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Core Curriculum in Dialysis 2013 Update

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Principles of Dialysis and How Modalities Differ

Kidney dialysis evolves as we learn more about the uremic condition. At its earliest versions the major transport process was diffusion, the spontaneous movement of particles down a concentration gradient, stimulated by thermal agitation, and affected by the collision of the particles with each other and with barriers such as dialysis membrane pore side walls. As dialysis was utilized to replace kidney function ultrafiltration (UF) was required, which could be generated by osmotic, oncotic, or hydrostatic pressures. Consequently, solvent drag effects of the UF led to an appreciation of the importance of convective transport and its advantageous property of increasing the removal of larger molecular sized (molecular weight + steric hindrance effects) species. Thus, modern dialysis generally utilizes both diffusive and convective transport and current devices and equipment allow for either process to occur independently or in combination. However, during convection solute is removed but concentrations in the retentate may not decrease unless substitution fluid is administered, a process called hemofiltration. Diffusion can occur without any UF. Appreciation of these extremes is important to the understanding of modern dialysis. Currently, dialysis cannot replace the endocrine or metabolic functions of the kidney so our discussion will be restricted to solute and fluid removal.

Hemodialysis (HD) utilizes synthetic membranes while peritoneal dialysis (PD) utilizes a biologic membrane which is complex and beyond this discussion. Synthetic and biologic membranes have pores varying in size, electrical charge, and other properties. The pores are transmembrane openings and under certain conditions can be designed and manipulated to achieve specific goals. An example of this is the glucose polymer icodextrin used in some PD solutions where the oncotic pressure of the macromolecule stimulates convection through small intercellular pores but insufficiently induces water movement across aquaporins. Such a solution could be helpful with disorders of aquaporin function.

The removal of a solute is measured in mass (e.g. grams). This can be determined by measuring the total body mass before and after dialysis. Usually this is done by extrapolation rather than direct measurement. Measuring the acquisition of solute in effluent dialysate is easier to perform. The difference between the mass acquired in the dialysate and that removed from the body is called mass balance error, usually reflecting binding of the solute to the dialyzer membrane. This can be clinically relevant for antibiotics and cytokines. Solute removal may also be measured as the extraction ratio (ER), the fraction

removed from the blood with a single pass through the dialyzer. This ER is determined as $(C_{in} - C_{out})/C_{in}$ where C_{in} is the solute concentration in the blood entering the dialyzer and C_{out} is the concentration in the blood exiting the dialyzer. The ER is dependent on blood (Q_b) and dialysate (Q_d) flow rates, the dialyzer membrane and intrinsic properties of the solute such as molecular size and protein binding. The ER is high in traditional thrice weekly and lower in short daily HD. We use a variation of this formula to measure urea removal during HD when we measure the urea reduction ratio (URR).

Another method of indirectly assessing solute removal is the concept of clearance, which is the volume (of plasma, serum, blood or entire body) from which all of the solute was removed during a specific time period; hence the units are volume/time. Plasma is the fraction of blood that is not cellular and plasma water makes up about 94% of plasma. Generally, we dialyze plasma water. When there is a concentration gradient from blood cells to plasma water (e.g. potassium), the amount removed during dialysis or hemofiltration may exceed that in plasma water. For urea we often evaluate dialysis dose by total body clearance which is the K in the 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 clearance in HD is determined from what was removed from the blood while in PD it is determined by what is acquired in the dialysate.

Instantaneous blood clearance in HD is the ER times Q_b . In clinical practice we have simplified this measurement by simply assessing the blood level of urea before and after HD. Clearance does not change during a HD session unless operating conditions are altered. As the solute is removed the C_{in} declines such that the fraction of total removal declines over the course of the dialysis but the clearance remains constant. Because C_{in} is highest at the start of dialysis, the greatest amount of mass removed is early in the treatment, hence frequently repeated dialysis such as short daily HD may be very effective in total solute removal over a week. Dialysis clearance can never exceed Q_b . If all of the blood is cleared, clearance is the Q_b . Clearance can never exceed the Q_d . If the dialysate is 100% saturated (equilibrated) with solute, then the clearance is the Q_d . This concept is important when dialysate is limited such as in PD and some short daily HD systems (e.g. NxStageTM).

Body clearance in PD is: $(D/P) \times$ dialysate effluent volume/time where D is the concentration in the dialysate and P is the concentration in the plasma.

Clearance comparison across different dialysis modalities is best done by using an entire week as the time period, then adjusting for the continuous nature of PD versus the intermittent nature of HD and accounting for the frequency of the applied intermittent treatments, as first proposed by Frank Gotch.

In PD and short daily HD using the most popular system in the US (NxStage System 1TM) the limit to clearance is the availability of dialysate. In each therapy the goal is to use dialysate as efficiently as possible, which in most circumstances means equilibrating dialysate with the solutes of uremia. In PD the peritoneal blood flow is limited so saturating dialysate takes more time than in short daily NxStageTM where Q_b is about three fold greater

than Qd. Both of these therapies differ from standard thrice weekly HD where dialysate is relatively unlimited. In PD the saturation is defined by the D/P whereas in NxStage™ it is derived from the ratio of Qd/Qb labeled flow fraction. When the flow fraction is < 40% the dialysate saturation with urea is > 90%. For urea the per treatment Kt/V for NxStage™ is about 0.45 so for 5 or 6 treatments/week, this is at least equivalent to thrice weekly traditional HD. A comparison of Kt/V for urea over different modalities is shown in Figure 1.

PD Update

The Teitelbaum and Burkart Core Curriculum in PD from this Journal in 2003 is outstanding, still fully applicable ten years later and selected topics only will be briefly updated here.

The long term technical survival of the PD technique depends in part on preservation of residual kidney function (RKF) and avoidance of complications which may damage the peritoneal membrane. The positive role of ACE inhibitors and ARBs in both areas is gaining significance. In addition “biocompatible” PD dialysates have been studied extensively now in clinical trials. The initial hope was that such solutions would benefit patients in diverse ways such as long term preservation of peritoneal membrane function, less exposure and absorption of glucose degradation products, and possibly better preservation of RKF. Unfortunately, these benefits have not been proven in clinical trials, at least not to the extent that the benefit can justify the extra cost. Similarly, glucose sparing regimens using amino acid solutions and icodextrin instead of dextrose reduce glucose exposure without jeopardizing the efficacy of PD. Recently the concern for encapsulating peritoneal sclerosis has grown, especially in long term PD patients. Some have advocated limiting the duration of PD to 5 to seven years, but this opinion is not universally accepted.

Regarding PD urea clearance “adequacy” in 2006 NKF-KDOQI changed its recommendation to an absolute acceptable minimum weekly Kt/V of 1.7 which could be 100% from PD if anuric, or a combination of RKF + PD. Creatinine clearance targets were not emphasized to simplify understanding and measuring process especially in light of the regulatory misuse of NKF-KDOQI Guidelines. To enhance PD dose in this era of popularity of automated PD, the gradual increase of inflow volume per cycled exchange is highly effective and well-accepted. Increasing fill volume each exchange by 100 mL each week for several weeks generally is not noticeable to the patient and the supine position generally allows more tolerance of larger fill volumes.

The International Society of Peritoneal Dialysis updates its peritonitis management guidelines frequently and again in 2010 recommended center specific empiric treatment regimens based on surveillance of the frequency, prevalence and antimicrobial sensitivities of the organisms observed in that center. There are circumstances when antibiotic prophylaxis is beneficial. Numerous studies suggest that mupirocin or gentamicin cream (rather than ointment, which can damage some catheter materials) applied daily to the catheter exit site reduces the risk of peritonitis. Prophylactic antibiotics are also recommended for dental, gynecologic, and gastrointestinal procedures, and that for

gynecologic or gastrointestinal procedures the abdomen additionally be empty of dialysate to enhance natural host defense mechanisms.

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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 blood, then to the dialyzer, and then to the dialysate for discarding. Each of these sequential steps is affected by the properties of the molecular species itself and the dialytic operating conditions. Those concepts will be described utilizing urea as the example.

Solute transport within the body

Urea, a 60 Dalton unbound, uncharged, water soluble, end-product of protein catabolism distributes from the liver to nearly all tissues. Generation is slow enough for equilibration to occur between extracellular (interstitial and plasma) and cellular water. During HD blood levels fall sharply but blood re-equilibrates as urea is recruited from the body. However, urea movement out of tissues into blood may be limited by tissue perfusion as well as intrinsic transport lag, the latter mooted as the etiology 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 minutes to hours, called “urea rebound”. Blood levels immediately after dialysis do not perfectly reflect urea levels in all tissues giving rise to two different indices: a single-pool Kt/V (spKt/V), based on the urea level at the conclusion of HD, and an equilibrated Kt/V, (eKt/V), based on urea levels measured 30 or 60 minutes after HD.

Solute Transport Within the Dialyzer

A roller pumps blood through the HD circuit probably with an accuracy of 95% of that displayed by the machine. Dialysate moves from the proportioning system to the dialyzer, and then a second pump moves it out of the dialyzer to a drain. The difference in pumping rates between the two dialysate pumps determines the amount of fluid ultrafiltered. A sensor evaluates conductivity as a surrogate for ionic strength, to assure proper proportioning. Another sensor detects blood in dialysate indicating rupture in the circuit, usually in the hollow fibers. A temperature sensor will be discussed later.

Most modern dialyzers utilize hollow fibers made of highly biocompatible synthetic material and this 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 (high vs. low) refer to the dialyzer's urea clearance now almost exclusively dependent upon the operating conditions of dialyzer surface area and Q_b . The ability of a dialyzer to remove urea is reported by the manufacturer as the "KoA", which has units of mL/min. Conceptually, KoA can be considered the urea clearance at infinitely high Q_b and Q_d , and 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 definition of high versus low flux is not precise, but a large prospective clinical trial chose a β_2 -microglobulin (12,800 Daltons) clearance of at least 20 mL/min as definition of a high-flux dialyzer, whereas dialyzers with β_2 -microglobulin clearances < 10 mL/min were described as 'low-flux.' High-efficiency as well as high flux dialyzers are also highly water permeable and must be used in conjunction with UFR controllers. The ability of a dialyzer to remove "middle molecules" between 500 and 5000 Daltons 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 improvements have gradually achieved this goal.

Clearance of a uremic solute depends on whether the solute is small enough to pass through the membrane's pores. Urea passes freely, albumin is blocked, and β_2 -microglobulin is partially blocked. Smaller species diffuse faster than larger while in convection this size effect is less and has led to the use of convective or mixed convective-diffusive therapies.

Dialyzer Performance

The National Cooperative Dialysis Study, the Hemodialysis Study, and observational epidemiology of the US Renal Data System have led to a "guideline" expectation that each episode of thrice weekly HD achieve a minimum single-pool Kt/V of 1.2. To minimize treatment time, Q_d is twice Q_b allowing urea clearance and total removal to be a strong function of achieved Q_b .

Dialyzer Selection

The major clinical factors to consider in dialyzer selection are the membrane material, sterilization method, dialyzer area, and the preferred flux. Cellulosic (e.g. cellulose triacetate), polysulfone, polyethersulfone, and polyacrylonitrile (PAN or AN69) membranes all perform adequately, and choice is primarily driven by idiosyncrasies and cost. However, ACE Inhibitorss predispose patients to anaphylactic reactions when exposed to polyacrylonitrile membranes and idiosyncratic reactions to polysulfone or polyethersulfone do rarely occur. Dialyzers are sterilized by ethylene oxide (EO), steam, radiation, or by chemical reprocessing. EO and reprocessing chemicals must be completely flushed from the device as remnants are toxic. Consequently, using steam or radiation sterilized dialyzers may be simpler than mandating all that extra maintenance and practice activity.

Assessment of Inadequate Urea Clearance

The failure to deliver a thrice weekly Kt/V of >1.2 should prompt an evaluation and action plan. The first evaluation concerns the ability of the access to deliver an appropriate Qb, usually > 300 mL/min. With a moderate sized and especially with a large surface area dialyzer at this rate a Qd to Qb ratio of 2 should lead to dialyzer C_{out} urea level < 10 mg/dL. If this does not occur and Qb and dialyzer size are maximized, then increasing dialysis time is necessary. Many clinicians think that increasing time should be an earlier step because of its slower (and safer) UFR and better chance to clear molecules larger than urea. Labor costs and patient reluctance to increase time are the two main barriers to this approach

The HEMO and 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 for patients with dialysis vintage over 3.7 years. Conditions attributed to middle sized molecules may take years of ESRD to emerge. Since the cost is hardly different, the only reason to use low flux dialyzers would be when water purity is suspect.

Anticoagulant Selection

Weight-based unfractionated heparin is the most common agent used for anticoagulation, as it is inexpensive and has a short half-life. However, recurrent exposure risks bleeding and heparin-induced thrombocytopenia. Alternatives include low-molecular weight heparins, direct thrombin inhibitors, or regional anticoagulation with citrate or prostacyclin. The direct thrombin inhibitors bivalirudin, and argatroban have short half-lives and may be monitored by the activated partial thromboplastin time, whereas danaparoid has a longer half life in renal failure and is monitored with anti-factor Xa levels. None have FDA labeling for anticoagulation in HD. Regional anticoagulation with prostacyclin is not commonly performed in the US, and regional anticoagulation with citrate and calcium infusions is too tedious and expensive for routine use, and limited often 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 an entire section on More Intensive Dialysis. The rationale for such therapies is that the removal of molecules contributing to uremia may not be represented by urea. They may be considerably larger and their removal is limited by slow diffusion from tissue to blood (e.g. phosphorus). Plasma inorganic phosphorus levels fall precipitously during HD and then rebound nearly to predialysis levels. Thus, the limiting step in phosphorus removal by HD is intercompartmental transfer.

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Sodium

Sodium is the primary determinant of plasma and extracellular fluid osmolality. This can be regulated in HD patients by controlling sodium and fluid intake and by the dialysate sodium concentration. From epidemiologic studies 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 valued asset to manage of HD patients, especially in helping to reduce interdialytic weight gain (IDWG), the need for antihypertensive medications, and mortality.

The role of dialysate Na concentration uniquely affects HD patients. Sodium is the most abundant exchangeable plasma cation. Before the advent of modern dialyzers with safe and predictable UF controls, Na concentration in the dialysate was between 126 and 130 mEq/L. Much of the sodium removed was due to diffusion. As much as 250 to 450 mEq of sodium and 5 to 8 liters of water could be removed with a dialysate sodium concentration of 126 mEq/L. As the HD devices improved and were able to withstand greater hydrostatic

pressures without expanding and requiring a larger extracorporeal blood volume commitment, a larger amount of volume could be ultrafiltrated in a shorter time period. Thus, Na removal shifted to primarily convection with 1 liter of ultrafiltrate removing approximately 140 mEq of sodium.

As a consequence of faster and more aggressive UF with shorter dialysis times, side effects such as muscle cramps, hypotension, thirst, and the dialysis disequilibrium syndrome increased in frequency and severity. Thus, the dialysate sodium concentration was increased to counteract these effects. This could be accomplished by fixing the sodium dialysate at a higher concentration for the entire HD session, periodic infusions of 0.9% saline or hypertonic saline, or changing the dialysate Na concentration over the course of the HD session (Na modeling).

The goal of sodium modeling is to shift water from within cells to the extracellular compartment. For example, one method of sodium modeling will use a dialysate sodium concentration of 160 mEq/L in the first period of dialysis, switching 120 mEq/L in the second equal period and repeating the cycle throughout the session such that the average dialysate Na concentration is 140 mEq/L. Ideally, the changes in plasma sodium should be limited to 4–5 mEq/L. The potential benefits include a reduced incidence of dialysis disequilibrium, vascular instability, and muscle cramps. Periodic infusions of D₅W, 0.9% or 23% NaCl provide other means for treating intradialytic hypotension and muscle cramps attributed to Na removal. Increasing the concentration of extracellular sodium pulls water from the cells increasing intravascular volume and BP. Each of these techniques can potentially lead to intradialytic accumulation of sodium, which is responsible for greater IDWG, hypertension and thirst.

Repeated high IDWG increases cardiovascular morbidity and mortality. Thus, focus has been redirected toward lowering the dialysate sodium concentration to reduce its role in this problem. The concept of sodium individualization focuses on matching the dialysate sodium concentration with the patient's predialysis serum concentration. Small uncontrolled trials have suggested that individualization of dialysate Na concentration decrease IDWG and BP, and may offer a mortality benefit. The Dialysis Outcomes and Practice Patterns Study (DOPPS) observed a 45% higher risk of death in patients with predialysis plasma sodium levels <137 mEq/L compared with sodium levels 140 mEq/L. However, there was a mortality benefit in using higher dialysate sodium concentrations in these patients, speculated to be due to increased cardiovascular stability.

Sodium removal in HD patients presents a challenge. Dietary sodium has to be restricted and the amount of sodium delivered through the dialysate must be taken into consideration. Removing sodium by convection can be difficult to increase. Advances in dialysis technology may aid in the process of individualizing a patient's dialysate sodium concentration to their plasma sodium concentration. Dialysis machines can monitor and alter dialysate inlet and outlet conductivity and ionic dialysance (effective solute clearance). Knowing the above values and ultrafiltration rates, the machine's software programs can determine and alter plasma conductivity, which is a surrogate for plasma sodium

concentration. This may provide a more precise method for tailoring a dialysis prescription to the individual patient.

Perhaps the serum sodium is not the only contributor to mortality in HD patients. Increasing attention is being drawn to the interstitial storage of sodium and its role in hypertension. Rat studies demonstrate that sodium is stored in the muscle and skin and that this can be reversed by lowering sodium intake. This “osmotically inactive” sodium is stored in greater proportion than that residing in water. Recently, tissue sodium content has been measured in normal and hypertensive humans using a sodium MRI technique. Sodium was found to be higher in the muscle and skin in older and hypertensive subjects, and was stored in excess of that in water.

Tight regulation of sodium metabolism is crucial for preventing excessive IDWG and controlling BP. Managing this while preventing unwanted side effects can be frustrating for all parties. Na balance does not appear to be as straightforward as previously thought. Emerging evidence suggests that tissue stores may provide other pathologic effects outside of IDWG and volume overload. Fortunately, imaging techniques such as the sodium MRI are available to quantify tissue sodium content. Additional studies validating the use of such a technique are required before implementing it in the clinical setting. However, this would provide a simple, noninvasive manner to monitor tissues sodium content, and add another valuable tool for managing such complex patients.

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Potassium

Potassium removal during dialysis is dependent on the potassium gradient created between the extracellular fluid and the dialysate. Intracellular potassium effluxes extracellularly to reestablish equilibrium as extracellular potassium is removed by dialysis resulting in an overall reduction in total body potassium. Skeletal muscle and the liver are the major organ sites of potassium. Should either of these organs be small or diseased, there may be a delayed or decreased replenishing of extracellular and plasma potassium. The dialysate glucose concentration affects the removal of potassium as glucose stimulates insulin release which in turn increases potassium cellular influx. This influx leads to a reduced potassium

gradient and a subsequent decrease in dialytic removal. Acid-base status also affects the potassium gradient. An acidic extracellular environment leads to cellular potassium efflux and an increased gradient. Correction of the acidosis by dialysis will result in an influx of potassium to reestablish equilibrium. Too rapid of a correction especially in the setting of a low potassium dialysate concentration will quickly reduce extracellular potassium and can result in serious hypokalemia. On the other hand, chronic excessive bicarbonate can create an alkaline extracellular environment causing potassium cellular influx which decreases the gradient resulting in a lower removal of potassium during dialysis as well as persistent hypokalemia.

The dialysate potassium concentration utilized depends on the patient's predialysis potassium concentration. The "rule of 7's" is a basic approach where the potassium level of the patient plus the dialysate potassium concentration should equal approximately 7. This approach is acceptable as long as consideration is given to the individual patient and care is taken in patients with a propensity for arrhythmias. The range of dialysate concentrations most utilized in chronic dialysis is 2 to 4 mEq/L. Both 0 and 1 mEq/L dialysate concentrations can be used in situations with life threatening acute hyperkalemia but only with extreme caution and frequent interdialytic potassium level checks to avoid severe hypokalemia.

Mild hypokalemia is generally asymptomatic but as blood levels fall below 3 mEq/L, weakness and muscle pain develop with further decreases causing rhabdomyolysis, paralysis, cardiac arrhythmias, and cardiopulmonary arrest. In patients prone to cardiac arrhythmias, such as those with cardiovascular disease or those taking digoxin, even mild hypokalemia can induce serious arrhythmias. Immediate postdialysis hypokalemia does not warrant treatment unless symptoms are present as a rebound increase in serum potassium will occur within 1–2 hours after dialysis as equilibrium is reestablished. Premature correction could result in hyperkalemia.

There is no absolute recommended value for a predialysis potassium level. Previous observations have associated greater survival with predialysis serum potassium levels of 4.6 to 5.3 mEq/L with higher levels associated with increased all-cause and cardiovascular mortality; therefore, attention to these details will allow individualized therapy. However, individualized potassium management demands that redundant safety checks be in place so that one patient does not receive another patient's potassium prescription.

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Bicarbonate

ESRD results in the net retention of hydrogen ions yielding a persistent metabolic acidosis. Dialysis amends metabolic acidosis via addition of base across the dialysis membrane in addition to the removal of acid. In the interdialytic interval, the serum bicarbonate level continually declines as it neutralizes endogenous acid production. The predialysis serum bicarbonate level varies from patient to patient and depends not only on factors such as the post-dialysis serum bicarbonate concentration, rate of endogenous acid production, food content and quantity, and duration between dialysis sessions, but also on the extent of ultrafiltration occurring during dialysis.

Buffer base loss occurs by convection during ultrafiltration and is proportional to the amount of ultrafiltrate removed. A reduced ultrafiltration requirement due to smaller interdialytic weight gain results in a more stable predialytic acid-base status when compared to large interdialytic weight gainers which require substantially more ultrafiltration. The buffer concentration in the dialysate therefore should compensate for the bicarbonate needed to buffer acid generation between dialysis sessions plus account for that lost during ultrafiltration.

Overly aggressive management of chronic metabolic acidosis may result in acute metabolic alkalosis. A lower base concentration should be utilized in patients susceptible to alkalosis, such as patients with poor protein intake, small muscle mass, receiving total parenteral nutrition, or with persistent vomiting. Symptoms of metabolic alkalosis can range from cramping, paresthesias and fatigue to hypoventilation, altered mental status and lethargy. Metabolic alkalosis can also predispose to cardiopulmonary arrest in the dialysis patient.

The dialysate buffer most utilized in hemodialysis is bicarbonate which is relatively inexpensive and generally better tolerated than is acetate. The usual dialysate bicarbonate concentration is 35 mEq/L. Modern dialysis machines are capable of delivering bicarbonate concentrations over a wide range (20 to 40 mEq/L) and able to amply meet specific individual acid-base requirements. KDOQI 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 between 18 to 23 mEq/L with an increase in mortality risk for both very low (< 18 mEq/L) and very high (> 27 mEq/L) values. While low predialysis plasma values can usually 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 thoroughly reviewed in these patients.

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Calcium

Plasma calcium is approximately 40% protein bound, 10% anion complexed and 50% ionized with only the complexed and ionized portions being dialyzable. The ionized calcium gradient between the dialysate and plasma water is the driving force of calcium mass transfer during dialysis with equilibration occurring by diffusion. The most common dialysate concentrations utilized for hemodialysis are 2.5, 3.0 or 3.5 mEq/L. The concentration selected should be dictated by the calcium mass balance of an individual patient.

Calcium homeostasis is essential for bone health and its disruption leads to secondary hyperparathyroidism and renal osteodystrophy. Phosphate binders, vitamin D analogues and calcimimetics are commonly utilized in the attempt to maintain normal mineral metabolism within KDOQI guidelines. Choosing the calcium concentration of the dialysate should also be viewed as a component of therapy. The dialysate should assist in achieving an overall goal of a mildly positive calcium balance, normal serum calcium levels and plasma PTH values within 2–3 times above normal while at the same time avoiding hypercalcemia, soft-tissue calcifications and over suppression of PTH with subsequent development of adynamic bone disease. To achieve this goal, frequent reassessment and adjustments must be considered. Large ultrafiltration volumes remove ionized calcium and this must also be appreciated

The dialysate calcium concentration can also have significant hemodynamic effects. The calcium ion is important for the contraction of both vascular smooth muscle and cardiac myocytes which in turn affect blood pressure. Lower dialysate calcium concentrations may predispose certain individuals to intradialytic hypotension as well as acute arrhythmias and sudden cardiac death. These potential complications might be avoided in cardiac-compromised patients with a higher dialysate calcium concentration; however care must be taken as long-term use of higher dialysate calcium increases risk of vascular calcifications in addition to the bone mineralization complications discussed above.

Acid-base status is another consideration of calcium homeostasis in the dialysis patient as extracellular pH affects the binding of calcium to albumin. Acidemia decreases and alkalemia 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. Care must be taken however with acidosis particularly in the setting of a low plasma ionized calcium level as rapid correction of the acidosis could lead to life-threatening hypocalcemia manifesting as neuromuscular excitability and seizures. Likewise, dialysate bicarbonate can induce alkalosis and lead to clinically significant hypocalcemia during and immediately following dialysis.

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Complications of Hemodialysis

HD has evolved into a relatively safe procedure, with an estimated 1 death in 75,000 treatments as a result of technical error. Some complications are immediate, occurring during or shortly after the dialysis procedure itself, whereas others become apparent only after several years and are responsible for considerable morbidity.

Hypotension

Hypotension is the most common acute complication. Dialytic and patient-related factors influence BP during treatment. The incidence of hypotension in the dialysis population ranges between 15% and 30%, being more common in women and the elderly. The hemodynamic response to HD must be reviewed for an understanding of hypotension. The dialysis procedure is made up of two separable processes: convection and diffusion. Convection refers to the movement of fluid and solute brought about by hydraulic pressure across the dialysis membrane (transmembrane pressure, TMP) and is termed “ultrafiltration” (UF). The higher the TMP, the greater is the rate of convection/UF. During isolated UF a progressive increase in total systemic vascular resistance maintains BP as fluid is removed. When diffusion is added to UF in the usual dialysis treatment, thermal energy transfers from the heated dialysate to blood. Furthermore, HD is a catabolic event generating heat, stimulating vasodilatation and increased blood flow to the skin. Cardiac output and BP must be maintained by an increase in heart rate and when possible by 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 are often present. The afferent arm of the baroreceptor reflex is blunted in hypotension-prone HD patients, who do not mount reflex vasoconstriction during hypotension. The efferent arm of this reflex involves sympathetic output, believed to be normal or even overactive in patients with CKD, but in patients who are prone to intradialytic hypotension, this arm has also been shown to fail.

Ultrafiltration Rate (UFR)

Hypotension results when the rate of intravascular volume removal exceeds its rate of refilling, especially if total peripheral resistance cannot compensate for the loss of intravascular volume. Thus, during combined UF and diffusion when vasoconstriction is not evident, the ability to ultrafilter during HD is primarily dependent on the ability to refill the intravascular space. Frequently, hypotension is experienced when the UFR exceeds 1.5 L/hour.

Hypotension can occur when the weight of the patient is at or below the “estimated dry weight,” that weight below which the patient develops symptomatic hypotension, *in the absence of edema and excessive IDWG*. The assessment of volume status by physical

examination can be augmented by echocardiographic measurement of inferior vena cava diameter.

Dialysate Composition

Dialysate composition can influence BP. Sodium, calcium bicarbonate and acetate are discussed in detail elsewhere. Plasma osmolality declines because of diffusive solute removal. The magnitude (10–25 mOsm/kg) creates an osmotic gradient between plasma and the interstitial and intracellular spaces. Fluid moves from plasma into cells and the interstitium, resulting in a further reduction in plasma volume to that imposed by UF, accounting for as much as 1.5 liters during the treatment. This shift is opposed by the UF-induced increase in plasma and interstitial oncotic pressure. Increases in the concentration of sodium, the principal osmotic agent in the dialysate, will reduce this osmotic gradient, as discussed in the Na section. Theoretically, vasoactive substances may be removed during the treatment. However, during HD the changes in plasma norepinephrine levels or potassium concentration have not been shown to play an important role in dialysis-induced hypotension.

Medication

ESRD patients often receive antihypertensive agents or other medications that can interfere with the normal hemodynamic response to UF. α -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 supporting BP during dialysis. Vasodilators can prevent vasoconstriction in response to UF.

Other Factors

The patient's health is another important variable that directly influences the frequency of hypotension. Patients at increased risk for hypotension are those who have arrhythmias, which can often be exacerbated by HD, those with poor cardiac function or pericarditis, or those with autonomic dysfunction such as diabetics. 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. In a previously stable patient without edema or heart failure in whom hypotension occurs late in the treatment, the most common cause will be that the patient's dry weight has been underestimated. Reducing the UF volume and raising the post dialysis dry weight will correct the hypotension. In contrast, the patient with excessive IDWGs may become hypotensive before the 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 which may lower BP should not be administered at least 4 hours before the HD treatment.

Bicarbonate does not have the vasodilatory properties of acetate. Higher dialysate Na concentrations help mobilize intracellular water and aid in managing dialysis hypotension,

but not without consequences, as discussed in the Na section. HD is a catabolic event that raises body temperature and induces vasodilation. Dialysate cooled to 35° C reduces the frequency and/or severity of hypotensive episodes because vasoconstriction is potentiated with cooling. This is generally tolerated by the patient and often results in a more stable treatment. Lowering the dialysate temperature is superior to the chronic use of 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 HD. Fludrocortisone at a dose of 1 mg/day can also be useful in maintaining intradialytic blood pressure in patients with autonomic dysfunction.

Cramps

Muscle cramps occur in as many as 20% of dialysis treatments. Although their pathogenesis is uncertain, cramps are known to be more frequent when UFRs are high and when low Na dialysate is employed, suggesting a volume related etiology. Thus effective therapies include the reduction of the UFR (which may mandate increased dialysis time), 200 mL bolus of 0.9% NaCl, 5 mL of 23% hypertonic saline, or D₅₀W (50% dextrose in water). In nondiabetic patients D₅₀W is especially useful, particularly toward the conclusion of the dialysis treatment, 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 administration of agents such as 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 to 2 hours before dialysis. Patients using quinine must be observed for thrombocytopenia. The 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.

Arrhythmias and Angina

Patients with ESRD 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 upon 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 nonsustained ventricular tachycardia is seen most frequently in patients receiving digoxin, particularly with predialysis hypokalemia or when dialysate potassium concentration is < 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 are not always appropriate in dialysis patients with atrial fibrillation. There is emerging evidence that acid concentrate used to prevent precipitation of calcium salts in bicarbonate based dialysate can induce metabolic alkalosis in HD patients (due to conversion of acetic acid, acetate and citrate to bicarbonate), causing potentially fatal arrhythmias and sudden death in the postdialysis period.

Hypoxia

HD- associated hypoxia is related to the buffer and/or the membrane used. The Pco₂ in acetate-buffered dialysate is low, creating a diffusion gradient from blood to dialysate,

lowering blood P_{CO_2} and decreasing respiratory drive with resultant hypoventilation and hypoxia. In contrast to the low P_{CO_2} of acetate-buffered dialysate, the P_{CO_2} of bicarbonate-buffered dialysate is nearly 100 mmHg, leading to the net transfer of CO_2 into the blood, stimulating respiratory drive.

Hypoglycemia

Carbohydrate metabolism is abnormal in patients with CKD. Although there is a peripheral resistance to the effects of insulin in uremia, the half-life of insulin is significantly prolonged when the glomerular filtration rate (GFR) is less than 20 mL/min. Finally, the effect of a given dose of insulin is enhanced once 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 dialysis against a bath with a fixed glucose concentration and too low for the amount of insulin being administered. It is frequently necessary to decrease the dose of insulin on dialysis days. Furthermore, diabetic patients should not be dialyzed against a bath that has a glucose concentration of less than 100 mg/dL.

Hemorrhage

Gastrointestinal blood loss, subdural and retroperitoneal hematomas, and the 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 who have had recent surgery, or who have an underlying coagulopathy or thrombocytopenia are at particular risk. Furthermore, HD patients are exposed to chronic blood loss with each dialysis treatment because 5 to 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 lab tests. Estimates of total blood loss per treatment vary from 5 to 50 mL.

Dialysate Composition and Integrity of the Extracorporeal Circuit

Constant monitoring of the composition and the temperature of the dialysate is necessary. Highly supervised and standardized water treatment before dialysate is reconstituted and the machine's integral safety systems are critical to ensure safe treatments. During each HD, the patient's blood is exposed to 120 to 200 liters of dialysate. So dialysate must receive the same consideration as medications. Given the magnitude of the water exposure even small amounts of trace elements or organic material may be harmful. Chloramines in water purification and copper have been associated with anemia. Aluminum has been associated with severe osteomalacia and fatal encephalopathy. Outbreaks of infection caused by agents such as *Mycobacterium chelonae* have been reported with improper reuse techniques or ineffective maintenance of the water treatment system. 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.

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 ultraviolet light. Periodic surveillance cultures are obtained at various points of the water and dialysate circuit and the entire water circuit disinfected on a regular basis.

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Higher Intensity Hemodialysis (HD)

Multiple observational studies have shown an association between higher dose of dialysis as measured by urea clearance, and better survival. Randomized controlled trials, using urea clearance to measure HD dose, have failed to confirm the observational data. Despite this, many clinicians think that longer and more frequent dialysis treatments, do improve survival. The technique of continuous HD, introduced over 50 years ago, has allowed over a million people with ESRD to survive, and in hundreds of thousands of cases, to survive to receive a renal transplant and be able to stop dialysis for a period of time. As the delivery of large scale, commercial dialysis has evolved over the past half-century, the drive to extend survival as well as improve quality of life has fueled interest in schedules that go beyond 4 hours, thrice weekly, during the day. Ample observational data in samples of patients from different patient populations, countries, and decades provide strong and compelling arguments that longer treatment time improves survival. Specifically, alternative treatment schedules may be beneficial in mitigating cardiovascular disease, the dominant cause of mortality in dialysis patients. At the same time, alternative schedules allow patients to sleep at night, and have their days free from HD treatments to work, care for family, or participate in other activities during regular daytime business hours. The dialysis community has responded to both the clinical and socioeconomic limitations of the 3–4 hours, thrice weekly schedule by developing a multiplicity of regimens that provide both a more intensive dialysis dose, opportunity for slower, more gradual UFR, and also furnish patients with temporal flexibility and choice. The three dominant more frequent and longer regimens are home HD, short daily HD, and nocturnal HD.

How to perform more intensive HD

Home HD

The main requirements for home HD are a caregiver in the home who can be present for the treatment, an HD machine, and access to purified, disinfected water. Over the past decade, in response to the demand for home HD, several machines for home use have been developed that provide for water recycling and conservation, decreasing the need for high volume, purified water. Once the machine has been chosen and the water system is in place, the nephrologist and the patient can work together to design a schedule which could range from 1–2 hours 6–7 nights a week, to 7–8 hours 3–6 nights a week, depending on the commitment and comfort level of both the patient and the caregiver. Accessing a fistula, a graft, or a catheter at home can be done by either the patient or the caregiver, once they have training and confidence. Many programs use a fluid sensing, or enuresis, device on the access with an alarm, to assist the caregiver in monitoring patients for bleeding during treatments.

In-Center Nocturnal HD

Most in-center nocturnal units are started in a dialysis unit with an existing daytime program. This means that the existing water system, machines, and dialysis chairs can be used to provide treatments at night. One plan that works well is 7–8 hours overnight on Sunday, Tuesday, and Thursday. This schedule leaves time for about 2 hours of downtime for disinfecting the water system and regenerating water between the last day shift on Tuesdays and Thursdays, and the start of the nocturnal shifts. Increased demand will be placed on the RO system, since RO water will be used during the overnight shift, and then a sufficient amount of water will be needed for the first morning shift Mondays, Wednesdays, and Fridays. The team has to calculate how much RO water will be needed overnight and then immediately the next day, factoring in the rate at which water is regenerated and the amount that can be stored.

Factors related to patient selection include whether they have both evening and early morning transportation, and whether they are able to adapt to sleeping in the unit at night. It can take as long as 5–6 weeks for a patient to successfully adapt to a nocturnal schedule. Patients often bring their own bedding, and the unit's thermostat may need to be adjusted so that the unit is warm enough for the patients to sleep comfortably. Orders are straightforward. The duration should be 7 or 8 hours. Providing nocturnal dialysis for less than 6 hours is inadvisable for 2 reasons: (1) Six hours may not be enough time for nocturnal patients to experience the dramatic improvement in subjective well-being, impressively well-tolerated volume removal, and normalized sleep schedule that is possible with 7–8 hours, and (2) it is easier for patients to have reliable and safe transportation at about 5AM, rather than at 2AM. It is reasonable to start with a 2 mEq/L K^+ , 2.5 mEq/L Ca^{++} bath, and then adjust the prescription as indicated by subsequent laboratory data. An initial heparin bolus is followed by a maintenance infusion until the last hour. An additional heparin bolus part way through the treatment may be needed. It is common for patients to UF 4–6 liters without difficulty, but surveillance is mandatory and adjustments likely.

A written plan for communication between the nocturnal staff and the daytime staff is invaluable, particularly for sign-out of any issues related to maintenance of the water system, and pending clinical issues from overnight, such as a clotted access.

More Intensive HD: Why it works so well

Longer, slower dialysis treatments and shorter, more frequent dialysis treatments make possible removal of larger amounts of fluid during the week without the patient experiencing as much hypotension and cramping. Patients who have fluid removed in either more frequent or longer treatments simply spend less time during their week in a volume overloaded state. Some data suggest that that this reduces left ventricular hypertrophy, and may reduce cardiac morbidity and mortality. In response to regular removal of larger amounts of fluid, patients often liberalize their fluid and food intake between treatments.

Urea clearance is certainly improved with longer and more frequent treatments. However, some data suggest that longer and/or more frequent treatments make possible removal of different and molecules larger than urea. In patients who are receiving HD treatments 6–7 days a week, phosphorus control is dramatically improved, and patients are often able to discontinue binders.

In-center nocturnal units leverage existing infrastructure. Unless there are changes needed to the water system, opening of an in-center nocturnal shift can be done with relatively little capital outlay. In terms of running the unit, there is often a period of a few hours after all the patients are on when staff responsibilities are lighter and staff may have time to do other work for the unit, such as filing papers, audits or performing inventories.

One of the reasons that longer and/or more frequent HD treatments work so well is that the economics are compelling. Patients who dialyze at night, either in-center or at home, have their days free to work or provide childcare for their families. There may be a medication cost savings, as patients who are less volume overloaded can often discontinue some of their blood pressure medicines. Observational data also show fewer hospitalizations in patients who have longer treatment times.

Targets for urea clearance can usually be achieved with conventional HD, for 3–4 hours during the day. The survival benefits shown in multiple observational studies with more frequent and/or longer HD treatments over the past 2 decades seem to be related to characteristics of the HD treatments other than urea clearance. More research is needed to better understand how longer and/or more frequent HD treatments improve survival, and what parameters other than urea clearance can be used to measure adequacy.

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Figure 1.

Using standard Kt/V as originally proposed by Frank Gotch, one can compare frequency and intensity of differing dialysis modalities.