Chapter 7
Managing Blood Pressure in the Elderly: What Is Different?

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Introduction

Blood pressure (BP) management is essential in patients with end-stage kidney disease (ESKD) on maintenance dialysis as hypertension is the most common cardiovascular risk factor in this population. Even though this is true across all age groups, the aging process adds challenges to the evaluation and management of BP in dialysis patients. In this chapter, we will review aspects related to the management of BP and the treatment of hypertension in patients on chronic maintenance dialysis, with a focus on issues that are modified by the aging process, being mindful of the caveat that data restricted to elderly patients are scanty.

Epidemiology

The relationship between BP and outcomes in dialysis patients is complex. Many observational studies have shown an inverse relationship between BP and mortality in HD patients [1]. Fewer studies are available in PD cohorts, but the available literature shows similar results [2]. In summary, these studies suggest that the lowest mortality rates in HD patients occur with BP in the range that would be classified as hypertension in the general population (140–160/70–90 mmHg). In these observational studies, the highest mortality rates occur in patients with BP below 120/80 mmHg. Increased mortality in the high BP ranges is only observed when BP is above 180/100 mmHg. With relevance to the elderly, a recent cohort study noted

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this pattern to be more pronounced in the elderly [3]; in other words, *the older the patient group*, *the greater the impact of low BP on mortality risk*, *especially among those aged 70 and older*. In patients under age 60, low BP was not associated with increased risk. These findings raise concern that aggressive BP control in dialysis patients, particularly the elderly, could put them at risk for worse outcomes and certainly complicate efforts to establish BP targets (see below).

There are several possible explanations for this apparent paradox [1, 4]. The most commonly raised is that low BP is associated with congestive heart failure and other severe comorbidities and these observational studies are uniformly flawed by the absence of adjustment for cardiac function. In the only observational study where echocardiographic data were available, no such U-shaped relationship was noted [5]. In addition, there may be a time lag bias; patients have a high mortality in the early stages after initiation of dialysis due to other reasons, and patients with higher BP may take several years to have an impact of high BP levels on mortality. Lastly, there may be a role of the type of BP measurement used, as studies using 48-h ambulatory or home BP monitoring have identified a direct relationship between BP and mortality, differently from BP values obtained in the dialysis unit.

Approximately 90 % of patients with chronic kidney disease have a diagnosis of hypertension by the time they reach ESKD. Contemporary cross-sectional surveys indicate the prevalence of uncontrolled hypertension in hemodialysis (HD) patients to be ~70 %. Similar estimates apply to patients undergoing peritoneal dialysis (PD) (60–90 %) [2, 4]. Interestingly and contrary to what is observed in the general population, the prevalence of hypertension in dialysis patients has no linear relationship with age. Some reports reflect on the very low prevalence of hypertension among patients receiving daily HD, long nocturnal HD, and in selected populations undergoing conventional HD or PD while adhering to aggressive salt restriction. We are not aware of data exploring an interaction between age and blood pressure (BP) in these very selected populations.

Unfortunately, limited clinical trial data are available to isolate the effects of BP lowering as beneficial or detrimental in dialysis patients, and all clinical trials have been underpowered to answer this question. However, two meta-analyses have compiled results from clinical trials in HD patients [6, 7]. In these trials, active antihypertensive drug treatment resulted in BP that was 4.5/2.7 mmHg lower than in the control group. Aggregate results that include both hypertensive and normotensive patients indicate a decrease in risk of death or cardiovascular events of ~20–29 % among patients receiving active treatment. As one would expect, this effect was more prominent among patients who have hypertension (51 % risk reduction). Results from these meta-analyses, while not conclusive, dispel some of the concerns clinicians may have about treating hypertension in dialysis patients. We do not have specific trial data restricted to elderly patients.

Pathophysiology of Hypertension

The pathophysiology of hypertension in dialysis patients is complex, and there are a variety of factors contributing to it. Table 7.1 outlines some of the known factors involved.

Table 7.1 Factors contributing to pathogenesis of hypertension in dialysis patients

Sodium and water retention leading to extracellular volume expansion
Excessive vasoconstriction:
↑Renin-angiotensin system activity
↑Sympathetic nervous system activity
↑Ouabain-like factor
↑Vasopressin
↑Endothelin-1
Decreased vasodilation:
↓Nitric oxide
↓Kinins
Increased intracellular calcium
Increased arterial stiffness
Obstructive sleep apnea
Hyperparathyroidism
Erythropoietin therapy
Renovascular disease

Extracellular Volume Overload

This is the most common and most recognized reason for hypertension in dialysis patients. Increased extracellular fluid (ECF) volume measured with different methods is associated with increased BP levels, and that seems to be *more pronounced in older patients* [8]. Patients receiving daily or prolonged HD reach better BP control at least in part through improved ECF volume status, though other mechanisms are likely operative as well. In a randomized clinical trial in patients receiving conventional HD, increased ultrafiltration resulting in a 1 kg difference in dry weight between groups translated into a 6.6/3.3 mmHg reduction in BP over a 2-month period [9]. In PD patients, patients with peritoneal membrane characteristics leading to faster solute transport are predisposed to volume overload and hypertension [2]. In such patients, improvement of sodium balance with better ultrafiltration (e.g., through the use of icodextrin) results in lower BP levels. Likewise, sodium restriction is associated with improved BP levels in hypertensive HD and PD patients. Overall, volume excess is an important mediator of hypertension in dialysis patients and is particularly relevant because of it can be manipulated clinically in order to lower BP.

Imbalance Between Vasoconstrictive and Vasodilatory Systems

This is a complex area of research involving multiple pathways, and to date, all the elements at play are incompletely understood, but it is apparent that as noted in Table 7.1, several vasoconstrictor systems are commonly overactive in ESKD, whereas vasodilating mechanisms are typically blunted [4, 10]. Of relevance to therapy, the renin-angiotensin system is not usually overactive but fails to suppress

in the face of the attendant volume overload. In addition, intrarenal renin activity is markedly increased in dialysis patients. Also of relevance is the well-demonstrated overactivity of the sympathetic nervous system, including output from renal afferents. This can be manipulated pharmacologically and, more recently, with renal sympathetic denervation.

Role of Dialysate Prescription in HD

Dialysate concentration of sodium, calcium, magnesium, and potassium all have effects on intradialytic BP in HD patients [10]. BP increases upon exposure to high sodium or calcium and falls when the dialysate is high in potassium or magnesium. The impact of interdialytic BP is less clearly defined, though it appears that high sodium and calcium also have an effect on longer-term BP control. These observations have impact on treatment decisions (see below). The impact of dialysate composition on BP in PD patients has been less adequately studied, although the role of sodium and calcium appears similar to what is observed in HD.

Arterial Stiffness

Arterial stiffness is accelerated by kidney disease, and patients on dialysis have among the highest degrees of arterial stiffness [11]. This process is mediated largely by increased arterial wall calcification and decreased elastin content. Although aging is associated with arterial stiffening, the strength of this relationship is blunted in patients on dialysis. Arterial stiffness results in increased pulse wave velocity, which causes an increase in central arterial pressure as a consequence of faster reflection of pulse waves. BP lowering through any means but particularly through control of sodium excess and use of blockers of the renin-angiotensin system is an effective way of decreasing pulse wave velocity. However, there are no proven strategies to improve the fundamental abnormalities of the arterial wall.

The other mechanistic factors listed in Table 7.1 are also operative in some cases and need to be entertained as part of the evaluation of patients on dialysis, in particular those with difficult BP control.

Blood Pressure Measurement in Dialysis Patients

Method of BP Measurement

Either auscultatory or oscillometric measurements are acceptable in dialysis patients [12]. As with any hypertensive patient, close attention to recommended guidelines for BP measurement is needed (e.g., the American Heart Association

guidelines [13]), including avoidance of recent use of nicotine or caffeine. Because of the combined effects of aging and advanced kidney disease on arterial calcification, the possibility of noncompressibility of the brachial artery needs to be entertained as a cause of pseudohypertension. Patients should be screened by careful palpation of these vessels. Also, given the high prevalence of atherosclerotic peripheral arterial disease in ESKD, all patients should be screened periodically for interarm differences due to stenosis of the subclavian or axillary artery. If differences are observed, the arm with higher values should always be used. Unfortunately, performing this screen is problematic in HD patients with functional arteriovenous fistulae or grafts, which preclude BP measurement on their side. A means of bypassing this shortcoming is to check the BP in the thigh, using specific thigh cuffs. If the BP is higher in the thigh by >20 mmHg in the supine position, the patient should be monitored using the thigh, not the arm.

Orthostatic BP Measurement

Orthostatic hypotension (BP fall by >20/10 mmHg after 3 min of standing) is common in older patients, with or without a diagnosis of hypertension [14]. Among geriatric patients treated with antihypertensive drugs, orthostatic hypotension occurs in ~1/3 of patients. Patients on dialysis have impaired autonomic function and decreased baroreceptor sensitivity and are at increased risk for orthostatic hypotension. Furthermore, HD patients are at particularly increased risk of orthostasis following an HD session with ultrafiltration. All dialysis patients should have routine measurement of standing BP during all visits. HD patients must have standing BP measured prior to leaving the HD unit after a dialysis session.

"Location" of BP Measurement

There is growing evidence that the association between BP and outcomes is best assessed by BP measurements made outside of the office environment [1, 4, 10]. The most recent guidelines for patients with essential hypertension (2011 United Kingdom NICE guidelines and 2013 European Society of Hypertension guidelines) emphasize the importance of out-of-office BP monitoring for the diagnosis and management of hypertension. In dialysis patients, the observations are similar. Available cohort studies, although much smaller than in essential hypertension, corroborate the observations that out-of-office BP (48-h ambulatory BP or home BP) is a better predictor of mortality in HD patients. Data in PD are scarce but indicate greater ability of out-of-office BP to predict target organ damage (left ventricular hypertrophy, arterial stiffness) than conventional clinic BP measurements.

Besides the implications for prognosis, the following are relevant practical aspects of each type of monitoring:

- *Clinic* (*dialysis unit*) *BP*. This is by far the most applied in clinical practice, and it is the method adopted in the majority of studies that evaluated BP levels in maintenance HD. However, this method may be imprecise because HD facilities are very busy and BP measurements are usually not uniform and tend to overestimate BP compared with standardized measurements. Besides, in-center BP correlates poorly with interdialytic BP obtained by ambulatory BP monitoring. BP in peritoneal dialysis patients is more stable because PD patients do not have large variations in BP associated with fluid removal. Therefore, in PD patients BP can be better assessed by standard methods. When using clinic BP, it is important to make sure that devices are well calibrated, that cuff size matches the arm size of the patient, and that multiple readings are obtained and averaged. In HD patients, pre-, intra-, and post-HD values need to be integrated into the decision-making process (see below).
- *Home BP*. This is a simple and reliable method to estimate interdialytic BP profile and is superior to clinic BP as a guide to achieve BP control in HD patients. When performing home BP monitoring, patients should use a validated device (list available from www.dableducational.org) whose accuracy is confirmed by periodic matching with readings obtained by calibrated devices in the dialysis unit. Most guidelines recommend monitoring of BP twice a day (early in the morning before taking medications and in the evening before dinner) for a period of 5–7 days. If patients have symptoms suggestive of low BP, extra readings in the late morning and late evening can be added. We recommend that this monitoring be done once a month for HD patients and before every clinic visit for PD patients. Home systolic BP readings are typically 10/5 mmHg lower than office readings in the general population. In dialysis patients, however, the differences are smaller, typically less than 5 mmHg, possibly due to an underrepresentation of the white-coat effect and a higher prevalence of the "masked BP" effect in patients with advanced kidney disease.
- *Ambulatory BP monitoring* (*ABPM*). ABPM is considered the gold standard in BP measurement in dialysis patients. In HD patients, ABPM shows the actual BP burden that occurs during the interdialytic period. ABPM also has better reproducibility as compared with clinic BP and is the only method that evaluates BP during sleep, which provides relevant prognostic data. However, the use ABPM in clinical practice is limited by operational difficulties (patients are often resistant to wearing the monitor during the interdialytic period), limited availability, and lack of reimbursement.

BP Profile in Dialysis Patients

The analysis of 44-h interdialytic ABPM in HD patients shows that even in patients who lower their BP during ultrafiltration, about 50 % returns to hypertensive levels within 12 h after HD [4]. Both awake and sleep BP increase between HD sessions, so that BP is higher in the second interdialytic day in comparison with the first interdialytic day. In patients dialyzed thrice weekly, the BP rise in the longer

interdialytic period (72 h) in the third interdialytic day (measured by home BP) is attenuated in comparison with the first two interdialytic days.

The decrease in BP that normally happens during sleep is blunted in dialysis patients. Up to 80 % of HD patients are non-dippers (BP decrease less than 10 % during sleep), and a significant number of them are reverse dippers (BP higher during sleep). The possible causes of this abnormal circadian rhythm include volume overload, sleep-disordered breathing, and abnormalities in hormonal and neuroendocrine mediators mainly those associated with the sympathetic nervous system [4]. Non-dipping and reverse dipping may be associated with worse cardiovascular outcomes in dialysis patients. Due to fluctuations in cardiac output (intravascular volume changes) and increased arterial stiffness, systolic BP characteristically oscillates more than diastolic BP in dialysis patients, resulting in increased pulse pressure. No study has addressed BP profile specifically in the elderly dialysis patient.

BP Targets in Dialysis Patients

As noted above, many observational studies have shown an inverse relationship between BP and mortality in HD patients, whereas aggregate data from clinical trials actually suggest benefit from using antihypertensive agents in dialysis patients with hypertension. Reconciling these observations in the absence of definitive clinical trial data is difficult. Based on weak evidence, the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines recommended a target BP less than 140/90 mmHg pre-dialysis or less than 130/80 mmHg post-dialysis for HD patients [15]. These targets are reasonable, though one must understand that reaching these post-dialysis BP goals is associated with increased incidence of intradialytic hypotension.

One study compared the accuracy of the in-center BP measurements in conventional HD with interdialytic 44-h BP measured by ABPM, being considered hypertensive those patients with a 44-h average BP above 135/85 mmHg (levels extrapolated from the general population). In this study, pre-hemodialysis levels of 150/85 mmHg and post-hemodialysis levels of 130/75 mmHg had the best accuracy to diagnosis of interdialytic hypertension [16].

Overall, we do not disagree with the K/DOQI guidelines. However, we must be cognizant of the lack of data to support them. We find it more useful to use measures of interdialytic BP (home or ABPM) to assess overall BP control and to mitigate hypotension. As it relates to elderly patients, the situation is no different. However, given the evidence in the general population that elderly individuals may be at increased risk of worse outcomes when BP is lowered excessively, it may be prudent to use a more liberal approach to BP (i.e., higher BP targets, such as 150/90 mmHg) in elderly dialysis patients, particularly those aged 80 or older [17].

There are no specific guidelines for BP targets in PD patients; the K/DOQI guidelines do not provide any recommendations for this group of patients. We believe the practice should be similar to what is done in HD, using a clinic BP target of 140/90 mmHg in most patients (150/90 mmHg in older patients) [18].

Assessment of Target Organ Damage

We routinely evaluate target organ damage (heart, brain, large vessels, and eye) in dialysis patients. Patients should be routinely asked about symptoms related to these organs, including focal neurological deficits, symptoms of congestive heart failure, coronary disease, or peripheral arterial disease. Periodic examination of all patients should include a fundoscopic exam, with more detailed ophthalmologic evaluation in those with diabetes to identify the coexistence of retinal abnormalities. We obtain EKGs yearly, and all patients receive an echocardiogram to evaluate left ventricular mass and function, as these findings help guide treatment choices, such as the use of blockers of the renin-angiotensin system, vasodilating beta-blockers, and mineralocorticoid receptor antagonists in patients with systolic dysfunction.

Additionally, cardiovascular risk factor evaluation and modification is important, including advice about smoking cessation, increased aerobic exercise, evaluation and treatment of hyperlipidemia (preferably with a statin, although the clinical trial data in dialysis patients remain conflicting), and control of diabetes.

Management of Blood Pressure in Dialysis Patients

Knowledge of the multiple factors that can influence BP in dialysis patients (Table 7.1) and of disorders that are more prevalent in the elderly (Table 7.2) is important when making decisions regarding BP management in elderly dialysis patients. Mindful of these factors, the strategies to be used to control hypertension in dialysis involve four essential items: control of ECF volume through ultrafiltration, management of sodium balance through diet and dialysate prescription, judicious use of antihypertensive drugs, and consideration of alternative dialysis modalities, particularly daily and long-duration HD. Very limited data are specific to the elderly, so most of our recommendations listed below are based on data from the general dialysis population.

Table 7.2 Specific factors that can influence the management of blood pressure in elderly dialysis patients

Factor	Impact
Arterial stiffness	Difficult to control systolic BP
	Predisposition to intradialytic hypotension
Congestive heart failure	Dictates drug choices
	Predisposition to intradialytic hypotension
Cardiac arrhythmias	May dictate drug choices
Renovascular disease	Treatment may improve resistant hypertension (rare)
Thyroid disorders	If present, may increase BP. Screening and treatment is indicated
Sleep apnea (both obstructive and central)	Treatment with noninvasive positive-pressure ventilation improves BP

Control of Extracellular Fluid Volume

Sodium and water retention and their removal by the dialysis procedure have a pivotal role in determining BP levels and BP profile in dialysis patients. In dialysis patients with residual renal function, the use of diuretics can aid in the achievement of optimal volume control. The effective use of diuretics in dialysis patients often requires high oral doses of loop diuretics (e.g., furosemide 120–200 mg twice daily) in combination with a potent thiazide agent (e.g., metolazone 10 mg once or twice daily). This strategy could also avoid the need for aggressive ultrafiltration during dialysis.

In anuric dialysis patients, dietary sodium intake directly influences fluid ingestion and interdialytic weight gain [19]. This is because human physiology strives to preserve extracellular osmolality at an apparent fixed osmolar set point. In functionally anephric dialysis patients, the main osmolar regulator is thirst. For example, an HD patient who ingests 8 g of sodium chloride in one interdialytic day theoretically would have to ingest 1 l of water to maintain his or her osmolar homeostasis, and consequently, a small reduction of 2 g in sodium chloride ingestion a day may reduce 200 g in the daily weight gain. Thus, dietary sodium restriction, rather than fluid restriction, is critical in decreasing interdialytic weight gain and BP in HD patients. The same concept of an osmolar set point also determines the effect of dialysate sodium concentration on weight gain and BP. If the prescribed dialysate sodium concentration is higher than the patient's serum sodium concentration, then the high concentration gradient could result in unnecessary sodium load which in turn leads to fluid retention and hypertension [20]. Several studies in which the dialysate sodium prescription was reduced showed a reduction in interdialytic weight gain and BP. However, recent observational studies have raised concerns about the use of low dialysate sodium concentration [21]; therefore, large prospective studies will be necessary to guide the use of low dialysate sodium to control BP. It is safe to say, however, that high dialysate sodium or the use of sodium modeling should be avoided in hypertensive HD patients.

Assessment and Achievement of Dry Weight

The first step in BP control in HD patients is achieving the correct dry weight, which is the reference used in HD to determine the ultrafiltration volume in each HD session. In current clinical practice, dry weight is defined primarily as the weight at the end of the HD session that leaves the patient either without hypovolemia (hypotension and associated symptoms) or hypervolemia (hypertension or other evidence of volume overload). Although this approach seems reasonable, more specific estimations of extracellular volume have uncovered the inaccuracy of this clinical method [22, 23]. Bioimpedance analysis has shown that a large percentage (25–50 %) of patients have augmented ECF despite a normal clinical exam. Likewise,

hypertensive HD patients who appear to be at their clinical dry weight often have a significant reduction in BP with a stepwise reduction (probing) of dry weight [9].

Figure 7.1 summarizes our proposed approach to the hypertensive dialysis patient who does not have obvious evidence of volume overload on clinical exam (pulmonary congestion, jugular venous distension, and edema). Assuming maximal dietary sodium restriction and limited sodium influx through the dialysate are already operative, we then proceed with increased ultrafiltration to lower the dry weight. In patients on conventional HD, we push the ultrafiltration targets by 0.3–0.5 kg per session so as to progressively lower the target post-HD weight. This is continued until the achievement of normotension or the development of intradialytic symptoms such as cramping, nausea/vomiting, chest pain, or intradialytic hypotension. In the elderly, dry weight accomplishment has to be cautious because older patients are at increased risk of intradialytic hypotension (see discussion below). Therefore, smaller increments in ultrafiltration targets are often indicated. In PD patients, increased ultrafiltration is achieved by increased PD fluid osmolality, or preferably, through the use of icodextrin, particularly in patients with peritoneal membrane with rapid solute transport characteristics.

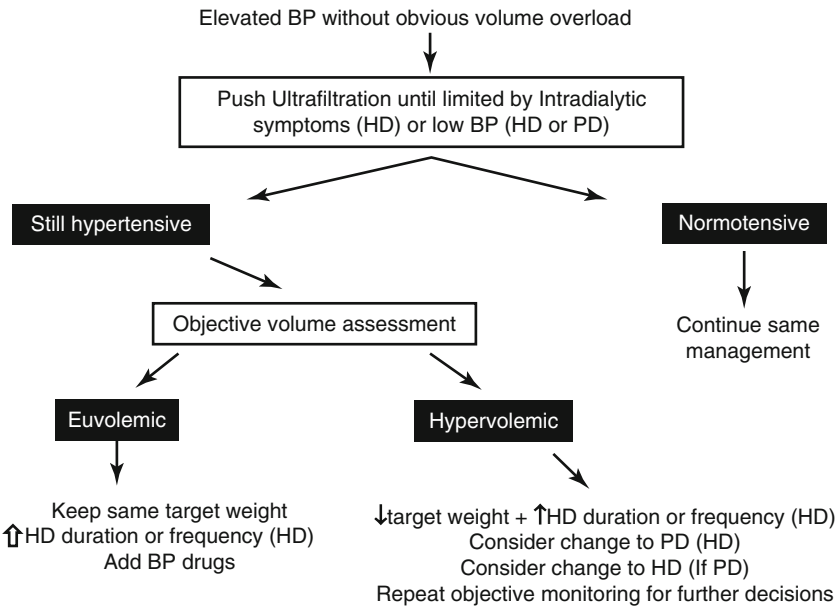

Fig. 7.1 Approach to blood pressure and volume management in dialysis patients. *BP* blood pressure, *HD* hemodialysis, *PD* peritoneal dialysis. Objective indicators of hypervolemia: inferior vena cava (IVC) ultrasound with inspiratory IVC collapse <25 %. Bioimpedance evidence of extracellular fluid volume excess (>25 % in women, >28 % in men). Blood volume (BV) monitoring evidence of flat residual BV slope (<1.33 %/h) during ultrafiltration). Can be used in hemodialysis patients only

If the patient remains hypertensive, objective assessment of ECF volume, if available, is indicated. The most accurate and best-studied method to determine ECF volume in dialysis patients is bioimpedance. The test provides a direct estimate of ECF volume with normative values for age and gender. A consensus position is that ECF volume expansion that is greater than 15 % of the predicted ECF volume is definitive evidence of volume overload. These measurements can be trended over time to evaluate the effectiveness of ultrafiltration. Inferior vena cava (IVC) ultrasound evaluates the changes in IVC diameter during the respiratory cycle as a marker of volume expansion. If the IVC diameter decreases by less than 25 % during inspiration, this is evidence of intravascular (and presumably ECF) volume expansion. Not as well studied but perhaps the most commonly available method to estimate ECF volume status is the analysis of blood volume changes during HD. Patients with ECF volume expansion have a flat slope of change in blood volume during ultrafiltration (less than 1.3 % per hour) [24]. As ultrafiltration rates are increased to achieve higher total ultrafiltration volumes, the slopes tend to change toward the target slope of 2.4–5.6 % per hour. When the slopes reach this range, there is no further benefit from ultrafiltration on BP reduction. For obvious reasons, blood volume monitoring cannot be used in PD patients.

After applying one of these objective measures of ECF volume expansion, we take the following approaches in case the patient remains hypertensive (Fig. 7.1):

1. In HD patients, if there is no evidence of ECF volume expansion, no further titration of dry weight is indicated. In such cases, the patient is declared resistant to pure control of ECF volume. There are two acceptable approaches to this problem: use of longer dialysis hours, use of short daily HD (e.g., 2 h/day 6 days/week), or addition of antihypertensive drugs. If it is a PD patient, the only possible resorts available are the use of drugs or conversion to long-hours HD or short daily HD. Because of issues regarding patient acceptance and lack of reimbursement for longer HD hours and/or increased HD frequency, these very effective options are largely underutilized in most countries, thus leading to the use of the second option, antihypertensive drugs (see below for details on their use).
2. If the patient remains hypertensive and the ECF volume is still expanded in an HD patient, dry weight needs to be titrated further down. The problem is that the reason why the dry weight could not be probed further was probably the development of intradialytic symptoms. In such case, the patient needs either a lower interdialytic weight gain to minimize ultrafiltration needs and improve HD tolerability or a slower means of volume removal, i.e., daily or long HD, or transfer to peritoneal dialysis.
3. By definition, patients who require objective measurement of ECF volume expansion cannot be adequately evaluated by the clinical exam. Therefore, if they remain hypertensive after changes outlined in #2, they require repeat objective assessment in order to delineate further treatment decisions.

Use of Antihypertensive Drugs in Elderly Dialysis Patients

Because of the limitations discussed above, drugs are often used to treat hypertension in the large majority of dialysis patients. As discussed before, two meta-analyses of randomized clinical trials have suggested cardiovascular and mortality benefit from antihypertensive drugs in dialysis patients. These trials included ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and the vasodilating beta-blocker carvedilol. More recent studies also suggest improved outcomes with the use of spironolactone [25, 26]. It is safe to say that most drug classes are effective in lowering BP in dialysis patients, with the exception of thiazides and loop diuretics in patients without residual renal function. In considering which drugs to use, we take into account the following elements:

1. Duration of action of the agent. Our preference is to use long-acting agents, as they make the treatment regimen easier for the patient. This is particularly important in elderly patients because of the frequent coexistence of cognitive impairment. In dialysis patients, the use of drugs that are excreted through the kidney is often preferable, as the absence of renal function increases their duration of action. For example, atenolol and lisinopril have been used with thrice weekly post-HD dosing in HD patients. This may be particularly useful in non-adherent patients, who can receive their medications immediately following HD under "directly observed therapy."
2. Removal of the agent by the dialysis procedure (relevant for HD patients). This has relevance to patients who have intradialytic hypertension (see below) and also to determine the need to provide any supplementation of agent following HD. Table 7.3 lists agents that are either not removed or only minimally removed by dialysis. It is important that the clinician becomes familiarized with the HD handling of the group of drugs that he/she preferentially uses in practice.
3. "Compelling" indications for a specific agent or drug class. This issue relates particularly to coexisting cardiovascular diseases (Table 7.4). Even though clinical trials in these conditions have rarely included dialysis patients, most experts agree that extrapolations from the general population are acceptable in the management of dialysis patients, thus guiding the choice of agent in many patients.
4. Potential relevance to problems commonly encountered in elderly patients. Table 7.5 lists clinical issues that are common in the elderly and that may call for a specific agent or drug class or may raise concerns about their use.

Table 7.3 Antihypertensive drugs that are not removed or only minimally removed by hemodialysis

ACE inhibitors	Benazepril, fosinopril
Angiotensin receptor blockers	Losartan, valsartan, telmisartan, candesartan
Calcium channel blockers	Amlodipine, felodipine, nifedipine, verapamil, diltiazem
α-blockers, β-blockers, and combined α- and β-blockers	Carvedilol, labetalol, bisoprolol, terazosin, doxazosin
Other agents	Clonidine, minoxidil

Table 7.4 Comorbid conditions that represent "compelling" indications for certain antihypertensive drug classes in hypertensive dialysis patients

Condition	Drug class(es) recommended
Heart failure with ↓ left ventricular systolic function	ACE inhibitors, angiotensin receptor blockers, vasodilating β-blockers, mineralocorticoid receptor antagonists
Coronary artery disease	β-blockers, ACE inhibitors
Left ventricular hypertrophy	Angiotensin receptor blockers, ACE inhibitors
Atrial fibrillation	β-blockers or non-DHP CCB (especially diltiazem) is the main agents used for heart rate control
Diabetes mellitus	ACE inhibitors or angiotensin receptor blockers
Stroke	ACE inhibitors (thiazides not indicated for this purpose in dialysis patients)

Table 7.5 Common clinical problems that may impact on antihypertensive drug choices in elderly dialysis patients

Condition	Comment
Cognitive dysfunction	Nonselective β-blockers (propranolol) and central antiadrenergic agents (clonidine, methyldopa) may rarely precipitate delirium
Depression	Lipophilic β-blockers (propranolol, metoprolol) may rarely increase depressive symptoms
High fall risk	Central antiadrenergics commonly cause excessive sedation and fatigue
Essential tremor	Nonselective β-blockers (propranolol) improve symptoms
Constipation (functional)	CCBs, especially non-DHP (diltiazem, verapamil), worsen colonic motility
Prostatic hyperplasia	α-blockers improve urine flow and obstructive voiding symptoms in dialysis patients who have residual urine output
Obstructive lung disease	β-blockers are generally safe, though may induce worsening symptoms in patients with significant airway reactivity

CCB calcium channel blocker, *DHP* dihydropyridines

Intradialytic Hypertension

The existence of patients who have an increase in BP during HD has long been recognized. However, recent cohort studies have described an association between an intradialytic rise in systolic BP (post-dialysis-pre-dialysis BP) of ≥10 mmHg and risk of death and hospitalization in HD patients. As a result, the increase in ≥10 mmHg has been used to define HD patients with intradialytic hypertension (ID-HTN), a process that occurs in 10–15 % of patients on conventional HD [10]. Interestingly, this definition includes patients who are normotensive at baseline, and in fact, one study showed that ID-HTN was associated with mortality only in patients with pre-HD SBP <120 mmHg. Patients with ID-HTN seem to be older and have lower body weight and evidence of undernutrition (lower serum creatinine and albumin levels). It thus appears that patients with ID-HTN may be sicker than patients who respond to UF with a fall in BP.

While not fully elucidated, the pathophysiology of ID-HTN is associated primarily with increased peripheral vascular resistance (Table 7.6). Faster plasma refilling

Table 7.6 Potential mechanisms associated with intradialytic hypertension

Patient factors:
Failure to reach estimated dry weight (i.e., volume overload)
Endothelial dysfunction:
HD removal of antihypertensive drugs
Hypokalemia
Dialysis procedure factors:
Dialysate composition (high sodium, high calcium, low potassium)

associated with volume overload could facilitate BP increase, and this hypothesis is corroborated by studies demonstrating less ID-HTN after aggressive probing of dry weight. Endothelial dysfunction resulting in increased vasoconstriction is characteristic of ID-HTN.

The management of ID-HTN requires a multipronged approach. First, one must ascertain that the patient is not volume expanded. If volume expanded, dry weight probing should take place as described above. In addition, factors such as high dialysate sodium and calcium must be avoided in the HD prescription, and prescribing antihypertensive drugs that are not removed in HD is a rational method in the treatment of ID-HTN. Finally, the vasodilating beta-blocker carvedilol, in doses of up to 50 mg twice daily, reduced the episodes of ID-HTN and improved endothelial function in a prospective crossover study of patients with ID-HTN [27].

Management of Intradialytic Hypotension in the Elderly

Unfortunately, the search for BP control in hypertensive HD patients often results in the dreaded complication of intradialytic hypotension (IDH), which is the fall in systolic BP by at least 20 mmHg accompanied by symptoms of organ ischemia that require intervention. IDH is the most common complication of HD, occurring in ~25 % of cases and in even higher rates among elderly patients and those with heart disease, diabetes, and autonomic neuropathy [10]. It is a consequence of an inadequate cardiovascular response to the reduction in blood volume during ultrafiltration. Because of impaired baroreflex function, elderly patients are particularly prone to IDH. Moreover, the consequences of IDH may be more severe in the elderly: dizziness, fatigue, and weakness may predispose to falls; underlying cerebrovascular disease may facilitate the occurrence of syncope, seizures, transient ischemic attacks, or stroke during IDH episodes; underlying coronary artery disease may result in myocardial infarction or cardiac arrhythmias during IDH; and repetitive episodes of IDH may be associated with asymptomatic myocardial ischemia and irreversible cardiac damage over time.

One or more of the factors that control BP in HD and keep hemodynamic stability can be affected in IDH-prone patients. Patient-specific factors and HD-related

factors should be thought to prevent IDH episodes. These factors include aggressive ultrafiltration; decline in extracellular osmolality; impaired venoconstriction of the splanchnic circulation, which decreases venous pooling, impaired vascular response (decreased vasoconstriction or enhanced vasodilation); and structural heart disease. Identification of these processes is important in the mitigation of IDH.

Often in clinical practice, managing hypertension on the one hand and IDH on the other needs to take place. The management of IDH frequently requires multiple interventions that are summarized in Table 7.7. Finding the balance between BP control in the interdialytic period and BP "safety" during the HD session is a critical aspect of the care of complex elderly HD patients.

Table 7.7 Interventions for the management of intradialytic hypotension

Optimize dry weight, making sure that the patient is not volume depleted
Decrease interdialytic fluid gain
Treat reversible cardiac diseases (myocardial ischemia, aortic stenosis, pericardial effusion)
Adjust antihypertensive medications. Consider holding them on the days of HD. Consider evening dosing to minimize morning hypotension
High sodium dialysate or sodium modeling. Monitor interdialytic weight gain as it may increase
Ultrafiltration profiling (often combined with sodium modeling). Consider longer HD or addition of extra sessions to avoid the use of fast ultrafiltration rates
Avoid food during dialysis
Cool dialysate (~36° Celsius)
Avoid low-calcium dialysate
Correct severe anemia
Screen for and correct carnitine deficiency if present
Pharmacological therapy: midodrine (2.5–15 mg orally given 15 min prior to HD)

Key Points

1. Orthostatic hypotension is common in the elderly. HD patients must have standing BP measured prior to leaving the HD unit after a dialysis session.
2. Extracellular volume overload is the most important reason for hypertension in elderly dialysis patients.
3. Achievement of dry weight must be cautious in the elderly dialysis patient.
4. Choice of antihypertensive drugs often depends on comorbid conditions that are common in the elderly.
5. Intradialytic hypotension and intradialytic hypertension are adverse intradialytic events that are more frequent in the elderly.
6. Longer HD hours and short daily HD should be considered for a better BP control in the elderly dialysis patients.

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