Chapter (18)

Continuous Renal Replacement Therapy (CRRT)

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CHAPTER OUTLINES

- History of CRRT and future directions.
- Choosing a renal replacement therapy in acute kidney injury (AKI).
- Complications of CRRT.
- Anticoagulation for Continuous Renal Replacement Therapy.
- Volume Management in Continuous Renal Replacement Therapy.
- Dialysate and Replacement Fluids.
- Vascular access in renal replacement therapies.
- Machine comparisons

CHAPTER OBJECTIVES

- Describe the main modalities of renal replacement therapy in the treatment of acute kidney injury in the critically ill patient.
- Enumerate the pros and cons of each modality
- Describe the concepts of diffusion and convection and their application to fluid management and metabolic control
- List the desirable characteristics of the vascular access for CRRT to ensure safe delivery of an appropriate dialysis dose
- Describe the potential complications in the use of CRRT techniques.
- Enumerate the available anticoagulation modalities
- Compare the operational characteristics of the CRRT machines currently available to treat AKI

KEY TERMS

- Acute Kidney Injury
- Continuous Renal Replacement Therapies, CRRT
- Intermittent Hemodialysis
- Extracorporeal
- Diffusion
- Convection
- Adsorption
- Hemofiltration
- Ultrafiltration
- Fluid Balance Errors
- Hemodynamics
- Vascular Access
- Anticoagulation
- Complications
- Replacement Fluid
- Ultrasound Guidance

A.T. Azar (Ed.): Modeling and Control of Dialysis Systems, SCI 405, pp. 929–1009.
springerlink.com

ABSTRACT

This chapter will summarize current knowledge in renal replacement technologies in the treatment of critically ill patients with acute kidney injury. The mechanics of different treatment modalities with emphasis on continuous renal replacement therapies will be described, as well as the application of such technologies in the management of fluid overload and metabolic abnormalities. Appropriate composition of dialysate and replacement fluids, use of anticoagulation, choice of vascular access, and potential complications in the use of such technologies will be discussed. Finally, the chapter will compare the main features of the different currently available CRRT machines.

18.1 HISTORY OF CRRT AND FUTURE DIRECTIONS

This section briefly describes the history and future perspectives of the management of acute kidney injury (AKI) in the critically ill patient, utilizing extracorporeal technologies.

At the dawn of dialytic therapy, renal replacement therapy was seen as a way to temporarily support patients with acute renal failure until renal functional recovery. The development of external arteriovenous access by Scribner, and the arteriovenous fistula by Cimino and Brescia made repeated access to the circulation possible and focused the attention of the nephrologic world towards chronic renal disease. The challenge of end stage renal disease was resolved when -at least in Western countries- chronic dialysis was made widely available. Unfortunately, these events took AKI to a second place, both in terms of the number of patients treated as well as the development of specific dialytic therapies. For many years, instead of developing specific therapies it was felt that AKI patients should be treated with the same methodologies as patients with chronic renal disease. The persistently elevated mortality associated with AKI did not stimulate a critical analysis of the problem; rather, elevated mortality was attributed to high comorbidity or to the nature of the syndrome, instead of relating it to inadequate treatment. The strongly conservative management of AKI was also associated with extensive search into the pathogenesis and clinical presentation rather than on treatment, at a time when nephrology remained tightly linked with internal medicine. Towards the end of the seventies, clinical AKI began to change, together with the development of increasingly invasive and complex surgeries and the growth of intensive care therapies. In this context, the need for specific treatments of AKI became obvious.

Renal replacement therapies first evolved by the development of acute peritoneal dialysis, and later by extracorporeal technologies able to control blood flow and ultrafiltration rate. Newer machines were developed, with more adequate control of ultrafiltration and the use of bicarbonate buffers in the dialysis fluid. Unfortunately, such developments remained insufficient, and unable to confront the hemodynamic instability of the critical patient. Moreover, new problems became evident such as the need to utilize cumbersome water treatment systems, and the scant availability of dialysis facilities in smaller hospitals. At that time, the simultaneous development of newer high permeability dialysis membranes permitted the development of convective treatments such as hemoperfusion. With these, it became possible to provide renal functional substitution with the use of bagged replacement fluids, and without the need for dialysis fluid. In spite of such progress, there remained the problem of vascular access and the use of extracorporeal circulation in the intensive care unit (ICU) environment, at that time still lacking in expertise in such technologies. In 1977, Peter Kramer, while attempting to puncture the femoral vein, punctured the femoral artery by mistake (Kramer et al. 1977). He proceeded to advance the cannula into the artery and assembled a circuit utilizing a polysulphone Amicon 30 filter and venous return: continuous arteriovenous hemofiltration (CAVH) was born. The system had low efficiency and had to be applied continuously for 24 hours. Moreover, the low fluxes and the limited ultrafiltration regimens made CAVH the ideal treatment for unstable patients who could not even be considered candidates for intermittent hemodialysis (IHD). The absence of dialysis fluids, machines and extracorporeal pumps made this modality very popular in the intensive care setting. Towards the end of 1970's, first at Mount Sinai Medical Center in New York (under the direction of Juan Bosch) and later at the Hospital San Bortolo in Vicenza, Italy, many patients were treated with this modality. After that time, Ronco et al. started to disseminate the technology in Italy, not without significant resistance from colleagues.

In 1984 the first meeting on CAVH was organized; in those times, it was mostly a convention of a group of passionate physicians including Lee W. Henderson, Michael Lysaght, Robert Bartlett, Juan Bosch, Luciano Fecondini and many others. Luciano Fecondini, in particular, was the chief engineer at Amicon and this was the key to the development, during many sleepless nights on call at Vicenza, of filters specially dedicated to CAVH. The most important successes included the creation of a very low resistance filter with the use of special geometries and fibers, and the adaptation of a very novel minifilter dedicated to neonates. With the intensive use of CAVH many more severely ill patients were able to receive

treatment, thus creating the possibility of critically evaluating the results of the technique. Towards the end of the 1980's it became obvious that the dose of dialysis delivered by CAVH was insufficient by multiple reasons, including frequent clotting of the system and limited ultrafiltration rates. Contemporarily, newer double-lumen venous catheters were being developed and the use of a blood pump in the ICU was more widely accepted. Also, the newer filters had an additional port permitting the addition of slow-flow of dialysis fluid. This led to the development of continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF). All these techniques, originated in CAVH, were classified under the umbrella of continuous renal replacement therapies (CRRT), taking advantage of newer machine developments by industrial groups that saw the commercial potential of such devices. In the 1990's the collaboration between Dr. Claudio Ronco and Dr. Rinaldo Bellomo (an Italian who immigrated to Melbourne, Australia) led to important joint achievements and an extensive number of publications on CRRT (Ronco and Bellomo 1998). A crucial event in the development of the field was the publication of a 1600 page text on Critical Care Nephrology and the joint publication in Nephrology, Dialysis and Transplantation of an editorial[1] titled "*Critical care nephrology, the time has come"*, which led to newer concepts on diagnosis and interdisciplinary courses on the management of the critical patient with AKI. The desire to learn and the need to discuss critically clinical results, led to the organization of three international courses in Melbourne and Vicenza on Critical Care Nephrology, with enormous success. The courses in Vicenza were geared towards a multidisciplinary medical audience, with sporadic nursing participation. Conversely, other meetings such as the San Diego International Conference on CRRT had mixed participation of physicians, nursing and other allied health practitioners. The reassuringly good patient outcomes in critical patients treated with CRRT led to the development of randomized controlled trials which have helped to define indications and treatment guidelines. Thus, in the book Blood Purification in Intensive Care we stressed the need to find consensus in multiple fronts; such consensus was gathered around the ADQI (Acute Dialysis Quality Initiative, http://www.ADQI.net) conferences in New York and Vicenza, and later in the Acute Kidney Injury Network (http://www.akinet.org).

The possibility of removing solutes from blood to obtain blood purification has mainly focused over the years on classic hemodialysis. However, the characteristics of some solutes make their removal difficult, and the limited efficiency of some dialysis membranes have spurred a significant

interest in the use of further mechanisms of solute removal, hemadsorption. Materials with high capacity of adsorption (sorbents) have been utilized for about 50 years in extracorporeal blood treatments of acute poisoning or uremia. With the recognition of the role of cytokines in systemic inflammatory response syndrome (SIRS) and sepsis, and the fact that most cytokines are poorly removable by conventional diffusive or convective blood purification modalities, treatment of sepsis based on sorbent technique has recently been explored. Continuous treatments are currently being favorably applied to the management of multiorgan failure and sepsis, and the concept of Multiorgan Support Therapies (MOST) is being successfully developed, demonstrating that contemporary treatment modalities of AKI are always the fruit of interdisciplinary collaboration.

18.2 CHOOSING A RENAL REPLACEMENT THERAPY IN AKI

This section focuses on the different modalities of renal replacement therapy (RRT) and briefly reviews both the basic concepts and the newest approaches to the management of the critically ill patient with AKI. Intermittent hemodialysis, Slow Continuous Low Efficiency Dialysis (SLED/EDD) and Continuous Renal Replacement Therapies (CRRT) are modalities of renal functional replacement used to manage AKI in the critically ill patient. Depurative mechanisms include convection, diffusion and membrane adsorption utilizing low- or high-flux highly permeable biocompatible dialysis membranes. In hemofiltration, simultaneous infusion of replacement fluid permits fluid removal without intravascular contraction and provides better hemodynamic stability, metabolic control to almost normal parameters and removal of large-size toxins and cytokines. CRRT allows better long-term clearance of small and middle molecules than other dialysis modalities. Adjustments of RRT techniques to avoid exacerbation of hemodynamic instability and to decrease further renal injury are discussed, emphasizing the importance of RRT modality to ensure patient survival and renal functional recovery.

18.2.1 Introduction

Most hospital-acquired acute kidney injury occurs in the intensive care unit and is associated with elevated morbidity and mortality (Cerda et al. 2008a, b). A recent international survey (Uchino et al. 2007) showed that while 80% of patients with AKI in the ICU are treated with CRRT, 17% are managed with IHD and 3% with peritoneal dialysis or SLED. These novel techniques of renal substitution therapy have allowed a conceptual shift from renal “replacement” to renal “support” therapies (Mehta 2001),

whereby the strategies to treat AKI have become an integral part of the overall critically ill patient management, with 'renal' and 'non-renal' applications such as sepsis and acute respiratory distress syndrome (ARDS). Table 18.1 lists the characteristics of the ideal treatment modality of AKI in the ICU (Lameire et al. 1999). Although none of the currently available modalities of renal replacement therapy fulfills all the ideal characteristics, this chapter will discuss the best options in each patient scenario.

Table 18.1 Characteristics of the "ideal" treatment modality of AKI in the ICU (Lameire et al. 1999)

CHARACTERISTIC
Preserves Homeostasis
Does not increase co-morbidity
Does not worsen patient's underlying condition
Is inexpensive
Is simple to manage
Is not burdensome to the ICU staff

The hemodynamic stability of the critically ill patient is the main determinant of the most appropriate dialysis modality (see Table 18.2):

Table 18.2 Indications for Specific Renal Replacement Therapies (Murray and Hall 2000)

Therapeutic Goal	Hemodynamics	Preferred Therapy
Fluid Removal	Stable	Intermittent Isolated UF
	Unstable	Slow UF
Urea Clearance	Stable	Intermittent Hemodialysis
	Unstable	CRRT
		Convection: CAVH, CVVH
		Diffusion: CAVHD, CVVHD
		Both: CAVHDF, CVVHDF
Severe Hyperkalemia	Stable/Unstable	Intermittent Hemodialysis
Severe Metabolic Acidosis	Stable	Intermittent Hemodialysis
	Unstable	CRRT
Severe Hyperphosphoremia	Stable/Unstable	CRRT
Brain Edema	Unstable	CRRT

When choosing the modality of renal replacement therapy most appropriate for each patient, multiple considerations must be kept in mind (see Table 18.3).

Table 18.3 Considerations in Renal Replacement Therapy for AKI

Consideration	Components	Varieties
Dialysis Modality		
	Intermittent Hemodialysis	Daily, Every other day, SLED
	Continuous renal replacement therapies	AV, VV
	Peritoneal dialysis	
Dialysis Biocompatibility	Membrane characteristics	
Dialyzer Performance		
	Efficiency	
	Flux	
Dialysis Delivery		
	Timing of initiation	Early, Late
	Intensity of dialysis	Prescription vs. Delivery
	Adequacy of dialysis	Dialysis dose

In addition to the patient's hemodynamic stability, the choice between the various renal replacement modalities rests on solute clearance goals; volume control and anticoagulation (see Table 18.4):

Table 18.4 Advantages and disadvantages of various renal replacement modalities (Modified from Davenport 2008)

Modality	Use in hemodynamically unstable patients	Solute clearance	Volume control	Anti-coagulation
PD	Yes	++	++	No
IHD	Possible	++++	+++	Yes/no
IHF	Possible	+++	+++	Yes/no
Intermittent IHF	Possible	++++	+++	Yes/no
Hybrid techniques	Possible	++++	++++	Yes/no
CVVH	Yes	+++/++++	++++	Yes/no
CVVHD	Yes	+++/++++	++++	Yes/no
CVVHDF	Yes	++++	++++	Yes/no

HDF: Hemodiafiltration; CVVH: Continuous hemofiltration; CVVHD: Continuous hemodialysis; CVVHDF: Continuous hemodiafiltration; IHD: Intermittent hemodialysis; IHF: Intermittent hemofiltration; PD: Peritoneal dialysis.

For the purposes of this section, we will utilize the conventional view that RRT dose is a measure of the quantity of blood purification achieved by means of extracorporeal techniques (thoroughly discussed in Ricci, Bellomo and Ronco, 2005). As this broad concept is too difficult to measure and quantify, the operative view of RRT dose is that it is a measure of the quantity of a representative marker solute that is removed from a patient. This marker solute is taken to be reasonably representative of similar solutes, which require removal for blood purification to be considered adequate. This premise has several major flaws: the marker solute cannot and does not represent all of the solutes that accumulate in renal failure. Its kinetics and volume of distribution are also different from such solutes. Finally, its removal during RRT is not representative of the removal of other solutes. This is true for both end-stage renal failure and acute renal failure. However, a significant body of data in the end-stage renal failure literature suggests that, despite all of the above major limitations, single solute marker assessment of dose of dialysis seems to have a clinically meaningful relationship with patient outcome and, therefore, clinical utility.

This section will focus on RRT modalities, and review the basic concepts and the newest approaches to this technology and its application in the ICU. We intend to discuss convective and diffusive depurative mechanisms and address the use of membrane adsorption as an additional method of large molecule removal. Previous reviews (Palevsky et al. 2002; John and Eckardt 2007) have discussed the fundamental operational characteristics of CRRT.

Recently, the Acute Dialysis Quality Initiative (ADQI) (Kellum et al. 2008a) published a consensus on fluid (Gibney et al. 2008; Kellum et al. 2008b) and volume management (Gibney et al. 2008) which is relevant to the present discussion. A recent review (Cerda and Ronco 2009) discussed these issues in depth, and KDIGO guidelines will soon be available online http://www.kdigo.org/

18.2.2 Arterio-Venous or Veno-Venous Blood Circuits

Arterio-venous (AV) systems are not used except in emergent situations, when veno-venous (VV) systems are not available. AV system limitations include arterial damage, blood flow dependency on systemic hemodynamics and insufficient dialysis dose (Palevsky et al. 2002).

18.2.3 Choice of CRRT Modality

The different modalities of CRRT (see Fig 18.1) are defined by the main mechanism with which clearance is achieved: simple diffusion (continuous hemodialysis, CVVHD), convection (continuous hemofiltration, CVVH) or a combination of both (continuous hemodiafiltration, CVVHDF) (Ronco 2006).

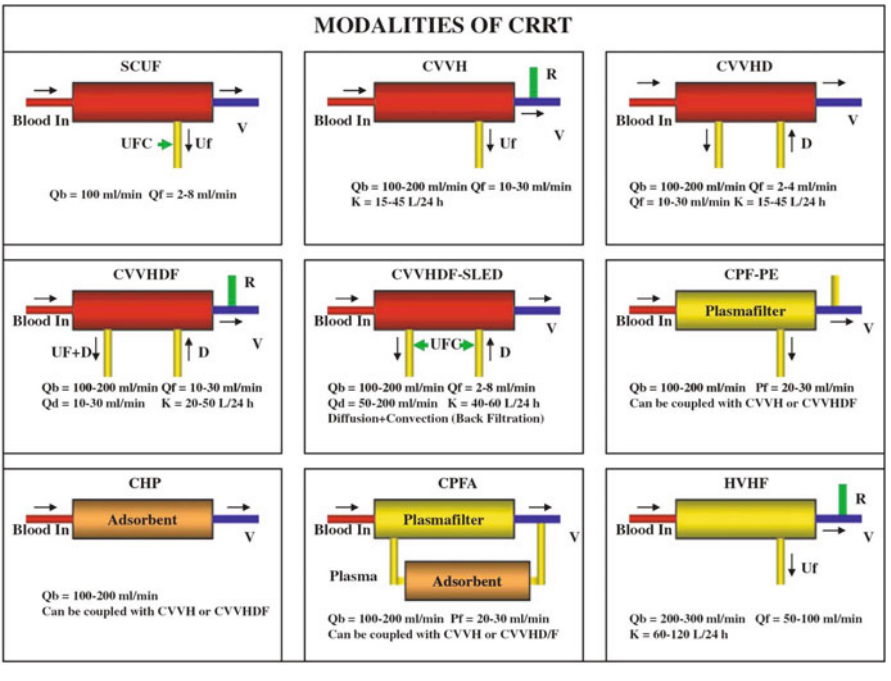

Fig. 18.1 Modalities of CRRT (Modified from (Cerda and Ronco 2009; Ronco 2006)

These modalities differ in the magnitude of the clearance achieved by convection or diffusion, the vascular access and the need for fluid replacement (hemofiltration) (see Table 18.5).

Table 18.5 Modalities of continuous renal replacement therapy

Technique	Clearance	Mechanism	Vascular	Fluid
	Convection	Diffusion	Access	Replacement
SCUF	+	-	Large vein	0
CAVH	++++	-	Artery and vein	+++
CVVH	++++	-	Large vein	+++
CAVHD	+	++++	Artery and vein	+++
CVVHD	+	++++	Large vein	+/0
CAVHDF	+++	+++	Artery and vein	++
CVVHDF	+++	+++	Large vein	++
CAVHFD	++	++++	Artery and vein	+/0
CVVHFD	++	++++	Large vein	+/0

CAVH=Continuous arteriovenous hemofiltration; CAVHD=Continuous arteriovenous hemodialysis; CAVHDF=Continuous arteriovenous hemodiafiltration; CAVHFD=continuous arteriovenous high-flux hemodialysis; CVVH=continuous venovenous hemofiltration; CVVHD=Continuous veno venous hemodialysis; CVVHDF=continuous venovenous hemodiafiltration; CVVHFD=Continuous venovenous high-flux hemodialysis; SCUF=Slow continuous ultrafiltration; 0=not required; +=negligible; ++=some; +++=marked; ++++=major

Given the absence of evidence of superiority among the different CRRT modalities, the choice rests on the available equipment (membranes, pump systems), and appropriate dialysate, and cost and conceptual considerations (Ricci et al. 2006).

18.2.3.1 Dialysis Membranes for CRRT

The main features of convective treatments are:

- High flux membranes
- High permeability to water
- High permeability to low and middle MW solutes (1,000-12,000 Dalton)
- High “biocompatibility”

Dialysis devices are designated as:

- Dialyzers working predominantly in diffusion with a countercurrent flow of blood and dialysate,
- Hemofilters working prevalently in convection.
- Newer designs allow powerful simultaneous convection and diffusion (high flux dialysis, hemodiafiltration).

Although it is widespread opinion that when considering physiological outcomes convective treatments like high-flux hemodialysis, hemodiafiltration and hemofiltration offer a clinical advantage over standard dialysis, studies have not been able to demonstrate superiority of these techniques on morbidity, mortality or quality of life (Palevsky et al. 2002; Locatelli et al. 2002).

18.2.3.2 Comparison between CRRT and Other Renal Replacement Modalities

CRRT techniques offer better long-term clearance of small and middle molecules than IHD or SLED. Modeling of these modalities shows (Liao et al. 2003):

- Small solute clearance is 8% and 60% higher with CVVH compared to SLED and IHD respectively
- CRRT and SLED allow effective azotemic control, while HD causes pronounced concentration peaks and poor time-averaged azotemic control
- Clearance results are even more different in the middle-molecule range of solutes, with superior middle-molecule clearance with CVVH compared with SLED or IHD
- The superior middle and large molecule removal for CVVH is due to a combination of convective clearance and continuous operation
- While on CRRT beta-2 microglobulin plasma concentration achieves steady state after 3 days, using SLED or IHD plasma concentration actually increases steadily, thus reflecting the inability of the latter modalities to clear large and middle molecular weight toxins.

The importance of the clearance of larger compounds is suggested by two treatment trials (Ronco et al. 2000) study and an earlier CRRT study (Storck et al. 1991) correlating convective dose (i.e. ultrafiltration rate) with survival. Large molecular clearance may have contributed substantially to the salutary effect of higher doses in these therapies. More recently,

studies (Saudan et al. 2006) have shown that the addition of diffusion to convective clearance resulted in further improvement in patient outcome.

Because the daily vs. every other day IHD study (Schiffl et al. 2002) was performed with high-flux dialyzers, the clearance of compounds significantly larger than urea may have played a role in the improved survival among the patients dialyzed daily. In spite of these suggestive findings, there is no firm evidence that enhanced removal of mid- or high-molecular weight patients leads to better patient outcomes (see below).

18.2.3.3 Convection and Diffusion

Convection-based replacement techniques (hemofiltration and hemodiafiltration) using high-flux membrane filters are aimed at maximizing the removal of so-called medium and high-molecular weight solutes (higher than 1,000 kDa up to several thousand kDa), as opposed to the so-called low molecular weight toxins (Colussi and Frattini 2007; Vanholder et al. 2008; Ledebo 2005).

Hemofiltration: A predominantly convective technique, when compared to diffusion, hemofiltration removes larger quantities of hydrophilic large molecular weight (MW) compounds. It leads to greater cytokine removal by adsorption and convection. Removal of inflammatory mediators has been postulated (but not demonstrated) to benefit patient outcome.

Hemodiafiltration: Utilizes partially hydrophilic high-flux membranes. Membranes with have high sieving coefficient and reduced wall thickness, and combine diffusive and convective clearance. Accurate UF control systems make safe large volume removal possible. Newer machines permit separate control of dialysate and UF/reinfusion, and on-line production of ultrapure dialysate and replacement fluid has made possible to deliver safe and less costly treatments.

With current CRRT machines, solute exchanges can be obtained by convection, diffusion or both, with easier and more precise control over each component of the therapy. Blood (Q_B), dialysate (Q_D) and ultrafiltrate (Q_{UF}) flow rates can be controlled accurately with integrated pumps, and greater dialysate or convective flows –and therefore greater diffusive and convective solute fluxes- can be achieved. During CRRT, diffusion is limited by Q_D, in contrast to intermittent hemodialysis (IHD) (Brunet et al. 1999; Clark and Ronco 1999) the addition of convection may improve the clearances or middle-molecular weight solutes.

18.2.3.3.1 Diffusion

The diffusivity of a solute, whether in solution or in an extracorporeal membrane, is:

- Inversely proportional to its molecular weight: as solute molecular weight increases, diffusion becomes a relatively inefficient dialytic removal mechanism and the relative importance of convection increases (Clark and Ronco 2004).
- Diffusion occurs whenever a concentration gradient (dc) exists for solutes not restricted in diffusion by the porosity of the membrane.
- Diffusion flux is also influenced by the characteristics of the membrane including:
  - Surface area (A)
  - Thickness (dx)
  - The temperature of the solution (T)
  - Diffusion coefficient of the solute (D).

The diffusion flux of a given solute (J_x) will therefore result from the equation (Clark and Ronco 2004):

$$J_X = D.T.A\left(\frac{d_C}{d_X}\right) \tag{18.1}$$

Other factors may influence the final clearance values including protein binding or electrical charges in the solute. Increased convection may contribute to greater solute transport, especially in the higher molecular weight range.

18.2.3.3.2 Convection

Convection requires movement of fluid across the membrane driven by a transmembrane pressure gradient (TMP). The fluid transport is defined as ultrafiltration is described by the equation:

$$J_f = K_f.TMP \tag{18.2}$$

Where K_f is the coefficient of hydraulic permeability of the membrane and $TMP = (P_b\text{-}P_{uf}) - \pi$, where P_b is the hydrostatic pressure of blood, P_{uf} the hydrostatic pressure of ultrafiltrate or dialysate and π the oncotic pressure of plasma proteins. The convective fluid of a solute x will therefore depend on:

- The amount of ultrafiltration (J_f),
- The concentration of the solute in plasma water (C_b) and
- The sieving characteristics of the membrane for the solute (S):

$$J_X = J_f C_b (1-\sigma) = J_f C_b S \tag{18.3}$$

The sieving coefficient (S) is regulated by the reflection coefficient of the membrane σ according to the equation:

$$S = 1-\sigma \tag{18.4}$$

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 expected from a simple theoretical calculation (Clark and Ronco 2004).

18.2.3.4 Pre-dilution or Post-dilution

In hemofiltration, replacement fluid can be infused either before the hemofilter ("pre-dilution") or after the hemofilter ("post-dilution").

In post-dilution CVVH, a purely convective therapy, the three primary determinants of solute clearance are:

- Ultrafiltration rate,
- Membrane sieving coefficient and
- Dilution mode (Clark and Ronco 2004).

Convection occurs by "solvent drag": solutes are swept (dragged) across the membrane in association with ultrafiltered plasma water, such that

$$K = Q_F.S \tag{18.5}$$

Where K is clearance (ml/min), Q_F is ultrafiltration rate (m/min) and S sieving coefficient. For small solutes, as S approaches unity clearance equals the ultrafiltration rate in post-dilution.

In post-dilution CVVH, filtration fraction (FF), the ratio of ultrafiltration rate (Q_{UF}) to plasma water flow rate is a limiting factor determined by blood flow (Q_B) rate and patient hematocrit (Htc):

$$F_F = \frac{Q_{uf}}{Q_b (1-H_{tc})} \tag{18.6}$$

Clinical practice indicates that a FF greater than 0.3 should be avoided because of hemoconcentration and protein-membrane interaction (Clark et al. 2003).

- Greater ultrafiltration rates require larger blood flows to avoid elevated FF and filter clotting and coating with accumulated proteins.
- Higher blood flows are usually difficult to reach with the temporary dialysis catheters and hemodynamic conditions commonly prevalent among critically ill patients. Reaching the higher doses recently demonstrated to affect survival are difficult to reach in post-dilution mode.

Pre-dilution mode has been introduced as a useful adjunct to prevent clotting of the extracorporeal circuit and to extend filter life, especially during high-volume CRRT, where filtration fraction would otherwise reach values greater than 0.3 and induce clotting and protein encroachment of the membranes.

Pre-dilution CRRT allows freedom from the constraints in blood flow and filtration rate imposed by pre-dilution. For small solutes dissolved in the water of the blood passing through the hemofilter (Brunet et al. 1999), clearance equals:

$$K = Q_F.S\left[\frac{Q_{BW}}{(Q_{BW} + Q_s)}\right] \tag{18.7}$$

Where Q_{BW} is blood water flow rate and Q_S the substitution (replacement) fluid rate.

At a given Q_F value,

- Pre-dilution is always less efficient than post-dilution CVVH with respect to fluid utilization.
- While pre-dilution attenuates hemoconcentration-related effects, it simultaneously reduces the efficiency of the treatment.
- Thus, the larger Q_s is relative to Q_{BW}, the smaller the entire fraction and the greater the loss of efficiency relative to post-dilution.

18.2.3.5 Importance of Achieving a High Blood Flow Q_B

In CVVH, given the direct relationship between Q_S and Q_F, great efforts are needed towards increasing the blood flow beyond that used traditionally in CRRT, usually close to 150 ml/min or less.

In pre-dilution mode, to attain doses of 35 ml/kg/h as described by Ronco et al (2000) it is necessary to achieve blood flows of 250 ml/min or higher, given that the decrease in efficiency inherent to pre-dilution mode can be as high as 35 to 40-45% for urea and creatinine respectively, when Q_B is 125-150 ml/min and Q_s is fixed at 75 ml/min (Troyanov et al. 2003).

Utilizing modeling analysis, (Clark et al. 2003) have shown that:

- As patient's weight increases, for low blood flow rates substitution fluid rates required to achieve this dose are impractically high in the majority of patients weighing more than 70 Kg.
- To achieve the dose target, the high ultrafiltration required determines high replacement fluid infusion rates, which in turn have a substantial dilutive effect on solute concentrations at low blood flows.
- Conversely, higher blood flows allow the delivery of higher doses without loss of efficiency.

Brunet et al (1999) studied the diffusive and convective solute clearances during CVVHDF at various dialysate and ultrafiltration rates. They demonstrated that convection is more effective than diffusion in removing middle-molecular weight solutes during CRRT, and that high convective flux should be applied if the goal is to remove middle molecules more efficiently.

18.2.3.6 Interaction between Convection and Diffusion

At the slow flow rates normally utilized in CRRT, there is no interaction between diffusive and convective clearances. Recent studies (Saudan et al. 2006) have shown that the addition of a diffusive component to dialysis "dose" resulted in improved survival. Up until recently, dose data were mainly limited to diffusion (Schiffl et al. 2002) and convection (Ronco et al. 2000). The results of Ronco et al led to the definition of a "standard dose" of CRRT of 35 ml/kg/hr, which was applied indiscriminately to diffusive and convective continuous modalities.

More recently, Palevsky et al (2008) in the ATN study, utilizing a combined diffusive and convective modality (pre-dilution CVVHDF) or intermittent hemodialysis depending on hemodynamic stability, failed to demonstrate a beneficial effect of a higher dose of renal replacement therapy (daily IHD or CVVHDF at 35 ml/Kg/hour compared with three times/week IHD or CVVHDF at 20 ml/Kg/hour). It must be emphasized that the ATN study was *not* designed to evaluate the different RRT modalities, but

rather to evaluate the effects of dose on survival and renal recovery function. The RENAL study, led by (Bellomo 2006; Bellomo et al. 2009) addressed similar dose questions utilizing post-dilution CVVHD and equally found that a higher dose of CRRT (40 ml/Kg/h) did not result in improved 90-day patient survival when compared to 25 ml/Kg/h.

- The premise of those studies is that dose is a solute clearance-related parameter (Clark et al. 2003).
- The studies were not designed to determine which toxin clearance led to better survival. Although small solute clearance is a possible explanation, substantial clearance of relatively large molecular weight toxins may also explain the survival benefit in the high dose arm of the Ronco study (Ronco et al. 2000).

Basing on the dosing scheme of normalizing effluent flow rate to body weight, other forms of CRRT such as CVVHD and CVVHDF may provide equivalent or nearly equivalent small solute clearances as post-dilution CVVH, but for a given effluent flow rate, the diffusive component of these therapies limits their ability to clear larger molecular weight toxins relative to hemofiltration (Clark et al. 2003). Consequently, extrapolating Ronco's data to other forms of CRRT, especially for dosing purposes, should be done with caution.

18.2.4 Nutrition and Outcome

Better management of volume and body fluid composition is easily achieved with CRRT. Given the importance of nutrition on the outcome of critically ill patients with AKI (Cerda 2008; Cerda et al. 2007) CRRT could offer a theoretical advantage over IHD in this setting.

18.2.5 Hemodynamic Stability

Older (Davenport et al. 1993) and very recent (Ronco 2006) studies have consistently shown that the main advantage of continuous modalities is greater hemodynamic stability. In their recently published study, (Palevsky et al. 2008) chose CRRT (CVVHDF) as the modality of choice for hemodynamically unstable patients, a decision that reflects current practice in the US. In their study, although hemodynamically "stable" patients were allocated to IHD, hypotension occurred more frequently among patients treated with IHD than CRRT and may have had an impact on their lower rate of recovery of renal function.

CRRT is associated with better tolerance to fluid removal because:

- The rate of fluid removal is much slower in CRRT than in IHD
  - The main determinant of hemodynamic instability during RRT is the maintenance of intravascular compartment volume.
  - The volume of that compartment is the result of the balance between convective removal of fluid (ultrafiltration) from plasma and the rate of replenishment from the interstitium.
  - Therefore, whenever the UF rate exceeds the rate of interstitium-to-plasma flow (refilling), the patient will experience hypovolemia and hemodynamic instability (Gibney et al., 2008).

- In IHD rapid diffusion of urea creates a plasma-to-interstitium and interstitium-to-cell osmotic gradient that drives water to the interstitium and to the intracellular compartment, such that plasma volume decreases and cell edema (including neuronal edema) occurs.
  - With CRRT, the slower rate of urea clearance allows for equalization of urea concentrations between compartments and therefore, lessened water shifts and cell edema.
  - This is particularly important in patients with intracranial hypertension, such as head trauma and severe liver failure (Davenport et al. 1993, 1989; Ronco et al. 1999).

- A decrease in core temperature and peripheral vasoconstriction has been shown to decrease hypotensive episodes and may play a role in hemodynamic stability (Santoro et al. 2003).

- With either pre- or post-dilution hemofiltration, the magnitude of sodium removal is less than the amount of sodium removed with hemodialysis, a factor which may contribute to better cardiovascular stability in hemofiltration (Gibey et al. 2008; Kellum et al. 2008b; Di Filippo et al. 2003)

- Although hypovolemia is the first step in dialysis-related hypotension, the ultimate arterial pressure response to hypovolemia is the result of a complex interplay between active and passive mechanisms including decreased venous vessel capacity to sustain cardiac filling; increased arterial vascular resistances to ensure organ perfusion; and increased myocardial contractility and heart rate to maintain cardiac stroke volume (Santoro et al. 2003). Any factor

interfering with one or more of these compensatory mechanisms may foster cardiovascular instability. In this context, it is possible that convective removal of inflammatory mediators could contribute to hemodynamic stability, especially in the early phases of septic shock (see below).

18.2.6 Other Modalities of Renal Replacement Therapy

Modality selection for renal support in critically ill patients with acute kidney injury continues to be a controversial subject. Both intermittent hemodialysis and continuous renal replacement therapy are established therapies for such patients. While application of IHD to AKI patients is very similar to therapy delivery in end-stage renal disease (ESRD), CRRT was developed specifically to address the unique needs of critically ill AKI patients. A more recently proposed dialysis modality for the AKI population is sustained low-efficiency dialysis (SLED), also known as extended daily dialysis (EDD). This approach was first described in the mid-1990s as a "hybrid" therapy combining characteristics of both IHD and CRRT. In relation to CRRT, proponents have claimed that SLED is an equivalent modality, which can be provided at substantially lower treatment costs. The recent landmark ATN and RENAL trials consolidate the evidence base for the established modalities of CRRT and IHD. However, these trials add essentially nothing to the clinical community's understanding of the effect of SLED on AKI patient outcomes. Because an evidence base relating to the effect of SLED on patient outcomes is largely non-existent, the prescription of this modality continues to be based upon small and uncontrolled reports. In this era of evidence-based medicine, it would appear mandatory that randomized controlled trials assessing the effect of SLED on patient outcomes should be promptly designed and conducted. Until such trials provide relevant AKI patient outcome data, the argument that SLED is clinically equivalent to CRRT should be viewed with skepticism.

18.2.7 Renal Replacement Therapies in Special Situations

18.2.7.1 Sepsis

18.2.7.1.1 Hemofiltration of Large Molecules

- Middle molecules,
  - Mostly of peptides and small proteins with molecular weight in the range of 1,000 to 600,000 Daltons

- Accumulate in renal failure and contribute to the uremic toxic state (Vanholder et al. 2008; Tattersall 2007).
- Beta-2 microglobulin, with a molecular weight of 11,000 Dalton, considered a representative of these middle molecules (Gejyo et al. 1986), is not well cleared by low-flux dialysis
- High flux dialysis will clear middle molecules partly by internal filtration (convection); the convective component of high-flux dialysis can be enhanced in a predictable way by hemodiafiltration (Winchester and Audia 2006; Winchester et al. 2003).

In the last decade, it has been postulated that high convective dose therapies improve the management of sepsis (Ronco et al. 2000; Ledebo 2005; Ratanarat et al. 2006; Tetta et al. 2004; Silvester 1997; Ronco and Tetta 2007).

- Severe sepsis and septic shock are the primary causes of multiple organ dysfunction syndrome, the most frequent cause of death in intensive care unit patients.
- Many water-soluble mediators with pro- and anti-inflammatory action such as TNF, IL-6, IL-8, and IL-10 play a strategic role in the septic syndrome.
- In intensive care medicine, blocking any one mediator has not led to a measurable outcome improvement in patients with sepsis.
- CRRT is a continuously acting therapy, which removes pro- and anti-inflammatory mediators nonselectively. The *"peak concentration hypothes*is (Joannidis 2006; Ronco et al. 2003a, b) is the concept that cutting peaks of soluble mediators through continuous hemofiltration may help restore homeostasis.

This latter development proposes to use increased volume exchanges in hemofiltration or the combined use of adsorbent techniques.

- High volume hemofiltration (HVHF):
  - A variant of CVVH that requires higher surface area hemofilters and ultrafiltration volumes of 35 to 80 ml/kg/h.
  - Provides higher clearance for middle/high molecular weight solutes than simple diffusive transport (CVVHD) or convection-based transport at lower volumes (CVVH).
  - Associated with practical difficulties including machinery, replacement fluid availability and cost, and accurate monitoring systems to maintain safety (Gibney et al. 2008).

  - Studies utilizing this technique have shown preliminary evidence of benefit, but none of the studies are randomized trials of adequate statistical power to demonstrate effect conclusively.
  - Alternative technologies have utilized high cut-off hemofilters with increased effective pore size (Ronco 2006).
  - Drawbacks of such porous membranes include the loss of essential proteins such as albumin.

- Plasmafiltration coupled with adsorption (CPFA) has been recently utilized in septic patients (Bellomo et al. 2003).
  - In CPFA, plasma is separated from blood and the plasma is circulated through a sorbent bed; blood is subsequently reconstituted and dialyzed with standard techniques, thus achieving normalization of body fluid composition and increased removal of protein-bound solutes and high-molecular weight toxins.

- Recently, evidence has been obtained (Ronco et al. 2003a; Cole et al. 2002, 2001, 2004) that very high volume hemofiltration applied in pulses may improve the hemodynamic stability of septic patients in septic shock, but failed to show consistently improved survival.

18.2.7.1.2 Use of Sorbent Technologies

The possibility of removing solutes from blood to obtain blood purification has mainly focused over the years on classic hemodialysis. However, both the characteristics of some solutes that make their removal difficult, and the limited efficiency of some dialysis membranes, have spurred a significant interest in the use of newer mechanisms of solute removal such as hemadsorption (Cruz et al. 2008; Joannidis 2006; Ronco et al. 2003b).

Materials with high capacity of adsorption (sorbents) have been utilized for about 50 years in extracorporeal blood treatments of acute poisoning or uremia. With the recognition of the role of cytokines in systemic inflammatory response syndrome and sepsis, and the fact that most cytokines are poorly removable by conventional diffusive or convective blood purification modalities, treatment of sepsis based on sorbent techniques has recently been explored.

Conventional blood purification has been shown to be poorly effective in the removal of pathogenic factors and mediators involved in the sepsis process. This has aroused interest in many innovative approaches such as

high-volume hemofiltration, the use of super-permeable membranes, and sorbent-based hemoperfusion using polymyxin B-immobilized adsorber (PMX) (Shimizu et al. 2009) to eliminate serum endotoxins.

Recent preliminary studies in septic patients have shown benefit in the use of sorbent technologies utilizing membrane-bound polymixin-B (the EUPHAS Trial) (Cruz et al. 2009). In this preliminary study, polymixin B hemoperfusion added to conventional therapy significantly improved hemodynamics and organ dysfunction and reduced 28-day mortality in a targeted population with severe sepsis and/or septic shock from intrabdominal gram-negative infection.

Larger multicentre evidence will be necessary before such techniques are widely implemented. If benefit is demonstrated, the use of very high volume hemofiltration and hemadsorption will require special equipment and very capable nursing able to manage such large volumes (i.e. up to 5-6 liters/hr) of ultrapure replacement fluid without error (Gibney et al. 2008).

18.2.7.2 Hemofiltration in Congestive Heart Failure

The cardiorenal syndrome is a complicated and increasingly prevalent entity requiring a multidisciplinary approach. Renal replacement therapy in the form of slow ultrafiltration demonstrates promise for the treatment of acutely decompensated heart failure. Despite the lack of evidence for decreased mortality there is considerable short-term benefit in decreased re-hospitalizations and a restoration of diuretic responsiveness. Given the potential for improvement in quality of life and cost if hospitalizations are minimized, slow ultrafiltration should be considered in patients with repeated hospitalization for decompensated heart failure (Mathew and Cerda 2011).

18.2.7.3 Acute Neurologic Injury

Acute neurologic injury is a highly unstable state requiring strict adherence to evidence based guidelines to achieve the best possible functional outcomes. With improved short-term survival, a greater burden of non-neurologic injury may hinder long-term functional recovery. Acute kidney injury is among such important considerations that can lead to worsened neurological injury. Careful application of continuous modalities of therapy, probably early in the course of illness to avoid intradialytic osmolar shifts and provide hemodynamic stability, will allow for unimpeded neurologic recovery. Newer evidence on dose and RRT modality on patients with acute and chronic brain injury will certainly add important knowledge to this field (Mathew and Cerda 2011).

18.2.7.4 Extracorporeal Technologies in Patients with Liver Failure

Hepatorenal syndrome (HRS) type I is a unique form of acute kidney injury resulting from renal vasoconstriction in the setting of systemic and splanchnic arterial vasodilation in patients with end stage liver disease. The only definitive treatment currently available is liver or liver-kidney transplantation. The goal of extracorporeal support (ECS) systems in HRS is to bridge eligible liver failure patients to transplantation or functional recovery by means of detoxification, assistance with biosynthesis of key metabolic products, and regulation of inflammation (Cerda et al. 2011). ECS systems in liver disease can be divided into two broad categories: cell-based and non-cell based systems. While cell-based systems aim to provide functions similar to those of normal hepatocytes, non-cell based systems do not incorporate tissue and provide detoxification utilizing membranes and adsorbents. There are no standard guidelines to the application of ECS systems. Published studies are too small and show considerable differences in primary indication, primary endpoint, and treatment protocols for 'intervention' and 'standard' treatment groups.

18.3 COMPLICATIONS OF CONTINUOUS RENAL REPLACEMENT THERAPIES

This section describes the complications of the CRRT procedure relating to the vascular access, the extracorporeal circuit, hematological and anticoagulation related problems, fluid balance errors, acid-base disorders, nutritional losses and problems dependent upon excessive removal of drugs such as antibiotics.

18.3.1 Vascular Access

18.3.1.1 Infectious Complications

Central venous catheters (CVC) are the most common form of vascular access for patients undergoing CRRT. The estimated rate of infection is between 1.3 to 5.6 per 1000 catheter days (Edwards et al. 2009). Several mechanisms have been postulated (McGee and Gould 2003):

- Contamination of the catheter hub – leading to luminal colonization.
- Exit site infection – followed by migration of the organism along the external catheter surface.
- Hematogenous seeding of the catheter.

Infections have been classified as (McGee and Gould 2003):

- Catheter colonization – Growth of organisms from a catheter segment by either semi quantitative or quantitative culture.
- Catheter related blood stream infection (CRBSI) – Isolation of the same organism from a blood culture and from a catheter segment by either semi quantitative or quantitative culture accompanied by clinical symptoms of blood stream infections without any other apparent source.
- Exit-site infection – erythema, tenderness, induration or purulence within 2 cm of the exit site of the catheter.

Interventions to reduce infectious complications include stringent sterile placement techniques, appropriate catheter care, avoidance of femoral site and use of antimicrobial locking solutions when not in use (Vanholder et al. 2010).

18.3.1.2 Mechanical Complications

The incidence of mechanical complications during catheter insertion varies between 5 and 19% based on the site selected (Merrer et al. 2001; Mansfield et al. 1994; Sznajder et al. 1986). Arterial puncture, hematoma, hemothorax, pneumothorax etc. are the major common complications reported. Arterio-venous fistulas, aneurysms, thrombus formation, pericardial tamponade, arrhythmias and retroperitoneal hemorrhage have also been reported (Oliver 2001).

18.3.1.3 Thrombosis

Central venous thrombosis is a serious complication of CVCs. The incidence increases with the duration of catheterization. Various etiological factors have been implicated (Kaye and Smith 1988):

- Kink in catheter, tubing or tight sutures
- Catheter tip blockade by vessel wall
- Endothelial damage during procedure
- Insufficient / improper catheter lock
- Fibrin sheath or intraluminal clot
- Mural thrombus

An important factor to be considered is the site of catheterization. Femoral catheters carry the maximum risk of thrombosis when compared to subclavian or internal jugular venous catheters (Merrer et al. 2001).

18.3.1.4 Access Recirculation

In a patient with AKI undergoing CRRT, dialysis dosing is a priority. An important factor to be considered is access recirculation because of temporary dialysis catheters. Studies have shown that recirculation may be as high as 22% in short femoral catheters and over 12% in long femoral catheters. Least recirculation is seen with subclavian catheters (Leblanc et al. 1996).

18.3.2 Extracorporeal Circuit Factors

18.3.2.1 Air Embolism

Because of negative pressure in the venous side of the circuit, air embolism is possible. Even a small amount of air in the extracorporeal circuit can be fatal. It is usually manifested by chest pain, dyspnea, cough, cyanosis, hypoxia and cardiopulmonary arrest. Most modern machines have alarm systems that stop the flow of blood when air is detected within the circuit.

18.3.2.2 Immune Activation

Prolonged exposure of blood to the filter and extracorporeal circuit can potentially activate several inflammatory mediators (Freyria et al. 1988).

18.3.2.3 Hypothermia

During CRRT, the patient's blood leaves the body, travels along a plastic tube to a filter and is exposed to cooler ambient temperatures and CRRT fluids. Studies (Yagi et al. 1998; Matamis et al. 1994) have shown that a significant number of patients develop hypothermia while on CRRT. The resulting heat loss may increase daily energy requirements, mask fevers and delay the recognition of infection.

18.3.2.4 Circuit Leaks

Rupture of the circuit may occasionally cause blood loss and contamination of the extracorporeal circuit. Circuit rupture may especially occur in the section of tubing in contact with the blood pump whenever the circuit is utilized for prolonged periods of time.

18.3.3 Hematologic

18.3.3.1 Bleeding

Critically ill patients with multi-organ dysfunction syndrome develop a procoagulant state due to activation of the coagulation system by proinflammatory cytokines (Levi and Opal 2006). Therefore, anticoagulation of the extracorporeal circuit is usually required. The most commonly used anticoagulant is heparin. However, it is associated with the risk of excessive bleeding.

18.3.3.2 Hemolysis

During CRRT, due to the effect of shearing forces generated by the roller pump or other parts of the extracorporeal circuit, a certain degree of hemolysis can occur. Treatment-related electrolyte imbalances such as hypophosphatemia, hypokalemia and hyponatremia can also promote hemolysis (Finkel and Podoll 2009). If clinically significant, hemolysis can delay recovery of renal function by causing pigment-induced nephropathy.

18.3.3.3 Related to Anticoagulation

18.3.3.3.1 Heparin Induced Thrombocytopenia (HIT)

Up to a quarter of patients experiencing repeated clotting of the extracorporeal circuit may have a positive HIT antibody (Lasocki et al. 2008). The diagnosis is primarily made on clinical grounds and serological confirmation. If not treated appropriately, it has devastating complications, including loss of limbs and even death(Arepally and Ortel 2006).

18.3.3.3.2 Hypocalcemia

Regional anticoagulation using tri-sodium citrate is a good alternative to systemic heparinization. It chelates calcium in the extracorporeal circuit, providing effective anticoagulation. Asymptomatic hypocalcemia has been reported by several authors (Mehta et al. 1990; Kutsogiannis et al. 2000). The importance of close monitoring of iCa^{++} levels cannot be overestimated. Critically ill patients who cannot metabolize citrate may require even more aggressive monitoring and repletion of calcium.

18.3.3.3.3 Metabolic Alkalosis

In patients with normal liver function, each ion of citrate is converted to three bicarbonate ions by the liver. If not sufficiently cleared by dialysis, citrate overload may lead to metabolic alkalosis.

18.3.3.3.4 Hypernatremia

When used as a 4% solution, trisodium citrate is hypertonic (560 mOsm/L) and hypernatremic (420 mmol/L) and can result in significant hypernatremia(Tolwani et al. 2001) unless baths of special composition (lower sodium) are used.

18.3.3.3.5 Citrate Toxicity

Occasionally, patients may exhibit citrate toxicity characterized by low serum-ionized calcium levels and a high serum anion gap (Palsson and Niles 1999).

18.3.4 Fluid Balance Errors

One of the most common indications of CRRT is fluid overload. Most modern machines monitor the fluids within the system. However, some patients require significant pre- or postfilter replacement fluids. If these are not accounted for properly, gross volume imbalances can occur. It is also potentially dangerous to override fluid imbalance alarms because such situations can even result in patient death (Bagshaw et al. 2007; Ronco 2005; Gibney et al. 2008).

18.3.5 Acid-Base and Electrolyte Disturbances

Larger pore size and ongoing intercompartmental mass transfer commonly cause hypophosphatemia and hypomagnesemia in patients undergoing CRRT (Locatelli et al. 1998). Another common electrolyte imbalance is hypokalemia. These imbalances occur mostly because of inadequate monitoring and replacement (Fall and Szerlip 2010). The use of trisodium citrate as an anticoagulant can cause hypocalcemia, alkalosis, hypo and hypernatremia as described above.

18.3.6 Nutritional Losses

18.3.6.1 Proteins

Critically ill patients on CRRT are hypercatabolic and have increased nutritional demands. In addition, the larger pore size of the membranes and large ultrafiltration rates result in significant protein and amino acid losses. It is estimated that 10 to 17% protein is lost in the effluent (Wooley et al. 2005). The impact of malnutrition as an important mortality risk factor is well known (Obialo et al. 1999).

18.3.6.2 Trace Elements

Plasma levels of trace elements like zinc, selenium, copper, manganese and chromium are altered during CRRT (Wooley et al. 2005). These trace elements perform an important function in the body as antioxidants. However, the clinical impact of these losses is not well studied.

18.3.6.3 Vitamins and Minerals

Water soluble vitamins can become depleted because they are readily filtered. Thiamin, vitamin C and vitamin E are all reported to be lost during CRRT. However, the clinical significance of these changes is unknown.

18.3.7 Drug Removal

In critically ill patients in the ICU, drug pharmacokinetics may be affected by the disease process. There may be altered protein binding, increased volume of distribution of water-soluble drugs and sometimes hyperdynamic circulation in early sepsis. In addition, extracorporeal drug removal also needs to be taken into account. The major factor affecting extracorporeal drug removal is either diffusion or convection. Other minor factors like drug charge, membrane adsorption and Gibbs-Donan effect also come into play (Schetz 2007a). Because of these issues, the clinician should resort to appropriate drug monitoring to ensure efficacy and to prevent toxicity.

18.4 ANTICOAGULATION FOR CONTINUOUS RENAL REPLACEMENT THERAPY

This section describes the different anticoagulation methodologies available for CRRT, including unfractionated heparin, regional heparinization, low-molecular weight heparin and heparinoids, thrombin antagonists, citrate anticoagulation and platelet inhibitor medications. The choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring and pharmacy issues. There is no consensus on which anticoagulant should be first choice for all CRRT patients. However, citrate anticoagulation is gaining wide acceptance with the development of simpler and safer protocols. Monitoring should include evaluation of anticoagulant effect, filter efficacy, and circuit life and complications.

18.4.1 Introduction

CRRT commonly requires anticoagulation to prevent clotting of the extracorporeal circuit. Although CRRT without anticoagulation is feasible in patients with coagulopathy, most patients require some form of anticoagulation to ensure delivery of an appropriate dose of dialysis. The ideal anticoagulant should provide optimal anti-thrombotic activity with minimal bleeding complications and negligible systemic effects. It should be inexpensive, have a short half-life, and be easily reversed. Moreover, monitoring methods of the anticoagulant effect should be simple and readily available. The advantages and disadvantages of various reported methods of systemic and regional anticoagulation for CRRT are reviewed in this section.

18.4.2 Unfractionated Heparin

Unfractionated heparin (UFH), the most commonly used anticoagulant for CRRT, potentiates antithrombin III by a 1000-fold, resulting in inhibition of factors IIa (thrombin) and Xa. UFH is made up of heparin molecules of varied sizes (5-30 kDa). The larger fragments have predominantly anti-IIa activity and are cleared more rapidly than the smaller fragments. Anti-IIa activity is measured by the activated partial thromoboplastin time (aPPT). The smaller fragments principally inhibit Xa and may result in an anticoagulant effect in the setting of a normal aPPT due to its delayed clearance (Hirsh et al. 2001; Greaves 2002; Baker et al. 1997). UFH metabolites are eliminated by the kidneys. Plasma half-life is approximately 90 min but can increase up to 3 hours in the presence of renal insufficiency.

The advantages of UFH are that it is inexpensive, widely available and familiar to physicians, easy to administer, simple to monitor, and reversible with protamine. Disadvantages include the unpredictable and complex pharmacokinetics of UFH (resulting in dosing variability), the development of heparin-induced thrombocytopenia (HIT), heparin resistance due to low patient antithrombin levels, and the increased risk of hemorrhage (Hirsh et al. 2001). Considering all the administration methods of heparin, the incidence of bleeding episodes ranges from 10 - 50%, with mortality due to bleeding as high as 15% (Van de Wetering et al. 1996; Davenport et al. 1994; Martin et al. 1994).

Most of the publications using UFH in CRRT are small, non-randomized studies that used variable doses of heparin and variable aPTT targets (Hirsh et al. 2001; Davenport et al. 1994; Martin et al. 1994; Bellomo et al. 1993; Leslie et al. 1996; Tan et al. 2000). Circuit survival times ranging from 20 to 40 hours have been reported. UFH is generally administered as a bolus of 2000-5000 IU (30 IU/kg), followed by a continuous infusion of 5-10 IU/kg/hour into the arterial limb of the dialysis circuit. aPTT is maintained between 34 - 45 seconds, or aPPT of 1.5 - 2.0 times normal.

18.4.3 Regional Unfractionated Heparin-Protamine

Regional anticoagulation of the circuit is achieved by constant infusion of UFH into the hemofilter arterial line along with a constant infusion of protamine administered post-filter on the return line of the extracorporeal circuit. This approach requires measurement of both circuit and patient aPTT. The advantage of this method is that the anticoagulant effects of UFH are restricted to the extracorporeal circuit, thereby lowering the risk of systemic patient bleeding.

Regional heparinization is complicated because of the difficulty in estimating the amount of protamine required to antagonize post-filter heparin. For CRRT, an initial ratio of 100 between pre-filter heparin (in units) and post-filter protamine (in mg) has been recommended, with subsequent adjustment according to the aPTT. However, the amount of protamine needed to neutralize 100 IU of heparin varies substantially, making protocols cumbersome and difficult to standardize (Bellomo et al. 1993; Morabito et al. 2003; Biancofiore et al. 2003; Mehta et al. 1992; Kaplan and Petrillo 1987; Van der Voort et al. 2005). The heparin-protamine complex is taken up by the reticuloendothelial system and broken down, but then heparin and protamine are released back into the circulation. Protamine infusion is also associated with hypotension, anaphylaxis, cardiac depression,

leukopenia, and thrombocytopenia (Horrow 1985). In practice, UFH at 1000-1500 U/hour is infused pre-filter and neutralized with post-filter protamine at 10-12 mg/hour. Although several small studies have demonstrated that regional heparinization with protamine is feasible and safe, its efficacy in prolonging filter lifespan has been variable (Morabito et al. 2003; Biancofiore et al. 20036; Van der Voort et al. 2005).

18.4.4 Low Molecular Weight Heparins

Because of their reduced chain length, low molecular weight heparins (LMWHs) have higher anti-Xa/anti-IIa activity than UFH (Hirsh et al. 2001). The pharmacokinetics of LMWHs are more predictable than that of UFH because of less plasma protein binding. The advantages include a more reliable anticoagulant response and a lower incidence of HIT. Disadvantages include minimal reversal with protamine, prolonged duration in renal failure, need for special assays to monitor anti-Xa activity, and increased expense as compared to heparin.

Controlled studies of LMWHs in CRRT have utilized either fixed doses or doses based on anti-Xa levels (de Pont et al. 2000; Reeves et al. 1999; Journois et al. 1990; Joannidis et al. 2007). Studies have demonstrated mixed results as to whether anti-Xa levels correlate with circuit survival (de Pont et al. 2000; Reeves et al. 1999; Journois et al. 1990; Joannidis et al. 2007). Loading doses of 15-25 IU/kg of nadroparin and dalteparin have been used, with maintenance doses of 5 IU/kg/hour. Although some studies use LMWHs in a fixed dose, for safety reasons, monitoring of anti-Xa (target level 0.25-0.35 U/ml) is recommended with prolonged use. Levels of anti-Xa between 0.45 and 0.8 U/mL have been associated with bleeding complications (Jeffrey et al. 1993).

Four small randomized controlled trials (RCTs) have shown fixed-dose LMWHs to be as effective as, but not superior to, standard heparin in prolonging circuit life (Van der Voort et al. 2005; Reeves et al. 1999; Journois et al. 1990; Garces et al. 2010). One small RCT by Joannidis et al (2007) showed that enoxaprin (loading dose 0.15 mg/kg; maintenance dose 0.05 mg/kg/hour) extended circuit life, correlated with anti-Xa activity, and demonstrated less bleeding when compared to UFH.

18.4.5 Heparinoids

Danaparoid is a synthetic glycosaminoglycuron derived from pig intestine. It has a low-grade sulfation that reduces the incidence of platelet cross-reactivity with heparin-induced antibodies. It primarily has an anti-Xa,

rather than anti-IIa, effect. While danaparoid has been used for HIT, it has several disadvantages: cross-reactivity with heparin/platelet factor 4 (PF4) antibodies in 5-10% of patients; a prolonged half-life (up to 48 hours) in renal failure; and notably, no antidote.

For CRRT anticoagulation, danaparoid is administered as a bolus dose between 750 - 2500 U followed by a maintenance dose of 1-2 U/kg/hour. The dose is adjusted to achieve an anti-Xa level of between 0.25 and 0.35 IU/mL. One observational study of danaparoid in 13 patients on CRRT found a high rate of bleeding (46%) despite lower mean anti-Xa activity (0.4±0.2 U/ml) (Lindhoff-Last et al. 2001). Monitoring of anti-Xa activity is therefore critical with prolonged use.

18.4.6 Thrombin Antagonists

Recombinant (r) hirudin irreversibly inhibits bound and unbound thrombin independent of cofactors and PF4. The advantage is it can be used in patients with or suspected HIT. However the half-life of r-hirudin (normally 1-2 hours) is prolonged in patients with renal insufficiency since it is almost exclusively eliminated by the kidneys. Moreover, because it has a molecular weight of 6980 Da, it is negligibly removed by diffusion and variably removed with convection. No antidote exists. Since the anti-coagulation effect at higher doses of r-hirudin is not linearly related to the aPTT, the ecarin clotting time (ECT) is a more reliable test employed but not yet easily available (Nurmohamed et al. 1994; Potzsch et al. 1997). ECT uses the prothrombin-activating enzyme ecarin to monitor the concentration of r-hirudin plasma levels. Several authors have reported successful use of r-hirudin as an anticoagulant for CRRT in critically ill patients diagnosed with HIT (Fischer et al. 1999; Kern et al. 1999; Hein et al. 2001, 2004). For CRRT, it is administered either as a continuous infusion (0.005 – 0.01 mg/kg/hour) or delivered in bolus doses (0.002 g/kg) with a targeted ECT between 80-100 seconds (Wester 2004). In patients without HIT, two studies have demonstrated increased bleeding with continuous infusion, and less bleeding but a shorter circuit life with bolus doses (Hein et al. 2001, 2004). The use of hirudin as an anticoagulant in CRRT has been associated with hemorrhagic complications in up to 38% of patients (Kern et al. 1999; Hein et al. 2001).

Argatroban is a second generation direct thrombin inhibitor used in patients with HIT. Unlike hirudin, it is metabolized by the liver and has a 35 minute half-life in chronic dialysis (Murray et al. 2004). Furthermore, anti-coagulation can be effectively measured by aPTT levels. Similar to hirudin, no antidote exists. Studies are limited but describe a loading dose of

250 µg/kg and a maintenance dose of 0.5 – 2 µg/kg/minute with an aPTT 1-1.4 times normal (Reddy et al. 2005; Tang et al. 2005). Dose reduction is required in hepatic failure.

Compared to lepirudin and argatroban, bivalirudin is a thrombin inhibitor with a shorter half-life, reversible thrombin binding, and extrarenal and extrahepatic clearance mechanisms. A small RCT compared the safety and efficacy of bivalirudin to UFH for preventing CRRT hemofilter clotting and demonstrated prolonged circuit patency with no increase in bleeding (Kiser et al. 2010). Bivalirudin was administered at an initial rate of 2 mg/hr and titrated to maintain the prefilter aPTT to 1.5 to 2.5 times the patient's baseline aPTT. Bivalirudin may be a reasonable alternate to hirudin and argatroban in the setting of both renal and liver failure.

Recombinant human activated protein C (rhAPC) is a potent thrombin antagonist shown to reduce patient mortality in severe sepsis (Bernard et al. 2001). It inhibits thrombin formation by degrading coagulation factors Va and VIIIa. Few studies exist, and experience is limited. However, one study reported a mean circuit life of 55 ± 14 hours with rhAPC as compared to 66 ± 19 hours with UFH (de Pont et al. 2003).

18.4.7 Regional Citrate

Citrate is infused into the blood at the beginning of the extracorporeal circuit and provides anticoagulation by chelating ionized calcium (iCa^{++}). Optimal regional anticoagulation occurs when the iCa^{++} concentration in the extracorporeal circuit is below 0.35 mmol/l (measured as the post-filter iCa^{++} level). Since citrate is a small molecule, the majority of the calcium-citrate complex is freely filtered and lost in the effluent. Therefore, a systemic calcium infusion is necessary to replace the calcium lost with citrate. Any calcium-citrate complex remaining then returns to the patient and is metabolized to bicarbonate by the liver, kidney and skeletal muscle. Each citrate molecule potentially yields three bicarbonate molecules. Calcium released from the calcium-citrate complex helps restore normal iCa^{++} levels. Advantages of citrate anticoagulation include the avoidance of systemic anticoagulation and HIT. The disadvantage is that citrate adds complexity and labor intensity to CRRT due to requirements for customized dialysate or replacement solutions. Frequent monitoring of electrolytes, iCa^{++}, and acid-base status is required, due to the potential for hypernatremia, metabolic alkalosis, and systemic ionized hypocalcemia. Patients with severe liver failure and lactic acidosis may have difficulty with citrate metabolism and develop citrate toxicity, which is characterized by low systemic iCa^{++}, elevated total serum calcium, metabolic acidosis, and an

increased anion gap (Apsner et al. 1997; Kramer et al. 2003; Meier-Kriesche et al. 2001; Bakker et al. 2006). If properly monitored, complications associated with regional citrate are uncommon.

A variety of methods of regional citrate anticoagulation are described in the literature (Palsson and Niles 1999; Gabutti et al. 2002; Mehta et al. 1990; Tolwani et al. 2001; Bagshaw et al. 2005; Monchi et al. 2004; Kutsogiannis et al. 2000, 2005; Brophy et al. 2005; Mehta et al. 1991; Thoenen et al. 2002; Hofmann et al. 2002; Tobe et al. 2003; Mitchell et al. 2003; Swartz et al. 2004; Cointault et al. 2004; Morgera et al. 2004; Egi et al. 2005; Naka et al. 2005; Bihorac and Ross 2005;Tolwani et al. 2006). Citrate is administered either as a separate citrate solution or added to a calcium-free pre-dilution replacement fluid. We have reported a simple citrate anticoagulation protocol with CVVHDF (Tolwani et al. 2006). By using an isotonic dilute-citrate based replacement solution and a commercially available physiologic calcium-free bicarbonate-based dialysate, the incidence of metabolic abnormalities is reduced.

Overall, studies of regional citrate anticoagulation, as compared to UFH, report better filter survival times and less bleeding (Palsson and Niles 1999; Gabutti et al. 2002; Mehta et al. 1990; Tolwani et al. 2001; Bagshaw et al. 2005; Monchi et al. 2004; Kutsogiannis et al. 2000, 2005; Brophy et al. 2005; Mehta et al. 1991; Thoenen et al. 2002; Hofmann et al. 2002; Tobe et al. 2003; Mitchell et al. 2003; Swartz et al. 2004; Cointault et al. 2004; Morgera et al. 2004; Egi et al. 2005; Naka et al. 2005; Bihorac and Ross 2005;Tolwani et al. 2006). There is also some evidence for improved biocompatibility by decreased activation of coagulation and leukocytes (Bos et al. 1997; Hofbauer et al. 1999). Five RCTs (Monchi et al. 2004; Kutsogiannis et al 2005; Betjes et al. 2007; Oudemans et al. 2009; Hetzel et al. 2011) report similar or longer circuit survival with citrate compared to heparin and less bleeding. Oudemans-van Straaten and colleagues (Oudemans-van Straaten et al. 2009) conducted a RCT comparing citrate to the LMWH nadroparin in 200 critically ill acute kidney injury patients on CRRT and found that citrate was better tolerated than heparin and improved patient and kidney survival, especially in patients after surgery, with sepsis, a high degree of organ failure or younger age. This mortality benefit, however, was not demonstrated in a similar RCT of 174 patients (Hetzel et al. 2011).

18.4.8 Platelet-Inhibiting Agents

Prostacyclin (PGI_2) and its synthetic derivative epoprostenol inhibit platelet aggregation and adhesion. Prostacyclin can cause hypotension

from vasodilation at doses of 20 ng/kg/minute. While the vasodilator half-life is 2 minutes, the antiplatelet effect remains for 2 hours. Prostacyclin has been investigated alone or in combination with UFH (Davenport et al. 1994; Langenecker et al. 1994; Kozek-Langenecker et al. 1998, 1999, 2002; Fiaccadori et al. 2002; Balik et al. 2005). The usual dose is 2 to 8 ng/kg/minute infused pre-filter. Monitoring is not required unless UFH is used. Its main drawbacks include the risk of hypotension and expense of the drug.

Most authors have reported only limited clinical experience with prostacyclin, and published reports on its safety and efficacy are scant (Davenport et al. 1994; Langenecker et al. 1994; Kozek-Langenecker et al. 1998, 1999, 2002; Fiaccadori et al. 2002; Balik et al. 2005). Langenecker et al. compared the efficacy and safety of PGI_2 as an alternative to and combined with UFH in a RCT. While PGI_2 increased circuit life, it was associated with more hemodynamic instability compared to heparin alone or heparin combined with PGI_2. The median filter life with prostacyclin as a sole agent was about 15-19 hours and extended to 20-22 hours when combined with low-dose UFH at 5-6 IU/kg/hour (Fiaccadori et al. 2002).

Nafamostat mesilate, a synthetic serine protease inhibitor, is a prostacyclin analog without the hypotensive activity. It is not available in the United States but typically administered at a dose of 0.1 mg/kg/hour. However, studies have demonstrated that levels of thrombin-antithrombin III complex and prothrombin activation fragment 1 + 2 increase, while protein C activity decreases, leading to circuit clotting (Ohtake et al. 1991; Nakae and Tajimi 2003). Several side effects (anaphylaxis, agranulocytosis, hyperkalemia) have been reported with use of nafamostat (Okada et al. 1992; Ookawara et al. 1996; Higuchi et al. 2000). Nafamostat has been widely used as an anticoagulant in Japan.

18.4.9 Conclusion

The choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring and pharmacy issues. There is no consensus on which anticoagulant should be first choice for all CRRT patients. However, citrate anticoagulation is gaining wide acceptance with the development of simpler and safer protocols. Monitoring should include evaluation of anticoagulant effect, filter efficacy, and circuit life and complications.

18.5 VOLUME MANAGEMENT IN CONTINUOUS RENAL REPLACEMENT THERAPY

Fluid management with CRRT requires an understanding of the principles of fluid removal and fluid balance. Attention to fluid balance during CRRT is essential. Standardized order sets for prescription of the therapy, flow sheets for recording and monitoring fluid balance, and well trained nursing personnel are essential for the delivery of effective and safe CRRT. This section describes the hemodynamic implications of CRRT, the mechanics of fluid management, possible complications related to the procedure and the need for accurate recording to minimize such complications.

18.5.1 Introduction

Fluid management is a key component in the care of critically ill patients with AKI fluid overload represents one of the most frequent indications for the application of extracorporeal therapy in critically ill patients. Critically ill patients develop fluid overload in the setting of decreased urine output in AKI, congestive heart failure, sepsis, and other pathological conditions. Several observational studies, both in the pediatric and adult population (Foland et al. 2004; Gillespie et al. 2004; Goldstein et al. 2001; Payen et al. 2008; Bagshaw et al. 2008; Bouchard et al. 2009) suggest an association between fluid overload and increased mortality in critically ill patients with AKI.

Renal replacement therapies remove fluid from the intravascular compartment. Hemodynamic stability is dependent on refilling of the intravascular volume from the interstitial compartment. The plasma refill rate (PRR) limits fluid removal. In contrast to IHD, CRRT permits a slower and more constant fluid removal that can be targeted to match the PRR and minimize hemodynamic instability. Thus, CRRT techniques offer a significant advantage over IHD for fluid control in the critically ill patient. An understanding of the principles of fluid management with CRRT is necessary to ensure accurate management of fluid balance and prevent CRRT-related complications. Continuous clinical assessment of the patient's fluid status and adjustment of the CRRT prescription to optimize fluid balance are the keys to successful volume management with CRRT.

18.5.2 Fluid Removal in CRRT

The effluent is the total amount of fluid discarded by the CRRT device. It consists of the amount of fluid removed from the patient PLUS the

dialysate and/or replacement solution, depending on the modality of CRRT used. This is represented as follows: Total effluent = Replacement Fluid (RF) + Dialysate (D) + Fluid Removal (FR). The fluid removal rate is also known as the net ultrafiltrate. The replacement fluid and/or dialysate rate that is prescribed is automatically accounted for by the CRRT device and removed through the machine. In calculating the NET fluid removed from the CRRT device (or net ultrafiltrate), the dialysate and replacement fluid volumes should not be included in the calculation. In other words, the total effluent volume is NOT the net fluid removed from the patient. The fluid removal rate is the net amount of fluid the CRRT system removes from the patient each hour after accounting for any replacement fluid being used. Net fluid removal occurs whenever the operator sets the CRRT fluid removal rate to a value above zero. The CRRT device does not measure or account for non-CRRT sources of patient fluid intake (such as hyperalimentation, blood, or drug infusion) or fluid output (such as urine and wound drainage). It also does not account for anticoagulant solution infused via the anticoagulant syringe pump. The operator must account for these other sources when prescribing the patient fluid removal rate, as well as when calculating the patient's input/output totals. Overall fluid balance management in CRRT typically involves calculation of the patient's hourly total non-CRRT system intake (infusions, medications, etc.) minus the hourly total output. The hourly total output includes both the net fluid removal from the CRRT device and non-CRRT system output (urine, gastrointestinal losses, etc.). The patient fluid removal rate must be adjusted if the weight loss prescribed by the physician is changed or if the patient's non-CRRT fluid inputs or outputs change.

Patients on CRRT should have a complete assessment of the fluid status and the volume of fluid the patient is receiving each hour. Parameters for assessment include the patient's blood pressure, dosages of vasopressors, weight, presence of edema, central venous pressure (CVP), pulmonary artery occlusion pressures, cardiac index, and cardiac output if the patient has a pulmonary artery catheter in place. Other helpful measurements include arterial blood gases, arterial oxygen saturation, and mixed venous oxygen saturation.

Accurate CRRT-related fluid management requires the incorporation of a bedside CRRT flow sheet for calculating machine fluid balance. The flow sheet requires the recording of fluid balance changes and CRRT parameters on an hourly basis. Furthermore, the CRRT flow sheet should allow for a running hourly balance. The CRRT flow sheet ensures that treatment goals reflect 'machine' settings and 'patient' fluid inputs. For example, a treatment may be set for a 200 mL/hr fluid removal while the

intravenous inputs are also 200 mL/hr; this is considered patient 'even' or no net fluid loss. To achieve a patient negative fluid balance the machine fluid removal would need to exceed 200 mL/hr. A common misunderstanding and source of error is in prescribing fluid loss or determining desired negative fluid balance.

Scales or balancing chambers are used to manage the administration and removal of fluid through the CRRT device. If a scale system is used, the scales balance the weight of the volume of fluid programmed to be lost on the infusion scale and the weight gained on the output scale. In a balancing chamber system, the balance chambers empty and fill precisely, to balance the fluid volume programmed in and out, ensuring that the fluid volume desired is accurate. In either type of system, accuracy can be verified by monitoring the therapy history and comparing the volume of actual fluid removed at the end of each hour to the volume that was programmed. The volumes programmed to be infused and removed by the system should be within the manufacturer's error specifications of the system in use.

18.5.3 Management of Complications

When large net fluid removal rates are prescribed, ultrafiltration may exceed the refilling capacity of fluid movement into the intravascular compartment, resulting in hypotension, decreased CVP decreased pulmonary arterial wedge pressure, etc. Fluid removal should be decreased or stopped if these signs of hypovolemia occur. Excessive fluid removal, i.e. fluid removal greater than what is prescribed, has resulted in death and injuries when operators repeatedly overrode safety alarms intended to limit fluid removal when the gravimetric scales were being adjusted (Ronco et al. 2005). In these cases, an alarm called "incorrect weight change detected" was overridden without identifying the underlying cause. Most machines today are equipped with software that intervenes and stops the treatment after a fixed number of alarm overrides or when an absolute error in fluid balance has occurred. Regardless of this safety measure, a red alarm should never by overridden without identifying and correcting the cause of the alarm.

An increase in edema or weight gain may indicate that the therapy objectives are not being achieved or that the circuit is not functioning properly. Every time an alarm occurs, or the pumps stop on the system, the fluid removal is also stopped. Therefore, the programmed volume of fluid to be removed may not be the volume that was removed that hour. Frequent interruptions of therapy due to machine alarms may lead to extensive loss of treatment time and thus decreased fluid removal. Furthermore, adjustments

to the fluid removal prescription may need to be made if patients are off therapy for extensive amounts of time due to procedures or other issues. Prompt attention to fluid balance should always be a priority in patients treated with CRRT.

18.5.4 Conclusion

Fluid management with CRRT requires an understanding of the principles of fluid removal and fluid balance. Attention to fluid balance during CRRT is essential. Standardized order sets for prescription of the therapy, flow sheets for recording and monitoring fluid balance, and well trained nursing personnel are essential for the delivery of effective and safe CRRT.

18.6 DIALYSATE AND REPLACEMENT FLUIDS

A successful CRRT program is dependent on the proper and timely delivery of safe dialysate and replacement fluids. This section describes the composition of custom-made and commercially dialysate and replacement fluids currently available for CRRT. Fluids should be sterile and contain electrolytes in physiologic concentrations. Bicarbonate is the preferred buffer for CRRT solutions.

18.6.1 Introduction

CRRT solutions should restore acid-base balance and maintain physiological electrolyte concentrations while minimizing errors and maximizing safety. The U.S. drug Administration (FDA) classifies replacement solution as a drug since it is infused in the vascular space, and dialysate as a device. In general, there is little difference in the composition of dialysate and replacement fluids, and many commercially available dialysates are used off-label as replacement fluids. Whether replacement fluid or dialysate is utilized, the solution should be as pure as possible since significant backfiltration can occur with diffusive CRRT modalities. During backfiltration, dialysate flows from the dialysate compartment across the membrane into the blood compartment. Therefore, dialysate and replacement fluids need to be at least ultrapure and preferably sterile. Decisions regarding the generation and composition of CRRT solutions are discussed in this section.

18.6.2 Custom-Made versus Commercially Available Solutions

CRRT fluids can be custom-made by pharmacy, premade from a compounding company, or purchased prepackaged by a manufacturer. Customization of solutions, with subsequent adjustments based on or determined by patient clinical status, expends pharmacy resources and increases the risk for error. In 2004, two patients who were receiving CRRT died after potassium chloride, rather than sodium chloride, was added mistakenly to a custom-made dialysate (Johnston et al. 2004; Canada News Wire Group 2004). Because the FDA does not presently require batch testing for quality control, potentially hazardous CRRT solution errors may be unrecognized. Like customized pharmacy-made solutions, premade CRRT solutions obtained from a compounding company are associated with increased cost and a shorter shelf life as compared to commercially available prepackaged solutions. Furthermore, the quality and sterility of such fluids are questionable. As a result, the safest approach is to use commercially available CRRT fluids. These are significantly less expensive, have longer shelf life, available in 3 liter and 5 liter bags, and available from multiple manufacturers.

18.6.3 Electrolyte Composition

The Acute Dialysis Quality Initiative (ADQI) has published recommendations regarding the composition of CRRT solutions (Kellum et al. 2008b). These are reviewed below. In general, replacement and dialysate solutions should contain electrolytes in physiological ranges.

18.6.3.1 Sodium

In most cases, the sodium concentration in CRRT solutions should be physiologic. Commercially available solutions contain sodium concentrations in the range of 130 to 145 meq/L. When hypertonic citrate solutions are used as anticoagulation for CRRT, hyponatremic replacement and/or dialysate fluids are often needed. Adjustments of the sodium concentration of CRRT fluids may also be necessary in patients with hypo- or hypernatremia.

18.6.3.2 Potassium

CRRT fluids with potassium concentrations between 0 to 4 meq/L are commercially available. When initiating CRRT, potassium concentration of 0 to 2 meq/L may be needed in the setting of severe hyperkalemia. After steady state is reached with CRRT or the acute hyperkalemia resolves,

CRRT solutions with a potassium concentration of 4 meq/L should be used for maintenance.

18.6.3.3 Calcium, Magnesium, Phosphorous

Calcium should be present in physiological concentrations in CRRT solutions. Exceptions include patients with severe hypo- or hypercalcemia and/or patients treated with citrate anticoagulation. When using citrate anticoagulation, the CRRT solutions should not contain calcium; instead, calcium is replaced to the patient by an intravenous infusion. Commercially available solutions contain calcium in the ranges of 0 to 3.5 meq/L.

Magnesium in commercially available CRRT fluids ranges between 1 – 1.5 meq/L. This level is not well studied but has been clinically successful in use without significant hypermagnesemia or hypomagnesemia. Intravenous magnesium may be needed if magnesium levels fall below normal or at lower ends of the normal reported range.

Although hyperphosphatemia is a frequent complication of AKI, the majority of patients on CRRT will develop hypophosphatemia after CRRT initiation. Phosphorus is not a standard component of replacement or dialysate fluids in CRRT. The most appropriate way to supplement phosphorus is to use higher phosphorous enteral feedings or phosphate addition to hyperalimentation. Hypophosphatemia may also be treated with intravenous supplementation. Several authors have described the safe addition of phosphorous to CRRT fluids (Troyanov et al. 2004, Broman et al. 2011).

18.6.3.4 Glucose

Commercially available solutions contain glucose in the range of 0 to 110 mg/dL. Solutions with supraphysiologic glucose content should be avoided since they can induce hyperglycemia, which is associated with poorer outcomes. The predominate complications with the use of glucose-free solutions is hypoglycemia and inadequate nutritional supply.

18.6.3.5 Buffer

CRRT fluids require a buffer anion due to substantial loss of bicarbonate in the effluent. Buffer options include acetate, lactate, bicarbonate, and citrate. Both acetate and lactate are converted by the liver into bicarbonate in a 1:1 ratio. Acetate has been associated with hemodynamic instability and decreased cardiac function in IHD. It has not been frequently

used as a buffer for CRRT (Morgera et al. 1997). Although controlled trials have demonstrated similar efficacy of lactate- and bicarbonate-based CRRT solutions in correcting metabolic acidosis (Thomas et al. 1997; Heering et al. 1999; Zimmerman et al. 1999), serum lactate levels are typically higher when lactate-based solutions are used and can confuse the clinical interpretation of blood lactate levels. Moreover, lactate solutions may worsen metabolic acidosis in patients with metabolic derangements and hepatic failure (Kierdorf et al. 1999). Bicarbonate-based solutions are preferred for patients with hepatic failure who cannot metabolize the lactate and are also more physiological than are lactate solutions. Recent studies have shown better control of metabolic acidosis with bicarbonate-based solutions as compared to lactate-based solutions (McLean et al. 2000). Both lactate-based and bicarbonate-based solutions are commercially available as CRRT fluids. Bicarbonate is currently the preferred buffer. Commercially available CRRT fluids contain bicarbonate in the range of 22 to 35 meq/L.

Citrate is used for anticoagulation and not solely as a buffer for CRRT. However, since citrate generates three moles of bicarbonate per mole of citrate, the concentrations of other buffers in CRRT solutions need to be adjusted or eliminated to prevent metabolic alkalosis. The acid-base complications of citrate are discussed in detail in the 'Anticoagulation' section of this chapter.

18.6.4 Conclusion

A successful CRRT program is dependent on the proper and timely delivery of safe dialysate and replacement fluids. Fluids should be sterile and contain electrolytes in physiologic concentrations. Bicarbonate is the preferred buffer for CRRT solutions.

18.7 VASCULAR ACCESS IN RENAL REPLACEMENT THERAPIES

This section discusses the characteristics of vascular access to be used for renal replacement therapy in patients with AKI. Dual lumen venous temporary catheters are the access of choice. Tunneled catheters can be used in patients with AKI if the anticipated need is more than one week, and insertion must be done under ultrasound guidance utilizing strict sterile technique, and preparing the skin with 2% chlorhexidine .The right internal jugular vein is the preferred site of insertion. The role of antibiotic

'locks' and antiseptics embedded into the catheter material is currently in question.

18.7.1 Introduction

Renal-replacement therapies are among the most invasive techniques used in the intensive-care units. Increased safety can be expected from interventions in several areas. Teaching and training are probably the more important due to the complexity of both techniques and devices (Journois and Schortgen 2008). Safe insertion and management of the hemodialysis access is key to ensure good patient outcomes. A well- functioning vascular access is an essential component of the equipment necessary to deliver adequate renal replacement therapy in AKI (Schetz 2007b).

The three main issues to be discussed in this section will include:

1. Insertion in the acute setting
2. Adequacy of dialysis in relation to the kind of catheter utilized
3. Prevention of angioaccess-related morbidity

18.7.2 Characteristics of Catheters and Procedures for Insertion

Most of hemodialysis catheters are made of plastic polymers, either polyurethane or silicone (Tal and Ni 2008). Polyurethane catheters are more rigid and therefore associated with greater risk of vessel injury, but their rigidity makes them easier to insert percutaneously. Conversely, silicone catheters are semi-rigid and become softer at body temperature: although less likely to injure blood vessels, these catheters require more complicated procedures for percutaneous insertion. For tunneled insertion, silicone soft cuffed catheters are preferable because they offer an additional barrier to the entry of bacteria (Siegel 2008). These catheters are generally inserted percutaneously via the right internal jugular vein, are larger than temporary catheters and provide better blood flow and less clotting complications. Tunneled catheters can be used in patients with AKI if the anticipated need is more than one week, but given the lack of predictors of duration of AKI, initial insertion of tunneled catheters is appropriate (Coryell et al. 2009). Tunneled catheters are equally adequate among elderly and young patients (Forauer et al. 2009).

The size of catheters is usually between 11 and 14 French. Structurally, catheters are double-lumen with variable catheter and tip design, attempting to minimize resistance to flow by ensuring maximal diameter and avoidance of recirculation between the outflow and inflow branches (Tal and Ni 2008). Reliable data directly comparing different designs and coatings are currently lacking.

Ultrasound guidance should be mandatory for catheter insertion. It reduces placement failure, decreases the number of placement complications and the number of attempts, and reduces the number of catheter associated infections (Randolph et al. 1996; Karakitsos et al. 2006; Hassan et al. 2008) (see Table 18.6)

Table 18.6 Comparison of catheter placement complications with and without ultrasound guidance (Karakitsos et al. 2006)

Complications	No U/S Guidance	U/S Guidance
Carotid Injury	10.6%	1.1%
Hematoma	8.4%	0.4%
Hemothorax	1.7%	0%
Pneumothorax	2.4%	0%

18.7.2.1 Site of Insertion

The preferred site of insertion is the right internal jugular vein, where the trajectory of the vein is direct towards the right atrium. Left internal jugular vein insertions tend to be more problematic because of the longer and more circuitous vein trajectory. Subclavian vein location should be avoided in order to minimize the chances of vein stenosis, considering possible future insertion of an arteriovenous fistula on the upper extremity. The place of insertion determines the required minimal length of the catheter (see Table 18.7 and Fig. 18.2).

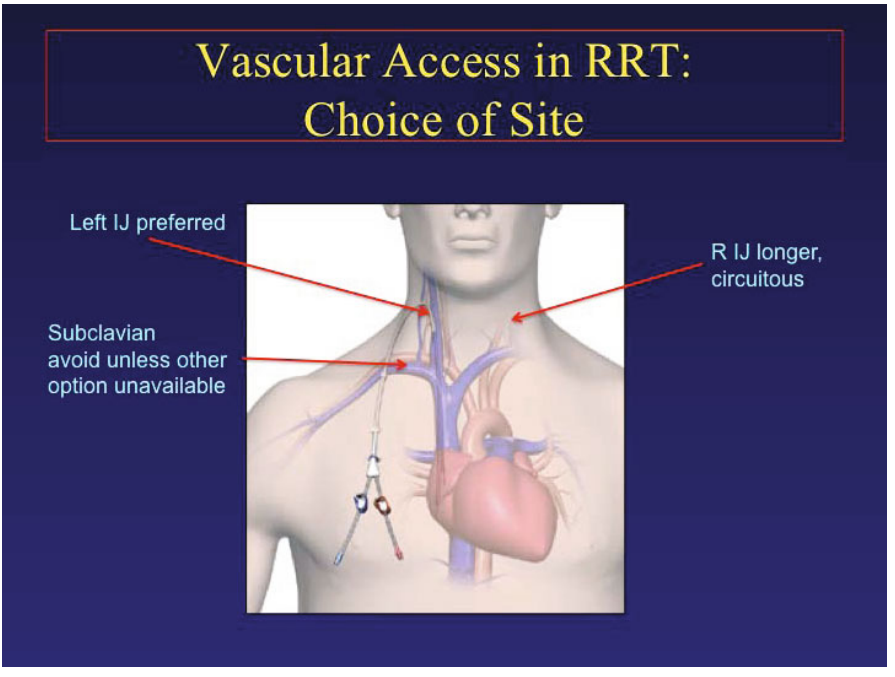

Fig. 18.2 Vascular access in RRT: choice of site

Table 18.7 Location of the dialysis line and preferred length of the catheter

Location		Preferred Length
Jugular	Right Internal	15-16 cm
	Right Internal	19-20 cm
Femoral		24-35 cm

18.7.2.2 Complications from Insertion

The complications of temporary dialysis catheters occur either during placement or long term.

During placement, complications include:

- Bleeding, hematoma formation, arterial puncture and risk of hemomediastinum.
- Air embolism.
- Recurrent laryngeal nerve paralysis.
- Atrial perforation.

- Arrhythmia and cardiac arrest: the electrocardiogram must be continuously monitored during catheter placement.

Long-term, complications include:

- Catheter thrombosis.
- Venous thrombosis, especially with femoral catheters (Brzosko et al. 2008).
- Venous stenosis.
- Fibrin sheath formation (Faintuch and Salazar 2008).
- Infection: the reported risk of bacteremia in nontunneled catheters ranges between 3 and 10%.

18.7.3 Adequacy of Dialysis in Relation to the Kind of Catheter Utilized

Multiple studies have shown a significant discrepancy between the prescribed and delivered dose of dialysis (Venkataraman et al. 2002; Vesconi et al. 2009). The type and location of hemodialysis access plays a key role in the delivery of an adequate dose of dialysis (Liangos et al. 2004). Klouche et al (2007) studied the effects of dialysis catheters on dialysis dose and patient survival, to evaluate the potential benefit of tunneled silicone catheters in femoral vein location. In patients with AKI, silicone tunneled catheters minimize catheter-related morbidity and improves dialysis efficiency, when compared to conventional femoral access (see Table 18.8).

Catheter recirculation plays a significant role in the delivery of dialysis. Canaud et al showed that while internal jugular and subclavian vein catheters show an average 10% recirculation, femoral catheter recirculation is higher (average 20% [range 5-38%]) and the inversion of dialysis lines increases recirculation up to 20-30% (Canaud et al. 2004). Utilizing the saline dilution technique, temporary femoral catheters less than 20 cm in length show three times as much recirculation than longer catheters, while internal jugular lines show minimal recirculation (Little et al. 2000). More recently, Parienti et al conducted a randomized control trial of catheter dysfunction and dialysis performance in critically ill patients and showed that as long as the femoral lines reach the inferior vena cava, they are an acceptable alternative to jugular access in bed-bound adults in the ICU (Parienti et al. 2010).

Table 18.8 Complications, effects on dialysis dose and survival of tunneled femoral catheters in acute kidney injury (Klouche et al. 2007)

Complications	Tunneled silicone catheters	Non tunneled polyurethane catheters
Time for insertion	Longer	Shorter
Vein thrombosis	Lower	Higher
Catheter related infection	Lower	Higher
Venous pressure/Q_b	Better	Worse
Recirculation	Same	Same
Dialysis dose (IHD or CRRT)	Higher	Lower
Catheter duration	Longer	Shorter

18.7.4 Catheter Related Infections

Bacteremia and the development of sepsis syndrome is second only to cardiovascular disease as the leading cause of death in patients on renal replacement therapy (Thomson et al. 2007). Catheter related infections are the second most common major complication of dialysis lines. Infection usually occurs due to migration of skin bacteria, although hematogenous colonization is possible (NKF-KDOQI 2006). Catheter related infections are more common with uncuffed dialysis lines.

Catheter infections occur from three sources: from the lumen (infected catheter hub); from the skin, in progression from infected exit site leading to tunnel and later catheter infection; or hematogenous such as during episodes of transient bacteremia and bacterial endocarditis (see Fig. 18.3).

The commonest agents of infection include gram-positive staphylococcus (S Aureus or Coagulase Negative Staphylococcus Epidermidis), followed by gram negative bacilli, gram positive bacilli such as the skin contaminant Corynebacterium, and fungi (usually Candida Spp) (Parienti et al. 2008).

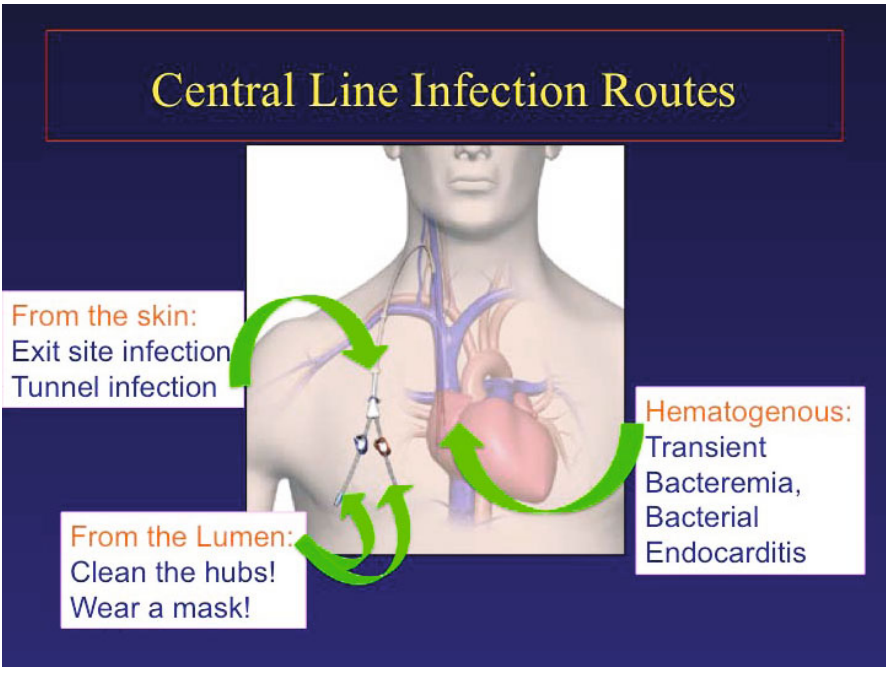

Fig. 18.3 Central line infection routes

Although prevalent opinion is that femoral catheters become infected more commonly than jugular catheters, a recent large randomized controlled trial (Parienti et al. 2008) has shown that jugular venous catheterization does not reduce risk of infection compared with femoral access except in obese adults. Also, in contradistinction to prevalent wisdom, the same authors demonstrated that catheter colonization and infection are random events without a time threshold: the incidence of infection increases linearly with time without inflection at any given time. This finding indicates that the current policy of systematic predetermined catheter exchange after a certain period of time is not justified unless infection is demonstrated.

Best demonstrated practices to avoid catheter related infectious complications include:

- Use of maximal sterile barrier precautions during insertion
- Use of ultrasound guidance for insertion
- Use of chlorhexidine skin desinfection and chlorhexidine impregnated disks in the exit site

- Careful desinfection of the catheter hub whenever used
- Use of dialysis catheter only for dialysis, forbidding their use for other purposes such as iv infusions or blood draws
- Pre-scheduled routine catheter exchanges are not necessary unless infection is demonstrated
- Remember to remove lines when no longer needed

When to remove the dialysis catheter?

- When systemic bacteremic infection is demonstrated
- Exit site infection requires temporary catheter removal and placement of a new line at a separate location
- Tunneled catheters must be removed if there is tunnel infection
- Sole exit site infection may be managed with a trial of topical antibiotics such as mupirocin

Complications of catheter related bacteremia (Maya and Allon 2008) are:

- Less likely with tunneled than non-tunneled
- Frequency 2 to 5.5 episodes/1000 catheter-days
- Suspected with fever/chills; confirmed with positive Blood Cultures
- Serious complications 5-10%: bacterial endocarditis, osteomyelitis, epidural abscess, and death.
- Etiology: 60-70% gram positive cocci, 30-40% gram negative rods
- Uncomplicated catheter-related bacteremia requires 3 weeks of intravenous antibiotics
- Systemic antibiotics alone (without replacement of dialysis catheter) lead to 75% recurrent infection
- Catheter removal is mandatory with persistent fever or bacteremia while on antibiotics, or tunnel infection
- Guidewire exchange is possible if fever resolves on antibiotic therapy
- Catheter biofilm is a major source of catheter-related bacteremia
- Antibiotic lock may kill bacteria in the biofilm but variable success depends on organism: 90% with gram negative, 80% with coagulase negative staphylococcus, 45% in S. Aureus infections

A procedure-related complication is an unanticipated adverse event that requires therapy. In order to analyze frequency and severity of complications in the process of quality assurance, it is useful to have a classification of complications, indicating the type and severity. The Clinical Practice Committee of American Society of Diagnostic and Interventional Nephrology has developed a Classification of Complications relating to Hemodialysis Vascular Access Procedures, based on the system first proposed by Beathard in 2006 (Vesely et al. 2007). In this system, the "type" refers to the procedure being performed or vessel entered, and the "grade" is based on the intensity of medical care needed to address the complication. This publication describes 10 Types and 4 Grades of complications. Development of a quality assurance system in each center is essential to minimize complications and to optimize dialysis access use.

18.8 MACHINE COMPARISONS

This section will briefly discuss machine comparisons among currently available CRRT machines.

18.8.1 Characteristics of the Ideal CRRT Device

The main characteristics of the ideal CRRT device include:

- Inexpensive cost
- User friendly
- Flexible to adapt for multiple renal replacement modalities
- Accurate measures
- Safe
- Available thermoregulation
- Exchangeable components
- Biocompatible

Newer CRRT machines have incorporated multiple newer characteristics:

- Integrated blood modules
- Fluid balance controls with gravimetric or volumetric measurement devices

- Capacity for intermittent and continuous therapy applications
- Ability to increase blood flow up to 500 ml/min
- Increased dialysate and replacement fluid flow rates
- Highly permeable membranes
- Highly surface area dialyzers
- Simplified priming procedures
- Friendly user interface
- Data extraction capabilities and possibility of downloading data to centralized servers
- Automating data printing

Currently available CRRT machines include:

- Gambro Prisma
- Gambro Prismaflex
- Braun Diapact
- Baxter Aquarius
- NxStage
- Fresenius 2008 K

Table 18.9 incorporates a side-by-side comparison among the different available CRRT machines.

Table 18.8 The main comparisons among different available CRRT machines

Manufacturer	Baxter	Gambro	BBraun	Gambro	Fresenius	Fresenius	Infomed
Model	Aquarius	Prisma	Diapact	Prismaflex	Multifiltrate	2008H, 2008K	HF 400
Weight				75 kg	80 kg		
Dimensions (cm)		H 145, W 41, D 30		H 162, W 49, D 30	H 150 , W 46, D 60		H 160, W 72, D 66
Battery backup		None	Optional	20 min	15 min		
Therapies provided	SCUF, CVVH, CVVHD, CVVHDF, TPE, IHD, IHFD	SCUF, CVVH, CVVHD, CVVHDF, TPE	SCUF, CVVH, CVVHD,	SCUF, CVVH, HVHF, CVVHD, CVVHDF, PEX	SCUF, CVVH, HVHF, CVVHD, CVVHDF, PEX	IHD, IHFD, SLED, SCUF, CVVHD	IHD, IHFD, IHF, SCUF, CVVH, CVVHD, CVVHFD, CVVHDF, PEX
Pumps	4	4	3	5	4	1+3	4
Display	Color, touchscreen	Monochrome, touchscreen	Monochrome	Color, touchscreen	Color, touchscreen	Color	Color, touchscreen

Table 18.8 (Continued)

Heater	Yes	Blood warmer	Yes	Yes, in-line	Yes, in-line	Yes	Yes
Heparin Pump	Yes	Yes	No	Yes	Yes	Yes	Yes
Reinfusion sites	Pre, Post, Pre-Post	Pre	Pre, Post	Pre, Post, Pre-Post	Pre, Post, Pre-Post	NA	Pre, Post, Pre-Post
Pressure sensors	4	4	4	5	4	3	4
Scales	2	3	1	4	4	Volumetric	2
RS-232	Yes	Yes	Yes	Yes	Yes	Yes	Yes
USB	No	No	No	No	No	No	No
Printer	No	No	No	No	No	No	No
Qb	0-450	0-180	10-500	0-450	0-500	0-500	0-450
Qd	0-165	0-40	0-400	0-133	0-70	0-300	0-200
Replacement			0-250	0-133	10-160	NA	
Effluent			0-300	0-33	0-100		
UF rate			0-2000 g/h	0-2000 ml/h	0-100		
Sensor Accuracy							

Table 18.8 (Continued)

Access			-400 to +300	-280 to +300			
Return			0 to +380	-80 to +500			
Pre-filter			0 to +650	0 to +750			
Filtrate			NA	NA			
Scale Range	10L		25 L	15L	24L	NA	12L
Air Detector	Yes		Yes	Yes	Yes	Yes	Yes
Blood leak detector	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Remarks						3 pumps for dialysate & fluid replacement are positioned inside the hydraulic circuit of the monitor	

Figures 18.4-18.13 describe the main characteristics, similarities and differences among the commonly used CRRT machines.

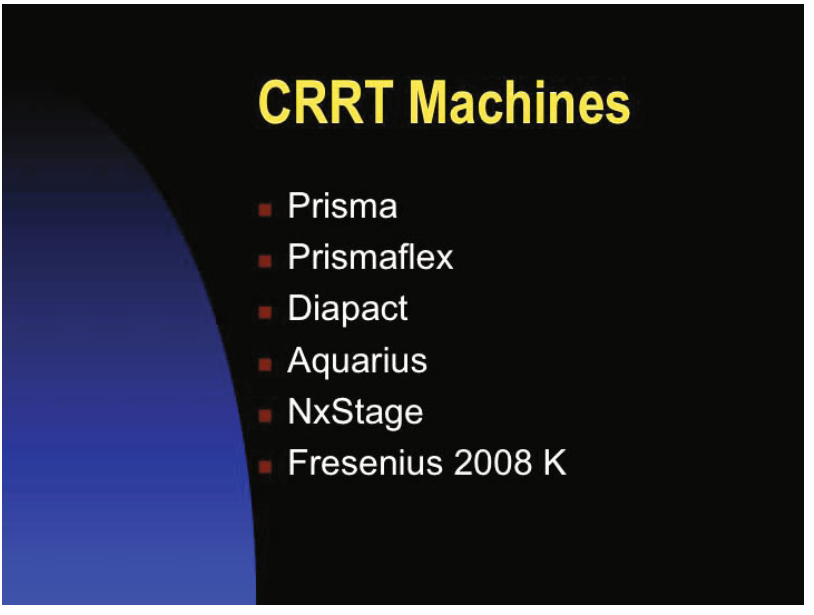

Fig. 18.4

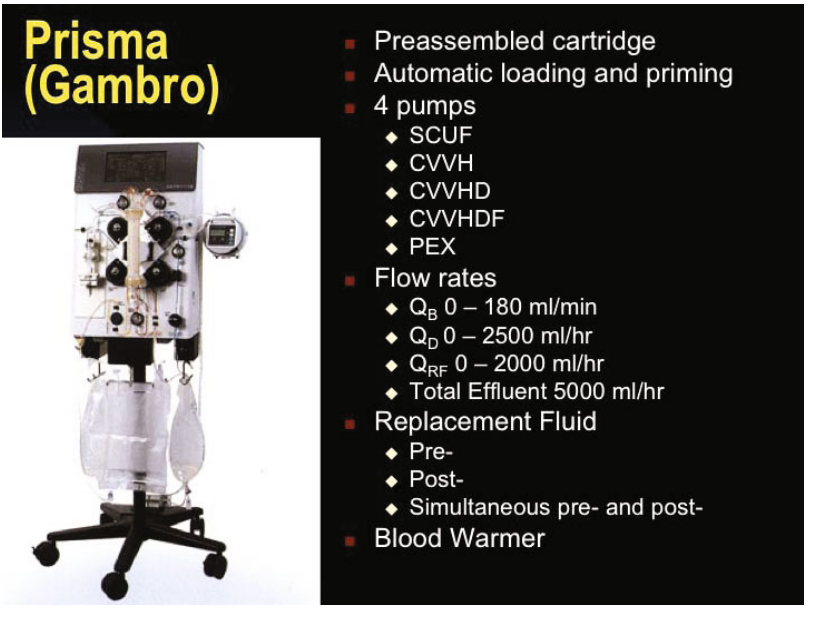

Fig. 18.5

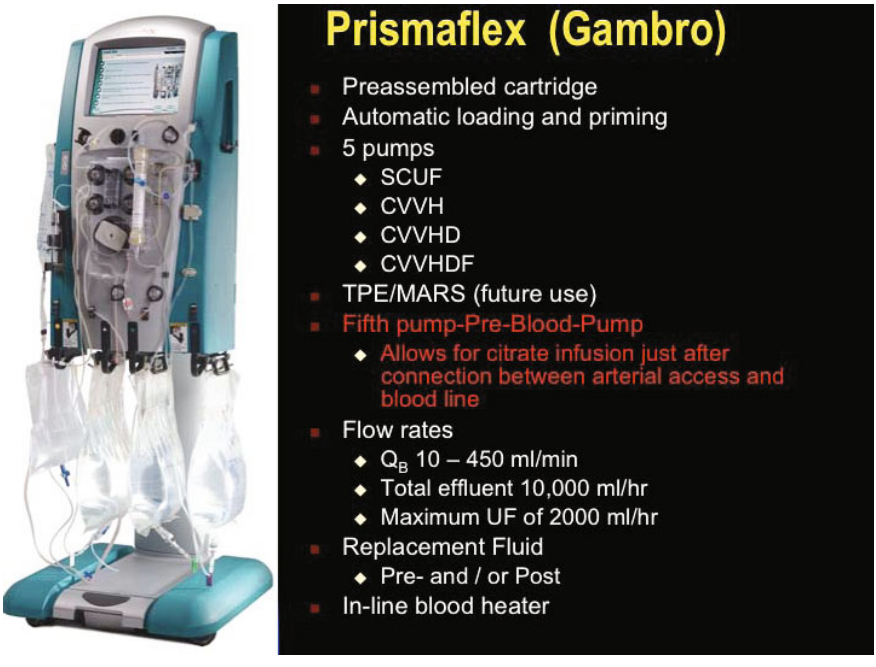

Fig. 18.6

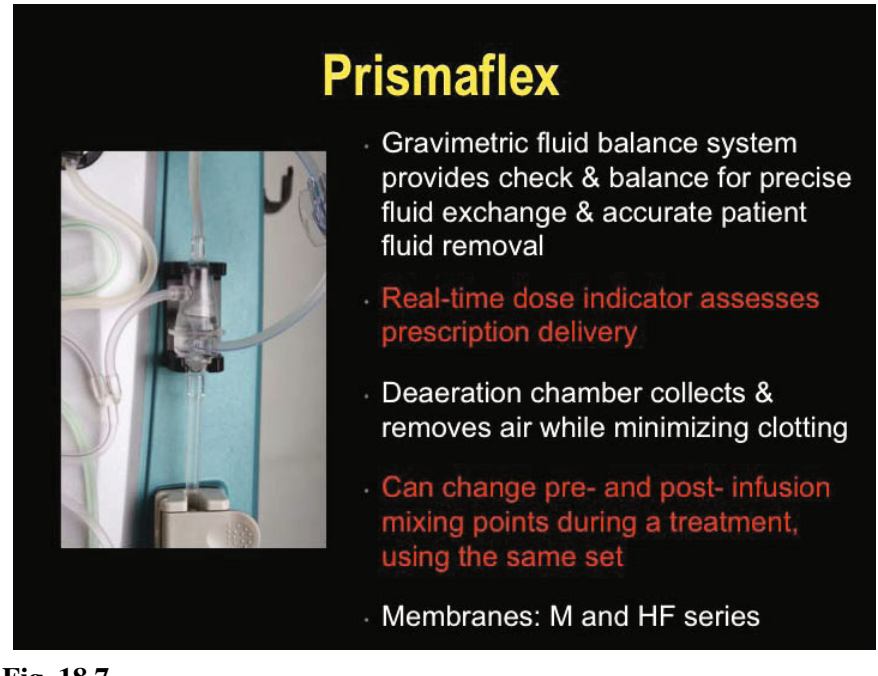

Fig. 18.7

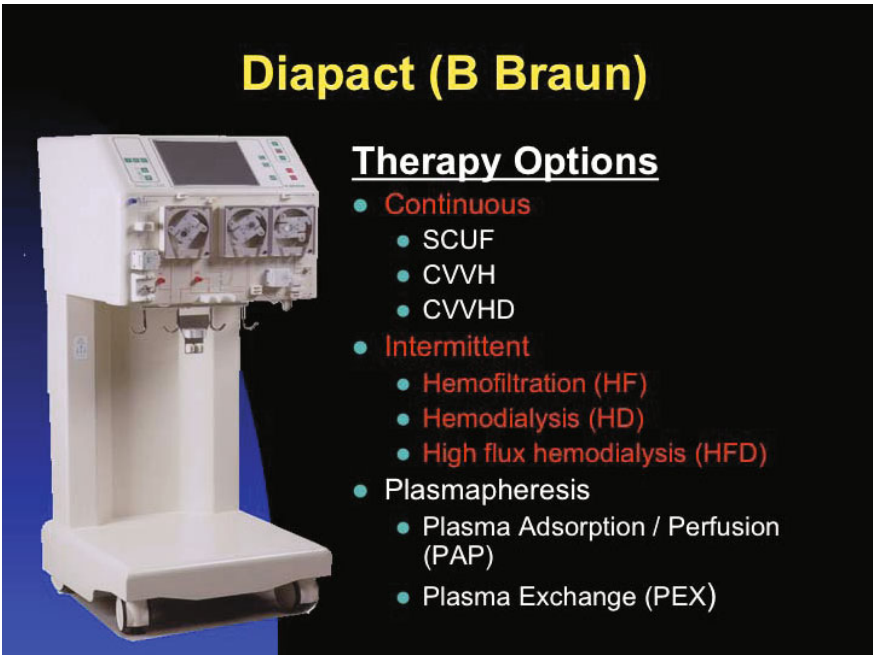

Fig. 18.8

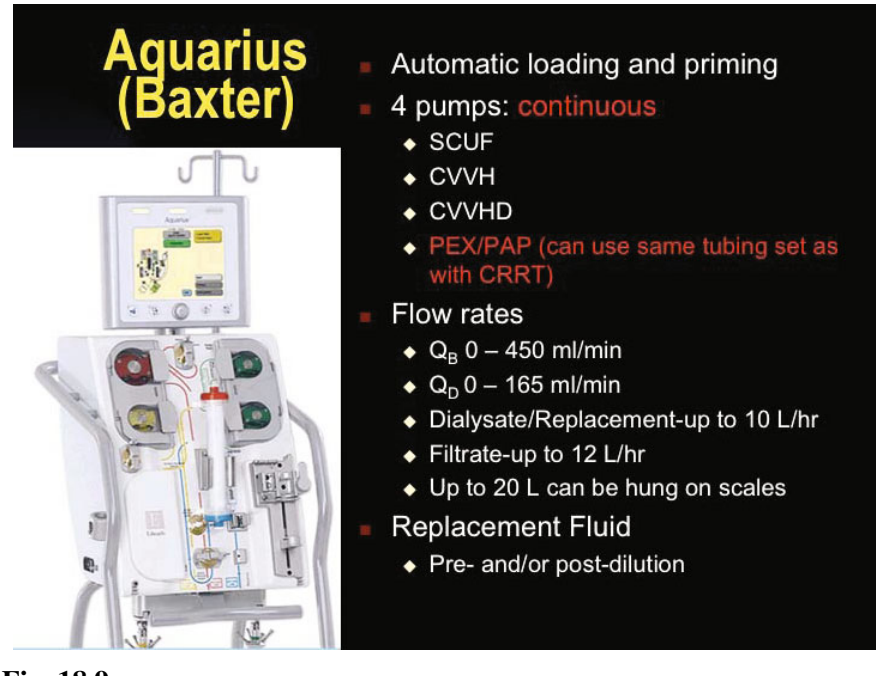

Fig. 18.9

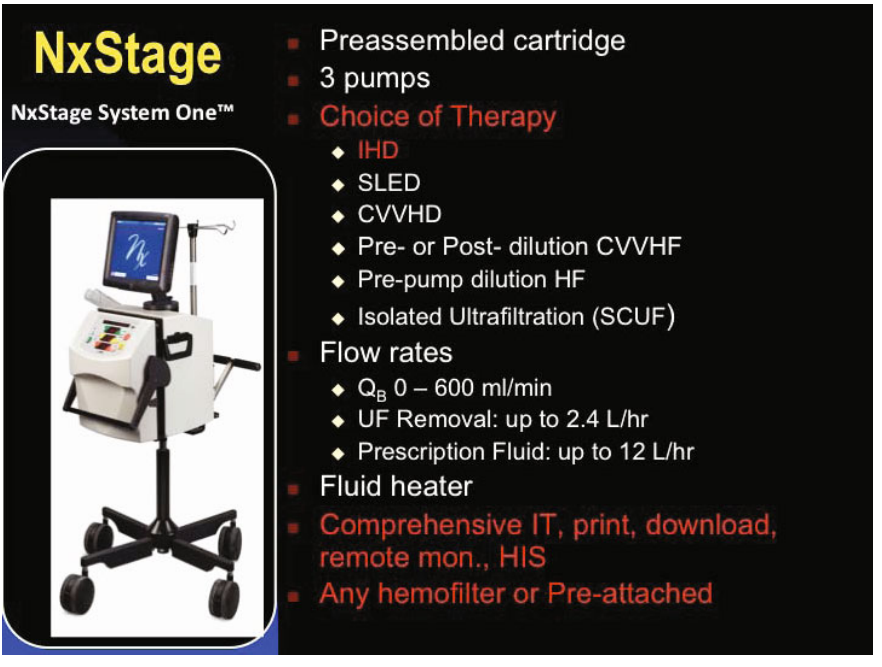

Fig. 18.10

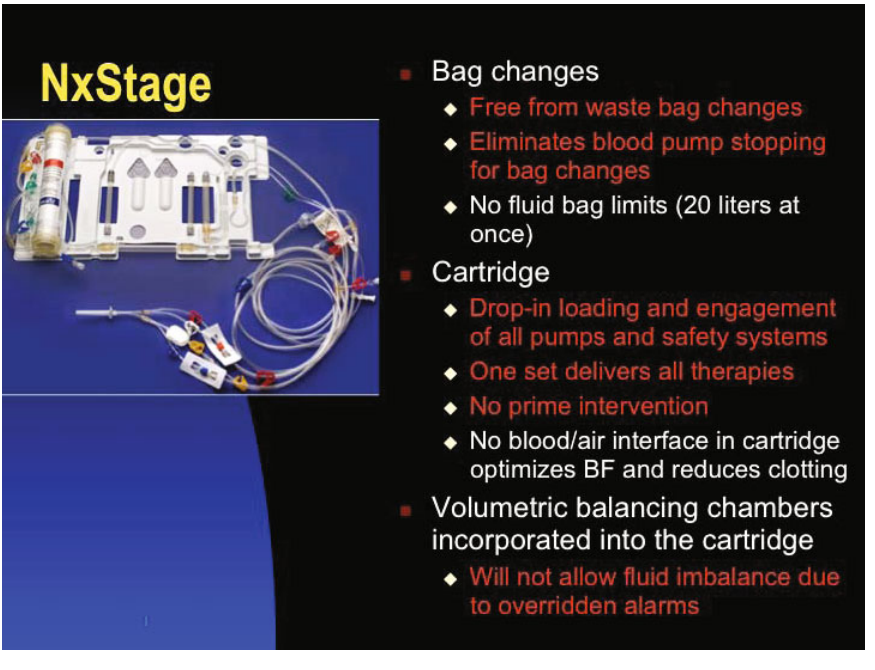

Fig. 18.11

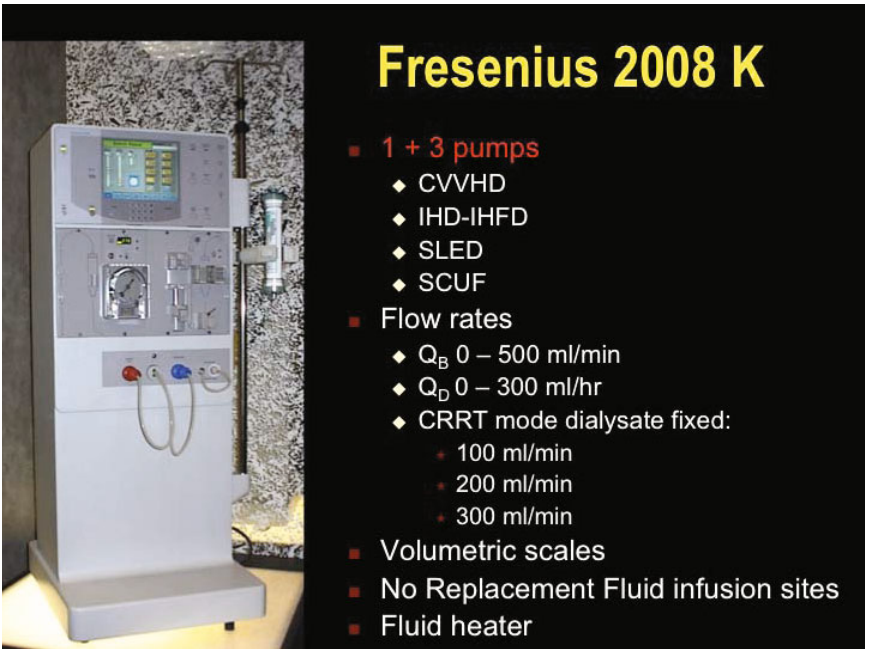

Fig. 18.12

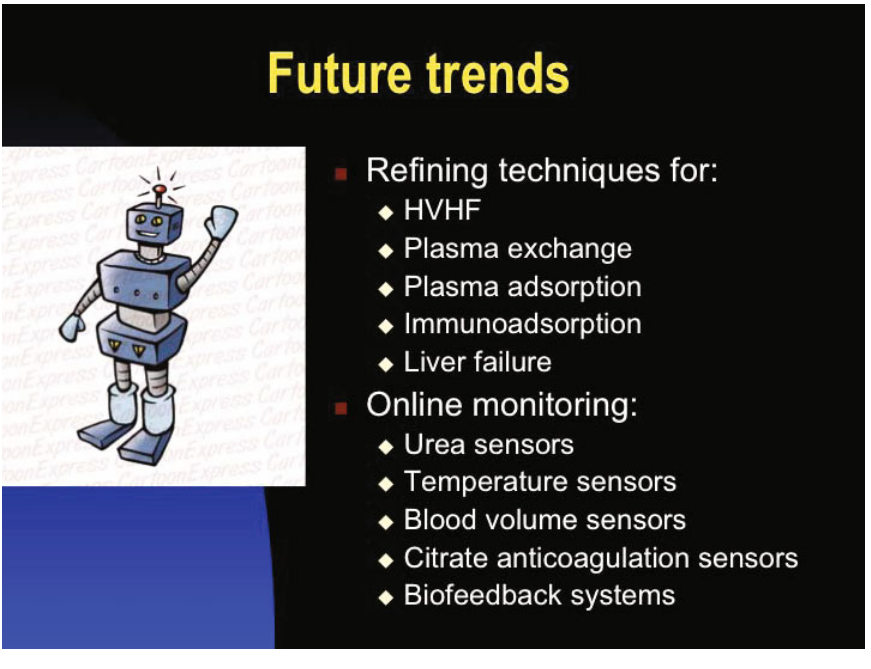

Fig. 18.13

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ESSAY QUESTIONS

1. Comprehensively describe the concepts of diffusion and dialysis and their application to the different CRRT modalities
2. Describe the operational characteristics of the different CRRT modalities, including CVVH, CVVHD and CVVHDF, and their implications in terms of diffusive and convective clearance and the optimization of dialysis dose
3. List the pros and cons of the following anticoagulation modalities: a. Heparin; b. Citrate; c. Prostacycline
4. Describe the ideal vascular access for dialysis, including catheter characteristics depending on site of insertion, tunneled vs. non-tunneled, and the advantages of ultrasound -guided catheter insertion
5. List the reasons why intermittent hemodialysis is associated with greater risk of hemodynamic instability than CRRT modalities
6. Compare the operational characteristics of the currently available CRRT machines
7. Discuss the effects of different sodium concentration in the dialysis and replacement fluid in terms of loss or gain of fluid during CRRT
8. List the pros and cons of the use of lactate, acetate or bicarbonate buffers in the dialysis and replacement fluid
9. Discuss the implications of convective versus dialytic technologies in terms of risk of brain edema
10. Discuss the possible uses of CRRT in patients with severe sepsis

MULTIPLE CHOICE QUESTIONS

Choose the best answer

1. As the expert initiating a new CRRT program at your institution, you need thorough understanding of the evidence supporting the use of these new techniques. *That is why you are here!*

Please indicate which ONE of these statements is true:

A. Recent randomized controlled trials demonstrate that early initiation of renal replacement therapy is associated with improved patient outcomes.
B. The recent ATN trial (VA/NIH Acute Renal Failure Trial Network, Dr. Palevsky et al) was a "modality" study, which demonstrated that there is no difference in survival between CRRT and IHD
C. Recent studies (the ATN and the RENAL trials) have shown that either "high" or "low", the dose of dialysis is unimportant and is not a determinant of patient survival.
D. Retrospective trials have shown that intermittent Hemodialysis is associated with fluid gains and increased hemodynamic instability, when compared with CRRT
E. Recent randomized controlled trials have conclusively demonstrated that renal functional recovery is superior among patients treated with CRRT, as compared with IHD.

2. As a model for the prescription and management of CRRT in a critically ill patient, it is preferable that:

A. Orders and follow up of the procedure be managed by the ***intensivist***, who is in the unit all the time and is the overall manager of patient treatment.
B. Orders and follow up decisions be managed by the ***nephrologist*** exclusively, as he is best trained to do so and "knows best" about extracorporeal treatments.
C. Decisions can be made by "the team", depending on the circumstances: ***all the practitioners involved in care of the critically ill patient*** should be involved in the decisions on CRRT, but a leader must be clearly identified.

3. Recent surveys and single center studies have shown that, on average, the delivered dose (based on various forms of urea clearance) of renal replacement therapy (IHD, CRRT or SLED):

A. Is measured in the majority (more than 75%) of the surveyed institutions
B. Is consistently about 85% to 90% of the prescribed dose
C. Is close to 25-30 ml/kg/hour

4. All of these factors can affect the delivery of an adequate dose of CVVHDF, **EXCEPT**:

A. Inability to raise the dialysis fluid flow above 800 ml/min
B. Catheter dysfunction limiting blood flow to below 100 ml/min
C. Catheter dysfunction inducing a recirculation greater than 20%
D. Femoral catheter shorter than 20 cm

5. The following are potential complications resulting from the use of heparin anticoagulation **EXCEPT**:

A. Bleeding
B. Hemolysis
C. Ineffective anticoagulation due to deficiency of antithrombin III
D. Induction of heparin induced antiplatelet antibodies

6. Which of the following is indicative of adequate anticoagulation of citrate for CRRT?

A. CRRT circuit ionized calcium level of 0.25 mmol/L
B. Systemic ionized calcium level of 0.7 mmol/L
C. Serum citrate level of 1 mmol/L
D. Total calcium level of 2.2 mmol/L

7. Risks associated with Heparin anticoagulation include:

A. Hypocalcemia
B. Thrombocytopenia
C. Hypolipidemia
D. Hypotension

8. A patient is on CRRT with the following parameters:
Modality: CVVHDF
Post dilution Replacement Fluid: 1500 ml/hr
Dialysate: 2000 ml/hr
Blood flow: 150 ml/min
Fluid Removal: 200 ml/hr

What is the total effluent rate in ml/hr?

A. 1500 ml/hr
B. 3500 ml/hr
C. 3700 ml/hr
D. 3850 ml/hr

9. Select the statement that is most appropriate regarding input and output (I&O) calculations in patients receiving CRRT

A. All I&O calculations are performed by the CRRT machine
B. The nurse must always manually calculate dialysate and replacement fluid use
C. I&O is not necessary for these patients
D. The nurse must be aware of which calculations are performed by the CRRT equipment

10. A patient is about to be started on CRRT. The total fluid input in 24 hours is 3.9 L. The total fluid output in 24 hours is 0.7 L. You want the patient to be 1 liter negative on CRRT by the next 24 hours. What should you prescribe as your fluid removal rate, assuming that the patient's 24 hour input and output will remain unchanged?

A. 75 ml/hr
B. 100 ml/hr
C. 175 ml/hr
D. 200 ml/hr

11. A mechanically ventilated patient with fulminant hepatic failure and acute kidney injury is started on CVVH for severe metabolic acidosis. His pH is 7.3, bicarbonate 10 mmol/L, and lactate 4.5 mmol/L. Which buffer is the best choice for the CVVH replacement fluid?

A. Acetate
B. Lactate
C. Bicarbonate
D. Citrate

12. A patient has severe Acute Respiratory Distress Syndrome (ARDS) and oliguric acute kidney injury. He is on a sodium bicarbonate infusion. You are starting CVVHD with citrate anticoagulation. Patient's pH is 7.1, pCO2 70 mmHg, serum sodium 132 mmol/L, serum bicarbonate 15 mmol/L, and serum potassium 4.9 mmol/L. Which of the following options is the best choice for dialysate? (All electrolyte options are in mmol/L)

A. PrismaSate BK 0/3.5 (Na 140, Cl 109.5, K 0, Mg 0.5, Ca 3.5, Lactate 3.0, HCO3 32)
B. Accusol 35 5B9251 (Na 140, Cl 116.3, K 2.0, Mg 0.75, Ca 2.8, Lactate 0, HCO3 30)
C. Baxter Hemodiafiltration dialysate (Na 140, Cl 117, K 2.0, Mg 0.75, Ca 3.5, Lactate 30)
D. PrismaSate BGK 4/0/1.2 (Na 140, Cl 110.2, K 4.0, Mg 0.6, Ca 0, Lactate 3.0, HCO3 32)

13. An anuric 98 kg patient is on continuous dialysis with Q_b 150, Q_d 2300 ml/hour and Q_{uf} 100 ml/hour. The patients small solute clearance is most nearly:
A. 145 ml/kg/hr
B. 40 ml/kg/hr
C. 30 ml/kg/hr
D. 25 ml/kg/hr

14. A 45 year old man with hepatitis C cirrhosis and hepatorenal syndrome is placed on Continuous Renal Replacement Therapy (CRRT) with no anticoagulation as a bridge to liver transplantation. He remains on CRRT for 7 days and his acid-base status is within normal limits prior to transplantation. He develops severe metabolic alkalosis immediately after liver transplantation. He is continued on CRRT intra- and post-operatively for persistent renal failure. The CRRT prescription has not changed from the pre-operative period.

Which ONE of the following is most likely to be responsible for the acid-base disturbance?
A. Transfusion of blood products
B. Increased ureagenesis by the transplanted liver
C. Increased urinary ammonium excretion
D. High bicarbonate CRRT solutions
E. Potassium depletion

15. Continuous renal replacement therapy is performed over a:
A. 3-4 hour period
B. 24 hour period
C. 6-8 hour period
D. 8-12 hour period

16. Continuous renal replacement therapy requires:
    A. A veno-venous central double lumen hemodialysis catheter
    B. An extracorporeal circuit and hemofilter
    C. A blood pump and effluent pump (dialysate and replacement pump, depending on therapy chosen)
    D. All of the above

17. Which therapy option does not require water hookup and hemodialysis nursing support?
    A. Continuous renal replacement therapy
    B. Sustained low efficiency dialysis
    C. Intermittent hemodialysis
    D. Intermittent hemofiltration

18. The movement of fluid through a semi-permeable membrane driven by a pressure gradient is called.
    A. Diffusion
    B. Convection
    C. Ultrafiltration
    D. Adsorption

19. The movement of solute from a higher concentration to a lower concentration is called:
    A. Convection
    B. Diffusion
    C. Ultrafiltration
    D. Adsorption

20. A 65 year-old man undergoes cardiac surgery with mitral valve replacement. His baseline serum creatinine is 2.7 mg/dl. Postoperatively he returns to the intensive care unit intubated and anuric on furosemide 20 mg/hr. His BP is 95/50 mmHg on vasopressin, dopamine, and norepinephrine infusions. He is mechanically ventilated and has an oxygen saturation of 90% on a fractional inspired oxygen of 0.8 with 15 cmH20 positive end-expiratory pressure. Central venous pressure (CVP) is 35 mmHg, and venous oxygen saturation is 50%. His weight has increased 12 kg from preoperatively, and the sternal wound has not been closed because of massive edema. His chest x-ray demonstrates bilateral pulmonary edema. His serum creatinine is 3.0 mg/dl. Other laboratory tests include sodium of 135 mEq/L, potassium of 5.1 mEq/L, chloride of 100 mEq/L. total CO2 of 12 mEq/L. blood urea nitrogen of 90 mg/dl and glucose of 80 mg/dl. The surgical team plans to transfuse 6 U of fresh-frozen plasma in preparation for

return to the operating room for sternal closure. You are asked to initiate emergent renal replacement therapy (RRT).

Which ONE of the following interventions is MOST appropriate in this setting?

A. Give intravenous boluses of 200 mg of furosemide with 500 mg of chlorothiazidc, and increase furosemide infusion to 40 mg/h.
B. Start a nesiritide infusion.
C. Initiate slow continuous ultrafiltration.
D. Initiate continuous venovenous hemofiltration (CVVH)