

## Hemodialysis: Core Curriculum 2014

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### PRINCIPLES OF DIALYSIS AND HOW MODALITIES DIFFER

Dialysis evolves as we learn more about the uremic condition. In its earliest versions, the major transport process was diffusion, the spontaneous movement of particles down a concentration gradient. This required concomitant ultrafiltration generated by osmotic, oncotic, or hydrostatic pressures. Consequently, ultrafiltration's solvent drag effects led to an appreciation of the importance of convective transport and its advantage in enhancing the removal of species of larger molecular size (that is, higher molecular weight plus steric hindrance; Fig 1). Thus, contemporary dialysis uses both diffusive and convective transport, and modern equipment allows for each process to occur independently or in combination. Currently, dialysis cannot replace the endocrine or metabolic functions of the kidney, so our discussion is restricted to solute and fluid removal.

Solute removal is measured in mass (eg, grams), which is determined by comparing total-body solute mass before and after dialysis, usually by extrapolation. Measuring the acquisition of solute in effluent dialysate is easier. The difference between the mass acquired in the dialysate and the mass removed from the body is called mass balance error and usually reflects the solute binding to the dialyzer membrane. This can be clinically relevant for antibiotics and cytokines. Solute removal also may be measured as the extraction ratio, which is the fraction of solutes removed from blood in a single pass through the dialyzer. Extraction ratio is determined as  $(C_{in} - C_{out})/C_{in}$ , where  $C_{in}$  is solute concentration in the blood entering the dialyzer and  $C_{out}$  is the concentration in the blood exiting the dialyzer. The extraction ratio is dependent on blood ( $Q_b$ ) and dialysate ( $Q_d$ ) flow rates, the dialyzer membrane, and the intrinsic properties of the solute, such as molecular size and protein binding. The extraction ratio is high in traditional thrice-weekly hemodialysis (HD) and lower in short daily HD. We use a variation of this formula, urea reduction ratio, to measure urea removal during HD.

Another method of indirectly assessing solute removal uses the concept of clearance, which is the volume (of plasma, serum, blood, or the entire body) from which all the solute was removed during a specific period; hence, the units are volume/time. Plasma is the fraction of blood that is not cellular, and plasma water makes up ~94% of plasma. Plasma

water is what is dialyzed. When a solute's concentration gradient is from blood cells to plasma water (eg, potassium), the amount removed during dialysis may exceed the amount in plasma water. For urea, we often evaluate dialysis dose by total-body clearance, which is the  $K$  in  $Kt/V$ . The  $t$  refers to the duration of the clearance period, and the  $V$ , to the volume of distribution of the substance (for urea,  $V$  = total-body water). The  $V$  term normalizes the  $Kt$  product to body size. In dialysis practice, in HD, clearance is determined from what was removed from the blood, whereas in peritoneal dialysis (PD), clearance is determined by what is acquired in the dialysate.

Instantaneous blood clearance in HD is extraction ratio multiplied by  $Q_b$  (Fig 2A). In clinical practice, we measure blood urea before and after HD. Clearance does not change during an HD session unless operating conditions are altered. As solute is removed,  $C_{in}$  declines such that the fraction of total removal declines over the course of the dialysis session, but clearance remains constant. Because  $C_{in}$  is highest at initiation, the greatest amount of mass removed is early in the treatment: hence, repeating HD frequently may be very effective in improving total weekly solute removal. Dialysis clearance can never exceed  $Q_b$ . If all the blood is cleared, clearance equals  $Q_b$ . Clearance can never exceed the  $Q_d$ . If the dialysate is 100% saturated (equilibrated) with solute, the clearance equals  $Q_d$ . This concept is important when dialysate is limited, as it is in PD and some short daily HD systems (eg, NxStage). Figure 2B shows the relationship between clearance,  $Q_d$ , and molecular size. Comparing clearance across different dialysis modalities is done best by using a week as the interval, adjusting for the continuous nature of PD versus the intermittent nature of HD and accounting for the frequency of the intermittent treatments, as first proposed by Gotch.

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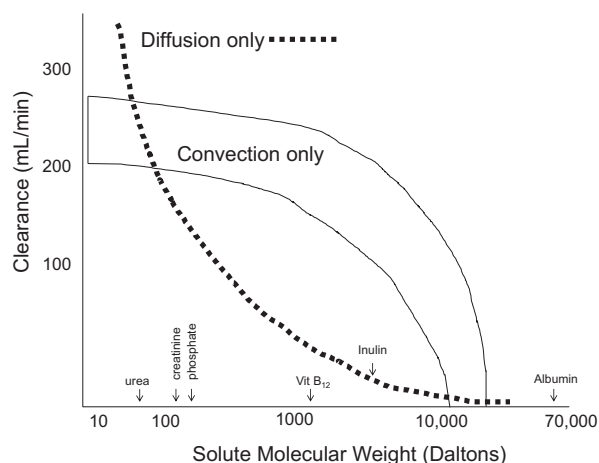
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**Figure 1.** An approximation of the difference in clearance between pure diffusive processes and pure convective process by the molecular weight of the solute. Abbreviation: Vit B<sub>12</sub>, vitamin B<sub>12</sub>.

In short daily HD using the most popular system in the United States, NxStage System 1, and PD, the limit to clearance is the availability of dialysate. In each therapy, the goal is to use dialysate efficiently, which means equilibrating dialysate with the solutes of uremia. In PD, peritoneal blood flow is limited, so saturating dialysate takes more time than in short daily HD, in which  $Q_b$  is 3 times  $Q_d$ . Both differ from standard thrice-weekly HD, in which dialysate is relatively unlimited. In PD, the saturation is defined by the dialysate to plasma concentration ratio, whereas in short daily HD, it is derived from the ratio of  $Q_d$  to  $Q_b$ , which is called flow fraction. When flow fraction is  $<40\%$ , dialysate saturation with urea is

$>90\%$ . The per-treatment  $Kt/V_{urea}$  for short daily HD is about 0.45, so 5 or 6 treatments per week is at least equivalent to thrice-weekly traditional HD. A comparison of weekly standardized  $Kt/V_{urea}$  over different modalities is shown in Fig 3.

### Additional Readings

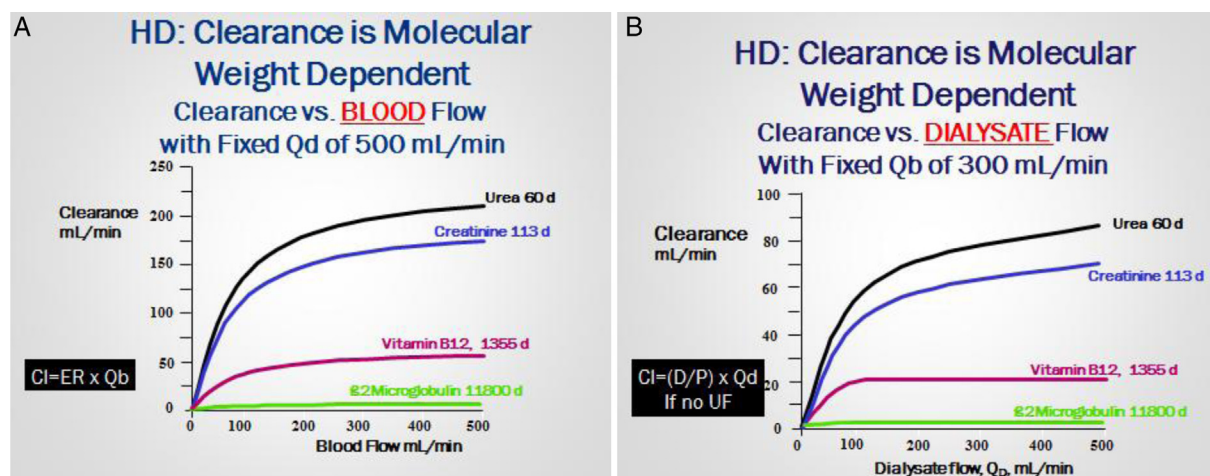
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### MECHANISMS OF SOLUTE TRANSPORT AND REMOVAL BY HD

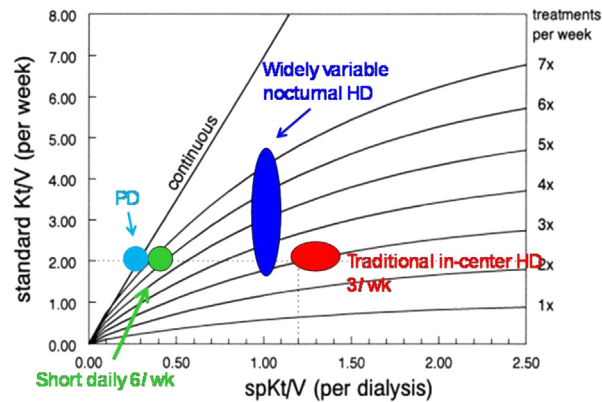
To be removed by HD, solute must move from its production/storage site to the blood, then to the dialyzer, and then to the dialysate. Each of these sequential steps is affected by the properties of the molecular species itself, as well as the dialytic operating conditions. These concepts are described using urea as an example.

#### Solute Transport Within the Body

Urea, a 60-Da, unbound, uncharged, water-soluble end product of protein catabolism, distributes from the liver to nearly all tissues. It is generated slowly enough for equilibration to occur between extracellular (interstitial and plasma) and cellular water. During HD, blood levels decrease sharply, but re-equilibrate as urea is recruited from the body.



**Figure 2.** (A) Instantaneous blood clearance (Cl) in hemodialysis (HD) is the extraction ratio (ER) times blood flow rate ( $Q_b$ ) and is dependent on solute molecular weight, among other things. (B) Cl in HD is the saturation fraction of dialysate concentration (D) over the plasma concentration (P) times dialysate flow rate ( $Q_d$ ) and is dependent on solute molecular weight, among other things. At greater  $Q_d$ , there is more turbulence, which reduces both dialysate “channeling” and boundary layer effects. Reproduced from Canaud B, Leray-Moragués H (“Conduite de l’hémodialyse et prévention de ses complications” [published online ahead of print October 28, 2013]. *EMC-Néphrologie.* Doi: 10.1016/S1762-0945(06)43988-7) with the permission of Elsevier. Copyright © 2013 Elsevier Masson SAS. All rights reserved. Abbreviations: d, dalton; UF, ultrafiltration.



**Figure 3.** Using standard Kt/V as originally proposed by Frank Gotch, one can compare frequency and intensity of differing dialysis modalities. Modified and reproduced from Gotch (“The current place of urea kinetic modeling with respect to different dialysis modalities.” *Nephrol Dial Transplant*. 1998;13 [suppl 6]:10-14), with permission of the Oxford University Press. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

However, urea movement out of tissues into blood may be limited by poor tissue perfusion, as well as other forms of intercompartmental transport delays, which is postulated as the cause of dialysis disequilibrium syndrome. Hypotension during dialysis may lead to underperfusion of solute-rich tissue such as skeletal muscle. After HD, tissue beds slowly equilibrate with blood over a course of minutes to hours and urea levels increase, a process called urea rebound. Blood levels immediately after dialysis do not perfectly reflect urea levels in all tissues, which gives rise to 2 different indexes: single-pool Kt/V (spKt/V) based on urea level at the conclusion of HD and equilibrated Kt/V based on urea levels measured 30-60 minutes after HD.

### Solute Transport Within the Dialyzer

A roller pump pushes blood through the HD circuit with probably 95% of the accuracy displayed by the machine. Dialysate moves from the proportioning system to the dialyzer, and a second pump moves it out of the dialyzer and into a drain. The difference in pumping rates between these 2 pumps determines the amount of fluid that gets ultrafiltered. A sensor evaluates conductivity as a surrogate for ionic strength to ensure proper proportioning. Another sensor detects blood in dialysate, which would indicate a rupture in the circuit, usually in the hollow fibers.

Most modern dialyzers use hollow fibers made of highly biocompatible synthetic material that maximizes surface area, does not expand under pressure, and has a relatively small extracorporeal blood volume commitment. Solute transport within the dialyzer is a function of blood flow distribution, blood-membrane interactions, membrane characteristics, and dialysate flow distribution.

### Dialyzer Characterization by Efficiency and Flux

Efficiency ratings refer to urea clearance, which is almost exclusively dependent on dialyzer surface area and  $Q_b$ . The manufacturer reports a dialyzer’s ability to remove urea as the KoA using milliliters per minute. Conceptually, KoA can be considered the urea clearance at infinitely high  $Q_b$  and  $Q_d$ ; it is meant to reflect intrinsic dialyzer characteristics. In actual use, dialyzers may have significantly impaired performance when contrasted to manufacturers’ reported values. Low-efficiency units have  $KoA < 450$  mL/min, whereas high-efficiency units have  $KoA > 700$  mL/min. The flux definition is not precise, but the HEMO (Hemodialysis) Study chose  $\beta_2$ -microglobulin (12,800 Da) clearance of at least 20 mL/min as their definition of high flux, whereas  $\beta_2$ -microglobulin clearance  $< 10$  mL/min was defined to be low flux. High-efficiency and high-flux dialyzers are very water permeable and must be used in conjunction with ultrafiltration rate controllers. The ability of a dialyzer to remove “middle molecules” (500-5,000 Da) must be balanced by the requirement that the dialyzer not leak important polypeptides. The sizes and shapes of the pores within the membrane are governed by the thermodynamics of the polymer, and advancements have gradually achieved this goal. Uremic solute clearance depends on whether the solute is small enough to pass through the membrane’s pores. Urea passes freely, albumin is reflected, and  $\beta_2$ -microglobulin is partially blocked. Smaller species diffuse faster than larger, while size effect is less significant with convection, leading to the use of convective or mixed convective-diffusive therapies (see Fig 1).

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### PRACTICAL ISSUES

The components of the necessary prescriptions for HD are discussed throughout the remainder of this Core Curriculum (Box 1).

### Dialyzer Performance and Selection

The National Cooperative Dialysis Study, the HEMO Study, and observational epidemiology of the US Renal Data System have led to a “guideline” expectation that each episode of thrice-weekly HD



**Box 1.** Components of the Hemodialysis Prescription

- Type of access and needle size
- Qb
- Qd
- Duration (time)
- Frequency
- Dialyzer size
- Dialyzer membrane material
- Anticoagulation regimen
- Dialysate composition of Na, K, bicarbonate, Ca
- Estimated dry weight
- Limitations to UFR
- Special medications

Abbreviations: Ca, calcium; K, potassium; Na, sodium; Qb, blood flow rate; Qd, dialysate flow rate; UFR, ultrafiltration rate.

achieve a minimum  $\text{spKt/V}$  of 1.2. To minimize treatment time, Qd is twice Qb, allowing urea clearance and total removal to be a strong function of achieved Qb.

The major clinical factors to consider in selecting a dialyzer are membrane material, sterilization method, surface area, and preferred flux. Cellulosic membranes perform adequately; choice is driven primarily by idiosyncrasies and cost. Angiotensin-converting enzyme inhibitors predispose patients to anaphylactic reactions when exposed to polyacrylonitrile membranes, and rare reactions to polysulfone or polyethersulfone occur. Dialyzers are sterilized by ethylene oxide, steam, radiation, or chemical reprocessing. Ethylene oxide and reprocessing chemicals must be completely flushed from the device because remnants are toxic. Consequently, using steam- or radiation-sterilized dialyzers may be simpler than mandating the additional maintenance and practice activity.

**Assessing Inadequate Urea Clearance**

The failure to deliver thrice-weekly  $\text{spKt/V} > 1.2$  deserves attention (Box 2). The blood pump is rarely an issue. Thus, the first concern is if the access is adequate to deliver  $\text{Qb} > 300 \text{ mL/min}$ . At this rate, a Qd to Qb ratio of 2 with a moderate or large surface area dialyzer should lead to dialyzer  $\text{C}_{\text{out}}$  urea level  $< 10 \text{ mg/dL}$ . If this does not occur while Qb and

**Box 2.** Items to Assess When Solute Clearance Per Session Is Marginal

- Adequacy of blood flow from the access
- Blood pump speed
- Qd
- Dialyzer surface area
- Duration of dialysis
- Fiber bundle clotting
- Dialysate pathway stagnation

Abbreviation: Qd, dialysate flow rate.

dialyzer size are maximized, it is necessary to increase dialysis time. Many clinicians think that increasing time should be an earlier step because longer sessions mean slower (and safer) ultrafiltration rate and a better chance to clear molecules larger than urea. Staff costs and patient reluctance are the main barriers to increasing time.

The HEMO and Membrane Permeability Outcomes (MPO) studies could not prove a clear benefit of high-versus low-flux dialyzers, but a subgroup analysis of the HEMO Study showed a statistically significant decrease in all-cause mortality in the high-flux arm with dialysis vintage longer than 3.7 years. It may take years of end-stage renal disease for conditions attributed to middle-sized molecules to emerge. Because the cost is hardly different, the only reason to use low-flux dialyzers would be when water purity is suspect.

**Anticoagulation**

Weight-based unfractionated heparin is the most commonly used anticoagulant because it is inexpensive and has a short half-life. Recurrent exposure risks bleeding and heparin-induced thrombocytopenia. Alternatives include low-molecular-weight heparins, direct thrombin inhibitors, regional anticoagulation with citrate or prostacyclin, and anticoagulation-free treatment, which often is accompanied by frequent saline flushes. Regional anticoagulation with prostacyclin is not commonly performed in the United States. Regional anticoagulation with citrate and calcium infusions is too tedious and expensive for routine use and thus often is limited to the intensive care setting. Citrate-containing dialysate solutions substitute citrate for acetate in the bicarbonate concentrate and may reduce heparin requirements.

**Treatment Time**

Below is a section on longer and/or more frequent HD. The rationale for such therapies is that urea levels may not represent removal of the molecules that contribute to uremia. These molecules may be considerably larger and their removal may be limited by slow diffusion from tissue to blood (eg, as is the case with phosphorus). Plasma inorganic phosphorus levels decrease precipitously during HD and then rebound to nearly predialysis levels. Thus, the limiting step in removing phosphorus by HD is intercompartmental transfer, and this also may be true for other uremic toxins.

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## SODIUM

The most abundant exchangeable plasma cation is sodium. Sodium is the primary determinant of plasma and extracellular osmolality, which can be regulated in HD patients by controlling sodium and fluid intake and by the dialysate sodium concentration. Epidemiologic studies have shown that a reduction in sodium intake can significantly reduce blood pressure (BP), cardiovascular morbidity, and mortality. We extrapolate this concept to HD patients. Therefore, dietary sodium restriction has been a major management strategy to help reduce interdialytic weight gain (IDWG), antihypertensive medications, and mortality.

Before the advent of modern dialysis machines with safe and predictable ultrafiltration controls, sodium concentration in dialysate was ~126 mEq/L and much of the sodium removed was due to diffusion. Modern nonexpanding dialyzers withstand greater hydrostatic pressures, require a smaller extracorporeal blood volume commitment, and achieve greater ultrafiltration in a shorter time. Thus, sodium removal shifted primarily to convection. As a consequence of faster and more aggressive ultrafiltration with shorter dialysis times, side effects such as muscle cramps, hypotension, thirst, and dialysis disequilibrium increased in frequency and severity. To counteract these effects, dialysate sodium concentration is increased by either fixing dialysate sodium at a higher concentration for the entire HD session or systematically varying the dialysate sodium concentration over the course of the HD session, a process called sodium modeling.

The goal of sodium modeling is to shift water from intracellular to extracellular compartments, where this added water supports circulation. Potential benefits include reduced incidences of dialysis disequilibrium, vascular instability, and muscle cramps. As an example, cycling a dialysate sodium concentration of 160 mEq/L in the first period of dialysis and 120 mEq/L in the second equal period and then repeating the cycle throughout the session leads to an average dialysate sodium concentration of 140 mEq/L. Periodic infusions of 50% dextrose in

water (D<sub>50</sub>W), 0.9% sodium chloride, or 23% sodium chloride solutions provide other means for treating intradialytic hypotension and muscle cramps attributed to sodium removal. Some of these techniques can lead to an intradialytic accumulation of sodium, which may cause greater thirst, IDWG, and hypertension.

Repeated high IDWG increases cardiovascular morbidity and mortality. Tightly regulating sodium metabolism is crucial for preventing excessive IDWG. Small uncontrolled trials have suggested that individualizing dialysate sodium concentration decreases IDWG and BP and may offer a mortality benefit. The DOPPS (Dialysis Outcomes and Practice Patterns Study) observed a 45% higher risk of death in patients with predialysis plasma sodium levels < 137 mEq/L compared with levels ≥ 140 mEq/L. However, there was a survival benefit in using higher dialysate sodium concentrations, speculated to be due to increased cardiovascular stability.

Sodium removal in HD patients presents a challenge. Dietary sodium is restricted and the amount of sodium delivered at dialysis must be minimized. Increasing sodium removal convectively means increasing ultrafiltration, which may be intolerable. Advances in dialysis technology may help individualize dialysate sodium concentration based on plasma sodium concentration. Dialysis machines can monitor and alter dialysate inlet and outlet conductivity and ionic dialysance (effective solute clearance). Knowing the sodium concentration and ultrafiltration rate, the machine's software can alter plasma conductivity, a surrogate for plasma sodium concentration.

Interstitial storage of sodium contributes to hypertension. Rat studies demonstrate that sodium is stored in muscle and skin, and lowering sodium intake can reverse this. This "osmotically inactive" sodium is a substantial portion of total-body sodium. Recently, tissue sodium content has been measured in healthy and hypertensive humans using sodium magnetic resonance imaging and is higher in muscle and skin of older and hypertensive individuals. Emerging evidence suggests that tissue stores may provide other pathologic effects besides IDWG and volume overload. Validating sodium magnetic resonance imaging is required before clinical implementation.

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## POTASSIUM

Dialytic potassium removal depends on the gradient created between extracellular fluid and dialysate. Intracellular potassium effluxes extracellularly to re-establish equilibrium as extracellular potassium is removed by dialysis. Liver and skeletal muscles are rich in potassium. If either is atrophied, there may be decreased post-HD extracellular potassium replenishment. The absorption of dialysate glucose decreases potassium removal by stimulating insulin, which drives potassium into cells and thus renders it unavailable for dialytic removal. Extracellular acidosis leads to cellular potassium efflux, which increases extracellular potassium concentration and enhances dialytic potassium removal. Dialytic acidosis correction results in a cellular influx of potassium to re-establish equilibrium. Rapid correction of acidosis in the setting of a low potassium dialysate concentration will quickly reduce extracellular potassium levels and can result in serious hypokalemia. The same consequence can occur from long-term excessive bicarbonate administration.

The prescribed dialysate potassium concentration depends on the patient's predialysis potassium concentration. The "rule of 7s" is a basic approach that states that the patient's potassium level plus dialysate potassium concentration should equal approximately 7. This approach is acceptable as long as individual care is taken in patients with a propensity for arrhythmias. A dialysate potassium concentration of zero should be used for only very short periods with monitoring and close surveillance, if at all. A stepped approach of progressively lowering the bath potassium concentration over the course of the treatment may be less arrhythmogenic. The range of most commonly used dialysate concentrations is 2-4 mEq/L. Lower concentrations can be used in the setting of life-threatening acute hyperkalemia, but only with extreme caution and frequent intradialytic potassium measurements.

As potassium blood levels decrease to <3 mEq/L, weakness and muscle pain develop; further decreases cause rhabdomyolysis, paralysis, cardiac arrhythmias,

and cardiopulmonary arrest. In patients prone to cardiac arrhythmias or those receiving digoxin, even mild hypokalemia can induce serious arrhythmias. Immediate postdialysis hypokalemia does not warrant treatment unless symptoms are present because a rebound increase in serum potassium level will occur within 1-2 hours. Premature correction could result in hyperkalemia.

There is no absolute recommended predialysis potassium level. Better survival is associated with predialysis serum potassium levels of 4.6-5.3 mEq/L. Individualized potassium management demands redundant safety systems so that no patient receives another person's potassium prescription.

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## BICARBONATE

Dialysis corrects metabolic acidosis by both adding base and removing acid. Between HD treatments, serum bicarbonate level declines as it neutralizes endogenous acid. The predialysis serum bicarbonate level varies depending on the factors elucidated in [Box 3](#). Buffer base loss occurs by convection during ultrafiltration and is proportional to the amount of ultrafiltration. The dialysate buffer concentration should compensate for the bicarbonate needed to buffer interdialytic acid generation plus account for that lost during ultrafiltration.

Managing chronic metabolic acidosis too aggressively may result in acute metabolic alkalosis. A lower base concentration should be used in patients susceptible to alkalosis, such as individuals with poor protein intake, small muscle mass, or persistent vomiting, or those receiving total parenteral nutrition. Symptoms of metabolic alkalosis can range from cramping, paresthesias, and fatigue to hypoventilation, altered mental status, and lethargy.

### Box 3. Influences to Predialysis Bicarbonate Concentration

- Postdialysis bicarbonate level
- Endogenous acid production
- Food content
- Food quantity
- Time between dialysis sessions
- Extent of bicarbonate loss with ultrafiltration

Metabolic alkalosis also can predispose to cardiopulmonary arrest.

In HD, the most commonly used dialysate buffer is bicarbonate, which is relatively inexpensive and generally better tolerated than acetate. The usual dialysate bicarbonate concentration is 35 mEq/L. To meet specific individualized requirements, modern dialysis machines are capable of delivering bicarbonate concentrations over the range of 20-40 mEq/L. The National Kidney Foundation's KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines recommend a midweek predialysis plasma bicarbonate level of 22 mEq/L. Lower mortality risk has been observed in patients with predialysis serum bicarbonate levels of 18-23 mEq/L, with an increase in mortality for both very low (<18 mEq/L) and very high (>27 mEq/L) values. Although low predialysis plasma values usually can be corrected by increasing the dialysate bicarbonate concentration, high plasma values likely reflect decreased protein intake and cannot be corrected by simply decreasing the dialysate bicarbonate concentration. Nutritional status and daily caloric intake should be reviewed thoroughly in this setting.

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### CALCIUM

Plasma calcium is ~40% protein bound, 10% anion complexed, and 50% ionized, and only the complexed and ionized portions are dialyzable. The ionized calcium gradient between dialysate and plasma water is the driving force of calcium transfer during dialysis; equilibration occurs by diffusion. The most commonly used dialysate concentrations for HD are 2.5-3.5 mEq/L. Calcium homeostasis is essential for bone health because its disruption leads to secondary hyperparathyroidism and metabolic bone disease. Phosphate binders, vitamin D analogues, calcimimetics, and dialysate calcium concentration are used to maintain normal mineral metabolism while avoiding hypercalcemia, soft-tissue calcifications, and oversuppression of parathyroid hormone with subsequent adynamic bone disease. Like bicarbonate, ionized calcium is removed convectively, so

large ultrafiltration volumes must be appreciated. Dialysate calcium concentration also can influence hemodynamics because calcium ion is important for contracting both vascular smooth muscle and cardiac myocytes, which affects BP. Lower dialysate calcium concentrations may cause intradialytic hypotension, acute arrhythmias, and sudden cardiac death. These complications might be avoided in cardiac-compromised patients with a higher dialysate calcium concentration. However, long-term use of higher dialysate calcium concentration increases the risk of calcification.

Acidosis decreases and alkalosis increases the binding of ionized calcium to albumin. Acidosis can induce signs of hypercalcemia ranging from mild nausea and vomiting to more serious symptoms, such as confusion and coma. However, care must be taken with acidosis, particularly in the setting of low plasma ionized calcium levels, because rapidly correcting the acidosis could lead to symptomatic hypocalcemia manifesting as neuromuscular excitability and seizures. Likewise, dialysate bicarbonate can induce alkalosis and lead to clinically significant hypocalcemia during and immediately following HD.

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### COMPLICATIONS OF HD

HD has evolved to be relatively safe. Some complications occur during or shortly after the procedure, whereas others become apparent only after several years and are responsible for considerable morbidity.

#### Hypotension

Hypotension is the most common acute complication of HD. Dialytic and patient-related factors influence BP during treatment. The incidence of hypotension in the dialysis population ranges from 15%-30% and is more common in women and the elderly. During isolated ultrafiltration, a progressive increase in total systemic vascular resistance maintains BP as fluid is removed. When diffusion is added to ultrafiltration in a usual HD treatment, thermal energy transfers from the heated dialysate to the blood. Furthermore, HD is a catabolic event that generates heat, stimulates vasodilatation, and

increases dermal blood flow. Cardiac output and BP must be maintained by an increase in heart rate and, when possible, an increase in myocardial contractility. However, the large burden of cardiovascular disease in this population often limits the appropriate cardiac responses. Additionally, abnormalities in autonomic function often are present. The baroreceptor reflex afferent arm is blunted in hypotension-prone HD patients, who do not mount reflex vasoconstriction during hypotension. The efferent arm of this reflex involves sympathetic output and is normal or even overactive in patients with chronic kidney disease, but has failed in patients who are prone to intradialytic hypotension.

**Ultrafiltration rate.** Hypotension results when the rate of intravascular volume removal exceeds its rate of refilling, especially if systemic vascular resistance cannot compensate for the loss of intravascular volume. Thus, during combined ultrafiltration and diffusion when vasoconstriction is not evident, the ability to ultrafilter during HD is dependent primarily on the ability to refill the intravascular space. Hypotension is frequent when ultrafiltration rate is  $>1.5$  L/h. Hypotension can occur when the patient's weight is at or less than the "estimated dry weight," the weight below which the patient develops symptomatic hypotension in the absence of edema and excessive IDWG. An echocardiographic measurement of inferior vena cava diameter can augment physical examination to assess volume status.

**Dialysate composition.** Dialysate composition can influence BP. Sodium, calcium, bicarbonate, and acetate are discussed elsewhere. Because of diffusive solute removal, plasma osmolality declines 10-25 mOsm/kg, creating an osmotic gradient between plasma, interstitial, and intracellular water. Thus, water moves from plasma into cells and the interstitium, which results in a further reduction in plasma volume in addition to that imposed by ultrafiltration, accounting for as much as 1.5 L of plasma volume loss during the treatment. This shift is opposed by the ultrafiltration-induced increase in plasma and interstitial oncotic pressure. A higher dialysate sodium concentration increases plasma sodium concentration and plasma osmolality, thus supporting plasma volume during HD (see the section on sodium). Theoretically, vasoactive substances may be removed during the treatment. However, during HD, the changes in plasma norepinephrine levels or potassium concentrations have not been shown to play an important role in dialysis-induced hypotension.

**Medication.** Patients with end-stage renal disease often receive antihypertensive agents or other medications that can interfere with the normal hemodynamic response to ultrafiltration.  $\beta$ -Adrenergic receptor blockers and verapamil reduce myocardial contractility and exert negative chronotropy. By preventing a

compensatory increase in heart rate, such agents interfere with the major defense that supports BP. Vasodilators can prevent vasoconstriction in response to ultrafiltration.

**Other factors.** Patients at increased risk for hypotension are those who have arrhythmias, which often can be exacerbated by HD; those with poor cardiac function or pericarditis; and those with an autonomic dysfunction, such as diabetes. Pericarditis and dysautonomias may prevent adequate changes in cardiac output or peripheral resistance to compensate for fluid removed during HD.

**Management.** The first step is to determine whether hypotension occurs early or late in the treatment. If hypotension occurs late in the treatment in a previously stable patient without edema or heart failure, the most common cause will be that the patient's dry weight has been underestimated. Reducing ultrafiltration volume or rate and increasing postdialysis dry weight will correct the hypotension. In contrast, a patient with excessive IDWG may become hypotensive before dry weight is achieved because the rate at which fluid can be mobilized to refill the intravascular space is limited. In this instance, increased dialysis time or frequency may be necessary. When possible, medications that can lower BP should not be administered within the 4 hours before HD treatment.

Bicarbonate does not have the vasodilatory properties of acetate, and sodium was discussed previously. As a catabolic event, HD increases body temperature and induces vasodilation. Dialysate cooled to  $35^{\circ}\text{C}$  reduces the frequency and/or severity of hypotensive episodes because cooling potentiates vasoconstriction. This generally is well tolerated and results in a more stable treatment. Cooling dialysate is superior to sodium modeling. For patients with persistent hypotension or autonomic insufficiency, the oral  $\alpha_1$ -adrenergic agonist midodrine can be effective at a dose of 5-10 mg given 30-60 minutes before beginning HD treatment. Anecdotally, fludrocortisone at a dose of 1 mg/d also can be helpful.

### Cramps

Muscle cramps occur in as many as 20% of HD treatments. Although their pathogenesis is uncertain, cramps are known to be more frequent when ultrafiltration rates are high and low sodium dialysate is used, which suggests a cause related to volume. Effective therapies include reducing ultrafiltration rate (which may mandate increased HD time), a 200-mL bolus of 0.9% sodium chloride solution, 5-mL increments of 23% hypertonic saline solution, or D<sub>50</sub>W solution. In nondiabetic patients, D<sub>50</sub>W solution is especially useful, particularly toward the conclusion of HD, because as glucose is metabolized, hyperosmolality and intravascular volume expansion in the



postdialysis period are avoided. The pain resulting from very severe cramps may be alleviated by administering diazepam, but at the risk of worsened hypotension. Quinine sulfate increases the refractory period and excitability of skeletal muscle and is effective in preventing cramping if administered 1-2 hours before dialysis. Patients using quinine must be observed for thrombocytopenia. The US Food and Drug Administration has issued a black box warning against the use of quinine for cramps. Alternatives to quinine in preventing cramps include vitamin E and L-carnitine, albeit with weak evidence.

### Arrhythmias and Angina

Patients with end-stage renal disease frequently have left ventricular hypertrophy, coronary artery and pericardial disease, and valvular sclerosis. The conduction system may be affected by calcific deposits, particularly in patients with adynamic bone disease. Superimposed on these pathologies are the rapid changes in electrolyte concentrations inherent in HD. It is not surprising that HD may provoke cardiac arrhythmias. Ventricular ectopy, including non-sustained ventricular tachycardia, is seen most frequently in patients receiving digoxin, particularly in the settings of predialysis hypokalemia or dialysate potassium concentrations  $< 2.0$  mEq/L. Supraventricular tachycardia and atrial fibrillation also can be precipitated by hypotension and coronary ischemia in a process called myocardial stunning. The classic indications for anticoagulation therapy with atrial fibrillation are not always appropriate in dialysis patients. There is emerging evidence that one specific formulation of acid concentrate used to prevent calcium salt precipitation in bicarbonate-based dialysate can induce metabolic alkalosis in HD patients due to acetic acid, acetate, and citrate converting to bicarbonate, which causes potentially fatal arrhythmias and sudden death in the postdialysis period.

### Hypoxia

HD-associated hypoxia is related to the buffer and/or membrane used.  $P_{CO_2}$  in acetate-buffered dialysate is low, which creates a diffusion gradient from blood to dialysate, lowers blood  $P_{CO_2}$ , and decreases respiratory drive, resulting in hypoventilation and hypoxia. In contrast to the low  $P_{CO_2}$  of acetate-buffered dialysate,  $P_{CO_2}$  of bicarbonate-buffered dialysate is nearly 100 mm Hg, which leads to the net transfer of carbon dioxide into the blood, stimulating respiratory drive.

### Hypoglycemia

Carbohydrate metabolism is abnormal in patients with chronic kidney disease. Although there is peripheral resistance to the effects of insulin in uremia,

the half-life of insulin is significantly prolonged when glomerular filtration rate is  $< 20$  mL/min/1.73 m<sup>2</sup>. The effect of a given dose of insulin is enhanced when dialysis is instituted because there is an improvement in peripheral responsiveness to insulin. Thus, a diabetic patient taking a usual dose of insulin may experience hypoglycemia when undergoing HD against a bath with a glucose concentration too low for the amount of insulin being administered. It frequently is necessary to decrease the patient's insulin dose on dialysis days. Furthermore, diabetic patients should not be dialyzed against a bath that has a glucose concentration  $< 100$  mg/dL.

### Hemorrhage

Gastrointestinal blood loss, subdural and retroperitoneal hematomas, and development of a hemopericardium may be life-threatening complications related to dialysis anticoagulation or the uremic state. Patients with acute inflammatory pericarditis, those who have had trauma or recent surgery, and those who have an underlying coagulopathy or thrombocytopenia are at particular risk. Furthermore, HD patients are exposed to long-term blood loss with each dialysis treatment because 5-10 mL of blood remains in the dialyzer and tubing even after thorough rinsing. There may be blood loss as needles are inserted and removed and from frequent laboratory tests. Estimates of total blood loss per treatment vary from 5-50 mL.

### Dialysate Composition and Integrity of the Extracorporeal Circuit

It is necessary to constantly monitor the composition and temperature of the dialysate. The machine's integral safety systems and highly supervised and standardized water treatment before dialysate is reconstituted are critical to ensure safe treatments. Blood exposure to massive quantities of dialysate mandates that the dialysate receive the same consideration as medications. Even small amounts of trace elements or organic material in dialysate can be harmful. Chloramines in water purification and copper have been associated with hemolysis. Aluminum has been associated with severe osteomalacia and fatal encephalopathy. Outbreaks of infection caused by *Mycobacterium chelonae* associated with improper reuse techniques or ineffective maintenance of the water treatment system have been reported. Bicarbonate-buffered dialysate has the potential to become contaminated by Gram-negative bacteria. Even if bacteria cannot cross an intact dialysis membrane, endotoxin fragments and other bacterial products can induce pyrogenic reactions, particularly when highly permeable synthetic membranes are used. Thus, strict guidelines exist for water treatment

and dialyzer reuse. A properly configured water-treatment system consists of carbon beds to remove organic material, filters, reverse osmosis, deionization, and UV light. Periodic surveillance cultures are obtained at various points of the water and dialysate circuit, and the entire water circuit is disinfected on a regular basis.

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### LONGER AND/OR MORE FREQUENT HD

Multiple observational studies have shown an association between higher dose of dialysis as measured by urea clearance and better survival. This association has not been confirmed by a randomized controlled trial. However, associations between longer treatment time and better survival have been shown in observational data from multiple countries, populations, and time periods. Many clinicians think that longer and more frequent dialysis treatments improve survival, and efforts to improve survival in HD patients are emphasizing increased treatment time per week in addition to small-solute kinetics. Alternative treatment schedules allow for lower ultrafiltration rates and more fluid removal per week, which may minimize long-term volume overload and hypertension, thus potentially diminishing the development of left ventricular hypertrophy and cardiovascular disease. Evening or nocturnal treatments make it possible for HD patients to have their days free for work, family, and other activities. There are several alternative regimens that provide greater clearances of urea and larger molecules, an opportunity for lower

ultrafiltration rates, and also furnish patients with schedule flexibility and choice. The 3 dominant more frequent and longer regimens are home HD, short daily HD, and nocturnal HD.

### Home HD

Home HD requires a partner who can be present to assist with treatments, the HD machine, and access to purified disinfected water. During the past decade, several machines have been developed that are simple to set up and provide for compact and safe water processing. Schedules range from 2-3 hours 5-6 times per week to 7-8 hours 3-6 nights per week, depending on the commitment and comfort level of the patient and partner. Accessing a fistula, graft, or catheter can be done by either the patient or partner. Some programs use an alarmed fluid sensing device on the access to assist with monitoring.

### In-Center Nocturnal HD

Most in-center nocturnal units exist in a dialysis facility with an existing daytime program, such that the water system, machines, and dialysis chairs are already present. One plan that works well is 7-8 hours overnight on Sunday, Tuesday, and Thursday, which leaves 2 hours for disinfecting the water system and regenerating dialysate between the last day shift and the start of the nocturnal shift. Increased demands are placed on the entire water processing system. Water generation capacity, storage, and use must be planned carefully.

Patient selection factors include transportation nuances and the ability to sleep in the unit at night. A patient may need 5 weeks to adapt to a nocturnal schedule. Patients bring their bedding and the facility must be warm enough for comfortable sleeping. Providing nocturnal HD for less than 6 hours is inadvisable because patients may not experience the improvement in subjective well-being, asymptomatic fluid removal, and normalized sleep schedule that are possible with 7- to 8-hour treatments. It also is easier to have reliable transportation at 5:00 AM than at 2:00 AM. Initial dialysate prescription is usually 2 mEq/L of K<sup>+</sup> and 2.5 mEq/L of Ca<sup>++</sup>, with subsequent adjustment as needed. Calcium balance particularly should be monitored on long dialysis regimens. The initial heparin bolus is followed by a maintenance infusion until the last hour of treatment. An additional heparin bolus during the treatment may be needed. It is common for patients to ultrafiltrate 4-6 L without difficulty, but surveillance still is important. A written plan for communication between nocturnal and daytime staff is mandatory, particularly for sign-out of any issues related to maintenance of the water system and pending clinical issues that occurred overnight.

### Why Alternate HD Schedules Work So Well

Greater treatment time per week makes the removal of larger amounts of fluid and phosphorus possible, which means that patients often can liberalize their diets. Because ultrafiltration rate is slower and/or more frequent, there is less hypotension and cramping during treatments and patients spend less time being volume overloaded between treatments. Better volume management may reduce left ventricular hypertrophy, cardiac morbidity, and mortality. Longer treatment times also are associated with fewer hospitalizations. Interestingly, longer treatments are associated with improved survival independent of urea clearance; the removal of middle and large molecules may contribute to this. For example, phosphorus control is improved in patients receiving HD treatments 6-7 days a week. Patients often are able to decrease their use of binders, as well as antihypertensive agents. More research is needed to understand how longer treatment times improve survival and what parameters other than urea clearance can be used to measure adequacy.

Finally, in-center nocturnal units are practical because they leverage existing infrastructure. Unless there are changes needed to the water system, opening an in-center nocturnal shift requires relatively little capital outlay. There often is a period of a few hours after all the patients are on HD when staff responsibilities are lighter and staff may have time to do other work for the facility, such as inventory and audits. With home HD, no funds are needed for staff during treatments. Overall, the economics and clinical

outcomes of longer and/or more frequent treatments are compelling.

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