Management of Hypertension in Pediatric Dialysis Patients

31

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Abbreviations

ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin converting enzyme inhibitor
BP	blood pressure
CAKUT	congenital anomalies of kidney and urinary tract
ESRD	end-stage renal disease
HD	hemodialysis
LVH	left ventricular hypertrophy
NO	nitric oxide
PD	peritoneal dialysis
PTH	parathyroid hormone
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone-system

Introduction

Patients on maintenance dialysis therapy have an excessively increased all-cause and cardiovascular morbidity and mortality compared with the general population. Adolescents and young adults may already have symptomatic cardiovascular disease, including ischemic heart disease and stroke, and at least every second child on dialysis presents with early signs of cardiovascular end-organ damage such as left ventricular hypertrophy (LVH) or alterations of vascular morphology and function. One of the main risk factors for the high cardiovascular morbidity and mortality is arterial hypertension. The percentage of hypertensive patients on maintenance dialysis is up to 80%, and while hypertension in mild-to-moderate chronic kidney disease (CKD) is mainly caused by underlying renal parenchymal disease, in dialysis patients the most important factor influencing blood pressure (BP) is fluid and salt overload.

The aim of this chapter is to review the prevalence and etiology of hypertension and associated cardiovascular morbidity and mortality in children on dialysis, as well as treatment strategies and targets.

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Prevalence of Hypertension in Pediatric Dialysis Patients

Hypertension is highly prevalent in the pediatric dialysis population. Almost 4 out of 5 children and adolescents requiring dialysis are hypertensive or have been prescribed antihypertensive medication.

In a survey of the European ERA/EDTA registry, comprising more than 1300 pediatric dialysis patients from 15 European countries, the prevalence of hypertension was 69.7% in hemodialysis (HD) and 68.2% in peritoneal dialysis (PD) patients. Forty-five percent of HD and 35% of PD patients had uncontrolled hypertension [72]. Similar findings have been seen in data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry. In an analysis including almost 3500 children, 67.9% of patients were found to be hypertensive 6 months after initiation of dialysis [49]. In another study in long-term HD patients, hypertension was present in 79% of patients. Sixty-two percent of patients were on antihypertensive medication; however, hypertension was uncontrolled in 74% of treated patients. [22].

It should be noted that these epidemiologic data were derived from casual/office BP measurements with single BP recordings per patient reported to the registries. Hypertension was commonly defined as either systolic or diastolic BP above the 95th percentile for sex, age and height. For the interpretation of these data, consideration of the time of BP measurement is important. Predialysis measurements are usually higher compared with post-dialysis measurements, resulting in a higher probability to be classified as hypertensive when only pre-dialysis measurements are available. In HD patients, the median (or mean) interdialytic BP measured by ambulatory BP monitoring (ABPM) is usually lower compared with casual pre-dialysis measurements, resulting in a lower number of patients being classified as hypertensive by ABPM [51]. When the ABPM measurement duration has been extended from the conventional 24 h to 44 h, covering a complete midweek interdialytic period, a higher percentage of patients were diagnosed with hypertension and all BP indexes and loads were significantly higher on interdialytic day 2 compared to day 1 [51]. Volume fluctuations and fluid overload are probably the most important factors responsible for the poor diagnostic value of pre- and post-dialytic BP measurements to predict hypertension in the interdialytic period [3, 125].

It should also be noted that ABPM may identify patients with nocturnal or masked hypertension [21] and patients with reversed nocturnal dipping or altered circadian and ultradian BP rhythms. Unfortunately, data on hypertension prevalence according to interdialytic ABPM are scarce [21, 77].

Etiology of Hypertension in Pediatric Dialysis Patients

The dominant factor contributing to hypertension in dialysis patients is volume overload; other contributing factors include activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, endothelial dysfunction, increased arterial stiffness, hyperparathyroidism, and exposure to BP elevating drugs.

Additionally, registry studies have identified young age, being on HD, having glomerulopathies as the primary renal disease, and shorter duration of renal replacement therapy as risk factors for dialysis-associated pediatric hypertension [22, 49, 72].

Volume overload plays a pivotal role in the development of hypertension in dialysis patients. Several studies in humans have demonstrated a direct effect of extracellular volume on BP in HD patients [4, 61, 133], and interdialytic weight gain has been shown to correlate with higher systolic BP load in 44-h ABPM profiles on the second day of the BP recording [51]. As might be expected, attainment of dry weight and normalization of sodium balance were able to normalize BP without the need for antihypertensive medication [16].

In dialysis patients, extracellular volume, cardiac output, and BP are increased by impaired or absent ability of the kidneys to excrete sodium and water. These alterations are worsened by

insufficient intradialytic removal of fluid and salt. Therefore, in addition to an adequate dialysis prescription, interdialytic fluid restriction and limited salt intake are therapeutic cornerstones for the attainment of dry weight as part of the management of hypertension in dialysis patients. However, efforts to compensate for decreasing residual renal function and diuresis by increasing intradialytic sodium and water removal are often insufficient, as seen in one recent study, in which 25% of dialysis-associated hypertension was felt to be related to factors other than volume overload [32].

Loss of residual renal function is another risk factor for the development of hypertension. BP is inversely correlated to residual renal function and hypertensive children on dialysis have less residual urine output compared to normotensive children [130].

Fluid balance is inextricably linked to serum *sodium* concentration. However, the hypertensive effects of sodium are exerted by mechanisms both related and unrelated to extracellular volume expansion; elevated sodium concentration may also induce vasoconstriction by altering endothelial cell responses and further contribute to the development of hypertension [99].

It has been demonstrated that intradialytic salt exposure (i.e., the sodium content of the dialysate) has a direct impact on BP. HD patients set to time-averaged dialysate sodium concentrations of 147 mEq/L were found to have higher 24-h systolic BP levels compared to patients set to a sodium concentration of 138 mEq/L [124]. Additionally, a higher dialysate-to-plasma-sodium gradient may increase thirst and interdialytic weight gain, impeding attainment and maintenance of dry weight [115].

Contrary to the physiologically expected suppression of the *renin-angiotensin-aldosterone system* (RAAS) in a state of salt or fluid overload, plasma renin activity was found to be significantly higher in a study comparing hypertensive to normotensive dialysis patients. The study results strongly suggested that the RAAS is an important factor involved in the pathogenesis of hypertension in end-stage renal disease (ESRD), when sodium balance is adequately controlled [71]. In addition, the significant decline in BP that occurs following bilateral nephrectomy [138] points to volume-independent mechanisms of hypertension in dialysis patients.

Children with end-stage renal disease showed a 25-fold increase in angiotensin (1–7) compared to control values. These marked changes in plasma angiotensin (1–7) were associated with the presence of hypertension and progression of kidney dysfunction [121], while angiotensin II levels were similar and plasma renin activity was lower compared to hypertensive patients with non-ESRD CKD. In dialysis patients, angiotensin II was only poorly suppressed by angiotensin converting enzyme inhibitor (ACEi) treatment. The significance of the elevated angiotensin (1–7) levels is still not clear, but might be a consequence of the altered RAAS pathway in pediatric ESRD patients.

Dialysis patients also have higher *sympathetic nervous system* (SNS) activity and vascular resistance than healthy controls or ESRD patients after bilateral nephrectomies [26]. An early manifestation of abnormal activation of the SNS activity is the absence of the physiological nocturnal BP dipping in 24 h ambulatory BP monitoring [79].

Endothelial dysfunction, which participates in accelerated atherosclerosis, is a hallmark of CKD. Patients with ESRD display impaired endothelium-dependent vasodilatation, elevated soluble biomarkers of endothelial dysfunction, and increased oxidative stress. Several uremic toxins, mostly protein-bound, have been shown to have specific endothelial toxicity: e.g., asymmetric dimethylarginine (ADMA), homocysteine, and advanced glycosylation end-products (AGEs). These toxins are insufficiently or not removed by dialysis, promote pro-oxidative and pro-inflammatory response, and inhibit endothelial repair, thereby inducing endothelial damage [64].

The most important vasodilatory substance is nitric oxide (NO). The disturbed balance between decreased NO (mediator of vasodilatation) and increased endothelin-1 (ET-1; mediator of vasoconstriction) in dialysis patients results in *endo-*

thelial cell dysfunction with increased vasoconstriction. NO release is reduced by CKD-induced elevation of ADMA, an endogenous inhibitor of endothelial NO synthase. Increased levels of ADMA have been found to be directly associated with increased cardiovascular and all-cause mortality in the ESRD population [12]. Oxidative stress with increased reactive oxygen species (ROS) can also interfere with NO synthesis and availability.

As a result, *arterial stiffness*, usually a problem of vascular aging and arteriosclerosis, is accentuated in the presence of end-stage renal disease and hypertension. The stiffened, non-compliant arteries transmit each ejected pulse wave so quickly that the reflected pressure wave, coming backwards from the peripheral circulation, coincides with the still ongoing systole. The consequence is increased systolic BP and pulse pressure resulting in LVH [80]. Higher pulse wave velocity (PWV) due to increased vascular stiffness is also present in pediatric ESRD. PWV is elevated compared to age-, height-, and weight-matched controls [68]. However, the elevated PWV in pediatric ESRD patients was not clearly correlated with the BP level and was found to be persistently elevated despite the use of pharmacological vasodilatation.

Another study in pediatric ESRD patients showed that aortic distensibility, another measure of arterial stiffness, was lower (i.e., higher arterial stiffness) in both HD and PD patients compared to healthy controls. Children on HD had more severe impairment than PD patients [110].

Plasma levels of *renalase,* a protein released by the kidneys and responsible for the degradation of catecholamines, are markedly decreased in ESRD. Renalase deficiency and the resulting increase of circulating catecholamine levels may also contribute to hypertension and cardiovascular disease in ESRD [30, 137].

Secondary *hyperparathyroidism*, a complication of CKD, may be yet another contributor to the high prevalence of hypertension. A retrospective study in adults with pre-dialysis CKD demonstrated that systolic and diastolic BP were significantly increased in patients with elevated parathyroid hormone (PTH) levels [108]. A possible mechanism might be increased platelet cytosolic calcium in patients with elevated PTH. Mean BP correlated highly with cytosolic calcium and PTH. In contrast, treatment with vitamin D lowered cytosolic calcium, PTH, and mean BP significantly.

Therapy with *erythropoiesis stimulating agents*, i.e., erythropoietin, is also associated with an increase of the BP level and development of hypertension. The prevalence of BP increase in adults on erythropoietin therapy is given as high as 10–75%. In a study in 23 pediatric dialysis patients, hypertension developed or worsened in 67% of CAPD patients and 36% of HD patients after initiation of erythropoietin, while no differences were observed in plasma level of aldosterone or plasma renin activity [69].

Mechanisms involved in the development of hypertension and cardiovascular end-organ damage in pediatric dialysis patients are summarized in Fig. 31.1.

While most pediatric dialysis patients lack the cardiovascular and metabolic comorbidities that lead to hypertension in adults with ESRD, *underlying renal disease* is another important factor influencing the BP level in children with ESRD.

In glomerulopathies, activation of the RAAS, present from the earliest stages of glomerular disease through ESRD, may complicate BP control. Patients with glomerular disease are also less likely to be normotensive compared to patients with congenital anomalies of the kidney and the urinary tract (CAKUT; 12% vs. 31%) [49] and to have an approximately two-fold higher risk of uncontrolled hypertension [49, 72].

Patients with autosomal-recessive polycystic kidney disease may have very severe or therapy refractory hypertension, necessitating bilateral nephrectomy in some cases. In contrast, patients suffering from CAKUT are less prone to renal hypertension, and attainment of dry weight often succeeds in achieving BP control without the need of additional antihypertensive medication.

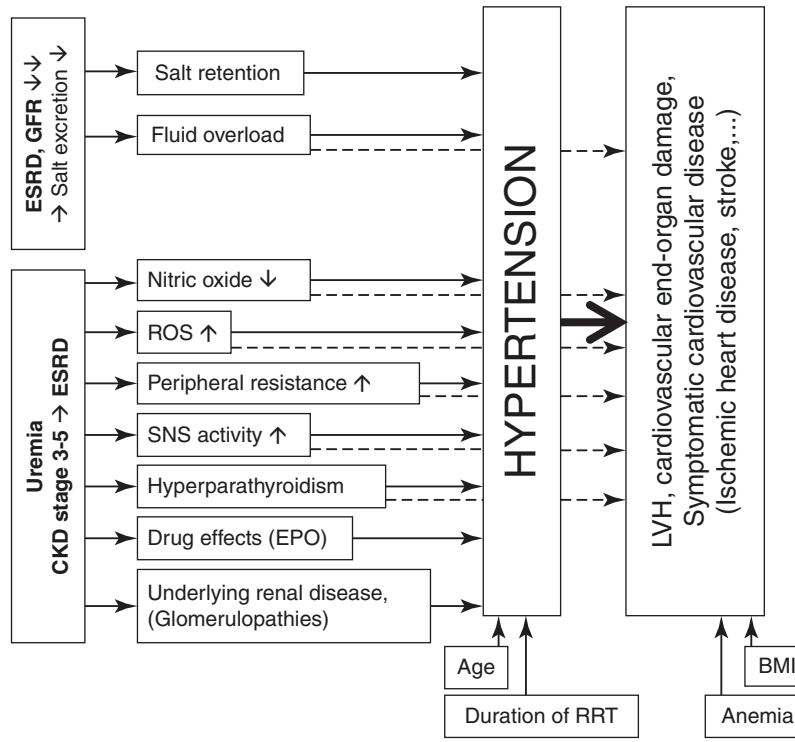

Fig. 31.1 Mechanisms involved in the development of hypertension in pediatric dialysis patients. BMI body mass index, CKD chronic kidney disease, EPO erythropoietin, ESRD end-stage renal disease, GFR glomerular filtration rate, ROS reactive oxygen species, RRT renal replacement therapy, SNS sympathetic nervous system

Short- and Long-Term Consequences of Hypertension

Hospitalization

Fluid overload and hypertension are a frequent cause for morbidity, accounting for 41% of hospitalizations in children on HD at the Texas Children's Hospital [44]. The risk of hospitalization correlated with the duration of the interdialytic interval. Children receiving chronic HD were more likely to be hospitalized for hypertension, fluid overload, or electrolyte abnormalities following a longer interdialytic interval. Accordingly, the odds ratio of hospital admission was 2.6 on Monday versus other days of the week, while the odds ratio of admission among PD patients was not significantly different on Mondays [126]. Thus, changes to the frequency and intensity of the dialysis treatment may effect admissions in this high-risk population.

Alterations of Vascular Morphology and Function

Increased arterial stiffness is a risk factor for mortality in adults with ESRD. A long-term outcome study including all living adult Dutch patients with childhood onset of ESRD between 1972 and 1992 at age 0–14 years showed a similar intima media thickness, but a reduced mean arterial wall distensibility and increased arterial stiffness compared to healthy controls. Systolic hypertension was the main determinant of these arterial wall changes [46].

The ESCAPE Trial group was able to provide clear evidence that CKD is associated with morphologic alterations of both muscular- and elastic-type arteries as early as in the second decade of life. The degree of pathology depended on the degree of renal dysfunction, correlated with systolic BP, and was most marked in patients on dialysis [78]. In another study including 39

children and adolescents on dialysis (15 HD, 24 PD), indexed diastolic BP was a significant predictor if cIMT [24].

Left Ventricular Hypertrophy

LVH is a common complication in dialysis patients. Forty-eight percent of PD patients were noted to have LVH and 75% had abnormal left ventricular geometry according to a registry analysis of the International Pediatric Peritoneal Dialysis Network (IPPN) [15]. In this analysis, hypertension, high body mass index, fluid overload, renal disease other than hypo/dysplasia, and hyperparathyroidism were predictors of LVH. The lower prevalence of LVH in patients with renal hypo/dysplasia is likely the result of lower BP and polyuria in these patients [15].

In HD patients, the prevalence of LVH was even higher at eighty-five percent, and abnormal left ventricular geometry was found in 80% of patients [91]. The impact of different BP parameters on LVH was analyzed in 25 PD patients, of whom 52% had LVH. Left ventricular mass index (LVMI) was significantly correlated with casual BP measurements and the majority of ABPM parameters [102]. In contrast, in 17 HD patients studied by casual BP measurements and 44-h ABPM, casual BP measurements did not correlate well with measures of cardiovascular end-organ damage, while nighttime BP during 44-h interdialytic ABPM most strongly predicted increased LVMI and LVH [66].

Forty-four-hour ABPM BP load was also correlated with a higher left ventricular mass index. Children with LVH had higher daytime and nighttime systolic BP loads, significantly higher daytime and nighttime diastolic BP loads, and a lesser degree of nocturnal dipping of systolic BP compared to children without LVH [51].

Cardiovascular Mortality

Twenty years ago, it was shown that overall mortality in children on dialysis was increased 1000-fold compared to the normal pediatric population [104] and 40–50% of deaths were from cardiovascular and cerebrovascular causes [47, 87, 101].

Encouragingly, over the past several decades the risk of death has decreased significantly in this population. For example, in the USRDS registry, cardiovascular mortality in pediatric dialysis patients has decreased significantly over the last 20 years, from 33.5/1000 patient-years in patients <5 years of age and 16.2/1000 patient-years in patients >5 years to 22.6 and 9.3/1000 patient-years, respectively [92].

In a European review, overall mortality was 28/1000 patient-years in children and adolescents who started dialysis between 2000 and 2013. Overall mortality risk was highest (36.0/1000) during the first year of dialysis and in the 0- to 5-year age group (49.4/1000), and cardiovascular events accounted for 18.3% of death. Children selected to start on HD had an increased mortality risk compared with those on PD, especially during the first year of dialysis [23].

Improved implementation of clinical practice guidelines, associated with better control of anemia, hyperparathyroidism, and BP, might have contributed to this reduction in mortality as recently shown by a NAPRTCS registry analysis [135]. Similarly, in a systematic review and meta-analysis of 8 trials including 1679 adult patients on dialysis and 495 cardiovascular events, BP lowering was associated with a lower risk of cardiovascular events, all cause-mortality and cardiovascular mortality [55].

Diagnosis of HTN in Dialysis Patients

Current European and American guidelines for evaluation and management of hypertension in children and adolescents [38, 82] do not specify different thresholds for diagnosing hypertension when it is known that the patient has a specific underlying diagnosis, such as renal disease; one would still make the diagnosis of hypertension once the BP had exceeded the specific age, sex, and height threshold. Given the close association

between CKD and hypertension in children and adolescents [119], it is likely that a pediatric dialysis patient would be hypertensive at the initiation of dialysis. Thus, the problem under consideration herein is more likely to be an issue of recognition of hypertension, as opposed to making an initial diagnosis of hypertension. Specifically, the problem is how to best diagnose hypertension in a dialysis patient when their measured BP in the clinic or dialysis unit does NOT exceed the thresholds found in the guidelines, but does at other times, a condition known as masked hypertension. Masked hypertension is particularly common in children and adolescents with pre-dialysis CKD [114].

Role of Ambulatory Blood Pressure Monitoring (ABPM)

24-h ABPM is a procedure whereby repeated BP measurements can be obtained outside of a clinical setting, including during sleep. A detailed discussion of ABPM is beyond the scope of this chapter; interested readers should consult other references [37, 83]. There are several distinct hypertension phenotypes that can be identified using the combination of clinic and ambulatory BP values (Table 31.1). All four phenotypes have been identified in adult HD patients [6]. While masked hypertension (and its opposite, white coat hypertension) can be diagnosed using resting BPs obtained in a non-clinical setting, ABPM is generally agreed to be the gold standard approach for identifying patients with these BP patterns [37]. As will be discussed in more detail below, widespread application of ABPM in patients undergoing dialysis is absolutely essential for optimal BP management in this high-risk population.

Table 31.1 Blood pressure phenotypes based on casual/office and ambulatory blood pressure values

Phenotype	Office BP	Ambulatory BP
Normotensive	Normal	Normal
Hypertensive	High	High
White coat hypertensive	High	Normal
Masked hypertensive	Normal	High

ABPM in Hemodialysis Patients

The assessment of BP in HD patients is challenging for many reasons, not the least of which is the timing of when BP is measured [74]. It is clear that pre- and post-dialysis BPs provide an inaccurate estimate of the interdialytic BP burden compared to assessment by ABPM [1]. Additionally, BPs obtained surrounding dialysis do not correlate with end organ damage such as elevated left ventricular mass index [2, 93, 94]. Forty-four-hour ABPM has demonstrated increased accuracy in detecting hypertension as compared to a 24-h assessment, likely due to the higher BPs seen in the day following dialysis (the second portion of 44-h ABPM). BP loads >25% on 44-h ABPM have been associated with higher left ventricular mass index in children on chronic HD as compared to assessment with 24-h ABPM [51]. Given these advantages, 44-h ABPM is felt to be the gold standard for BP assessment in HD patients [7].

ABPM in Peritoneal Dialysis Patients

Abnormal circadian BP patterns are common in adult PD patients, and blunted nocturnal dipping and higher BP loads on ABPM correlate with higher left ventricular mass index [13]. Similarly, among 47 children on PD, systolic BP loads on 24 h ABPM were associated with an increased risk of elevated left ventricular mass index [19]. In another study, ABPM was more sensitive in diagnosing hypertension as compared to clinic BPs among 25 pediatric PD patients (56 vs. 32%, $p < 0.05$) [102]. As with HD patients, these data support the routine use of ABPM in assessing BP in patients receiving PD.

Treatment of Hypertension

Adjustment of Dry Weight/Optimization of Dialysis

Dry Weight

Dry weight is defined as the lowest body weight at the end of dialysis at which the patient can remain normotensive without antihypertensive medication, despite fluid accumulation, until the

next dialysis treatment. Stated differently, dry weight is the lowest weight a patient can tolerate without having symptoms of hypotension [62]. When a patient is at their dry weight, it is thought that they are less likely to have hypertension from volume overload.

However, determination of dry weight is difficult. Typically, dry weight is often achieved by trial and error; dry weight is thought to have been achieved when the patient develops signs of hypotension, such as drop in BP, cramping, yawning, headache, abdominal pain, etc. Common clinical methods to assess dry weight include monitoring weight pre- and post-dialysis, examination for the presence of edema, jugular venous distension or crackles on lung auscultation, or detection of hypotension in those with intravascular volume depletion. Clinical assessment can be inaccurate in states of subtler volume excess/depletion. Markers such as change in weight are further confounded in a growing child. Due to the limitations of relying on clinical assessment to determine dry weight, different techniques have been studied to aid in the assessment and achievement of dry weight.

Biochemical markers of volume status include atrial natriuretic peptide, cyclic guanidine monophosphate, brain natriuretic peptide, and troponin T [31, 139]. Most of the biomarkers can be affected by various factors other than volume status, thus limiting their clinical utility. Ultrasound measurement of the inferior vena cava diameter and its collapsibility is a simple and noninvasive way to assess intravascular volume status. Challenges that prevent the broad use of this parameter include interoperator error and patient variability in diameter measurements [31, 62]. Bioelectrical impedance analysis, or bioimpedance, is a method that determines the electrical opposition (impedance) to the flow of an electric current through the body. Bioimpedance can be applied to both HD and PD patients [28]. In adults, bioimpedance analysis has shown that extracellular volume change correlated with the ultrafiltration volume [81]. Other studies in adults using bioimpedance have demonstrated the underestimation of ultrafiltration volumes by 30% based on ECF volumes pre and post HD [62].

Pediatric studies of bioimpedance have demonstrated the utility of this technique, showing good correlation of measured blood volume change to percentage body weight change [100], and serial clinical use to assess dry weight at a single center led to improvement in left ventricular mass index and reduction in LVH [103]. In one recent study, the assessment of dry weight by bioimpedance was compared to clinical assessment in 30 children with stage 5 CKD, 20 of whom were on dialysis (10 HD, 10 PD). Assessment by bioimpedance was felt to more accurately determine hydration status, and correlated with biomarkers of volume overload such as plasma N-terminal pro-B natriuretic peptide and cardiovascular markers such as LVH [32]. The technology does have limitations. Temperature and ion changes that occur during dialysis may effect electrical impedance, as may patient factors such as electrolyte imbalance, hematocrit values, and protein levels [62].

Relative plasma volume monitoring during HD provides insight into the relative rate of ultrafiltration compared to the rate of refilling of plasma volume from the extravascular space. Photo-optical technology measures hematocrit or protein values. An increase in hematocrit or protein concentration is inversely proportional to the change in plasma volume. The use of this technology in adults has led to mixed results, with some reporting improvement in determining and achieving dry weight [111, 127] and some reporting improvement in casual BPs [27] and lower systolic BP as measured by 44 h ABPM [122]. Several pediatric studies have studied the use of plasma volume monitoring [20, 63, 90, 105]. In a multicenter prospective study of 20 pediatric patients, plasma volume monitoring was used to target the 100% ultrafiltration goal, with 50% to be removed in the first hour (max plasma volume change of 8–12% per hour) and the remaining 50% over the subsequent time (max plasma volume change of 5% per hour). They demonstrated a decrease in dialysis-associated morbidity, reduction in antihypertensive medication usage, and improved ABPM profiles. There was no

change in weight or left ventricular mass index at the end of the 6-month study, which the authors attributed to somatic growth in their young patients [105]. In 9 pediatric HD patients, systematic use of plasma volume monitoring to challenge dry weight and reduce antihypertensive use resulted in mean dry weight reduction, decreased BP measured both casually and by ABPM, and a reduction in antihypertensive burden [20].

Lung ultrasound has also been used to assess volume status. In the setting of extracellular fluid excess, hydrostatic forces will create a transudative effusion that leads to a decrease in the acoustic mismatch between lung and surrounding tissues. This creates a partial reflection and discrete hyper-echogenic reverberation of the ultrasound beam arising from the pleural line known as "B-lines" [11]. In adults, lung ultrasound findings including B-lines correlated with other markers of fluid overload including: clinical parameters [98, 131], B type natriuretic peptide, inferior vena cava diameter, and bioimpedance [18, 134]. In a single-center study of 96 patients on HD where lung ultrasound, bioimpedance, and echocardiography were prospectively studied for their ability to predict mortality, predialysis B-line score and left ventricular mass index were significantly associated with survival [123]. A recent pediatric study that included patients with ESRD treated with both modalities of dialysis and patients with acute kidney injury demonstrated a significant correlation between B-lines and volume excess as determined by target weight [11]. Among 13 children on dialysis in which objective parameters of volume excess were studied including lung ultrasound, bioimpedance, clinical parameters, and inferior vena cava parameter, only lung ultrasound correlated significantly with volume overload [10, 11].

Clearly, each of these approaches to determining dry weight has advantages and disadvantages, many of which will depend on local expertise as well as the availability of each technique. While the utilization of a combination of techniques may be ideal [112], each dialysis center should follow a standardized approach that allows for longitudinal evaluation of each patient.

Optimization of Dialysis

For both HD and PD, optimization of dialysis with respect to control of BP means utilizing different approaches to reduce volume overload during the dialysis treatment. Just as important is avoidance of intradialytic hypotension, which may be associated with myocardial stunning [57, 58, 88], and prevention of excessive interdialytic weight gain.

Adjusting the duration of therapy and/or the concentration of dialysate sodium is the main strategy used in HD to improve fluid removal. Currently, there is increasing evidence that reduction in dialysate sodium at or slightly below the patient's pre-dialysis serum concentration leads to reduction in thirst, interdialytic weight gain, and hypertension [17, 97, 129]. A small pediatric study consisting of 5 patients demonstrated a reduction in interdialytic weight gain and predialysis BP when dialysate sodium was reduced from 140 to 138 mEq/L [85]. A systematic review of 23 studies comparing high vs. low dialysate sodium concentration in chronic adult HD patients demonstrated that while BP was unaffected by the concentration of dialysate sodium, there was an increase in interdialytic weight gain in the higher dialysate sodium group and increased intradialytic hypotension in the low dialysate sodium group [17]. It is, in turn, important not to reduce the dialysate sodium too far. Mortality was assessed in 3 observational studies and demonstrated reduced mortality overall with higher dialysate sodium concentrations, but was confounded by patients' serum sodium concentrations, which demonstrated an inverse relationship between serum sodium concentration and death [17, 53, 54]. Specifically, Hecking et al. demonstrated lower serum sodium (<137 mEq/L) was associated with the highest risk of death, while dialyzing against a bath >140 mEq/L was protective [54].

Increasing dialysis treatment time is another factor associated with improved outcomes. Adult and pediatric studies have demonstrated improved control of BP, faster achievement of dry weight, and reduction in medication burden including antihypertensive medications with increased

dialysis time in both adults [40, 42, 128] and children [45, 56]. Increasing time also allows for a reduction in the ultrafiltration rate, which reduces the risk of myocardial stunning [88]. The current recommendation in adult HD patients is to reduce the ultrafiltration rate to <13 ml/kg/h, although even rates <10 ml/kg/h have been associated with increased morbidity and mortality [95, 116].

It should be emphasized that the phenomenon of myocardial stunning is not limited to adult dialysis patients. Work by Hothi and colleagues has shown that excessive intradialytic BP reduction was associated with myocardial stunning in pediatric HD patients [57, 58]. However, no "ideal" rate of ultrafiltration has been determined for pediatric HD patients. In the absence of data, many pediatric dialysis centers, at least in the United States, have been following the recommendation for adults mentioned above. Further discussion on avoidance of intradialytic hypotension can be found in a recent review by Raina et al., in which the lack of evidence-based approaches to this issue in pediatric HD patients is emphasized [107].

Optimization of sodium and water removal in PD can be achieved by managing osmotic potential (dialysate dextrose concentration, dwell time) and surface area recruitment and hydrostatic pressure (fill volume). The 3 pore model theory of peritoneal transport [109] describes 3 various sized pores of the peritoneal endothelium through which transport of water and solutes occurs. The smallest pores are the aquaporin channels, via which only water can be transported; these are activated by intraperitoneal hyperosmolarity created by dextrose-based solutions. There are also small pores that allow transport of both small solutes and water, and large pores that transport macromolecules. Water removal is optimized by short dwell times to maintain the higher osmotic potential of the dialysate, and lower fill volumes to reduce hydrostatic pressure that would counteract the osmotic potential. In contrast, solute removal (including sodium) is optimized by increased fill volumes that increase the recruitment of peritoneal surface area, and longer dwell time [36].

The drawback of using higher dialysate dextrose concentrations is the production of glucose degradation products that are toxic to the peritoneum [33]. This can be avoided in part by the use of icodextrin, a maltodextrin polymer produced by the metabolism of cornstarch. Icodextrin is absorbed from the peritoneal space much more slowly via the lymphatics and thus maintains the osmotic potential longer. It further exerts its effect via colloid osmosis, and therefore exerts its effects via the small pores and not the aquaporin channels, thus leading to less sodium sieving [39]. However, icodextrin is only meant to be used for the long dwell, as metabolism over time increases its colloid potential. Studies in adults have demonstrated equivalent ultrafiltration of icodextrin over 10 h and superior ultrafiltration beyond that time as compared to 4.25% dextrose solutions [25, 96]. A recent retrospective study of 50 pediatric patients who used icodextrin for a long daytime dwell demonstrated improved ultrafiltration overall and improved ultrafiltration with increasing patient age [113].

Finally, adapted automated PD, where the PD cycler alternates between short dwells with low fill volumes to enhance ultrafiltration and long dwells with large fill volumes to enhance solute clearance [9, 34, 35], can be used to improve BP control. In a prospective, crossover study in adults, adapted PD resulted in increased sodium and water removal and improved BPs as compared to conventional PD [35]. To date, no studies of this approach to PD in children have been reported.

Dietary Intervention: Fluid and Salt Intake

The observation that dietary sodium restriction and ultrafiltration led to improved BP management was noted by Belding Scribner when treating the first patient to receive chronic dialysis, who suffered from malignant hypertension [118]. Controlling dietary sodium intake facilitates achievement of dry weight [70], and is associated with decreased thirst, lower interdialytic weight

gain, improved BP control, lower LVMI, and decreased mortality in adults [67, 84, 86]. It is important to recognize that fluid restriction will not be possible if sodium intake is not reduced, as increased sodium intake will inexorably increase thirst, which leads to greater interdialytic weight gain [76]. While most studies of sodium intake and dialysis have focused on HD patients, a limited number of studies in in adults undergoing PD have shown that a reduction in sodium intake reduces fluid overload and reduces BP in this population as well [60].

Restriction of sodium intake, although ideal, is difficult to achieve given the high sodium intake of many children, including those with CKD. Despite guidelines recommending limiting daily sodium intake in children with kidney disease and hypertension to between 1500 mg and 2300 mg [65], data from a registry of children with CKD stage 2–4 demonstrated that sodium intake was greater than 3000 mg daily, with 25% of adolescents consuming more than 5000 mg of sodium per day [59]. A study examining sodium intake among school-aged children found that the top ten food categories that contributed to 48% of the salt intake are from processed foods, with the exception of cow's milk, which naturally has sodium [106]. Similar studies in American adults demonstrated that 70.9% of the salt consumed was sodium added to food outside the home [50]. Renal dieticians are key members of the treatment team because of their role educating the patient and their family on low sodium food with high nutritional content. The social worker can also play a role by providing better access to these often more expensive foods.

Pharmacological Treatment

All classes of antihypertensive medications are useful for BP control in the dialysis population, although the choice of agent needs to be individualized [43]. Dosing of many agents may need to be adjusted in dialysis patients, as summarized in Table 31.2. However, it should be noted that antihypertensive medications are ineffective when volume excess is the etiology of hypertension, and studies have demonstrated that reliance on antihypertensive medications instead of correction of volume overload leads to persistent hypertension [5].

Antihypertensive medication use in dialysis patients has been shown to not only reduce BP, but to also improve intermediate markers of cardiovascular disease. In a recent randomized, controlled trial in hypertensive chronic adult HD patients with LVH, lisinopril or atenolol given three times a week after dialysis lowered BP on 44 h ABPM and led to regression of LVH. However, when monthly home BPs were assessed, the lisinopril group had higher BPs despite a greater number of antihypertensive agents and reduction in dry weight; this and other events in the study suggested that atenolol was overall superior to lisinopril [8].

In our experience in children, beta-adrenergic blockers and agents affecting the RAAS are the most effective classes of antihypertensive agents once volume overload has been corrected. Long-acting vasodilating medications (i.e., amlodipine, minoxidil) are best avoided as they may impair the ability to correct volume overload with fluid removal during dialysis. Clonidine may also have a role given the activation of the sympathetic nervous system in ESRD [117].

There has been an increased interest in the use of diuretics in dialysis patients who still have residual renal function [73, 132]. In patients with preserved residual renal function, loop diuretics may enhance urine output and limit interdialytic weight gain [75]. A recent study comparing patients who continued loop diuretics after HD initiation to those who did not showed that those who continued diuretics had lower rates of hospitalization and intradialytic hypotension, as well as lower interdialytic weight gain over the first year of dialysis, but there was no difference in mortality [120]. In PD, one small study showed that the use of oral loop diuretics led to better volume control in the first year after dialysis initiation [89]. There have also been studies showing that the use of potassium-sparing diuretics in PD patients is useful for correction of hypokalemia [41]. There is one study of pediatric PD patients in which diuretic

Table 31.2 Antihypertensive medication dosing in children on dialysis[a]

Class	Drug	Usual pediatric dosing range	Excretion	Modifications in dialysis
Angiotensin receptor blockers	Candesartan	*1–6 years:* 0.2 mg/kg/day up to 0.4 mg/kg/day *6–17 years: <50 kg*: 4–16 mg QD *>50 kg:* 8–32 mg QD	K (L)	No known recommended adjustment but clearance reduced if GFR <30 mL/min; not removed by dialysis; give 50% of usual dose; consider dosing after HD session
	Losartan	0.75 mg/kg/day to 1.4 mg/kg/day; maximum 100 mg daily	K (L)	Not recommended if GFR <30 mL/min; not removed by dialysis
	Olmesartan	*20–35 kg:* 10–20 mg QD ≥*35 kg:* 20–40 mg QD	K (L)	Clearance reduced if GFR <20 mL/min; do not exceed 20 mg daily in such patients; not removed by dialysis
	Valsartan	*<6 years:* 5–10 mg/day up to 80 mg daily *6–17 years:* 1.3 mg/kg/day up to 2.7 mg/kg/day; maximum 160 mg daily	K (L)	Clearance reduced if GFR <30 mL/min; not removed by dialysis
Angiotensin converting enzyme inhibitors	Benazepril	0.2 mg/kg/day up to 0.6 mg/kg/day; maximum 40 mg daily	K (L)	No pediatric data. 20–50% removed by dialysis; Give 25–50% of usual dose; consider dosing after HD session
	Captopril	0.3–0.5 mg/kg/dose TID up to 0.6 mg/kg/day; maximum 450 mg daily	K	No pediatric data. 50% removed by dialysis. Give 25% of usual dose in HD patients; consider dosing after HD session. Give 50% QD of usual daily dose in PD.
	Enalapril[†]	0.08 mg/kg/day up to 0.6 mg/kg/day; maximum 40 mg daily	K (L)	Not studied in children with GFR <30 mL/min. 50% removed by dialysis. Give 50% of usual dose; consider dosing after HD session
	Fosinopril	0.1 mg/kg/day (up to 10 mg/day) up to 0.6 mg/kg/day; maximum 40 mg/day	K (L)	No known adjustments; not removed by dialysis
	Lisinopril[†]	0.07 mg/kg/day (up to 5 mg/day) up to 0.6 mg/kg/day; maximum 40 mg daily	K	Not studied in children with GFR <30 mL/min. 50% removed by dialysis. Give 25% of usual dose; consider dosing after HD session
	Quinapril	5–10 mg/day up to 80 mg daily	K (L)	No pediatric data. For adults with GFR 10–30 mL/min, do not exceed 2.5 mg/day; no data for GFR <10 mL/min
	Ramipril	1.6 mg/M^2/day QD up to 6 mg/M^2/day; maximum 20 mg daily	K (L)	No pediatric data. In adults with GFR <40 mL/min, give 25% of usual dose; 20% removal by dialysis. Consider dosing after HD session
α- and β-adrenergic antagonists	Carvedilol	0.1 mg/kg/dose BID (up to 6.25 mg) up to 0.5 mg/kg/dose; maximum 25 mg BID	L (K)	No adjustment needed; not removed by dialysis

Table 31.2 (continued)

Class	Drug	Usual pediatric dosing range	Excretion	Modifications in dialysis
	Labetalol	2–3 mg/kg/day BID up to 10–12 mg/kg/day; maximum 1200 mg daily	K (L)	No adjustment needed; not removed by dialysis
β-adrenergic antagonists	Atenolol	0.5–1 mg/kg/day up to 100 mg daily	K (L)	If GFR 15–35 mL/min, do not exceed 50 mg daily (reduction to 50% of usual dose); if GFR <15 mL/min, do not exceed 25 mg daily (reduction to 25% of usual dose). 50% removed by dialysis; consider dosing after HD session.
	Metoprolol	Immediate release: 1–2 mg/kg/day BID up to 6 mg/kg/day; maximum 200 mg daily Extended release: 1 mg/kg/day up to 2 mg/kg/day; maximum 200 mg daily	K (L)	No adjustment needed; not removed by dialysis
	Propranolol[†]	1 mg/kg/day TID-QID up to 8 mg/kg/day; maximum 640 mg daily	K	No adjustment recommended but can accumulate in renal impairment; not removed by dialysis
Calcium channel blockers	Amlodipine	0.06 mg/kg/day up to 0.6 mg/kg/day; maximum 10 mg daily	L	No adjustment needed; not removed by dialysis
	Diltiazem	1.5–2 mg/kg/day up to 6 mg/kg/day; maximum 360 mg daily	L (K)	No adjustment needed; not removed by dialysis
	Felodipine	2.5–10 mg/day; maximum 10 mg daily	L	No adjustment needed; not removed by dialysis
	Isradipine	0.05–0.15 mg/kg/dose TID/QID up to 0.8 mg/kg/day; maximum 20 mg daily	L	No adjustment needed; not removed by dialysis
	Extended-release nifedipine	0.25–0.5 mg/kg/day up to 3 mg/kg/day; maximum 120 mg daily	L	No adjustment needed; not removed by dialysis
Central α-agonist	Clonidine	5–20 mcg/kg/day BID up to 15 mcg/kg/day; maximum 0.9 mg daily	K (L)	No known adjustments; 5% removed on HD
Peripheral α-blockers	Prazosin	0.05–0.1 mg/kg/day TID up to 0.5 mg/kg/day; maximum 20 mg daily	L	No known adjustments; not removed by dialysis

(continued)

Table 31.2 (continued)

Class	Drug	Usual pediatric dosing range	Excretion	Modifications in dialysis
	Doxazosin	1 mg QD up to 4 mg daily; maximum adult dose is 16 mg daily	L	No known adjustments; not removed by dialysis
	Terazosin	1 mg QD up to 20 mg daily	L	No known adjustments; 10% removed on HD
Vasodilators	Hydralazine	0.25 mg/kg/dose TID up to 7.5 mg/kg/day; maximum 200 mg daily	L	No known adjustments; 25–40% removed by dialysis. Consider dosing after HD session.
	Minoxidil	0.1–0.2 mg/kg/day QD-BID up to 1 mg/kg/day; maximum 50 mg daily	L	No known adjustments
Diuretics	Chlorthalidone	0.3 mg/kg/day up to 2 mg/kg/day; maximum 50 mg daily	K (L)	Avoid in oligoanuria or with GFR <10 mL/min
	Furosemide	0.5–2 mg/kg/dose QD-QID up to 6 mg/kg/day; maximum 600 mg daily	K (L)	Avoid in oligoanuria; not removed by dialysis

[a]Recommendations represent the authors' opinions although every effort has been made to confirm by consulting appropriate references. Manufacturers' prescribing information is frequently updated and should be consulted whenever possible

[†]Commercially prepared suspension formulation available

Abbreviations used in table: *BID* twice daily, *GFR* glomerular filtration rate, *HD* hemodialysis, *K* Kidney, *kg* kilogram, *L* Liver, *mcg* microgram, *mg* milligram, *PD* peritoneal dialysis, *QD* once daily, *QID* four times daily, *TID* three times daily

use was retrospectively studied [48]. Children who received diuretics from the initiation of PD were 80% less likely to develop oligoanuria compared to those who did not receive diuretics; other outcomes were not examined.

Native Nephrectomy

Native kidney nephrectomy is typically considered the last resort in the treatment of hypertension in dialysis patients, reserved for those who remain hypertensive despite the measures discussed above (Fig. 31.2). The procedure has been shown to be effective in treating hypertension in children with ESRD [14], and newer surgical techniques may allow quick resumption of dialysis in children on PD who require this procedure [29].

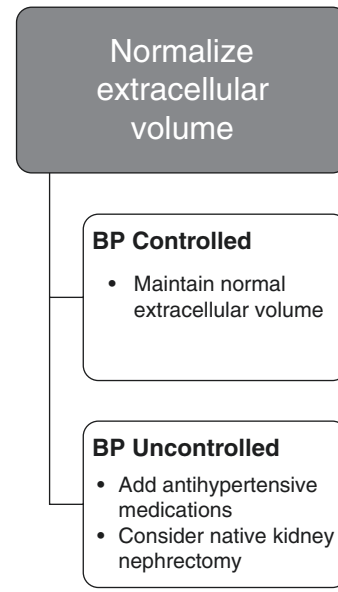

Fig. 31.2 Approach to management of hypertension in pediatric dialysis patients

There are two possible explanations for how nephrectomy can improve hypertension in patients on dialysis. As discussed earlier, the RAAS is a well-established cause of hypertension in CKD and in ESRD, and this may be related to the presence of native, diseased kidneys. Among 51 HD patients, plasma renin activity was higher among patients who had uncontrolled hypertension as compared to those whose BP was controlled by ultrafiltration and sodium restriction. Among the 18 who had uncontrolled hypertension, 17 had significant improvement in BPs after native nephrectomies [136]. In another study, treating patients with CKD with angiotensin converting enzyme inhibitors (ACEi) resulted in increased angiotensin 1–7 and decreased angiotensin II, whereas ESRD patients with ACEi therapy did not have a decrease in angiotensin II levels [121]. This may help explain why refractory hypertensive ESRD patients may benefit from native nephrectomies.

ESRD patients are also known to have increased sympathetic nervous system activity [26, 117]. The origin of the increased sympathetic nervous system activity may also be from the diseased native kidney. This was determined in an elegant study in transplant recipients who had continued activation of the sympathetic nervous system until they underwent native nephrectomies [52].

Summary

Hypertension is common among both PD and HD patients. It is an important modifiable condition, and one of the most important contributors to excess morbidity and mortality in this population. Accurate diagnosis with appropriate BP measurement, especially the use of ambulatory BP monitoring, is crucial in order to achieve optimal BP control. Management begins with the achievement of dry weight and avoidance of excessive interdialytic weight gain. When hypertension persists despite the achievement of euvolemia, antihypertensive medications may be required, and in some patients, native nephrectomies.

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