CHAPTER 165

Solute and Water Kinetics in Continuous Therapies

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OBJECTIVES

This chapter will:

1. Describe the basic mechanisms of fluid transport and solute removal (ultrafiltration, diffusion, convection, and adsorption) and the factors influencing these processes in continuous renal replacement therapy.
2. Describe the manner in which the basic principles of solute and water removal apply in the clinical application of the different continuous renal replacement therapy modalities.
3. Apply the above principles in relation to the concept of dose for a dialytic treatment, with specific reference to the various terms used to quantify therapy delivery.

Renal replacement therapy is required in a significant percentage of patients developing acute kidney injury (AKI) in an intensive care unit (ICU) setting.[1] Continuous renal replacement therapy (CRRT) is any extracorporeal blood purification therapy that aims to support kidney function over an extended period of time. One of the foremost objectives of CRRT is the removal of excess fluid and blood solutes that are retained as a consequence of decreased or absent glomerular filtration. In addition to CRRT, hybrid therapies can be performed. They share characteristics of intermittent and continuous techniques with respect to frequency and duration, having the goal of maximizing the desirable and minimizing the undesirable characteristics of each technique.

Because prescription of CRRT requires goals to be set with regard to the rate and extent of both solute and fluid removal, a thorough understanding of the mechanisms by which solute and fluid removal occurs during CRRT and of related therapies is necessary. From the combination of the different transport mechanisms, a number of CRRT modalities are identified. Finally, these principles are applied to provide a brief overview of the concept of CRRT dose.

TRANSPORT MECHANISM

Fluid Removal

Ultrafiltration

Ultrafiltration describes the transport of plasma water (solvent) through a semipermeable membrane driven by a pressure gradient between blood and dialysate/ultrafiltrate compartments. (The non-blood chamber of a CRRT filter typically is designated as the effluent compartment, and the rate at which fluid exits the filter from this space is equal to the sum of the dialysate flow rate and/or replacement fluid rate along with the patient's net fluid removal rate.) Quantitatively, ultrafiltration is defined by the ultrafiltration rate:

$$Q_{UF} = DK_{UF} \cdot TMP$$

where DK_{UF} is the filter ultrafiltration coefficient and TMP the transmembrane pressure.

Solute Removal

Diffusion

Diffusion is the process of transport in which molecules that are present in a solvent and can pass freely across a semipermeable membrane tend to move from the region of higher concentration into the region of lower concentration. In reality, molecules present a random movement. However, the number of particles crossing the membrane toward the region of lower concentration is statistically higher. Therefore this transport mechanism occurs for solutes that are not restricted completely in diffusion by the porosity of the membrane.[2] In addition to the concentration gradient (dc), the diffusive flux (J_d) is influenced by membrane thickness (dx) and the diffusion coefficient of the solute (D). The diffusive flux (by definition normalized to membrane surface area[3]) is defined as the solute mass removal rate resulting from diffusion, and it is described mathematically by Fick's law:

$$J_d = D\left(\frac{dc}{dx}\right)$$

Diffusion is an efficient transport mechanism for the removal of relatively small solutes, but as solute molecular weight increases, diffusion becomes limited and the relative importance of convection increases.

Convection

Convection is the mass transfer mechanism in which solutes pass across the semipermeable membrane in association with the plasma water ("solvent drag"), the movement of which is a consequence of a transmembrane pressure (TMP) gradient. Quantitatively, the ultrafiltration flux (J_F), defined as the ultrafiltration rate normalized to membrane surface area, can be described this way:

$$J_F = K_{UF} \times TMP$$

In this equation, K_{UF} is the membrane-specific hydraulic permeability (units: mL/hr/mm Hg/m^2), and TMP is a function of the hydrostatic and oncotic pressure gradients.

Under theoretical conditions, the convective flux of a given solute (J_c), defined as the solute mass removal rate resulting from convection normalized to membrane surface

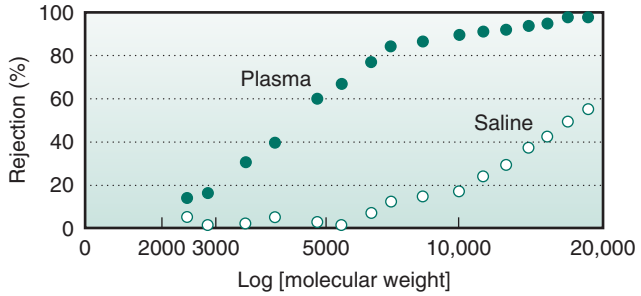

FIGURE 165.1 Effect of secondary membrane formation on membrane sieving properties.

area, is a function of J_F, the solute concentration in plasma water (C_{Pi}), and the sieving coefficient of the membrane (SC):

$$Jc = J_F \cdot C_{Pi} \cdot SC = J_F \cdot C_{Pi} \cdot (1 - RC)$$

For ideal conditions, SC is regulated by the rejection coefficient of the membrane (RC) according to:

$$SC = 1 - RC$$

In clinical practice, however, because plasma proteins and other factors modify the original reflection coefficient of the membrane, the final observed sieving coefficient is smaller than that expected from a simple theoretical calculation. Nonspecific adsorption of plasma proteins occurs instantaneously to an extracorporeal membrane after exposure to blood. This changes the effective permeability of the membrane from the perspective of water and solute permeability. This is explained by the action of proteins to essentially "plug" or block a certain percentage of membrane pores.

In Fig. 165.1, percent rejection, which is equal to (1 – SC) × 100, is plotted against solute molecular weight. Results for a protein-containing fluid (plasma) and a protein-free fluid (saline) are shown. For a test solute with a molecular weight of 5000, the percent rejection in saline is 0% (i.e., the sieving coefficient is 1). On the other hand, for that same solute, the percent rejection in plasma is approximately 60% (sieving coefficient of 0.4). This difference demonstrates the significant effect of secondary membrane formation on membrane function. Postdilution reinfusion techniques tend to accentuate secondary membrane effects because protein concentrations are increased within the membrane fibers (resulting from hemoconcentration). On the other hand, higher blood flow rates work to attenuate this process because the shear effect created by the blood lessens the binding of proteins to the membrane surface.

Adsorption

For certain membranes, adsorption (binding) may be the dominant or sole mechanism by which some hydrophobic compounds (i.e., peptides and proteins) are removed.[4] The adsorptive surface area of a membrane resides primarily in the pore structure rather than in the nominal surface area. As such, the adsorption of a low-molecular-weight protein is highly dependent on access of the protein to a membrane's internal pore structure. Consequently, adsorption of peptides and low-molecular-weight proteins, such as β_2-microglobulin, to low-flux membranes is not expected to be clinically significant, at least in comparison with that which occurs to high-flux membranes. The adsorption affinity of certain high-flux synthetic membranes for proteins and peptides is particularly high, attributable to the relative hydrophobicity of these membranes.

CONTINUOUS RENAL REPLACEMENT THERAPY TECHNIQUES

Several techniques are today available in the spectrum of CRRT. Techniques may differ in terms of vascular access and extracorporeal circuit design, frequency, and intensity of treatment, predominant mechanism of transport used, and type of membrane.

Slow Continuous Ultrafiltration

Slow continuous ultrafiltration (SCUF) typically is employed for 24 hours a day but also may be applied during some portion of the day. The treatment is carried out with high-flux membranes, and the objective is to achieve volume control in patients with severe, diuretic-resistant volume overload. Relative to hemofiltration, low filtration rates (typically 2–8 mL/min) are required. As such, filters of relatively small surface area and low blood flow rates can be employed. An ultrafiltration control system is required to prevent excessive ultrafiltration. Although very effective for volume reduction, the low filtration rates and lack of substitution fluids render this therapy ineffective as a blood purification modality.

Extracorporeal ultrafiltration is being used increasingly as an adjunctive therapy for patients with refractory heart failure.[5,6] In this context, an important consideration is the type of vascular access required. Because slow continuous ultrafiltration is not a blood-cleansing modality such that solute clearance is not a relevant consideration, it is possible to use a smaller-bore catheter in a peripheral vein as vascular access. From one perspective, the minimum blood flow rate is that required to avoid excessive hemoconcentration. To quantify this phenomenon, the filtration fraction (ratio of the ultrafiltration rate to the plasma flow rate delivered to the filter) has been employed traditionally. In general, a maximal filtration fraction of 25% usually guides prescription in acute postdilution hemofiltration, which is the relevant comparison in this instance. At filtration fractions beyond this value, hemoconcentration is associated with an environment that promotes interactions between formed elements and proteins in the blood and the filter membrane, leading to a high risk of filter resulting from widespread pore occlusion ("clogging"). However, the ultrafiltration rates typically employed in SCUF (<10 mL/min) are significantly less than those in hemofiltration, which may be 40 mL/min or higher. Therefore, although the minimum blood flow rate may be 200 mL/min or higher in the setting of postdilution hemofiltration, a blood flow rate of 50 mL/min in SCUF may be adequate to maintain the filtration fraction less than 25%.

Two caveats must be discussed. First, the filtration fraction calculation often is based on the hematocrit value at the start of therapy. However, as ultrafiltration proceeds and net volume removal occurs, hematocrit increases. Therefore, for a given volume of blood flowing through the filter, an increasing percentage of that volume is composed of red blood cells and a decreasing percentage is composed of plasma water during ongoing ultrafiltration therapy. At a fixed blood flow rate and ultrafiltration rate, this implies an increasing filtration fraction, because plasma water flow

rate is the denominator in the filtration fraction equation. Thus, from the relatively narrow perspective of filtration fraction, a seemingly adequate blood flow rate at the onset of ultrafiltration may be inadequate after several hours of therapy. A second important consideration related to blood flow rate involves its effect on blood rheology at the membrane surface. The velocity that blood achieves while passing through an individual hollow fiber membrane is directly proportional to its blood flow rate.[7] In turn, the velocity (or more rigorously, the velocity gradient) of blood at the membrane surface is directly proportional to its shear rate at that membrane-blood interface.

Continuous Venovenous Hemofiltration

Continuous venovenous hemofiltration (CVVH) normally is prescribed for 24 hours per day over an extended period of time. The technique uses high-flux membranes, and the prevalent mechanism of solute transport is convection. Ultrafiltration rates in excess of the amount required for volume control are prescribed, requiring partial or total replacement of ultrafiltrate losses with reinfusion (replacement) fluid. Replacement fluid can be infused either before the filter (predilution) or after the filter (postdilution). The location of reinfusion fluid delivery in the extracorporeal circuit has a significant impact on solute removal and therapy requirements.

Postdilution hemofiltration is limited inherently by the attainable blood flow rate and the associated filtration fraction constraint. For acute hemofiltration (usually delivered continuously as CVVH), the blood flow limitations imposed by the use of temporary catheters accentuates the filtration fraction–related constraints on maximally attainable ultrafiltration rate in the postdilution mode. Therefore the ultrafiltrate volumes shown by Ronco et al.[8] to improve survival frequently can be achieved only in the predilution mode, in which the efficiency of replacement fluid utilization is an important consideration (see later in this chapter).

From a mass transfer perspective, the use of predilution has several potential advantages over postdilution.[9] First, hematocrit and blood total protein concentration are reduced significantly before the entry of blood into the hemofilter. This effective reduction in the red cell and protein content of the blood attenuates the secondary membrane and concentration polarization phenomena, resulting in improved mass transfer. Predilution also favorably affects mass transfer because of augmented flow in the blood compartment, because prefilter mixing of blood and replacement fluid occurs. This achieves a relatively high membrane shear rate, which also reduces solute-membrane interactions. Finally, predilution also may enhance mass transfer for some compounds by creating concentration gradients that induce solute movement out of red blood cells. However, the major drawback of predilution hemofiltration is its relatively low efficiency, resulting in relatively high replacement fluid requirements to achieve a given solute clearance.[10]

Continuous Venovenous Hemodialysis

Continuous hemodialysis first was proposed by Scribner more than 40 years ago but not actually incorporated into general clinical use for many years because of technical limitations at that time.[11,12] Continuous arteriovenous hemodialysis, a pumpless system relying on the arteriovenous pressure gradient and a patient's cardiac output for blood flow through the system, initially was developed but has been superseded by continuous venovenous hemodialysis (CVVHD), which uses a blood pump and provides more reliable operation and solute clearance.[12–14] CVVHD is characterized by slow countercurrent dialysate flow into the ultrafiltrate/dialysate compartment of the dialyzer. Ultrapure dialysate may be produced using online proportioning systems, or bags containing sterile dialysate may be used. The prevalent mechanism of solute transport in this technique is diffusion, with the prescribed ultrafiltration rate targeted to achieve the patient's desired fluid balance (i.e., without requirement of fluid reinfusion).

For continuous venovenous hemodialysis, either a low-flux or high-flux filter can be used, although the latter typically is prescribed. When CVVHD is performed with a relatively small surface area filter (<0.5 m^2), saturation of the dialysate is achieved only at relatively low dialysate flow rates. For a 0.4 m^2 filter, Bonnardeaux et al.[15] showed that saturation of the effluent dialysate for urea and creatinine is preserved only up to a dialysate flow rate of approximately 16.7 mL/min (1 L/hr) (Fig. 165.2A). For dialysate flow (Q_D) values in the 2 to 3 L/hr range (33.3–50 mL/min), an increase in Q_D results in an increase in clearance. However, the divergence between the urea/creatinine clearance curves and the effluent dialysate curve indicates the degree to which the dialysate is "nonsaturated." Of course, the greater the degree of nonsaturation, the more inefficient is the procedure. Beyond a Q_D value of approximately 3 L/hr, the urea/creatinine clearance curves plateau, and further

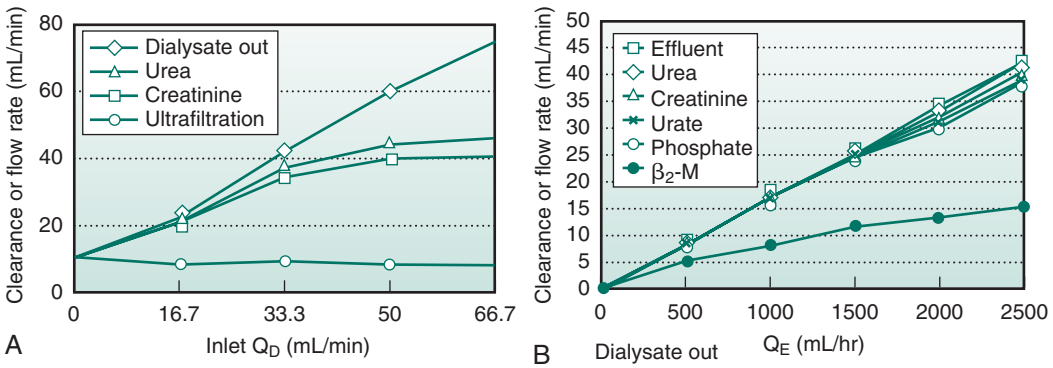

FIGURE 165.2 Relationship between solute clearance and dialysate flow rate for a 0.4 m^2 filter (A) and a 0.9 m^2 filter (B). *β_2-M,* β_2-microglobulin; *Q_D,* dialysate flow; *Q_E,* effluent flow. (A, Reprinted from Bonnardeaux A, Pichette V, Ouimet D, et al. Solute clearances with high dialysate flow rates and glucose absorption from the dialysate in continuous arteriovenous hemodialysis. *Am J Kidney Dis.* 1992;19:31–38. B, Reprinted from Brunet S, Leblanc M, Geadah D, et al. Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. *Am J Kidney Dis.* 1999;34:486–492.)

increases in Q_D no longer result in an increase in clearance when a filter with a relatively low surface area is used.

A more contemporary study involving a larger surface area filter (0.9 m^2) demonstrates clearly the important effect of surface area on preserving dialysate saturation (Fig. 165.2B).[16] For this larger filter, preservation of effluent dialysate saturation was achieved essentially over the entire Q_D range; the only exception was β_2-microglobulin. The high molecular weight of this compound (approximately 200 times that of urea) severely limits its diffusive capabilities and therefore its ability to saturate the dialysate. In contemporary CRRT (including CVVHD), filters having membranes with surface areas greater than 1.0 m^2 are used routinely.[17]

CVVHD has been used primarily to provide renal replacement therapy in critically ill, hemodynamically unstable adult patients with acute renal failure. It also has been used to treat infants and children with inborn errors of metabolism.[18,19] CVVHD also has been advocated as a means to effectively cool patients with hyperthermia or to improve hemodynamic stability in hypotensive patients, and it has been used to treat hypothermia using warmed dialysate.[20,21]

Membrane characteristics greatly influence solute clearance and, in this respect, some polyamide membranes are not designed for diffusive clearance.[22] Comparisons of CVVHD and CVVH using similar membranes have shown little difference in solute clearance for small- and middle-molecular-weight solutes. CVVHD is slightly more efficient than predilution CVVH at eliminating small-molecular-weight solutes but similar in efficiency to postdilution CVVH.[23] However, β_2-microglobulin is cleared more effectively with CVVH because of convection providing greater clearance of higher-molecular-weight solutes.[24,25] Dialyzer circuit survival tends to be extended during CVVHD, likely because of maintenance of a stable hematocrit across the dialyzer, in contrast to CVVH, where there is an increase in hematocrit toward the end of the hemofilters resulting from plasma water loss from ultrafiltration.[25]

Continuous Venovenous High-Flux Hemodialysis

Continuous venovenous high-flux hemodialysis (CVVHFD) is delivered at the same manner of CVVHD, but with the use of high-flux membranes (membranes and filters are defined as high-flux when the membrane ultrafiltration coefficient K_{UF} > 25 mL/hr/mm Hg/m^2). In addition to diffusive solute clearance there is also a major element of ultrafiltration and convective solute clearance. The rate of ultrafiltration is controlled by an ultrafiltration/dialysate volume control system and obviates replacement fluid. In this therapy, positive pressure in the dialysate compartment causes ultrafiltration in the proximal part of the dialyzer and backfiltration more distally. During backfiltration there is a flow of dialysate from the dialysate compartment across the membrane into the blood compartment.

Clearance of higher molecular-weight inflammatory mediators is achieved more effectively with high cutoff membranes during CVVHFD.[26] However, because many inflammatory mediators and cytokines are removed primarily by adsorption, there is some removal also during CVVHD and CVVH.[27–29]

Continuous Venovenous Hemodiafiltration

Continuous venovenous hemodiafiltration (CVVHDF) operates combining the principles of hemodialysis and hemofiltration and requires a high-flux hemodiafilter. As such, this therapy may allow for an optimal combination of diffusion and convection to provide clearances over a very broad range of solutes. Dialysate is circulated in countercurrent mode with respect to blood and, at the same time, ultrafiltration is obtained in excess of the desired fluid loss from the patient. The ultrafiltrate is replaced partially or totally with reinfusion fluid, either in predilution or postdilution mode. Later-generation CRRT machines allow a combination of predilution and postdilution with the aim of combining the advantages of both reinfusion techniques: information from the chronic hemodiafiltration literature suggests a combination of predilution and postdilution may be optimal in terms of clearance and operational parameters.[30] The optimal balance is dictated most likely by the specific set of CVVHDF operating conditions, namely blood flow rate, dialysate flow rate, ultrafiltration rate, and filter type.

The specific manner in which diffusion and convection interact in CVVHDF differs significantly from the situation when this treatment is applied in the end-stage renal disease setting. In the latter situation, diffusion and convection interact in such a manner that total solute removal is significantly less than what is expected if the individual components are simply added together.[31] This phenomenon is explained in the following way. Diffusive solute removal results in a decrease in solute concentration in the blood compartment of the filter along the axial length (i.e., from blood inlet to blood outlet) of the hemodiafilter. Because convective solute removal is directly proportional to the blood compartment concentration, convective solute removal decreases as a function of this axial concentration gradient. At the same time, hemoconcentration resulting from ultrafiltration of plasma water causes a progressive increase in plasma protein concentration and hematocrit along the axial length of the filter. This hemoconcentration and resultant hyperviscosity causes an increase in diffusive mass transfer resistance and a decrease in solute transport by this mechanism.

Because of the markedly lower flow rates used and clearances obtained in CVVHDF, the effect of simultaneous diffusion and convection on overall solute removal is different. Therefore the small-solute concentration gradient along the axial length of the filter (i.e., extraction) is minimal compared with that which is seen in chronic hemodiafiltration, in which extraction ratios of 50% or more are the norm. Thus the minimal diffusion-related change in small-solute concentrations along the filter length allows any additional clearance related to convection to be simply additive to the diffusive component. This has been demonstrated clearly in continuous hemodialysis[32] and continuous hemodiafiltration.[16]

Troyanov et al.[33] performed a direct clinical comparison of CVVHDF and predilution CVVH with respect to urea and β_2-microglobulin clearance at a traditional blood flow rate of 125 mL/min. The study compared clearances at the same effluent rate over an effluent range of up to 4.5 L/hr. As Fig. 165.3 indicates, urea clearance was higher in CVVHDF than in predilution CVVH and, in fact, the difference between the two therapies increased as effluent rate increased. These results are consistent with the "penalizing" effect of predilution, which is pronounced especially at low blood flow rates. For β_2-microglobulin, the results are contrary to the conventional wisdom, which would suggest a purely convective therapy such as CVVH inherently should be superior to a partly convective therapy such as CVVHDF for clearance of a molecule this size. However, once again, the penalty of predilution in CVVH is apparent, because the β_2-microglobulin clearances for the two modalities

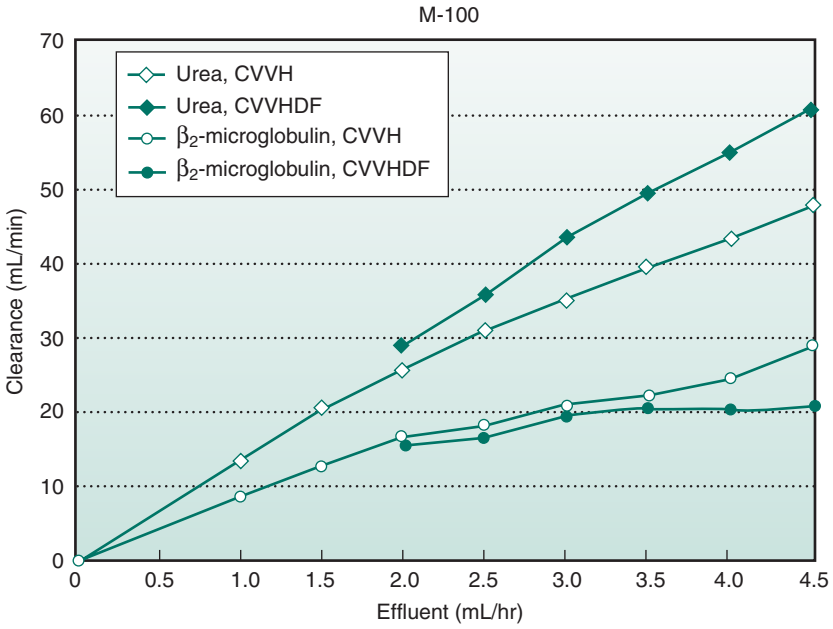

FIGURE 165.3 Comparison of solute clearance in predilution continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF). (Reprinted from Troyanov S, Cardinal J, Geadah D, et al. Solute clearances during continuous venovenous haemofiltration at various ultrafiltration flow rates using Multiflow-100 and HF1000 filters. *Nephrol Dial Transplant.* 2003;18:961–966.)

are equivalent except at very high effluent rates (>3.5 L/hr). Until the impact of higher blood flow rates on solute clearances in CRRT can be assessed, these and other data suggest CVVHDF is a logical modality choice to achieve the broadest spectrum of solute molecular-weight range in the most efficient way.

ADDITIONAL CONSIDERATIONS IN THE DELIVERY OF CONTINUOUS RENAL REPLACEMENT THERAPY

Anticoagulation

Although conventional wisdom in the past has suggested that anticoagulation is necessary for the adequate delivery of CRRT, recent data suggest clinical practice deviates substantially from this axiom. In fact, in a recent large, prospective trial,[34] the majority of treatments were performed with no anticoagulation. Unfortunately, these trials did not report the effect of a no-anticoagulation approach on filter longevity, and the question of filter performance over time as a function of anticoagulation type remain unsettled. Nevertheless, it is reasonable to perform CRRT without anticoagulation, although a circuit life of less than 18 hours can be expected.[35]

When anticoagulation is prescribed for CRRT, systemic heparin (either unfractionated or low-molecular-weight) and regional citrate anticoagulation (RCA) are used most commonly.[35] However, several recent prospective trials clearly have indicated the risk of bleeding when CRRT patients are exposed to systemic heparin is very high.[36] Moreover, it may be very difficult to prospectively identify patients at high risk of bleeding because of the nature of the underlying comorbidities in this population.

Although originally proposed for patients at high risk of bleeding if treated with systemic heparin, RCA now is used commonly as the standard anticoagulation technique at many institutions. Indeed, the use of RCA for CRRT with either trisodium citrate or acid citrate dextrose is becoming increasingly popular. This approach provides regional anticoagulation within the extracorporeal circuit by chelating ionized calcium, which is then unavailable to participate at numerous points in the coagulation cascade. In addition, because citrate is a small-molecular-weight compound, free citrate and citrate-calcium complexes are cleared to varying degrees according to the specific CRRT modality used. Regional citrate anticoagulation provides the longest dialyzer survival and minimizes interruptions of therapy caused by clotting.[37,38] Moreover, as suggested above, RCA is associated with a significantly decreased risk of bleeding in comparison with systemic heparin.[36] Direct thrombin inhibitors such as danaparoid, lepirudin, and argatroban also have been used to provide anticoagulation, usually in the setting of heparin-induced thrombocytopenia.[39,40]

Drug Removal During Continuous Renal Replacement Therapy

The pharmacokinetics of drug removal in critically ill patients receiving CRRT is complex; many variables affect clearance.[41] In general, protein-bound drugs have relatively high molecular weights and large volumes of distribution, resulting in limited removal. On the other hand, antimicrobials with lower protein binding are cleared more readily. In addition to flow rates, membrane pore size also significantly influences drug clearance. An additional consideration is the possibility that the individual components of combination agents (such as piperacillin-tazobactam or imipenem-cilastatin) have differential rates of removal, rendering difficult the dosing of such agents.

Efficiency, Intensity, and Efficacy

Identified as a clearance (K), the efficiency represents the volume of blood cleared of a solute over a given period of time. It can be expressed as the ratio of blood volume over time (e.g., mL/min, mL/hr, L/hr, l/24 hr) and generally is normalized to ideal patient weight (mL/kg/hr). Efficiency

depends on the reference molecules chosen (molecular size), removal mechanisms (diffusion, convection, or both) and circuit operational characteristics (i.e., flow rates and type of filter). Efficiency can be used to compare different RRT treatments applied with the same modality using different settings and operational characteristics. Intensity can be defined by the product "efficiency × time." In practice, intensity represents the blood volume cleared of a solute after a certain period of time; it can be expressed as mL or L. When comparing RRT modalities with different duration times, the use of intensity is more appropriate than the use of efficiency. For example, despite its low efficiency, use of CRRT for a long period of time results in increased treatment intensity. Because patients with AKI frequently require more than a single treatment, frequency of treatment should be considered when assessing dose. Specifically, the product of intensity times frequency (measured as treatment days/week [d/w]) is useful to obtain information beyond a single treatment.

Although intensity allows comparison between different treatments, it does not take into account the volume of the solute pool. Efficacy measures the removal of a specific solute achieved by a given treatment in a given patient. It can be identified as the ratio of the entire volume cleared during the treatment to the volume of distribution of that solute. In practice, efficacy is a dimensionless number and can be defined numerically as the ratio between intensity and the volume of distribution of a specific solute.

CONCLUSION

Rational prescription of CRRT to critically ill patients with AKI is predicated on an understanding of the basic principles of solute and water removal. In this chapter, the fundamental mechanisms for solute and fluid transport have been discussed. Then, these principles have been applied in a therapeutic context to the various CRRT modalities used by clinicians managing AKI patients. Finally, a brief explanation of various expressions used to express the dose of dialysis has been given.

Key Points

1. Continuous renal replacement therapy (CRRT) employs a variety of mechanisms, including ultrafiltration, diffusion, convection, and adsorption to achieve solute water elimination, the factors influencing these processes in continuous renal replacement therapy.
2. With respect to solute removal, the mechanism primarily responsible depends on the solute of interest and the modality used.
3. Solute clearance during continuous venovenous hemodialysis is determined primarily by dialysate flow rate and becomes progressively limited as solute molecular weight increases.
4. The location of reinfusion fluid delivery in continuous venovenous hemofiltration has a significant impact on clearance across, irrespective of solute molecular weight.
5. Efficiency, intensity, and efficacy can be used to characterize treatment dose in CRRT.

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