The Dialysis Prescription and Urea Modeling

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Hemodialysis is a life-sustaining procedure for the treatment of patients with end-stage renal disease. In acute renal failure the procedure provides for rapid correction of fluid and electrolyte abnormalities that pose an immediate threat to the patient's well-being. In chronic renal failure, hemodialysis results in a dramatic reversal of uremic symptoms and helps improve the patient's functional status and increase patient survival. To achieve these goals the dialysis prescription must ensure that an adequate amount of dialysis is delivered to the patient.

Numerous studies have shown a correlation between the delivered dose of hemodialysis and patient morbidity and mortality [1–4]. Therefore, the delivered dose should be measured and monitored routinely to ensure that the patient receives an adequate amount of dialysis. One method of assessing the amount of dialysis delivered is to calculate the Kt/V. The Kt/V is a unitless value that is indicative of the dose of hemodialysis. The Kt/V is best described as the fractional clearance of urea as a function of its distributional volume. The fractional clearance is operationally defined as the product of dialyzer clearance (K) and the treatment time (t). Recent guidelines suggest that the Kt/V be determined by either formal urea kinetic modeling using computational software or by use of the Kt/V natural logarithm formula [5]. The delivered dose also may be assessed using the urea reduction ratio (URR).

A number of factors contribute to the amount of dialysis delivered as measured by either the Kt/V or URR. Increasing blood flow rates to 400 mL/min or higher and increasing dialysate flow rates to 800 mL/min are effective ways to increase the amount of delivered dialysis. When increases in blood and dialysate flow rates are no longer effective, use of a high-efficiency membrane can further increase the dose of dialysis (KoA >600 mL/min, where KoA is the constant indicating the efficiency of dialyzers in removing urea). Eventually, increases in blood and dialysate flow rates, even when combined with a high-efficiency membrane, result in no further increase in the urea clearance rate. At this point the most important determinant affecting the dose of dialysis is the amount of time the patient is dialyzed.

CHAPTER 6

Ultrafiltration during dialysis is performed to remove volume that has accumulated during the interdialytic period so that patients can be returned to their dry weight. Dry weight is determined somewhat crudely, being based on clinical findings. The patient's dry weight is the weight just preceding the development of hypotension. The patient should be normotensive and show no evidence of pulmonary or peripheral edema. A patient's dry weight frequently changes over time and therefore must be assessed regularly to avoid hypotension or progressive volume overload.

During ultrafiltration the driving force for fluid removal is the establishment of a pressure gradient across the dialysis membrane. The water permeability of a dialysis membrane is a function of membrane thickness and pore size and is indicated by its ultrafiltration coefficient (KUf). During ultrafiltration additional solute removal occurs by solvent drag or convection. Because of increased pore size, high-flux membranes (KUf >20 mL/h/mm Hg) are associated with much higher clearances of average to high molecular weight solutes such as β_2 microglobulin. Because blood flow rates over 50 to 100 mL/min result in little or no further increase in the clearance of these molecules, clearance is primarily membrane-limited. In contrast, clearance values for urea are not significantly greater with a high-flux membrane compared with a high-efficiency membrane because the blood flow rate, and not the membrane, is the principal determinant of small solute clearance.

The biocompatibility of the dialysis membrane is another consideration in the dialysis prescription. A biocompatible dialysis membrane is one in which minimal reaction occurs between the humoral and cellular components of blood as they come into contact with the surface of the dialyzer [6]. One such reaction that has been used as a marker of biocompatibility is evidence of complement activation. Cellulosic membranes generally tend to be bioincompatible, whereas noncellulosic or synthetic membranes have more biocompatible characteristics. Whether any clinical difference exists in acute or chronic outcomes between biocompatible and bioincompatible membranes is still a matter of debate. Trials designed to address this issue have been mostly uncontrolled, limited in sample size, and often retrospective in nature. Nevertheless, some evidence exists to suggest that bioincompatible membranes may have a greater association with β_2 microglobulin-induced amyloidosis, susceptibility to infection, enhanced protein catabolism, and increased patient mortality [5–9].

Another aspect of the dialysis prescription is the composition of the dialysate. The concentrations of sodium, potassium, calcium, and bicarbonate in the dialysate can be individualized such that ionic composition of the body is restored toward normal during the dialytic procedure. This topic is discussed in detail in chapter 2.

Although hemodialysis is effective in removing uremic toxins and provides adequate control of fluid and electrolyte abnormalities, the procedure does not provide for the endocrine or metabolic functions of the normal kidney. Therefore, the dialysis prescription often includes medications such as erythropoietin and $1,25(OH)_2$ vitamin D. The dose of erythropoietin should be adjusted to maintain the hematocrit between 33% and 36% (hemoglobin of 11 g/dL and 12 g/dL, respectively) [10]. Vitamin D therapy is often used in patients undergoing dialysis to help limit the severity of secondary hyperparathyroidism. Dosages usually range from 1 to 2 µg given intravenously with each treatment.

Treatment

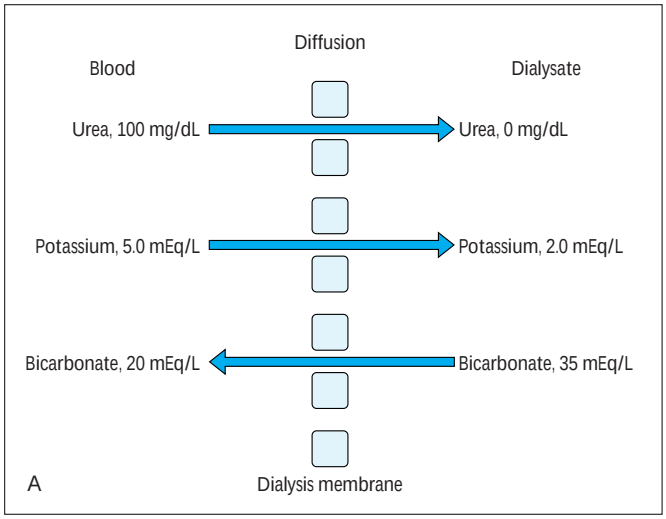

FIGURE 6-1

Diffusional and convective flux in hemodialysis. Dialysis is a process whereby the composition of blood is altered by exposing it to dialysate through a semipermeable membrane. Solutes are transported across this membrane by either diffusional or convective flux. **A,** In diffusive solute transport, solutes cross the dialysis membrane in a direction dictated by the concentration gradient established across the membrane of the hemodialyzer. For example, urea and potassium diffuse from blood to dialysate, whereas bicarbonate diffuses from dialysate to blood. At a given temperature, diffusive transport is directly proportional to both the solute concentration gradient across the membrane and the membrane surface area and inversely proportional to membrane thickness.

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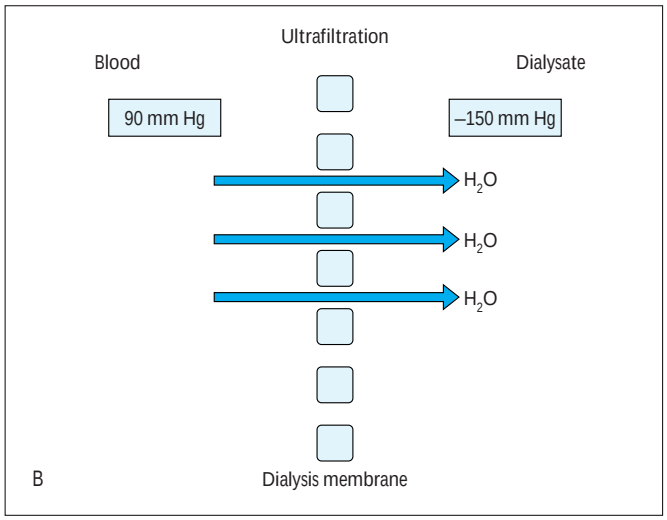

FIGURE 6-1 (*Continued*)

B, During hemodialysis water moves from blood to dialysate driven by a hydrostatic pressure gradient between the blood and dialysate compartments, a process referred to as ultrafiltration. The rate of ultrafiltration is determined by the magnitude of this pressure gradient. Movement of water tends to drag solute across the membrane, a process referred to as convective transport or solvent drag. The contribution of convective transport to total solute transport is only significant for average-to-high molecular weight solutes because they tend to have a smaller diffusive flux.

TREATMENT OF HEMODYNAMIC INSTABILITY

- Exclude nondialysis-related causes (*eg*, cardiac ischemia, pericardial effusion, infection)
- Set the dry weight accurately
- Optimize the dialysate composition
  - Use a sodium concentration of ≥140 mEq/L
  - Use sodium modeling
  - Use a bicarbonate buffer
  - Avoid low magnesium dialysate
  - Avoid low calcium dialysate
- Optimize the method of ultrafiltration
  - Use volume-controlled ultrafiltration
  - Use ultrafiltration modeling
  - Use sequential ultrafiltration and isovolemic dialysis
- Use cool temperature dialysate
- Maximize cardiac performance
- Have patients avoid food on day of dialysis
- Have patients avoid antihypertensive medicines on day of dialysis
- Pharmacologic prevention
  - Erythropoietin therapy to keep hematocrit >30%
  - Experimental (*eg*,caffeine, midodrine, ephedrine, phenylephrine, carnitine)

FIGURE 6-2

The common treatments for hemodynamic instability of patients undergoing dialysis. It is important to begin by excluding reversible causes associated with hypotension because failure to recognize these abnormalities can be lethal. Perhaps the most common reason for hemodynamic instability is an inaccurate setting of the dry weight. Once these conditions have been dealt with, the use of a high sodium dialysate, sodium modeling, cool temperature dialysis, and perhaps the administration of midodrine may be attempted. All of these maneuvers are effective in stabilizing blood pressure in dialysis patients.

ACCEPTABLE METHODS TO MEASURE HEMODIALYSIS ADEQUACY*

- Formal urea kinetic modeling (Kt/V) using computational software
- $Kt/V = -Ln\,(R - 0.008 \times t) + (4 - 3.5 \times R) \times Uf/w^{t}$
- Urea reduction ratio

*Recommended by the National Kidney Foundation Dialysis Outcomes Quality Initiative Clinical Practice Guidelines, which suggest a prescribed minimum Kt/V of 1.3 and a minimum urea reduction ratio of 70%.

†*Ln* is the natural logarithm; *R* is postdialysis blood urea nitrogen (BUN)/predialysis BUN; *t* is time in hours, *Uf* is ultrafiltration volume in liters; *w* is postdialysis weight in kilograms.

FIGURE 6-3

Acceptable methods to measure hemodialysis adequacy as recommended in the Dialysis Outcomes Quality Initiative (DOQI) Clinical Practice Guidelines. These guidelines may change as new information on the benefit of increasing the dialysis prescription becomes available. For the present, however, they should be considered the minimum targets.

Considerations in Choice of Membranes

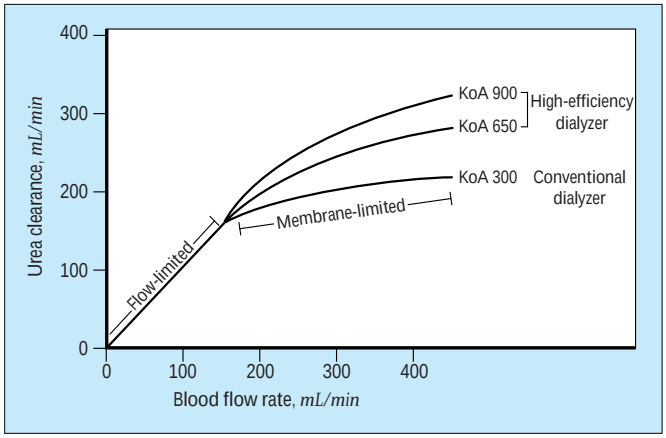

FIGURE 6-4

Relationships between membrane efficiency and clearance and blood flow rates in hemodialysis. When prescribing the blood flow rate for a hemodialysis procedure the following must be considered: the relationship between the type of dialysis membrane used, blood flow rate, and clearance rate of a given solute. For a small solute such as urea (molecular weight, 60) initially a linear relationship exists between clearance and blood flow rates. Small solutes are therefore said to be flow-limited because their clearance is highly flow-dependent. At higher blood flow rates, increases in clearance rates progressively decrease as the characteristics of the dialysis membrane become the limiting factor. The efficiency of a dialyzer in removing urea can be described by a constant referred to as KoA, which is determined by factors such as surface area, pore size, and membrane thickness. Use of a high-efficiency membrane (KoA >600 mL/min) can result in further increases in urea clearance rates at high blood flow rates. In contrast, at low blood flow rates no significant difference exists in urea clearance between a conventional and a high-efficiency membrane because blood flow, and not the membrane, is the primary determinant of clearance.

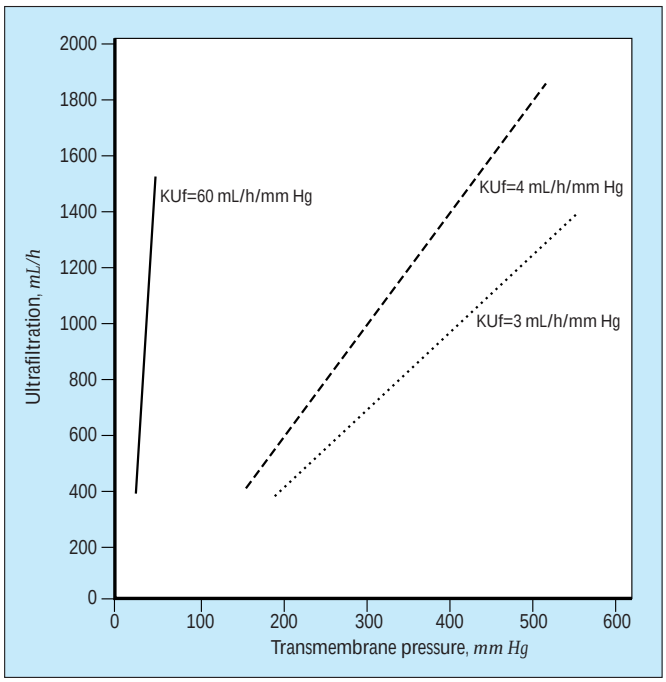

FIGURE 6-5

Water permeability of a membrane and control of volumetric ultrafiltration in hemodialysis. The water permeability of a dialysis membrane can vary considerably and is a function of membrane thickness and pore size. The water permeability is indicated by its ultrafiltration coefficient (KUf). The KUf is defined as the number of milliliters of fluid per hour that will be transferred across the membrane per mm Hg pressure gradient across the membrane. A high-flux membrane is characterized by an ultrafiltration coefficient of over 20 mL/h /mm Hg. With such a high water permeability value a small error in setting the transmembrane pressure can result in excessively large amounts of fluid to be removed. As a result, use of these membranes should be restricted to dialysis machines that have volumetric ultrafiltration controls so that the amount of ultrafiltration can be precisely controlled.

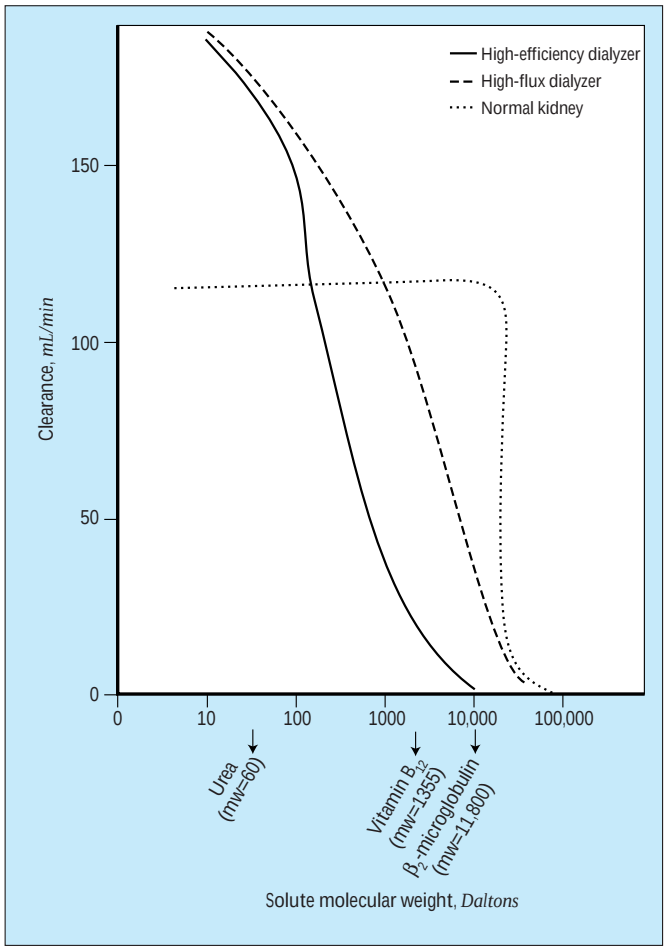

FIGURE 6-6

High-efficiency and high-flux membranes in hemodialysis. These membranes have similar clearance values for low molecular weight solutes such as urea (molecular weight, 60). In this respect both types of membranes have similar KoA values (over 600 mL/min), where KoA is the constant indicating the efficiency of the dialyzer in removing urea. As a result of increased pore size, use of high-flux membranes can lead to significantly greater clearance rates of high molecular weight solutes. For example, β_2-microglobulin is not removed during dialysis using low-flux membranes (KUf <10 mL/h/mm Hg, where KUf is the ultrafiltration coefficient). With some high-flux membranes, 400 to 600 mg/wk of β_2-microglobulin can be removed. The clinical significance of enhanced clearance of β_2-microglobulin and other middle molecules using a high-flux dialyzer is currently being studied in a national multicenter hemodialysis trial.

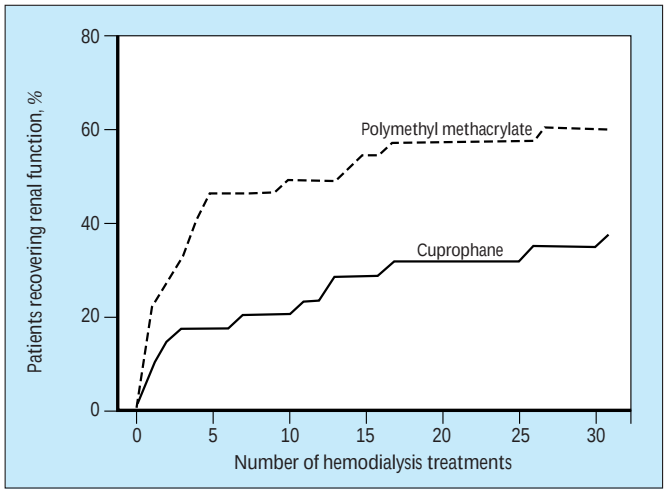

FIGURE 6-7

Effects of membrane biocompatibility in hemodialysis. Another consideration in the choice of a dialysis membrane is whether it is biocompatible. In chronic renal failure some evidence exists to suggest that long-term use of biocompatible membranes may be associated with favorable effects on nutrition, infectious risk, and possibly mortality when compared with bioincompatible membranes [5–9]. In the study results shown here, the effect of biocompatibility on renal outcome in a group of patients with acute renal failure who required hemodialysis was examined. Patients received dialysis with a cuprophane membrane (a bioincompatible membrane known to activate complement and neutrophils) or a synthetic membrane made of polymethyl methacrylate (a biocompatible membrane associated with more limited complement and neutrophil activation). The two groups of patients were similar in age, degree of renal failure, and severity of the underlying disease as defined by the Acute Physiology and Chronic Health Evaluation (APACHE) II score. As compared with the bioincompatible membrane, those patients treated with the synthetic biocompatible membrane had a significantly shorter duration of renal failure in terms of number of treatments and duration of dialysis. In the setting of acute renal failure, particularly in patients after transplantation, a biocompatible membrane may be the preferred dialyzer. (*From* Hakim and coworkers [11]; with permission.)

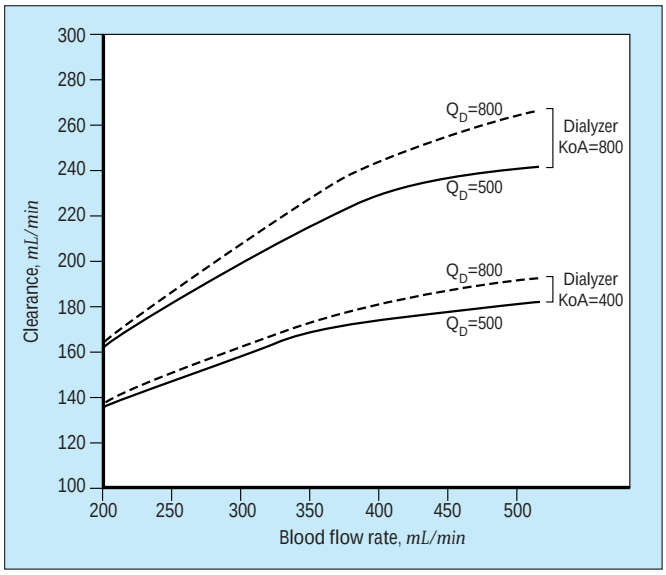

FIGURE 6-8

Dialysate flow rate in hemodialysis. The clearance of urea also is influenced by the dialysate flow rate. Increased flow rates help maximize the urea concentration gradient along the entire length of the dialysis membrane. Increasing the dialysate flow rate from 500 to 800 mL/min can be expected to increase the urea clearance rate on the order of 10% to 15%. This effect is most pronounced at high blood flow rates and with use of high KoA dialyzers. KoA—constant indicating the efficiency of the dialyzer in removing urea; Q_D—dialysate flow rate.

Prescription for Dose Delivery

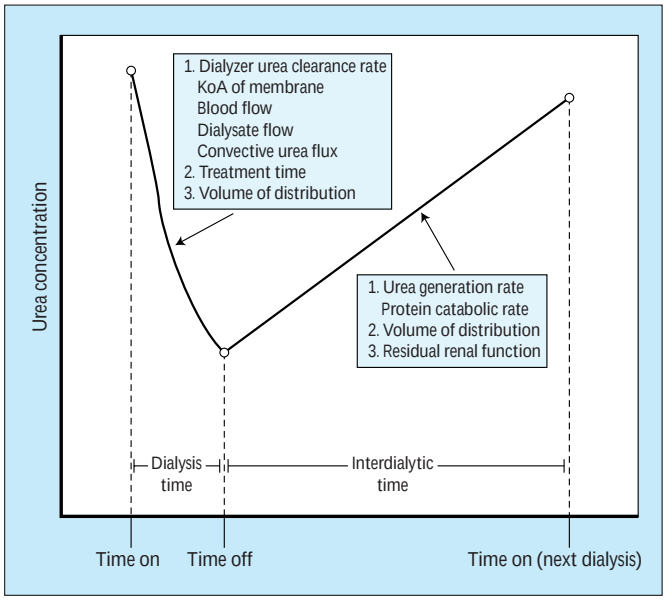

FIGURE 6-9

Delivering an adequate dose of dialysis in hemodialysis. Providing an adequate amount of dialysis is an important part of the dialysis prescription. During the dialytic procedure a sharp decrease in the concentration of urea occurs followed by a gradual increase during the interdialytic period. The decrease in urea during dialysis is determined by three main parameters: dialyzer urea clearance rate (K), dialysis treatment time (t), and the volume of urea distribution (V). The dialyzer urea clearance rate (K) is influenced by the characteristics of the dialysis membrane (KoA), blood flow rate, dialysate flow rate, and convective urea flux that occurs with ultrafiltration. The gradual increase in urea during the interdialytic period depends on the rate of urea generation that, in an otherwise stable patient, reflects the dietary protein intake, distribution volume of urea, and presence or absence of residual renal function.

FACTORS RESULTING IN A REDUCTION OF THE PRESCRIBED DOSE OF HEMODIALYSIS DELIVERED

- Compromised urea clearance
  - Access recirculation
  - Inadequate blood flow from the vascular access
  - Dialyzer clotting during dialysis (reduction of effective surface area)
  - Blood pump or dialysate flow calibration error
- Reduction in treatment time
  - Premature discontinuation of dialysis for staff or unit convenience
  - Premature discontinuation of dialysis per patient request
  - Delay in starting treatment owing to patient or staff tardiness
  - Time on dialysis calculated incorrectly
- Laboratory or blood sampling errors
  - Dilution of predialysis BUN blood sample with saline
  - Drawing of predialysis BUN blood sample after start of the procedure
  - Drawing postdialysis BUN >5 minutes after the procedure

BUN—blood urea nitrogen.

FIGURE 6-10

Each of the factors listed may play a major role in the reduction of delivered dialysis dose. Particular attention should be paid to the vascular access and to a reduction in the effective surface area of the dialyzer. Perhaps the most important cause for reduction in dialysis time has to do with premature discontinuation of dialysis for the convenience of the patient or staff. Delays in starting dialysis treatment are frequent and may result in a significant loss of dialysis prescription. Finally, particular attention should be paid to the correct sampling of the blood urea nitrogen level and the site from which the sample is drawn.

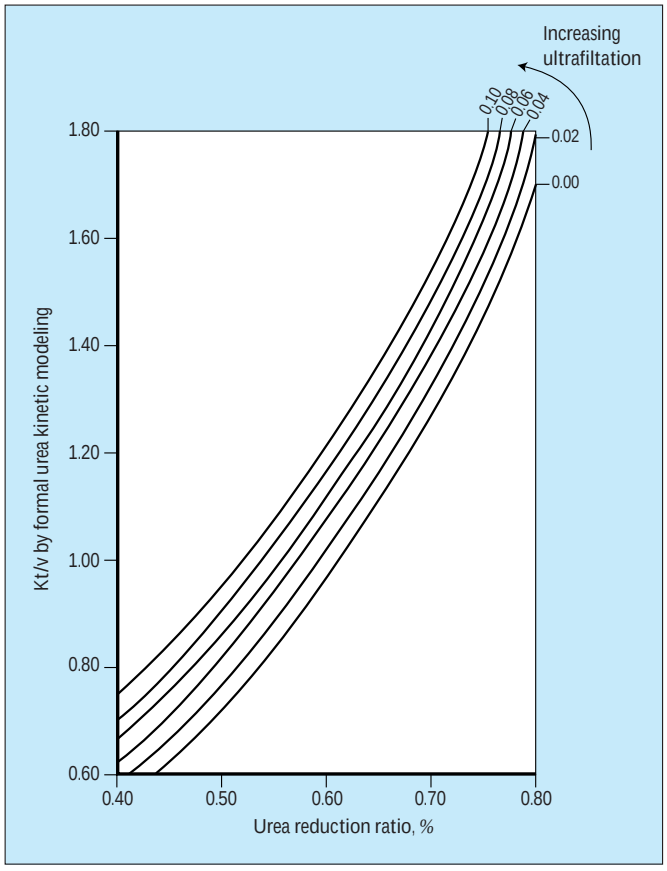

FIGURE 6-11

Monitoring the delivered dose in hemodialysis. Use of the urea reduction ratio (URR) is the simplest way to monitor the delivered dose of hemodialysis. However, a shortcoming of this method compared with formal urea kinetic modeling is that the URR does not account for the contribution of ultrafiltration to the final delivered dose of dialysis. During ultrafiltration, convective transfer of urea from blood to dialysate occurs without a decrease in urea concentration. As a result, with increasing ultrafiltration volumes the Kt/V, as determined by formal urea kinetic modeling, progressively increases at any given URR. For example, a URR of 65% may correspond to a Kt/V as low as 1.1 in the absence of ultrafiltration or as high as 1.35 when ultrafiltration of 10% of body weight occurs.

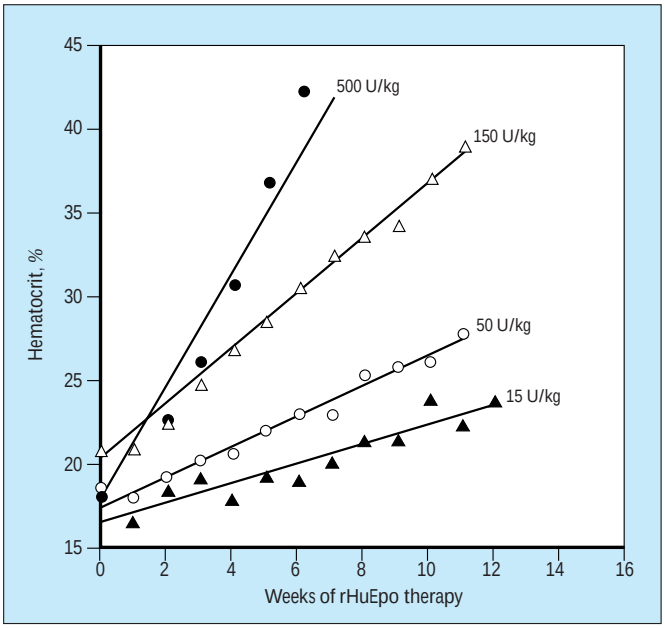

FIGURE 6-12

Correction of anemia in chronic renal failure. Anemia is a predictable complication of chronic renal failure that is due partly to reduction in erythropoietin production. Use of recombinant erythropoietin to correct the anemia in patients with chronic renal failure has become standard therapy. The rate of increase in hematocrit is dose-dependent. The indicated doses were given intravenously three times per week. Current guidelines for the initiation of intravenous therapy suggest a starting dosage of 120 to 180 U/kg/wk (typically 9000 U/wk) administered in three divided doses. Administration of erythropoietin subcutaneously has been shown to be more efficient than is intravenous administration. That is, on average, any given increment in hematocrit can be achieved with less erythropoietin when it is given subcutaneously as compared with intravenously. In adults, the subcutaneous dosage of erythropoietin is 80 to 120 U/kg/wk (typically 6000 U/wk) in two to three divided doses. rHuEpo—recombinant human erythropoietin. *Data from* Eschbach and coworkers [12]; with permission.

MAJOR COMPONENTS OF DIALYSIS PRESCRIPTION

- Choose a biocompatible membrane
- Prescribe a Kt/V ≥1.3 or a URR ≥70%
- Rigorously ensure that the delivered dose equals the amount prescribed
- When the delivered dose is less than that prescribed do the following:
  - Exclude factors listed in Figure 6-10
  - Increase blood flow rate ≥400 mL/min
  - Increase dialysate flow rate to ≥800 mL/min
  - Use a high-efficiency dialyzer
  - Increase treatment time
- Choose dialysate composition: sodium, potassium, bicarbonate, and calcium
- Adjust ultrafiltration rate to achieve patients' dry weight (assess dry weight regularly)
- Adjust recombinant erythropoietin to maintain hematocrit between 33% and 36%
- When indicated, use $1,25(OH)_2$ vitamin D for treatment of secondary hyperparathyroidism
- Use normal saline, hypertonic saline, or mannitol for treatment of intradialytic hypotension

URR–urea reduction ratio.

FIGURE 6-13

All these components are important as contributors to a successful dialysis prescription. The Dialysis Outcomes Quality Initiative (DOQI) recommendations should be followed to achieve an adequate dialysis prescription, and the time on dialysis should be monitored carefully. When the delivered dialysis dose is less that prescribed, the reversible factors listed in Figure 6-10 should be addressed first. Subsequently, an increase in blood flow to 400 mL/min should be attempted. Increases in dialyzer surface area and treatment time also may be attempted. In addition, attention should be paid to the correct dialysis composition and to the ultrafiltration rate to make certain that patients achieve a weight as close as possible to their dry weight. Hematocrit should be sustained at 33% to 36%. Finally, vitamin D supplementation to prevent secondary hyperparathyroidism and use of normal saline or other volume expanders are encouraged to treat hypotension during dialysis. KoA—constant indicating the efficiency of the dialyzer in removing urea.

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