normotension with volume expansion in 10%. The remaining had reasonably controlled BP and volume state. Volume expansion in follow-up of a cohort of 269 patients found expanded extracellular fluid volume to be associated with increased mortality (Wizemann et al., 2009).

Relative plasma volume monitoring

RPV monitoring utilizes photo-optical technology to non-invasively measure absolute haematocrit through a transparent chamber affixed to the arterial end of the dialyser. The assumption underlying this technology is that in the absence of blood loss and uniform mixing of blood, the rise in haematocrit is proportional to the amount of fluid withdrawn during the dialysis procedure. Accordingly, percentage blood volume change during the dialysis procedure can be calculated in real time. RPV slope then is a function of ultrafiltration rate and the plasma refill rate. Patients who are 'wet' have large interstitial fluid volumes and therefore a high plasma refill rate; their RPV slope will be flat. Patients with a low plasma refill rate will have steeper slopes and are more likely to be at their 'dry weight'. Prospective, randomized trials suggest that relative blood volume-controlled dialysis can improve pre-dialysis BP, reduce the frequency of intradialytic hypotension, as well as reduce cardiothoracic ratio (Dasselaar et al., 2007).

In the Dry-weight Reduction In hypertensive hemodialysis Patients (DRIP) trial (discussed later in the chapter), RPV monitoring was performed in all patients at the beginning and end of the study (Sinha et al., 2010). RPV slopes were defined as flat when they were less than the median (1.33% per hour) at the baseline visit. The study found that flat RPV slopes may indicate a volume-overloaded state. This is because of the following four reasons: (1) probing dry weight in these patients leads to steeper slopes; (2) those with flatter slopes at baseline have greater weight loss; (3) both baseline RPV slopes and the intensity of weight loss are important for subsequent change in RPV slopes; and, most importantly, (4) RPV slopes predict the subsequent reduction in interdialytic ambulatory systolic BP; those with the flattest slopes have the greatest decline in BP on probing dry weight. Thus, RPV slope monitoring may be useful to assess dry weight among hypertensive haemodialysis patients. RPV monitoring, combined with clinical assessment of intradialytic hypovolaemia, and post-dialytic fatigue, can help assess patient dry weight and optimize volume status while reducing dialysis-associated morbidity (Rodriguez et al., 2005). Several studies in hypertensive paediatric haemodialysis patients have successfully utilized RPV monitoring to improve BP control (Patel et al., 2007; Candan et al., 2009).

A multi-centre randomized trial, the Crit-Line Intradialytic Monitoring Benefit (CLIMB) study, tested the notion whether RPV-guided therapy can improve outcomes (Reddan et al., 2005). Contrary to expectations, the trial demonstrated that RPV-guided therapy was associated with worse outcomes. The trial randomized 227 haemodialysis patients to RPV monitoring and 216 to conventional monitoring for 6 months to test the hypothesis that RPV-guided monitoring would mitigate hospitalization rates. Hospitalization occurred 1.53 times per year in the RPV-guided monitoring group and 1.03 times per year in the conventional group. Mortality was 8.7% and 3.3% (P = 0.021) in the RPV-guided monitoring and conventional monitoring group respectively. An elaborate protocol was available to guide fluid management based on RPV-guided monitoring. The investigators state, 'algorithm use was encouraged but not mandated, in contrast to earlier studies. This design was intended to assess the therapeutic efficacy of Crit-Line in a trial that permitted voluntary nonuse of the information from the device …. Therefore, Crit-Line was studied as a voluntary adjunct to care.' Furthermore, they state, 'highly variable implementation of the monitoring and interventional algorithm occurred within and across dialysis units; the causes were not collected'. Uncertain adherence to the protocol by the investigators makes it difficult to conclude that RPV-guided monitoring was a cause of higher complication rates. In fact, at baseline, as determined by RPV slope patterns, patients in the conventional group were more volume overloaded compared to the RPV-guided group. At 6 months, both groups had similar RPV slopes. In other words, the conventional group appeared to have had greater volume challenge than the intervention group. Since this study appears to be more observational than interventional because of uncertain adherence to protocol, a more valid evaluation of this technology would have been to compare the RPV slope data as an association. No causal inference is possible from this trial.

Blood pressure monitoring

According to Guyton, chronic volume overload triggers a compensatory increase in systemic vascular resistance and hypertension (Guyton, et al. 1972). Thus, the presence of hypertension among dialysis patients strongly indicates volume excess. BP measured during dialysis is not very reliable in detecting the presence or absence of hypertension (Agarwal et al., 2006c, 2009c). On the other hand, out-of-office BP measurements serve as an excellent way to diagnose hypertension among dialysis patients (Drawz et al., 2012; Roberts et al., 2012).

Ambulatory BP measurement

Ambulatory BP monitoring allows the assessment of BP over the entire interdialytic interval. Measurements every 20–30 minutes are averaged allowing a more stable mean. Furthermore, the patterns of BP can be analysed. Ambulatory BP is predictive of both left ventricular hypertrophy (Agarwal et al., 2006b) and all-cause mortality (Alborzi et al., 2007; Agarwal, 2010). Furthermore, volume excess may confer a unique BP 'signature' that can be detected by analysing the pattern of BP change (Agarwal, 2009). Using 400 ambulatory BP recordings over 8 weeks, composed of 35,302 measurements among 145 patients participating in the DRIP randomized, controlled trial, the trended cosinor model was found to be the best descriptor of BP chronobiology (Agarwal, 2009). The trended cosinor model may be described as a pattern of sinusoidal oscillation around a straight line with an upward trend during the interdialytic period that has an intercept at the post-dialysis time. Augmented volume removal therapy reduced the intercept systolic BP and increased the rate of rise in systolic BP over the interdialytic interval but had no effect on the systolic BP fluctuation (amplitude). Thus, an elevated intercept and blunted slope pattern characterize the 'volume-overload BP pattern' on ambulatory BP monitoring. Similar changes were seen for diastolic BP.

Home BP monitoring

Home BP monitoring is a practical way to diagnose hypertension among dialysis patients. Systolic home BP of 150 mmHg or more has a sensitivity of 80% and specificity of 84% in diagnosing interdialytic ambulatory hypertension (Agarwal et al., 2006a). Home BP can accurately track changes in dry weight among dialysis patients (Agarwal et al., 2009b). Home BP also are similar to ambulatory BP in predicting both left ventricular hypertrophy (Agarwal et al., 2006b) and all-cause mortality (Alborzi et al., 2007; Agarwal, 2010). Due to the chronobiology of BP changes following dialysis, measurement of home BP twice daily following mid-week dialysis for 4 days is desirable to make an accurate diagnosis of hypertension (Agarwal and Light, 2009).

Intradialytic hypertension

The notion that intradialytic changes in BP reflect excess volume was tested in the post hoc analysis of the DRIP trial (Agarwal and Light, 2010). In this study, dry weight was probed in 100 prevalent haemodialysis patients; 50 patients who did not have their dry weight probed served as time controls. The slope of intradialytic BP over dialysis was calculated by the log of BP regressed over time. At baseline, intradialytic systolic and diastolic BP dropped at a rate of about 3%/hour ($P < 0.0001$). Over the course of the trial, compared to the control group, the slopes steepened in the ultrafiltration group for systolic but not diastolic BP. Those who lost the most post-dialysis weight from baseline to 4 weeks and baseline to 8 weeks also experienced the greatest steepening of slopes. Each percent per hour steepening of the intradialytic systolic BP slope was associated with a 0.71 mmHg (95% confidence interval (CI) 0.01–1.42, $P = 0.048$) reduction in interdialytic ambulatory systolic pressure. Thus, intradialytic BP changes appear to be associated with change in dry weight; among long-term haemodialysis patients, intradialytic hypertension may, thus, be a sign of volume overload

Echocardiographic assessment

Direct imaging of cardiac structures can provide an accurate tool to assess volume. Some more commonly imaged structures are reviewed further.

Inferior vena cava diameter

Certain echocardiographic parameters have been reported to assess volume among haemodialysis patients. Cheriex et al. in a small study of 18 haemodialysis patients first reported the usefulness of IVC diameter and its collapse with inspiration as a marker of volume (Cheriex et al., 1989). A good relationship was found both between IVC diameter and right atrial pressure and between collapse index and right atrial pressure; the right atrial pressure was measured invasively. However, the collapse index was found not to correlate with changes in blood volume. These results were confirmed by Agarwal et al. in the context of a larger randomized trial (Agarwal et al., 2011a). The endpoint was not right atrial pressure but the relationship of reduction in IVC diameter and interdialytic ambulatory BP.

Not all studies have given such encouraging results. For example, Katzarski et al. suggest that IVC diameter measured at the end of dialysis or shortly thereafter gives a misleading indication of volume overload in these patients (Katzarski et al., 1997). Among children on chronic haemodialysis, IVC diameter also did not vary significantly after changing dry weight (Krause et al., 2001). Another problem with the use of IVC diameter is that there is no uniform definition of the threshold used to classify patients into hypovolaemic, euvolaemic, or hypervolaemic groups. For example, depending on the criterion used, before dialysis, hypovolaemia was found in an astounding 39–47% of the patients (Brennan et al., 2006). An additional 21–25% were euvolaemic before dialysis despite being above dry weight. Thus, further evaluation is needed before this test can be become mainstream in the determining dry weight.

Left atrial diameter

Left atrial diameter is a part of routine echocardiographic evaluation that is volume responsive (Agarwal et al., 2011a). Thus, this measurement can be easily used among patients who do have other reasons to have left atrial enlargement such as mitral regurgitation. Furthermore, left atrial volume has been reported to be a correlate of fatal and non-fatal cardiovascular events among haemodialysis patients (Tripepi et al., 2007). Hepatic vein Doppler evaluation can also assess right atrial pressure but has been found to be of value to determine dry weight. One reason for this may be the technical difficulty associated with its measurement especially in the post-dialysis state where the hepatic veins may be so collapsed that they are hard to visualize.

In the DRIP trial, both IVC diameter and left atrial diameter were responsive to volume (Agarwal et al., 2011a). However, improvement in volaemia as judged by these structures was not predictive of improvement in interdialytic ambulatory BP. In other words, although indicative of volume excess, neither of these parameters could accurately predict BP response to probing dry weight.

Lung comets

The 'comet-tail' sign is detectable with lung ultrasound in which wedge-shaped comet-tails fan out from the lung surface (Jambrik et al., 2004). It is thought that fluid-thickened interlobular septa similar to Kerley B lines are the precursor of this sign. Accordingly, the test is an assessment of extravascular lung water. Zoccali et al. (2013) followed 392 haemodialysis patients and detected moderate-to-severe lung congestion in 45% and very severe congestion in 14% of the patients. Among those patients with moderate-to-severe lung congestion, 71% were asymptomatic or presented slight symptoms of heart failure. Compared with those patients having mild or no congestion, patients with very severe congestion had a 4.2-fold risk of death and a 3.2-fold risk of cardiac events adjusted for New York Heart Association class and other risk factors. Including the degree of pulmonary congestion in the model significantly improved the risk reclassification for cardiac events by 10% ($P < 0.015$). Randomized trials are planned to evaluate this non-invasive sign to detect and treat patients with volume excess.

Establishing the diagnostic utility of volume markers

From the above review it is clear that we do not have any tool for the day-to-day management of dry weight for dialysis patients. This is because no single test has all diagnostic parameters established. For example, knowledge of the following parameters for any test would be desirable: the range of normality, the prevalence and determinants (e.g. age, sex, race, and co-morbidities) of hypervolaemia using this range of normality, short-term and long-term variability

in volume over time and its determinants, the independent prognostic value of the test, and finally whether targeting a normal test result can alleviate symptoms associated with hypovolaemia or hypervolaemia and improve long-term volume-related outcomes.

Management of hypervolaemia

Among dialysis patients, the reduction of volume can be facilitated when interdialytic weight gain is limited through limitation of dietary or dialysate sodium intake. However, to reduce volume, probing dry weight is required. Simply limiting sodium intake without probing dry weight is unlikely to improve the volume state.

Dietary sodium intake

Dietary sodium restriction limits interdialytic weight gain and improves the feasibility of achieving dry weight (Krautzig et al., 1998; Kooman et al., 2003). Although no randomized trials have been performed among patients with end-stage renal disease (ESRD), observational studies among long-term haemodialysis patients suggest that the combined strategy of restricting dietary sodium and achieving dry weight can improve left ventricular hypertrophy (Ozkahya et al., 2002).

Recent guidelines suggest that the elderly and those with chronic kidney disease are most likely to derive the greatest benefits of dietary sodium restriction (Bibbins-Domingo et al., 2010). These guidelines are even stricter on sodium intake than those advocated earlier (2 g/day). Dietary sodium restriction to no more than 1.5 g sodium (or about 65 mmol) per day is now recommended. Implementing such severe sodium restriction will require substantial education and training of dialysis patients and without participation of trained dieticians and periodic monitoring is unlikely to be successful.

Instead of restricting dietary sodium, patients on haemodialysis are sometimes prescribed fluid-restricted diets. With the exception of treating hyponatraemia, there is no scientific basis for prescribing a fluid-restricted diet in these patients (Tomson, 2001).

Although dietary sodium intake remains a common cause of excess volume accumulation, an often overlooked source of sodium loading among haemodialysis patients is through the prescription of dialysate sodium.

Dialysate sodium reduction

Short dialysis treatment sessions provoke haemodynamic instability; hypertonic dialysate is often prescribed to stabilize the haemodynamics. However, the prescription of hypertonic dialysate provokes thirst and therefore interdialytic weight gain (Barre et al., 1988). This may trigger the need for increased fluid volume removal, haemodynamic instability, and prescription of even higher dialysate sodium (Flanigan, 2004). Reducing interdialytic weight gain will require a lower ultrafiltration rate to facilitate that achievement of post-dialysis weight. A lower ultrafiltration rate may make the dialysis therapy more comfortable (Munoz et al., 2011).

Sodium ramping is associated with fewer hypotensive episodes on dialysis but greater interdialytic fatigue and thirst, greater interdialytic weight gain and hypertension (Sang et al., 1997). Interdialytic 24-hour ambulatory BP increased with time averaged concentration of sodium was extremely elevated at 147 mEq/dL (Song et al., 2002).

Some studies show that the prescription of high dialysate sodium in some patients leads to worsening of BP control (Cybulsky et al., 1985). Individualizing dialysate sodium concentration (Santos et al., 2008) may improve BP control (de Paula et al., 2004). In a pilot non-randomized study of 16 patients, dialysate sodium at end dialysis was decreased in four phases from 137.8 mmol to 135.6 mmol (Manlucu et al., 2010). As a result of this manoeuvre, the net sodium loss increased nearly 100 mmol from 383 to 480 mmol; this also reduced interdialytic weight gain and BP (Manlucu et al., 2010). This proof-of-concept study suggests that facilitating diffusive sodium losses through reducing dialysate sodium can increase net sodium removal and therefore hypertension control. Therefore, one sodium prescription may not fit all patients.

In a non-randomized trial, improvement in nocturnal mean arterial pressure was found among patients who were prescribed a low dialysate sodium (Davies et al., 2009). However, if the low dialysate sodium was not accompanied by reduction in dry weight, BP did not change. Simply prescribing low dialysate sodium without altering dry weight may not improve BP control. On the other hand, BP increments provoked by higher sodium dialysate can be adequately controlled by adjustment of dry weight (Stewart and Fleming, 1974).

Probing dry weight

The management of dry weight poses several challenges. First and foremost, there is no universally agreed upon definition of dry weight. Several definitions have been proposed.

Definition of dry weight: history of the concept

The concept of dry weight was proposed in the early years of dialysis (Thomson et al., 1967). The evolution of this definition is reviewed.

In 1967, Thomson and colleagues defined dry weight as reduction of BP to hypotensive levels during ultrafiltration and unassociated with other obvious causes (Thomson et al., 1967). Whereas this definition may have worked in the early years of dialysis when a low-salt diet was the rule, the hypotensive dialysis patient was often the one with high interdialytic weight gain, hypertension, and left ventricular hypertrophy. Such a patient is quite likely to be volume overloaded.

In 1980, dry weight was defined by Henderson as the weight obtained at the conclusion of a regular dialysis treatment below which the patient more often than not will become symptomatic and go into shock. This definition does not take into account that high interdialytic weight gain and poor ventricular compliance may not lead to an adequate volume removal during dialysis and leave the patient hypervolaemic. Such a volume overloaded patient may still go into shock if a bit more volume is removed. Yet such a patient is volume overloaded.

In 1996, dry weight was defined by Charra and colleagues as the body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis despite the retention of saline and ideally without the use of antihypertensive medications (Charra et al., 1996). This definition was an important evolution since it focused on the achievement of normotension rather than precipitating shock.

In 2008, Raimann et al. proposed a definition of dry weight defined by continuous calf BIA during dialysis. They defined dry weight as a flattening of the baseline/instantaneous impedance ratio curve for at least 20 minutes in the presence of ongoing

ultrafiltration. This definition in departure from the prior ones did not consider measureable surrogates of volume such as normotension or shock. Instead, the as yet incompletely validated measure of volume was used.

In 2009, Sinha and Agarwal proposed a definition that combined subjective and objective measurements (Sinha and Agarwal, 2009). According to this definition, dry weight is defined as the lowest tolerated post dialysis weight achieved via gradual change in post-dialysis weight at which there are minimal signs or symptoms of either hypovolaemia or hypervolaemia. The definition requires probing the dry weight and therefore cannot be established cross-sectionally.

The technique for probing dry weight

According to the newest definition of dry weight noted in the previous section, probing is the current gold standard which defines dry weight. Briefly, dry weight is the lowest tolerated post-dialysis weight achieved via gradual change in post-dialysis weight at which there are minimal signs or symptoms of either hypovolaemia or hypervolaemia. The assessment and achievement of dry weight is an iterative process that often provokes uncomfortable intradialytic symptoms such as hypotension, dizziness, cramps, nausea, and vomiting. These symptoms often lead to interventions such as cessation of ultrafiltration, administration of saline, the premature cessation of dialysis, or placing the patient in the head-down (Trendelenburg) position. Interestingly, placing the patient in the head-down position does little to protect the BP (Bridges and Jarquin-Valdivia, 2005); whereas raising the leg passively without lowering the head can be effective in raising ventricular filling pressure (Monnet and Teboul, 2008). Often physicians will respond to these distressing symptoms by raising dry weight, which may result in the necessity of adding more antihypertensive medication. Paradoxically, this may make subsequent achievement of dry weight even more difficult. However, strategies to gently reduce target weight by setting the ultrafiltration goal slightly above the post-dialysis weight from the previous treatment (by ~ 0.2–0.3 kg in an adult) optimally by prolonging the dialysis time to allow for slower ultrafiltration then dry weight can often be successfully achieved without troublesome symptoms

Effect of probing dry weight on BP

To test the hypothesis that hypertension among haemodialysis patients who do not manifest overt signs of volume overload is mediated by excess volume, dry weight was probed without changing the dialysis time in the only randomized controlled trial to date among hypertensive haemodialysis patients (Agarwal et al., 2009a). Notably, in this study, patients with obvious volume overload were excluded. Interdialytic ambulatory BP monitoring was performed at baseline, 4 weeks, and 8 weeks among 50 patients randomized to a control group and 100 patients randomized to the ultrafiltration group. In the intervention group, ambulatory BP was reduced within 4 weeks by 11/6 mmHg (Agarwal et al., 2009a). This level of BP reduction was achieved despite stable concurrent use of 2.7 antihypertensive drugs. The magnitude of reduction in BP was therefore much larger than what would be expected by adding an additional antihypertensive agent. Since the control group had a placebo effect, a correction for this effect was made. Even after this correction, ambulatory BP reduction was significantly reduced from baseline by 7/3 mmHg within 4 weeks. This antihypertensive effect was sustained for 8 weeks of the trial. Despite provoking occasional uncomfortable intradialytic symptoms, the quality of life was not impaired. Even in this randomized trial, the presence or absence of oedema, a physical sign deemed to be a reliable sign of volume overload, had no predictive value in separating the responders from non-responders. Furthermore, 10% of the patients in the control group developed accelerated hypertension defined as BP ≥ 175/105 mmHg by interdialytic ambulatory monitoring. This study provides strong support for the hypothesis that among haemodialysis patients, probing dry weight is an effective strategy for reducing BP.

Observational studies also support the practice of probing dry weight. In 1969, Vertes et al. reported that 35 of 40 patients became normotensive by achieving dry weight (Vertes et al., 1969). In a more recent report from Turkey, Kayikcioglu et al. compared the benefit of non-pharmacologic to pharmacologic therapy for control of left ventricular mass among haemodialysis patients (Kayikcioglu et al., 2009). In a case–control study, patients who had been treated at one centre with salt restriction and dry-weight reduction were compared to patients at another centre where antihypertensive-based therapy was the primary method for management of hypertension. The centre using dry weight and salt restriction as a primary strategy had the following benefits: lower antihypertensive drug use (7% vs 42%), lower interdialytic weight gain, lower left ventricular mass, better diastolic and systolic left ventricular function, and fewer episodes of intradialytic hypotension. These observations are important and of clinical relevance; they suggest that probing for dry weight as opposed to adding more antihypertensive drugs perhaps diminishes the risk for cardiac remodelling and mitigates left ventricular hypertrophy and preserves systolic and diastolic left ventricular function. Although a case–control study cannot assert causation, the results of this study support the use of non-pharmacologic therapies in the management of patients with ESRD.

Importance of the duration of dialysis

Dry weight is difficult to achieve when interdialytic weight gains are excessive and/or dialysis duration is short. The European Best Practice Guidelines recommend that dialysis should be delivered at least three times a week and the total duration should be at least 12 hours per week, unless substantial residual renal function is present (Tattersall et al., 2007). An increase in treatment time or frequency or both should be considered in patients who experience haemodynamic instability or remain hypertensive despite maximal possible fluid removal.

In the United States, a recent study reported that the average duration of dialysis among 32,065 participants in the ESRD Clinical Performance Measures Project was 217 minutes (Foley et al., 2011). The IQR was 195–240 minutes. This means that one-quarter of the patients were receiving < 3 hours and 15 minutes of dialysis and only one-quarter of the patients were receiving > 4 hours of dialysis.

Although the adequacy of dialysis is still debated, it is clear that patients who shorten treatment have hypertension that is more difficult to control (Chazot et al., 1995). Patients that are dialysed for 8 hours three times a week have excellent BP control, minimal requirement for antihypertensive drugs, and excellent long-term survival (Charra et al., 1992; Chazot et al., 1995). In a randomized cross-over trial of 38 patients, the effects of 4 hours versus 5 hours of dialysis were evaluated (Brunet et al., 1996). Haemodynamic stability and hypotensive episodes were fewer with longer dialysis

especially among older patients (> 65 years old). However, these data are difficult to generalize since treatment was evaluated only over 2 weeks and those requiring > 4 L ultrafiltration were excluded. Longer or more frequent dialysis sessions, in general, are associated with less haemodynamic instability, better achievement of post-dialysis weight, better control of BP, and the reduced need for antihypertensive drugs. These are discussed further in the next section, 'Frequent dialysis and its effect on blood pressure'.

Frequent dialysis and its effect on BP

Observational studies suggest that conversion of patients from thrice-weekly conventional dialysis to nocturnal dialysis may improve BP and left ventricular mass (Chan et al., 2002). In a cumulative analysis of 72 patients from nine centres it was noted that pre-dialysis systolic and diastolic BP falls within 1 month of dialysis by 13/7 mmHg from 163/94 mmHg (Woods et al., 1999). This reduction was accompanied by a 1% decline in post-dialysis weight. Although BP did not change after 1 month, the number of antihypertensive agents declined significantly. At baseline, 46% were taking antihypertensive drugs whereas at 12 months after switching to daily dialysis, only 25% were taking antihypertensive agents.

Several observations have suggested improvements in BP and left ventricular mass among patients undergoing more frequent dialysis. For example, Chan et l. reported an improvement in both systolic and diastolic BP, reduction in antihypertensive drugs and doses, and reduction in left ventricular mass in patients undergoing nocturnal dialysis (Chan et al., 2002). This group has also reported an improvement in pharyngeal size among nocturnally dialysed patients (Beecroft et al., 2008). This may improve airflow through the upper airway, relieve obstructive sleep apnoea, and consequently ambulatory BP. Another mechanism of BP reduction with long-duration dialysis is suggested to be an improvement in arterial compliance and consequent improvement in baroreflex sensitivity (Chan et al., 2005). Others may be better volume and toxin removal (Saad et al., 2004). In a small study, both systolic and diastolic BP improved with six times per week compared to thrice-weekly dialysis, whether they were recorded pre-dialysis or post-dialysis. The number of medications and pre-dialysis and post-dialysis weight remained unchanged. Intradialytic symptoms commonly attributed to volume shifts also improved. A randomized two-period crossover study compared the effect of short daily haemodialysis versus standard haemodialysis on BP and left ventricular mass index among 12 hypertensive patients with ESRD (Fagugli et al., 2001). At the end of 6 months of standard haemodialysis and 6 months of daily dialysis, 24-hour ambulatory BP monitoring, echocardiography, and BIA were performed. Interdialytic ambulatory BP declined by 20/6 mmHg with daily dialysis. The decrease in BP was accompanied by the withdrawal of antihypertensive therapy in seven of eight patients during daily dialysis. Left ventricular mass index decreased by 28.6 g/m^2 from 148.7 g/m^2. Extracellular water content decreased 5.1% from 52.7% and correlated with 24-hour improvements in left ventricular mass index and systolic BP.

A randomized controlled trial assigned 52 haemodialysis patients to either frequent dialysis, 6 nights per week, or conventional thrice-weekly treatment. In the frequent dialysis group, improvement was seen in cardiac magnetic resonance imaged left ventricular mass and reduction in the need for BP medications (Culleton et al., 2007).

The Frequent Hemodialysis Network (FHN) study randomized haemodialysis patients to either conventional thrice-weekly dialysis or more frequent in-centre dialysis; the primary endpoint was an improvement in both left ventricular hypertrophy and physical health composite. The primary endpoint was met but perhaps the most notable finding was an improvement in systolic BP, reduction in antihypertensive drug use, and improvement in left ventricular mass (Chertow et al., 2010). These findings suggest better achievement of dry weight in these patients (Agarwal, 2011). Increasing the treatment duration may improve haemodynamic stability of dialysis and make the procedure more tolerable but is not a requirement for improvement in left ventricular mass. Shortening the procedure to tailor dialysis to a minimum Kt/V may provoke intradialytic symptoms, post-dialysis fatigue, and non-adherence to therapy; thus this is not recommended (Twardowski, 2007). Normotension can be achieved independently of the duration of dialysis if the control of volume is adequate (Katzarski et al., 1999). In fact, left ventricular mass index was also improved to a comparable degree in the DRIP trial participants where the duration of dialysis was not altered but the dry weight was aggressively challenged (Agarwal et al., 2011b).

Potential benefits of probing dry weight

Studies among haemodialysis patients in both adults and children suggest that managing intradialytic RPV may reduce the number of hospital admissions due to fluid overload (Goldstein et al., 2003; Rodriguez et al., 2005), improve BP control, and decrease hypotension-associated dialysis symptoms (Patel et al., 2007). It is possible that the latter benefit is, in part, related to diminished use of antihypertensive medication. Accordingly, monthly monitoring of RPV and home BP may offer an attractive way to assess the adequacy of volume control among haemodialysis patients.

To study the effect of volume status on mortality, Wizeman et al. followed 269 prevalent haemodialysis patients for several years (Wizeman et al., 2009). They measured volume state using a body composition analyser. If there was > 15% excess of extracellular fluid volume (2.5 L volume excess), they classified such patients as volume overloaded; 25% of the patients had excess extracellular fluid volume. In a multivariate adjusted analysis, they found that excess volume was associated with a higher mortality. Compared to those without excess extracellular fluid volume, the hazard ratio of mortality with excess fluid volume was 2.1 ($P = 0.003$). Although the study did not examine reduction in extracellular fluid volume on subsequent outcomes, such studies need to be performed in the future. Also, it is unclear whether targeting normovolaemia in an interventional study can improve outcomes.

Inrig et al. compared the change in pulse pressure during dialysis as a risk factor for hospitalization and mortality among prevalent haemodialysis patients participating in a randomized controlled trial (Inrig et al., 2009). They found that patients who had the least change in pulse pressure from before to after dialysis had clinical characteristics indicating volume overload. Among these patients, lowering of the pulse pressure from before to after dialysis was associated with lower hospitalization and mortality outcomes. Since pulse pressure is largely driven by systolic BP, it is likely that lowering of pulse pressure with dialysis reflects more volume loss, a lower extracellular fluid volume state, and this may provide better cardiovascular outcomes, perhaps through less pressure/volume stress on the heart. Given that this is the only study of its kind, at present it is unclear if pulse pressure reduction with dialysis can

be used as a surrogate of volaemia. Further research is needed to establish a cause-and-effect relationship.

Potential risks of probing dry weight

There are potential hazards related to probing dry weight, none of which have been adequately examined. These include the following: (1) increased risk of clotted angioaccess, (2) increased rate of attrition in residual renal function, and (3) complications related to interdialytic hypotension. Intradialytic hypotension, besides requiring more nursing interventions, can be complicated by cerebral hypoperfusion, seizures, myocardial dysfunction, and mesenteric ischaemia. Furthermore, it has been associated with mortality (Shoji et al., 2004). Thus the relative risks and benefits of probing dry weight need to be examined in long-term randomized trials.

Summary

In summary, the assessment of volume among dialysis patients remains more of an art; it remains an imperfect science. Whereas hypovolaemia can be uncomfortable (e.g. cramping, dizziness, and syncope during dialysis) and occasionally have more sinister consequences (access thrombosis, occult myocardial dysfunction), hypervolaemia if left unrecognized can lead to recurrent hospitalization for heart failure, progressive myocardial dysfunction, and death. Accordingly, at least a proportion of hospitalizations for heart failure can be avoided with management of dry weight. The DRIP trial has demonstrated that probing dry weight can improve ambulatory BP. Future studies should assess whether this strategy can also reduce the morbidity and mortality associated with hypervolaemia among dialysis patients.

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CHAPTER 274

Nutritional screening and nutritional management in dialysis patients

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Introduction

Patients with chronic kidney disease (CKD), mainly those undergoing dialysis, are prone to the development of nutritional disturbances, collectively termed as the protein-energy wasting (PEW) syndrome. The prevalence of PEW ranges from 18% to 80% in dialysis patients depending on the characteristics of the population studied (i.e. CKD stage, dialysis modality, presence of comorbidities, and ethnicity) and on the method applied for diagnosis of PEW. Regardless of the factors influencing this high prevalence, PEW invariably associates with increased rates of morbidity and mortality, being one of the strongest risk factors for adverse outcomes (Kalantar-Zadeh et al., 2011). In the pathophysiology of PEW, a number of factors lead to increased protein catabolism and increased energy expenditure, while patients often have a concomitant decrease in energy and nutrient intake (Mak et al., 2011). Due to the multifactorial nature of PEW (Fig. 274.1), the treatment of this condition requires a multifaceted approach, combining clinical, nutritional, and pharmacological strategies (Mak et al., 2011).

By contrast, overweight and obesity are also frequent nutritional disturbances in CKD patients, which, as opposed to PEW, are not a consequence of uraemia but a consequence of overnutrition, a major problem in the general population and an important risk factor for developing metabolic syndrome, cardiovascular disease (CVD), and also CKD. It has been estimated that 20–60% of CKD patients have a body mass index (BMI) ≥ 25 kg/m^2 (Iglesias and Diez, 2010) with a substantial increase in this proportion prognosticated for the next decade (Kramer et al., 2006). Obesity has been found by some authors to represent a survival advantage in late CKD stages (Kalantar-Zadeh et al., 2003, 2006). The interpretation of this apparent paradox has to do with the overwhelming effect of PEW on the short-term mortality risk. Although overweight patients are thought to be less likely to suffer from PEW, it can be speculated that dialysis patients with PEW will die of causes that are related to the short-term consequences of PEW and do not live long enough to die of cardiovascular and metabolic complications related to overweight. In the case of obesity, a confounded protection is probably observed because the patients have larger energy stores to resist the severe wasting syndrome (Beddhu et al., 2003). Finally, it should be acknowledged that a considerable portion of obese dialysis patients show signs of muscle wasting, that is, obese sarcopenia (Honda et al., 2007). With the contradiction regarding the role of obesity on adverse outcome, clinicians dealing with dialysed patients do get a mixed message about how to best treat this specific population.

Nutritional assessment of dialysed patients

Ideally, a nutritional marker should not only predict outcome, but also identify patients at nutritional risk, be sensible enough to evaluate the impact of a nutritional intervention, and detect longitudinal changes. In addition, in order to ascertain high applicability in the routine care, other desirable characteristics include low cost, high reproducibility, and the use of instruments that can be easily applied bedside. Currently there is no single method that combines all the above characteristics and provides complete and unambiguous assessment of the nutritional status of dialysed patients. This is due to specific conditions related to the disease and/or to the dialysis treatment per se such as fluid retention, bone osteodystrophy, and chronic inflammatory conditions that can interfere with some of the methods used for assessment of nutritional status. With this in mind, the assessment of the nutritional status of dialysed patients should include a combination of methods that evaluate body composition, laboratory parameters, food intake, and composite indices of nutritional status, in order to guarantee a precise nutritional diagnosis in a given patient (Fouque et al., 2007).

Body composition assessment

Monitoring body composition is an important tool for nutritional screening. The method of choice for the assessment of body composition depends on the body compartment to be measured, for example, *water* (total, intra-, and extracellular), *fat* (total and regional fat stores, such as subcutaneous or abdominal fat), *bone* or *lean body mass* or *muscle*, and on the reasons why nutritional assessment is performed (research or clinical practice).

Methods for assessing body composition can be classified by their applicability. In general, methods with high applicability such as anthropometry, bioimpedance analysis (BIA), and near

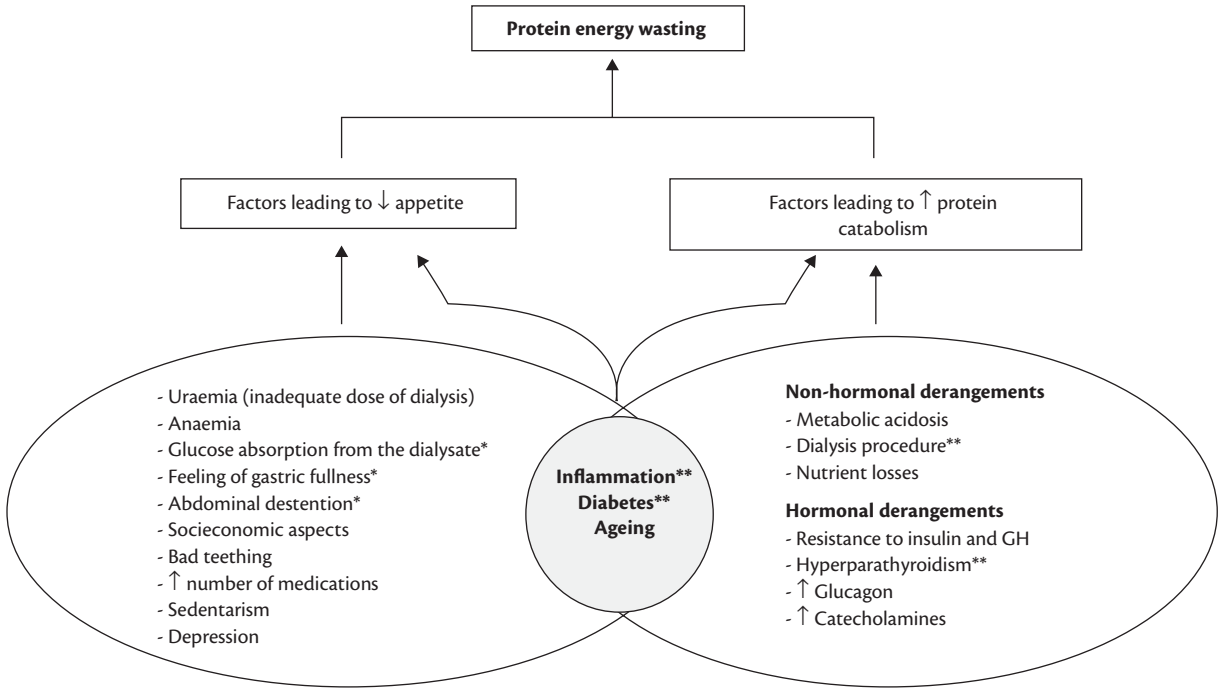

Fig. 274.1 Causes of protein energy wasting in dialysed patients. GH = growth hormone; PTH = parathyroid hormone. * For patients on peritoneal dialysis. ** Factors associated with increased resting energy expenditure.

infrared interactance, have relatively low precision. On the other hand, a more precise assessment in general requires more sophisticated methods with low applicability, due to high costs, complexity, and unavailability. Examples include computed tomography, nuclear magnetic resonance, hydrodensitometry, neutron activation analysis, isotopic dilution, and total potassium counting. Dual-energy X-ray absorptiometry (DXA) has been considered as a method of intermediate applicability and has been largely used for research purposes (Ellis, 2000). Regardless of the applicability of a given method, all of them can be used to assess body composition, as long as we acknowledge their limitations and try to overcome them.

Anthropometry

Anthropometric measurements include body weight, height, skinfold thicknesses (triceps, biceps, subscapular, suprailiac) and circumferences (arm and waist). The equipment used for such measurements (weight scale balance, skinfold caliper, and non-stretchable metric tape) are simple, have low cost and could be applied bedside. With these measurements it is possible to monitor somatic protein stores, body fat (total and abdominal), and a rough assessment of body water. Because of these features, anthropometric measurements are highly applicable for both routine care and research purposes. In order to increase the precision of anthropometric measurements, it is important to provide continuous training for those performing the measurements. In addition, for patients on haemodialysis (HD), the measurements should be performed after the dialysis session and for those on peritoneal dialysis (PD), it is desirable to perform these measurements with an empty abdominal cavity, in particular when assessing body weight and waist circumference (WC). To diminish intra-observer variation the same observer should perform longitudinal measurements.

Bioelectrical impedance

The method of BIA has the advantage that it can be readily performed, and, in addition, BIA is less dependent on the skills of the person performing the examination. By measuring body *resistance* (opposition offered by the body to the flow of an alternating electrical current) and *reactance* (capacitance properties of the cell membrane depending on its integrity, function, and composition), BIA provides measurements of body water (total, extra-, and intracellular), lean body mass, and body fat. The main principle for the assessment of body composition by BIA is its relationship with the body water content. Moreover, BIA relies on several static assumptions and dynamic relationships regarding electrical properties of the body, such as its composition and hydration status (Ellis, 2000). As the hydration status of dialysed patients is highly variable, the accuracy of BIA for assessing body composition can be subject to errors. Moreover, one should also consider that the BIA equipment use equations to assess the body compartments that may not be valid for dialysed patients. In order to diminish the errors coming from alterations in the hydration status, it is important to perform the BIA measurement approximately 30 minutes after the dialysis session, or for PD patients, with a dry abdominal cavity. Moreover, it is preferable to use BIA equipment based on equations that have been validated for dialysed patients.

Among the measurements coming from BIA, the *phase angle* may be especially important from a nutritional point of view. Phase angle is obtained from resistance and reactance, which are direct measurements of BIA. The biological and pathogenic meanings of phase angle are not completely understood, but it has been interpreted as an indicator of membrane integrity and water distribution between the intra- and extracellular spaces. Phase angle has also been used to predict body cell mass; for this reason, it is used

as a nutritional indicator in adults (Barbosa-Silva et al., 2005). In fact, studies in dialysed patients have shown that a low phase angle is highly associated with increased morbidity and mortality (Mushnick et al., 2003; Pupim et al., 2004). Although there is as yet no reference range for phase angle in dialysis patients, its longitudinal measurements should be encouraged, as decreasing values over time may signal increased risk of a poor nutritional status.

Dual-energy X-ray absorptiometry

DXA has been widely used in clinical research as a means of quantifying body composition. The underlying concept of DXA is that the photon attenuation *in vivo* is a function of tissue composition. It was first developed as a single photon absorptiometry to quantify appendicular bone mass. Later, it became available as DXA enabling the assessment of bone and soft tissue mass. DXA combines non-invasive assessment in a three-compartment body composition model (bone mineral content, lean body mass, and fat mass) with a high precision and low radiation dose. In addition, the body scanning is fast, taking 5–10 minutes. The attenuation coefficient for a scanned pixel depends on the relative amount of fat, lean tissue, and bone. Nevertheless, as two energy pixels cannot assess, directly, the three body compartments, some assumptions of the hydration distribution is taken into account (Ellis, 2000): DXA soft tissue analysis algorithms assume that 73.2% of lean body mass is water (Abrahamsen et al., 1996). This therefore leads to potential errors in patients with fluid retention, such as dialysis patients (Abrahamsen et al., 1996). For this reason, although DXA is considered a reference method for assessing body composition, results obtained in uraemic patients with gross imbalances in hydration status should be interpreted with caution, and, to reduce the influence of hydration status, DXA assessment should be performed in patients who have reached their so-called *dry body weight*.

An advantage of DXA is that it allows segmental measurements of the body (total, trunk, arms, and legs). This feature has been largely explored in clinical research for the assessment of truncal and total fat. However, the need of a trained operator, the large size of the equipment, and its high maintenance cost makes it difficult to use this method in the routine clinical care (Ellis, 2000).

Which method should be preferably used for clinical routine care in dialysed patients?

Anthropometry and BIA are methods that gather important characteristics for use in clinical practice. Both are relatively low cost, are portable, non-invasive, and are not cumbersome for the patient. In addition, they enable measurements of body fat, lean body mass, body water, and also of health indicators (i.e. phase angle from BIA), somatic protein, and visceral fat (i.e. mid-arm muscle circumference and WC, respectively, both from anthropometry). Although the precision of these methods for the assessment of body compartments can be questioned, they are useful tools in the clinical routine care. Whereas the assessment of total body fat by anthropometry, using measurements of skinfold thicknesses, may be preferable to BIA (Kamimura et al., 2003), BIA may be a better method for the assessment of lean body mass (Woodrow et al., 1996), and therefore, for a more thorough assessment of PEW. In very obese patient (e.g. BMI > 35 kg/m^2) both methods have equally low precision and, if possible, equations specific to this population should be used.

Another anthropometric measurement that deserves attention is *waist circumference* (WC). It can be easily measured as it requires only a non-stretchable metric tape and minimum collaboration from the patient. WC has been demonstrated to have high predictive value for tracing traditional and non-traditional CVD risk factors in non-dialysed CKD patients (Sanches et al., 2008) and also to predict all-cause and CVD-related mortality in dialysed patients (Postorino et al., 2009). Moreover, in non-dialysed CKD patients, WC showed a strong association with abdominal fat (visceral and subcutaneous fat) assessed by computed tomography (Sanches et al., 2008). However, its value as a means to assess changes in visceral and subcutaneous fat was questioned as there was a poor agreement between WC and computed tomography when assessing changes in abdominal fat (Velludo et al., 2010). Despite this limitation, assessment of WC should be encouraged, as besides its predictive values for CVD risk factors and outcome, it also enables the assessment of the *conicity index*, which is an easily obtained marker of fat distribution and abdominal fat deposition, which may be used as a predictor of clinical outcome in CKD (Cordeiro et al., 2010).

Altogether, anthropometry and BIA can be used to assess body composition in clinical practice. One should, however, consider the limitations of both methods. As mentioned before, the measurements should be performed with the patient being close to dry body weight (in case of BIA, measurements should be performed 30 minutes after the HD session) and by skilled and trained professionals in order to diminish measurement errors.

Handgrip strength

Decreased muscle mass is an important criterion for the presence of PEW. However, assessment of muscle mass in CKD patients can be hampered by limitations inherent to the body composition methods. Handgrip strength (HGS) with measurement of the maximal voluntary force of the hand and arm assessed by a dynamometer is a useful tool to assess muscle function (Silva et al., 2011). In addition, HGS has important advantages for use in clinical practice such as being a non-invasive, rapid, relatively objective (albeit subject to patient motivation and mental status), and inexpensive procedure. This technique has been used to predict mortality and complications in surgical patients (Bohannon, 2001) and in the elderly (Stalenhoef et al., 2002). Many studies have assessed HGS in dialysed patients and results show a high association between values coming from HGS and those from lean body mass assessed by DXA (Heimburger et al., 2000), as well with results obtained by composite methods to assess nutritional status, such as the subjective global assessment (SGA) (Carrero et al., 2008) and the malnutrition-inflammation index (MIS) (Silva et al., 2011). Similarly to phase angle, there are as yet no normal range values for HGS. Therefore, assessment of changes over time should be encouraged, with decreasing values signalling higher risk of PEW.

Biochemical parameters

Biochemical parameters can be routinely used to assess and monitor nutritional status in CKD patients. Biochemical parameters have the potential to be useful biomarkers in the sense that they are molecules that can be objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic interventions. An ideal biochemical marker to use in the clinic should be inexpensive, directly linked to the pathophysiological process that it represents, closely correlated to symptom severity, and be sensitive and specific. It is clear that biologically and even more so in the context

of the complex uraemic milieu, it will be highly difficult to reach such standards for any biomarker. Indeed, currently favoured biomarkers imperfectly reflect nutritional status in CKD, being influenced by systemic inflammation, and by the important role of the kidney in metabolizing circulating peptides, as well as by fluid status and losses of the biomarker in urine or dialysate. Thus, biochemical indicators of malnutrition should be studied in terms of temporal trends and as a whole, information provided by a single biomarker at a single time point, may be deceiving.

Serum albumin

Albumin constitutes about 60% of human plasma protein and has a relatively long half-life (~14–20 days). The amount of circulating serum *albumin* is determined by its synthesis, breakdown, and volume of distribution (Klein, 1990). In CKD patients, factors such as overhydration, proteinuria, and losses into the dialysate and urine may cause a decrease in plasma protein concentration. Counter-regulatory mechanisms may also influence the serum albumin concentration: whereas in the short term, protein deficiency decreases the rate of albumin synthesis (Kaysen et al., 2004), compensation in the long term may occur through a decrease in albumin breakdown and a shift of albumin from the extravascular to the intravascular space. As an acute-phase reactant, inflammation and inflammatory stimuli are also important factors affecting its production. For these reasons, the utility of serum albumin as a marker of malnutrition in dialysis patients has been questioned (Mak and Cheung, 2006).

Notwithstanding these limitations, measurement of serum albumin is a simple test, which is readily available in most clinical settings, and, as the PEW syndrome represents not only malnutrition but also inflammation, and other factors influencing the serum albumin concentration, such as fluid retention, albumin remains an outcome marker that reflects the severity of disease. In most countries, serum albumin is usually measured monthly to quarterly, making it an easily accessible biomarker. In addition, its actionability and responsiveness to nutritional interventions makes it a relevant index of health. Randomized controlled trials designed to improve nutritional status in CKD patients and with serum albumin as a surrogate outcome measure reported significant improvement in hypoalbuminaemia (Aguirre Galindo et al., 2003; Cano et al., 2007).

There is a strong association between hypoalbuminaemia (and albumin losses) and morbidity and mortality in CKD patients. A low serum albumin concentration is a strong predictor of poor outcomes in dialysis patients, also when compared to other risk factors, be it the traditional risk factors (hypertension, hypercholesterolaemia, diabetes, and obesity) or non-conventional ones (presence of anaemia, CKD-bone and mineral disorders, and even systemic inflammation) (Kalantar-Zadeh et al., 2011). In conclusion, serum albumin is a useful marker of morbidity and mortality in CKD patients, but one needs to be aware of the limitations of albumin as a marker of pure malnutrition. We therefore propose to evaluate temporal trends and to always combine serum albumin measurements with additional complementary markers of malnutrition in patient monitoring (see additional information in 'Setting up easy screening tools for nutritional status assessment').

Pre-albumin

Pre-albumin (also known as transthyretin which today is the preferred term), a transporter of thyroxine and retinol, is mainly synthesized in the liver, and a reduced protein intake is associated with a decline in its serum concentrations, which can be rather rapidly restored by re-feeding, due to its lower concentration and shorter half-life (2–3 days) (Chertow et al., 2000). However, serum transthyretin levels are also affected by inflammation (Ingenbleek et al., 1972). In CKD, reduced renal catabolism also contributes to altered serum transthyretin concentrations. Two recent studies showed that change in serum transthyretin over time is associated with changes in survival of dialysis patients (Cano et al., 2007; Rambod et al., 2008). Even if baseline serum transthyretin may not be superior to albumin in predicting mortality in HD patients, transthyretin concentrations < 20 mg/dL are associated with death risk even in normoalbuminaemic patients, and a fall in serum transthyretin over 6 months is independently associated with increased death risk (Rambod et al., 2008). In a trial by Cano et al. (2007), 186 malnourished HD patients were randomized to intradialytic parenteral nutrition (IDPN) versus no IDPN, while both arms received oral nutritional supplements. Despite apparently negative results for the IDPN, serum albumin and transthyretin levels increased in both groups under oral supplement therapy, and greater survival was observed at month 3 in those whose serum transthyretin increased by > 3 mg/dL (Cano et al., 2007). These data underline the plausible utility of serum transthyretin in the follow-up of patients during nutritional support.

Creatinine

The primary source of serum creatinine is skeletal muscle, and serum creatinine concentrations are elevated in individuals with greater muscle mass, independent of renal function (Macdonald et al., 2006). Serum creatinine level is a function of creatinine production and renal excretion, and therefore its association with kidney function may limit its utility as a marker of muscle mass in CKD patients not requiring dialysis (Keshaviah et al., 1994). However, in patients receiving long-term dialysis who have minimal or no residual renal function and who undergo a stable dialysis treatment regimen, time-averaged serum creatinine concentration is a more likely surrogate of muscle mass, and its changes over time may represent parallel changes in skeletal muscle mass (Macdonald et al., 2006). Low serum creatinine in this setting is a powerful risk factor for death, both in cross-sectional (Macdonald et al., 2006) and longitudinal (Kalantar-Zadeh et al., 2010) studies.

Creatinine kinetics is based on the principle that creatinine production is proportional to lean body mass, and the sum of creatinine excretion (urinary and dialytic) and metabolic degradation represents a simple and reliable tool for the assessment of protein nutritional status and muscle mass. In HD patients, creatinine kinetics can be easily coupled to urea kinetics modelling (Keshaviah et al., 1994). Indices derived from creatinine kinetics are strongly associated with the patient's nutritional status and are prognostic markers of mortality in HD patients. In HD patients, creatinine kinetics can be easily coupled to urea kinetics modelling allowing estimation of protein equivalent of nitrogen appearance (previously often called protein catabolic rate) and dietary protein intake (Keshaviah et al., 1994).

Assessment of energy and nutrient intake

Assessment of energy and nutrient intake with quantitative and qualitative information about the patient's usual diet enables monitoring of the dietary intake of energy, protein, phosphorous, potassium and fluid intake, which are all important to control in dialysis patients (Bross et al., 2010).

The methods applied to assess energy and nutrient intake include 24-hour food recalls, 3–7-day food records, and food questionnaires (Bross et al., 2010). The assessment of energy and protein intake by these methods has been shown to predict outcome (Kovesdy et al., 2010). In addition, particularly for the assessment of protein intake, the protein equivalent of nitrogen appearance (PNA) can also be used in dialysed patients. It relies on the principle that during steady-state conditions, nitrogen intake is equal to or slightly greater than total nitrogen appearance (National Kidney Foundation, 2000). Therefore, in the clinically stable patient, PNA can be used to estimate protein intake. As the estimation of protein intake by the PNA does not rely on reports from patients, PNA is theoretically subject to less error. However, this is based on the presence of neutral nitrogen balance; which means that in patients with concurrent catabolic illnesses, the PNA will be increased and will falsely indicate increased protein intake, whereas during periods of anabolism, PNA may underestimate protein intake. In addition, a single assessment of PNA may not be representative of the usual protein intake. Because protein intake is usually prescribed according to oedema-free body weight, PNA is commonly normalized by body weight, and known as normalized PNA (nPNA). The detailed equations for assessment PNA are described elsewhere (National Kidney Foundation, 2000).

Composite indices of nutritional status in CKD

The 7-point SGA and the MIS score are the most frequent composite methods used to assess PEW in dialysed patients. They can be seen as 'composite indices' because both combine assessments of the medical history (loss of body weight, changes in appetite, presence of nausea, vomiting, presence of comorbidities) as well as functional capacity, dietary history, and physical examination (loss of subcutaneous fat and muscle wasting) (Steiber et al., 2004). Both are commonly used by clinicians and researchers and have features that make their use attractive for clinical and research settings: they are inexpensive and can be easily performed by healthcare providers from many disciplines. In addition, they have been shown to be valid, reliable, and with a good degree of reproducibility in CKD population (Kalantar-Zadeh et al., 2001; Steiber et al., 2007). SGA differs from MIS in some aspects: while SGA requires no laboratory testing and has a score system that does not rely on summing points, MIS includes three objective components (body mass index, serum albumin, and total iron binding capacity) or transferrin. In addition, the scoring system of MIS is based on summing up the total amount of points obtained from each parameter assessed (Kalantar-Zadeh et al., 2001; Steiber et al., 2004, 2007). Some researchers consider MIS as a more complete method to assess PEW, because it includes the measurement of laboratory parameters that can predict outcome (Yamada et al., 2008). One critique of both methods is, however, that they may not be sensitive to detect small changes over time.

Setting up easy screening tools for nutritional status assessment

A significant hurdle in preventing and treating malnutrition is accurate clinical detection, particularly at early stages when interventions may be more effective. A crucial feature of clinical patient monitoring is the importance of following trends over time. Without previous values, numbers can be deceiving. In addition, biochemical markers and other nutritional estimations should be studied in the entire clinical context and, if a particular value does not make sense in the clinical picture, it should be disregarded. This being said, and in the absence of dedicated personnel (like dieticians) or specialized equipment (like skinfold caliper, BIA, dynamometer, or others), some simple inexpensive tools can be proposed for basic screening and monitoring of nutritional status, such as combining both the use of biomarkers and anthropometric measures.

Firstly we should emphasize and bring upfront the importance of patient reporting and clinical judgement, and the need to take this information into account in the patient's nutritional assessment. For instance, patients' reports on appetite were associated with nutritional status and predicted an increased mortality or hospitalization risk in dialysis patients (Carrero et al., 2007). Also, nurses' visual inspection of characteristics of muscle atrophy in dialysis patients strongly predicted objective measures of muscle mass and strength and short-term mortality risk of patients (Carrero et al., 2008). Last, but not least, the answer to the 'surprise question' by healthcare professionals (e.g. 'Would you be surprised if this patient died within 1 year?') is a clear and undeniable predictor of poor outcomes (Moss et al., 2008).

The regular screening of nutritional status in the clinical setting should be based on simple available tools. Combining information based on laboratory parameters, body composition, especially muscle mass, and dietary intake seems to be an ideal way to assess nutritional status. It was shown in a large American dialysis cohort that taking into consideration concurrent estimates of body weight and creatinine trimestral variation could provide additional diagnostic information: both gaining muscle (increase in creatinine) and gaining fat (concurrent increase in dry weight) were associated with a survival benefit. However, the biggest survival benefit was observed for patients gaining both dry weight and creatinine (Kalantar-Zadeh et al., 2010). The International Society of Renal Nutrition and Metabolism (ISRNM) organized an expert panel to re-examine terms and criteria used for the diagnosis of PEW (Fouque et al., 2008a). Similarly, the European Best Practice Guideline (EBPG) in Nutrition also proposed a panel to combine different methods to assess nutritional status (Fouque et al., 2007). In summary, combining these simple tools can represent a starting point towards more thorough investigations of the nutritional status (Table 274.1).

Nutritional requirements in dialysed patients

Energy

The recommended energy intake for dialysed patients according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) nutrition guidelines is 35 kcal/kg/day for patients aged < 60 years old and 30–35 kcal/kg/day for those aged > 60 years (National Kidney Foundation, 2000). These recommendations were set in 2000, based upon the very few published studies assessing energy expenditure. Subsequent studies seem to confirm this range, as discussed elsewhere (Byham-Gray, 2006; Avesani et al., 2011). However, it is important to individualize the energy recommendation, particularly taking into consideration patients' sedentary lifestyles and their reportedly low

Table 274.1 Recommended criteria for the clinical diagnosis of PEW proposed by the International Society of Renal Nutrition and Metabolism (ISRNM) (Fouque et al., 2008a) and by the European Best Practice Guideline (EBPG) in Nutrition (Fouque et al., 2007)

Panel for Screening PEW by the ISRNM	Panel for Screening PEW by the EBPG
At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease-related PEW.	PEW should be diagnosed by a number of assessment tools including:
Criteria	(A) Dietary assessment
Serum chemistry	(B) Body mass index
Serum albumin < 3.8 g per 100 mL (Bromcresol Green)	(C) Subjective global assessment
Serum pre-albumin (transthyretin) < 30 mg per 100 mL (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2–5)	(D) Anthropometry
Serum cholesterol < 100 mg per 100 mL	(E) nPNA[a]
Body mass	(F) Serum albumin and serum pre-albumin
BMI < 23 kg/m^2	(G) Serum cholesterol
Unintentional weight loss over time: 5% over 3 months or 10% over 6 months	(H) Technical investigations (bioelectrical impedance, dual-energy X-ray absorptiometry, near-infrared reactance)
Total body fat percentage < 10%	
Muscle mass	
Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months	
Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population)	
Dietary intake	
Unintentional low DPI < 0.80 g/kg/day for at least 2 months for dialysis patients or < 0.6 g/kg/day for patients with CKD stages 2–5	
Unintentional low DEI < 25 kcal/kg/day for at least 2 months	

DEI = dietary energy intake; DPI = dietary protein intake.

[a]Normalized protein equivalent of nitrogen appearance.

physical activity-related energy expenditure (Baria et al., 2011; Avesani et al., 2012). According to the EBPG in Nutrition, one way to achieve this individualized recommendations is by first estimating the resting energy expenditure (either with the Harris-Benedict equation or Schoefield equation) and then multiplying this by a factor of physical activity close to the patient's lifestyle (light activity, active or moderately activity, and vigorous activity) (Table 274.2) (Fouque et al., 2007). Particularly for obese patients on PD, it may be appropriate to discount the energy coming from the absorption of glucose from the dialysate from the total recommended energy intake.

Protein and phosphorous intake

The suggested recommended protein intake for dialysed patients by the NKF-KDOQI guidelines is 1.2 g/kg/day in patients on HD and 1.3 g/kg/day in patients on PD (National Kidney Foundation, 2000). Most studies show that patients fail to achieve this protein intake. This can be a sign either that protein intake is underreported or that the protein needs of these patients are lower than the recommended values. As it was found that HD patients maintaining their nutritional status were ingesting 1.44 ± 0.12 g of protein/kg/day (Kloppenburg et al., 2002) it is likely that their protein need is between 1.2 to 1.4 g/kg/day. One important issue while planning and counselling the protein intake is to control phosphorous intake as well, since the many food sources of protein are also food sources of phosphate. According to the EBPG on Nutrition, a daily intake of 1.1 g/kg/day of protein and up to 800–1000 mg of dietary phosphate is recommended (Fouque et al., 2007). To reach this goal, it is important to develop nutritional educational programmes that teach the patient about the choice of food sources of protein with low phosphate content.

Nutritional support in dialysed patients

According to the European Society for Parenteral and Enteral Nutrition guidelines, nutritional support should be considered for patients with signs of PEW, such as BMI < 20 kg/m^2, body weight loss > 10% over 6 months, serum albumin < 35 g/L, and serum transthyretin < 300 mg/L (Cano et al., 2006). Nutritional support should aim to ensure that the energy and nutrient needs are being fulfilled, according to that recommended by the guidelines. Oral nutritional support (by drinking enteral formula) should be the first option for treating PEW. It can provide approximately an additional 7–10 kcal/kg/day of energy and 0.3–0.4 g/kg/day of protein (Kalantar-Zadeh et al., 2011). To reach this level of oral supplementation, the supplement should be given three to four times daily in small doses after the meal, and should never replace a meal. When there is low adherence, the supplement can be given during the dialysis session. Studies investigating the effect of oral supplements for about 6 months show improvements in SGA score, serum albumin, and functional scoring. In addition, an increase in spontaneous energy and protein intake was also reported (Stratton et al., 2005; Fouque et al., 2008b). If adequate intake cannot be achieved by oral supplementation and nutritional status continues to deteriorate, enteral nutrition with tube feeding should considered (Cano et al., 2006). However, as this is a more invasive intervention, with the need of home care or hospitalization, many patients are reluctant to accept this treatment. Studies with tube feeding are scarce and with small sample sizes. In one study, an improvement in serum

Table 274.2 Estimating daily energy needs according to the European Best Practice Guideline in Nutrition (Fouque et al., 2007)

Step 1: Estimating resting energy expenditure(eREE) by Schoefield or Harris & Benedict equation	
eREE: Schofield tables (Food and Agriculture Organization of the United Nations (2004)	
Males	*Females*
18–30 years: 15.3 × body weight (kg) + 679	14.7 × body weight (kg) + 496
30–60 years: 11.6 × body weight (kg) + 879	8.7 × body weight (kg) + 829
> 60 years: 13.5 × body weight (kg) + 487	10.5 × body weight (kg) + 596
eREE: Harris & Benedict equation (Harris and Benedict, 1918)	
Males	*Females*
66 + (13.7 × body weight (kg)) + (5 × Height (cm)) – (6.8 × age (years))	655.1 + (9.6 × body weight (kg)) + (1.8 × height (cm)) – (4.7 × age (years))
Step 2: Estimating daily energy needs (eDEN)	
eDEN: eREE (kcal/day) × physical activity level (PAL)[a]	
[a]Classification of lifestyles in relation to the intensity of habitual physical activity, or PAL (Food and Agriculture Organization of the United Nations, 2004)	
Sedentary or light activity lifestyle: 1.40–1.69	
Active or moderately active lifestyle: 1.70–1.99	
Vigorous or vigorously active lifestyle: 2.00–2.40	

albumin with tube feeding was shown (Cockram et al., 1998). For both interventions, oral or enteral supplementation, formulas specifically designed for dialysed patients are preferred, as they have higher energy density (and therefore reduced volume) and protein content, but reduced potassium and phosphate concentration (Cano et al., 2006). The use of IDPN may represent an additional option for treating PEW, but the effectiveness of this treatment is not clear yet. Its main advantages are easy administration through pre-existing vascular access, control of nutritional content, and prevention of net loss of amino acids and water-soluble vitamins. However, during IDPN, nutrients are rapidly removed from blood; and it can be seen as a non-physiologic circumvention of the normal nutrient–gut interactions. Additionally, IDPN is expensive, requires time and effort from the nursing staff, and may lead to bacterial contamination and reactive hypoglycaemia (Kalantar-Zadeh et al., 2011). In one review about studies treating malnourished dialysed patients with IDPN, it was concluded that this treatment provided improvement in nutritional parameters, such as albumin, transthyretin, and dry body weight, but the limited amount of studies impairs a more conclusive answer about the effectiveness of this approach (Dukkipati et al., 2010).

A final comment is that regardless of the modality chosen for nutritional support (oral or intradialytic parenteral), it is important that the oral intake should cover at least 50–80% of the patient's energy and protein needs (Kalantar-Zadeh et al., 2011). Occasionally, total enteral or parenteral nutrition may be implemented to nourish patients with very low energy and nutrient intake.

Conclusion

The nutritional management of dialysed patients is of high importance and should be carefully planned. This includes the assessment of the nutritional status and the prescription of a diet that fulfils the recommended intake of energy and nutrients. Periodic follow-up is also necessary, so that early changes in nutritional status can be diagnosed and treated accordingly. The whole team at the renal unit must be aware of the nutritional derangements that these patients are prone to have, and a multidisciplinary teamwork (ideally with a renal dietician) is recommendable.

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