Acute Kidney Injury: Diagnosis and Treatment with Peritoneal Dialysis, Hemodialysis, and CRRT

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In response to growing evidence that even small declines in kidney function can adversely affect outcome in severely ill patients, the term acute kidney injury (AKI) was introduced in 2005 to better represent the dynamic clinical entity traditionally known as acute renal failure (ARF). Acute kidney injury affects an increasing proportion of critically ill pediatric and adult patients who now survive medical conditions and surgical complications that once were often fatal. Identifying the pathophysiologic principles underlying the development, progression, and resolution of AKI is the focus of much ongoing investigation. Improvements in classification systems along with consistency of applied defining criteria will enhance our understanding of the etiology and progressive nature of AKI in children and help define the role of early intervention. Advances in diagnosis, most notably the introduction of newer biomarkers, and the widespread availability of an increasing number of effective renal replacement treatment modalities have raised hopes of improved outcomes. This chapter focuses on the diagnosis and medical and dialytic management of pediatric AKI.

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Definition of Acute Kidney Injury (AKI)

Acute kidney injury has been classically defined as an abrupt, prolonged yet often reversible loss of the ability of the kidneys to maintain homeostasis of the body fluids. Retention of nitrogenous wastes is a consistent feature of AKI; significant reduction in urine output is not [1, 2]. Objective diagnostic criteria have ranged from a change in a biomarker (e.g., increase in serum creatinine), to a clinical sign (reduction in urine output), to a therapeutic maneuver (need for dialysis support) [3–5]. In fact, by the year 2002, more than 30 different definitions of AKI had been published [6].

This lack of consensus on AKI diagnostic criteria has confounded efforts to study the condition, establish incidence and prevalence rates,

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Table 37.1 The RIFLE AKI classification systema

AKI stage	Serum creatinine criteria	Urine output criteria
1 (***Risk***)	Absolute increase ≥ 0.3 mg/dL or Value is 1.5× baseline value or GFR decrease by >25%	<0.5 mL/kg/h for >6 h
2 (***Injury***)	Value is 2× baseline value or GFR decrease by >50%	<0.5 mL/kg/h for >12 h
3 (***Failure***)	Value is ≥3× baseline value or GFR decrease by >75% or Value ≥4 mg/dL with absolute increase ≥0.5 mg/dL or Patient is receiving renal Replacement therapy	<0.3 mL/kg/h for 24 h or Anuria for 12 h
Loss	Persistent AKI = complete loss of renal function for >4 weeks	
ESRD	End-stage renal disease	

[a]With AKIN modifications; see text

define risk factors, and monitor outcomes. Following a series of consensus conferences beginning in 2000 known as the "Acute Dialysis Quality Initiative" (ADQI), a sensitive definition of AKI was developed based on five degrees of increasing severity and worsening outcome (the "RIFLE" criteria): Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease. (Table 37.1) The RIFLE criteria are based on absolute values and changes in serum creatinine levels, estimated glomerular filtration rates and/or urine output, reflecting the dynamic process of AKI, which can progress from mild to severe forms [6].

Initial application and validation of the RIFLE criteria in the adult critical care population demonstrated reasonable predictive correlation between the different degrees of AKI according to the RIFLE criteria and mortality [7, 8]. Modifications of the original criteria were proposed in 2005 by the Acute Kidney Injury Network (AKIN) both to broaden consensus and reflect new evidence that discrete changes in serum creatinine levels in adults as small as 0.3 mg/dL were associated with worsening outcomes [9]. Table 37.1 incorporates both the original RIFLE category definitions (in italics) with the AKIN modifications which replace RIFLE levels R, I, and F with AKIN stages 1, 2, and 3.

In a landmark study of 150 critically ill children, Akcan-Arikan and Goldstein and their colleagues in Houston developed a pediatric-specific AKI classification system that is shown in Table 37.2 [10].

In all three AKI staging systems (RIFLE, AKIN, and pRIFLE) patients are classified according to either urine output or serum creatinine/estimated creatinine clearance (cCcl) criteria, whichever is worse.

The relative simplicity of the pRIFLE is attractive, but to be successful a clinical condition definition and severity classification system must also prove to be a sensitive and valid predictor of outcomes. Subsequent reports from Europe and North America have confirmed the pRIFLE's ability to identify children at greater risk for AKI and poorer outcomes in a variety of clinical settings, including burn injury and following cardiac surgery [11–13]. The potential utility of the pRIFLE is shown in another study of 103 consecutive patients admitted to a pediatric intensive care unit in Amsterdam [14]. Plotz and colleagues identified 60 patients with AKI by pRIFLE at a

Table 37.2 Pediatric-modified (pRIFLE) criteria

AKI category	Estimated creatinine clearance (eCcl)	Urine output
Risk	eCcl decrease by 25%	<0.5 mL/kg/h for
Injury	eCcl decrease by 50%	<0.5 mL/kg/h for 16 h
Failure	eCcl decrease by 75% or eCcl < 35 mL/min/1.73 m2	<0.3 mL/kg/h for 24 h or Anuric for 12 h
Loss	Persistent loss >4 weeks	
ESRD	End-stage renal disease defined As persistent failure >3 months	

eCcl estimated creatinine clearance

mean of 1.9 ± 1.6 days after admission. These patients had a five times greater risk of dying (25% vs. 5%) compared to patients without AKI. A recent report has demonstrated successful extension of the use of the pRIFLE to non-critically ill children at risk for AKI due to aminoglycoside exposure [15].

Based on these encouraging reports, widespread use of the pRIFLE should promote early recognition of AKI in pediatric patients and may prove useful in preventing progression of renal failure by identifying those patients who could benefit from earlier treatment. In addition, the widespread acceptance of pRIFLE will facilitate progress in research on this complex clinical condition.

The Epidemiology of AKI in Children

The incidence and prevalence of AKI varies according to the pediatric population studied, the definition of AKI employed, and the country of origin of the report, making comparative analysis difficult. For example, a retrospective study from Italy reported an incidence of AKI (defined as need for dialysis) of 2.7% in children undergoing cardiopulmonary bypass surgery [16], while another similarly designed study from the United Kingdom found an overall AKI incidence of 3.2 per 100,000 children [17]. A prospective study validating the Pediatric Logistic Organ Dysfunction (PELOD) score in pediatric intensive care units (PICU), demonstrated an incidence of AKI (defined as serum creatinine levels above 55–140 μmol/L depending on age of the child) of 129 per 1,000 admissions [18]. The absence of a common definition for pediatric AKI makes these and many other studies difficult to interpret or compare.

Pathophysiology of AKI

Several key pathophysiological processes thought to be important in the development of AKI are briefly described in the next section of this chapter. For a more detailed discussion the reader is encouraged to see the excellent reviews by Lamiere, van Biesen and van Holder [1], Boneventure and Weinberg [19] and Sutton et al. [20] upon which the following discussion is largely based.

Renal Blood Flow (RBF) Autoregulation

Autoregulatory mechanisms in the kidney act to preserve renal blood flow (RBF) and glomerular capillary perfusion pressure during periods of hypotension or hypoperfusion by adjusting afferent and efferent glomerular arteriolar vascular resistances to produce a pressure gradient at the level of the glomerular capillary bed. In states of hypoperfusion, the afferent arteriole dilates and the efferent arteriole vasoconstricts to maintain the transglomerular pressure gradient, thereby maintaining glomerular filtration.

Mediators that serve as regulators of renal blood flow by acting as vasoconstrictors include angiotensin II, thromboxane A2, and endothelin. Catecholamines may also exert a vasoconstrictive

effect indirectly by altering production of both vasoconstrictors and vasodilators. Unopposed vasoconstriction of both afferent and efferent renal arterioles eliminates the transglomerular pressure gradient necessary for glomerular filtration which is consequently dependent on afferent arteriolar vasodilatation. Prostaglandins appear to play a substantial role as renal vasodilators, along with nitric oxide (NO) produced locally by vascular endothelium. Diffuse endothelial damage, as is seen in states of inflammation such as sepsis, alter organ autoregulatory function through diminished NO production. Additionally, the macula densa has a direct reflex vasodilation effect on the afferent arteriole, the "myogenic reflex," which causes relaxation in response to the same stimuli as renin release. Finally, atrial naturetic peptide (ANP) released from myocytes in response to atrial stretch in states of volume overload acts to dilate the afferent arterioles and increase glomerular filtration.

The Classical Theory of Ischemic AKI

Ischemic acute renal injury ranges from mild prerenal azotemia to acute tubular necrosis and is caused by an absolute or relative reduction in renal perfusion resulting in reduction in glomerular filtration rate (GFR) and increases in serum creatinine and blood urea nitrogen levels. Oliguria occurs frequently, but not always. At first, compensatory mechanisms affecting RBF autoregulation attempt to restore renal perfusion and GFR to normal by vasodilation of the afferent arteriole and maintenance of fluid delivery to the distal nephron. In the setting of generalized hypotension, multiple potent systemic compensatory mechanisms are activated that establish a generalized milieu of vasoconstriction in an effort to restore blood pressure to normal. If renal hypoperfusion persists, vasoconstriction of the efferent arteriole occurs in an effort to maintain a constant glomerular capillary hydrostatic pressure. The intricate balance of autoregulatory vasoconstriction and vasodilation at the level of the glomerulus needed to sustain a reversible state of prerenal azotemia requires a symphony of physiologic forces acting in harmony to sustain renal function until normal perfusion and blood pressure can be restored.

When hypoperfusion is not corrected in time, RBF autoregulation fails, resulting in conversion of reversible prerenal azotemia to acute tubular necrosis. Persistent afferent and efferent arteriolar vasoconstriction is relatively unopposed as vascular relaxation mechanisms become less effective, leading to congestion in the outer medulla and causing tubular injury. Tubular cells swell, lose their brush border membranes and begin to exfoliate, resulting in tubular obstruction. Activation of endothelial cells by ischemic injury upregulates adhesion molecules, trapping leukocytes and platelets while launching a cytokine-driven inflammatory cascade that causes further endothelial injury and worsening ischemia.

Vascular Response to Ischemia and Cell Energetics

In normal function, the kidneys receive approximately 20–30% of cardiac output, and consume 7% of delivered oxygen. In times of physiologic stress, oxygen consumption by the kidney may increase dramatically with little means of increasing total renal blood flow, unlike myocardial blood flow, which under similar conditions may increase as much as tenfold to meet metabolic demands. These factors place the metabolically active nephron units at great risk for oxygen debt in the presence of global hypoperfusion and/or hypoxemia. Cortical nephrons are at the greatest risk for oxygen debt, perhaps because their blood supply is the most distal from the renal artery and they are the most metabolically active. During these periods of hypoxic/ischemic stress, kidney adenosine triphosphate (ATP) stores are consumed rapidly, and energy availability becomes dependent on local mitochondrial regeneration of ATP from adenosine diphosphate, along with neosynthesis and/or regeneration of ATP from purine precursors and adenosine monophosphate (AMP).

Cellular recovery from an ischemic event is dependent upon the length of the insult and the prior metabolic status of the patient. For example, an unstressed patient with normal cardiac output will recover renal function quickly following aortic or renal artery cross clamping with rapid local regeneration of ATP, while a patient in a low cardiac output state with a high metabolic demand, as is seen in sepsis, will not recover as rapidly from an acute ischemic event, in part because the ability to regenerate ATP from local precursors is diminished. During these periods, AMP is shunted away metabolically to form adenosine and inosine, from which regeneration of ATP requires extensive metabolic remodeling. Hence, energetic recovery is hampered, extending the injury period beyond the period of acute ischemia.

Free Radical Injury

During periods of recovery from oxidative stress, toxic by-products are created, such as oxygen free radicals. Highly reactive species, such as hydroxyl radical (OH) and superoxide anion (O_2–) cause direct injury to proteins by oxidizing amino acid residues and changing the structure or function of important enzymes. Additionally, the lipoprotein bilayer and ultrastructure of the cell is affected, causing cell rupture and an increase in cell membrane permeability, thereby reducing the cell's ability to isolate the cytosol from the surrounding milieu. Direct DNA damage can occur which limits the ability of a cell to perform important reparative functions. Hence, through a variety of mechanisms, further cell injury and death is incurred during the reperfusion phase after an acute ischemic event.

Tubular Cell Alterations

Renal tubular epithelial cells are highly metabolically active in order to provide the energy required to fuel active solute transport. The straight proximal segment of the renal tubule (S3 segment) is highly susceptible to injury, as it contains many Na+/K + ATPase-dependent transport channels. These channels are found predominantly on the basolateral surface of the cell, and are anchored in place by cytoskeletal elements. Injury to the cell, either through primary ischemia/hypoxia, or due to reactive oxygen species, causes the Na+/K/+ ATPase to mislocate through the fluid lipoprotein bilayer and come to reside on the apical surface. Additionally, energy needs for this ATPase are not met, and function is reduced. Particularly, damaging is the loss of active calcium transport that normally sequesters calcium predominantly in the extracellular fluid. This calcium gradient is also maintained via metabolically active transport channels, including a Ca++ ATPase. Protein migration from the basolateral to apical surface and reduced activity of Ca++ ion channels disrupt the polarity of the electrochemical gradient established by the tubular epithelium which is vital to normal function. This loss in polarity may explain the increased solute delivery to the distal nephron seen in AKI. Changes in cytoskeleton structure are also seen in arteries, arterioles, and in the vasa recta. These changes may play a role in the loss of autoregulation of renal blood flow.

Renal Tubule Obstruction/Backflow

Insults to the renal tubular epithelium cause cell death and diminished or absent regeneration. The resultant cellular debris sloughs off and enters the tubular lumen. In some cases, this debris is felt to obstruct the tubular lumen, especially in the inferior segment of the Loop of Henle thereby raising tubule intra-lumenal pressure and further reducing the gradient from the glomerular capillary to Bowman's space necessary for effective glomerular filtration. Due to the loss of the integrity of tubular epithelium, tubular obstruction may also cause back flow of ultrafiltrate into the surrounding interstitium. Extruded tubular fluid may alter the interstitial milieu substantially, affecting corticomedullary osmolarity and local electrochemical gradients, as well as causing direct cell injury and further propagating renal dysfunction.

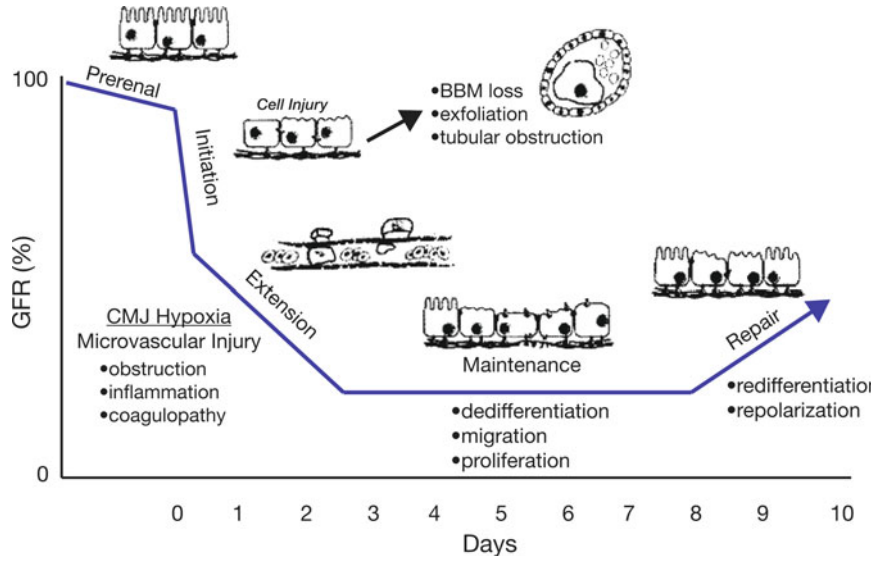

Fig. 37.1 Stages of ischemic acute kidney injury (Adapted with permission from Ref. [20]) depicting the relationship between the clinical phases and the cellular phases of ischemic acute renal failure (ARF), and the temporal impact on organ function as represented by the glomerular filtration rate (GFR). See text for details. *BBM* brush border membrane; *CMJ* corticomedullary junction

Summary of the Classical Theory

Taken together, there are classically four phases to the progression of parenchymal injury during ischemic AKI [20] (Fig. 37.1). The first phase ("initiation") follows the decrease in perfusion and ATP depletion caused by the acute ischemic insult. The second phase ("extension") is marked by ischemia reperfusion injuries that may cause further damage. During this phase, inflammation leads to prolongation of ischemia and aggravation of injury. Proximal tubules regenerate during the extension phase, but cells from the S3 segment of the same proximal tubule and from the medullary thick ascending limb can undergo necrosis and apoptosis. The differential effects of therapy if applied during the extension phase in experimental models supports the notion that severity of injury during this phase is closely correlated with prognosis of renal recovery. During the third phase ("maintenance"), necrosis and apoptosis persist via inflammation and cell injury. Finally, during the last phase ("recovery"), several mechanisms occur concomitantly resulting in repair, regeneration, and proliferation of injured cells. The degree and extent of injury likely determine whether or not the kidneys will recover fully, progress to end-stage renal disease, or leave the patient with chronic kidney disease.

The Clinical Syndrome of Acute Kidney Injury

The clinical syndrome of acute kidney injury may be divided into prerenal, intrinsic renal, and postrenal categories (see Table 37.3), and further subdivided into oliguric and nonoliguric forms. AKI may also be categorized as primary or secondary. AKI is primary when kidney dysfunction is due, for example, to acute glomerulonephritis or to hemolytic-uremic syndrome (HUS). AKI is secondary when it is caused by a systemic disorder such as sepsis or shock. In developed nations, primary AKI [23, 24] was once the most common form seen in children. In recent years, with advances in the treatment of other childhood pathologies, secondary AKI due to sepsis,

Table 37.3 Causes of acute kidney injury (Adapted from Refs. [21, 22])

Prerenal
Intravascular volume depletion
Bleeding, trauma
GI losses: diarrhea, vomiting
Renal losses: diabetes insipidus
Skin/mucous membrane losses: burns, fever (prolonged)
Third space losses: pancreatitis, hypoalbuminemia, crush injuries
Decreased cardiac output
Congestive heart failure
Cardiomyopathy
Sepsis
Drugs (overdose), anesthetics
Anaphylaxis
Renal vasoconstriction
Liver disease, sepsis, hypercalcemia
Drugs
Angiotensin-converting enzyme inhibitors
Nonsteroidal anti-inflammatory drugs
Renal (intrinsic)
Acute tubular necrosis (ATN)
Hemolytic-uremic syndrome (HUS)
Glomerulonephritis/rapidly progressive glomerulonephritis
Post-infectious glomerulonephritis
Systemic lupus erythematosis
Membranoproliferative glomerulonephritis
IgA nephropathy
Henoch-Schonlein purpura
Pulmonary-renal syndromes
Wegner's granulomatosis
Goodpasture's syndrome
Acute interstitial nephritis
Nephrotoxins
Drugs: aminoglycosides, cyclosporine A, amphotericin B, cisplatinum
Toxins: ethylene glycol, heavy metals, herbal remedies
Pigments: hemolysis, rhabdomyolysis
Postrenal (obstructive)
Ureter
Nephrolithiasis, sloughed renal papillae
Post-operative ureteric surgery
Hemorrhage, tumor
Bladder
Calculi, blood clots, bladder catheter obstruction
Neurogenic bladder
Tumor
Urethral
Valves, phimosis, strictures

nephrotoxic drugs, and renal ischemia in children undergoing hematopoetic stem cell transplantation, solid organ transplantation, or cardiac surgery represent the majority of cases of AKI [25, 26].

Demographics of AKI in Children

Geographical location and cultural traditions influence the causes of AKI in children (Table 37.3). In developing countries, infectious diseases are the main causes of AKI. Two studies from Nigeria observed that 71% of cases of AKI were secondary [27, 28] with malaria the most common cause. Other common causes were gastroenteritis and human immunodeficiency virus (HIV) nephropathy [28]. In India, HUS and glomerulonephritis still represent the predominant cases of AKI [23]. Some long standing local customs [29] such as use of herbal medicines in developing countries are associated with AKI. In recent years, herbal medicine-induced AKI is seen with increasing frequency in developed countries [30, 31].

Risk Factors and Associated Causes of AKI

Risk factors for AKI are varied and dependent on the patient population studied. In most circumstances, more than one risk factor is present prior to the development of AKI [32, 33].

Primary risk factors for AKI seen in adults are septic shock (40–50%) [32, 34, 35], other types of shock (e.g., cardiogenic, hypovolemic) [34], and nephrotoxic drugs [34]. An international multicenter prospective observational study of 29,269 critically ill adults identified increased risk for AKI in patients with septic shock (47.5%), cardiogenic shock (27%), hypovolemia (26%), and nephrotoxic drugs such as aminoglycosides, antifungal agents, calcineurin inhibitors, and angiotensin-converting enzyme inhibitors in cases of associated hypovolemia (19%) [4].

Information on risk factors for AKI in children is sparse and largely limited to single center reports. Sepsis, hypovolemia, cardiac dysfunction, cardiac bypass surgery, and nephrotoxic medications have been implicated [36, 37]. Sepsis, septic shock, and nephrotoxic drug-induced AKI stand apart from other causes due to the increasing frequency with which these entities are seen in the pediatric critical care setting. Drug-induced AKI accounts for up to 16% of

pediatric AKI [26], becoming more prevalent in sicker populations [38].

AKI induced by drugs occurs by two predominant mechanisms: direct toxicity to renal tubular epithelium, as is seen with aminoglycosides and amphotericin, and interference with autoregulatory mechanisms leading to unrestricted vasoconstriction and reduced renal blood flow, as is seen with nonsteroidal anti-inflammatory drug (NSAID) toxicity. Prevention of drug-induced AKI is more effective than any available therapy; recognition of high risk patients is therefore necessary. A detailed discussion of specific drugs known to cause AKI is beyond the scope of this chapter and may be found in several excellent reviews [38, 39].

Contrast Nephropathy

A syndrome of acute kidney injury associated with exposure to radiocontrast materials is known as contrast nephropathy. Contrast nephropathy results in AKI requiring hospitalization in 12 % of adult patients who have undergone imaging with contrast agents [40], and is associated with an increased risk of mortality in the year following the episode of AKI [41]. The incidence in children is unknown. Patients with chronic kidney disease or diabetes are at increased risk [41]. Volume and osmolality of contrast administered is directly associated with risk of AKI [42, 43], and non ionic agents are thought to be safer, especially in patients with chronic renal disease [44].

The pathophysiology of contrast nephropathy is still largely unknown. Severe vasoconstriction following contrast administration has been implicated [45, 46], as has direct cytotoxicity via oxygen free radical generation [47]. The rise in serum creatinine occurs 1–2 days after the imaging procedure and is usually unaccompanied by a decrease in urine output [48]. Dialysis is required in a minority of patients. No treatment exists other than support if AKI occurs. However, in recent years, attention has focused on prevention [38, 49]. A recent meta-analysis of prevention strategies recommends pre- and post-contrast intravenous hydration with bicarbonate-containing fluids and use of low or iso-osmolar contrast agents in the smallest volume possible in patients with pre-existing kidney disease who are at increased risk. N-acetylcysteine and ascorbic acid have also been suggested for use as free radical scavengers in the higher risk populations [44].

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is seen in patients undergoing the first cycle of chemotherapy where rapid tumor destruction occurs. It is more frequent in certain tumors such as lymphoma and acute lymphoblastic leukemia, with an incidence in these high risk patients approaching 10% [50]. Patients usually present with a metabolic disorder linked to the rapid cell turnover, such as hyperuricemia, hyperkalemia, hyperphosphatemia, and resulting hypocalcemia. Prevention and early recognition of patients at risk for TLS is critical. Avoidance of nephrotoxic drugs and volume depletion is also important [51], as is prevention of hyperuricemia with drugs such as allopurinol and more recently recombinant urate oxidase (Rasburicase®) [52, 53]. Early and aggressive use of Rasburicase® has all but eliminated TLS in some pediatric oncology centers. Urinary alkalinization to diminish uric acid precipitation in the tubule has been recommended, but should be used with caution as it may increase precipitation of calcium phosphate crystals. Targeting the urinary pH to around 7 is usually sufficient to aid uric acid elimination; alkalinization of the urine should be stopped once a normal serum uric acid level is reached [54]. When severe AKI occurs and RRT is required, intermittent hemodialysis will effectively reduce uric acid and phosphate levels; however, rebound often occurs. As a result, continuous renal replacement therapy (CRRT) is often recommended in this situation [54]. The need for RRT of any type usually can be avoided by prompt recognition of TLS risk and early Rasburicase® treatment.

AKI Due to Urinary Tract Obstruction

Obstruction to flow of tubular ultrafiltrate can cause significant renal dysfunction. Glomerular

filtration is a product of the balance between hydrostatic and oncotic pressure gradients at Bowman's space. Intratubular pressure is normally very low compared to the driving hydrostatic pressure across the glomerular capillary bed. However, with obstruction to tubular ultrafiltrate flow, the pressure in Bowman's space rises and becomes a significant inhibitor of glomerular filtration. Obstruction to ultrafiltrate flow may occur at the tubular level, as is seen with ATN or intratubular crystal precipitation, or may occur in the renal collecting system, ureter, bladder, or urethra. Unilateral obstruction may not be clinically evident due to compensatory alterations in function of the unaffected kidney [55]. However, in cases of bilateral obstruction or obstruction occurring in a solitary kidney, clinically significant changes in renal function will occur, leading to AKI.

Diagnosis of Pre-renal Versus Intrinsic Versus Postrenal AKI

Prompt determination of pre-renal or postrenal AKI should be the goal of initial evaluation in patients with acutely diminished renal function in the critical care setting, as these conditions are most amenable to therapy. The history and physical exam will be helpful in some cases, but in many critically ill patients history and physical findings can be difficult to interpret.

The ready availability of bedside ultrasonography has made determination of postrenal failure due to urinary tract obstruction the simplest of these diagnoses to make. All patients with AKI should have a renal sonogram performed within 12 h of onset of AKI, and in patients where the index of suspicion for obstruction is high, the sonogram should be obtained immediately. Delay in relief of urinary tract obstruction risks permanent renal injury. Similarly, prompt determination of renal tubular function indices such as the fractional excretion of sodium (FE_{Na}) or urea (FE_{UN}) can also be helpful in differentiating pre-renal from intrinsic AKI (see below). When history, physical examination, renal sonography, and renal tubular function indices suggest pre-renal AKI, attention can be turned to measures designed to increase renal perfusion. In general, the child with pre-renal AKI is not likely to benefit from the use of diuretics which may result in further renal damage. When signs and indices point to intrinsic AKI, attention should be turned to conservative management strategies (e.g., dietary and fluid restriction, adjustment of drug doses, etc.) in which judicious use of diuretics can be helpful while plans are made for possible renal replacement therapy (RRT).

Fractional Excretion of Sodium (FE_{Na})

FE_{Na} is easily calculated from a random urine sample. In cases of pre-renal AKI due to hypovolemia, most sodium should be reabsorbed in the proximal tubule and thus the FE_{Na} should be less than 1%. If the tubules are damaged as seen in acute tubular necrosis, the FE_{Na} is often in the range of 2–3% [56, 57]. The FE_{Na} can be calculated as follows [58]:

$$\mathrm{Fe_{Na}}(\%) = \frac{\text{Quantity of } \mathrm{Na^+} \text{excreted}}{\text{Quantity of } \mathrm{Na^+} \text{filtered}} \times 100$$

$$\mathrm{FE_{Na}}(\%) = \frac{\mathrm{U_{Na}} \times \mathrm{V}}{\mathrm{P_{Na}} \times \left(\mathrm{Ucr} \times \frac{\mathrm{V}}{\mathrm{Pcr}} \right)} \times 100$$

$$= \frac{\mathrm{U_{Na}} \times \mathrm{Pcr}}{\mathrm{P_{Na}} \times \mathrm{Ucr}} \times 100$$

where, the amount of Na excreted is equal to the product of urine concentration of Na (U_{Na}) and urine volume (V); the amount of Na filtered is equal to the product of the plasma concentration of Na (P_{Na}) and the glomerular filtration rate(Ucr × V/Pcr).

FE_{Na} can be less than 1% in conditions other than hypovolemia such as congestive heart failure, nephrotic syndrome or cirrhosis [56]. It can also be less than 1% in contrast nephropathy or heme pigment nephropathy [56].

Urine sodium and FE_{Na} are unreliable if diuretics are given. If measured, urine should be collected based on the half-life of the diuretics administered. For example, in the case of furosemide, the urine sample should be taken at least 6 h after the most recent dose. Caution should

also be exercised in the neonatal population when using this ratio. FE_{Na} is appropriately elevated in newborns making the transition from intra- to extra-uterine life. This ratio is even less reliable in those infants born preterm.

Fractional Excretion of Urea (FE_{UN})

Due to the limited value of the FE_{Na} in circumstances where diuretics have been administered, the concept of measuring fractional excretion of urea (FE_{UN}) has been proposed. In states of clinical dehydration, the urinary excretion of urea should also decrease [59]. The FE_{UN} should be less than 35% in hypovolemic states of prerenal AKI while in the case of ATN it should be above 50%. A hospital based prospective study conducted comparative analysis of FE_{Na} and FE_{UN} in their respective abilities to differentiate between prerenal AKI and acute tubular necrosis in the presence of diuretics [60]. In this study, FE_{UN} (<35%) had a better sensitivity and specificity (85% and 92%, respectively) in differentiating AKI due to pre-renal causes vs. ATN particularly where diuretics were employed. More importantly, a high positive predictive value of 98% was noted for the FE_{UN}. Studies evaluating FE_{UN} in children with AKI are limited.

Newer Biomarkers of AKI

Serum creatinine concentration, while an easily measured biomarker of AKI, is relatively insensitive, since a rise in creatinine signifies that damage has already occurred. Recent identification of a series of novel, increasingly specific and sensitive biomarkers has sparked renewed interest in the early diagnosis and management of AKI. The principal utility of these markers is to detect early signs of injury that could lead the clinician to alter management in order to prevent further damage to the kidneys. Early markers may also serve to predict severity of injury and help in monitoring the effect of an intervention. An excellent review of biomarkers in AKI has been recently published [61].

Biomarkers should ideally be noninvasive, reproducible, accurate, reliable, and have a high predictive ability (specific and sensitive). They should also be easy to perform, relatively inexpensive, and the results rapidly available. Several AKI biomarkers currently being evaluated will be discussed briefly.

Cystatin C

Cystatin C is a cysteine protease inhibitor that unlike serum creatinine is freely filtered, completely reabsorbed and catabolyzed by the tubular epithelial cells, and not secreted. It is stable and not influenced by body mass, gender, or age. More interestingly, its measurement is simple, automated, and easily available [62]. One prospective study in an adult population at risk for AKI showed that an increase of 50% in serum cystatin C level predicted AKI 1–2 days prior to a rise in serum creatinine [63]. Another study demonstrated that cystatin C had a better correlation with GFR than serum creatinine in critically ill adults [64]. Cystatin C levels were also able to predict the need for renal replacement therapy but could not differentiate among various causes of AKI. Cystatin C measurement has also been useful in kidney transplantation [65]. Cystatin C has also been demonstrated to correlate with AKI in children suffering from malaria [66]. So far, no prospective study of the value of cystatin C in predicting AKI in children has been published.

Kidney Injury Molecule (KIM-1)

KIM-1 is a transmembrane receptor that undergoes cleavage and is found in urine following ischemic injury [67]. In a small study, KIM-1 was able to differentiate ischemic renal injury from prerenal causes and chronic kidney disease [67]. To date, no large study has validated the predictive value of KIM-1 in AKI in adults. KIM-1 is also undergoing analysis and evaluation for its usefulness as a predictive tool for AKI in children.

Neutrophil Gelatinase–Associated Lipocalin (NGAL)

NGAL is a protein bound to gelatinase first described in neutrophils [68]. Circulating NGAL is normally reabsorbed at the level of the proximal tubule. Following ischemia, NGAL is secreted in the thick ascending limb and is found in the urine. A study in 71 children undergoing cardiopulmonary bypass surgery measured urinary NGAL 2 h post surgery [69]. Twenty children had an increase in urinary NGAL that preceded a rise in serum creatinine by 2–4 days. The specificity and sensitivity were excellent at 98 % and 100%, respectively. NGAL has been shown to be useful as a predictor of AKI in patients with HUS [70]. However, NGAL may be increased in patients with infections, limiting its value in diagnosing early AKI in septic patients. Urinary NGAL measurement has recently become commercially available.

Interleukin-18 (IL-18)

IL-18 is a pro-inflammatory cytokine cleaved to the mature form by caspase-1 and found in the urine following ischemia [71]. Many studies have observed an increase in urinary IL-18 that predicts an increase in serum creatinine in diverse patient populations [72–74]. It has also been used to differentiate among the diverse causes of AKI [72]. When combined with NGAL, IL-18 predicted the duration of AKI in children following cardiac surgery [69]. A commercial assay is available.

Other Biomarkers

Other markers such as sodium/hydrogen exchanger isoform 3 (NHE3), N-acetyl-β-glucosaminidase (NAG), and matrix metalloproteinase 9 (MMP-9) may be useful in early detection of AKI, but to date assays are not easily performed nor is there enough preliminary data to support their clinical use [67, 75].

Utility of Biomarkers of AKI

The value of these biomarkers in predicting AKI is under intense study. While urinary IL-18 and NGAL are good predictors of AKI in many clinical settings, in situations of complex pediatric patients their value may be diminished. Serum cystatin C measurement is promising, but large prospective studies in patient populations with complex diseases need to be performed before its utility can be fully established. Before these markers make a significant impact on clinical management in pediatric patients developing AKI, there is a need for simple, accurate, inexpensive, and rapid methods of measuring them. Additionally, prospective studies in diverse pediatric patient groups developing AKI are required.

Imaging the Kidneys in AKI

Renal Ultrasonography

Renal ultrasonography remains the renal imaging modality of choice for pediatric patients with newly diagnosed or worsening AKI. Resolution of anatomic detail by ultrasound (US) is generally excellent and avoids exposure to contrast agents or radiation. However, the US assessment of renal function is limited. In AKI, its primary role is to initially identify postrenal causes of AKI by demonstrating hydronephrosis [76–78]. Ultrasound abnormalities may not be appreciated in cases of prerenal AKI, but intrinsic AKI can be appreciated by a variety of anatomic changes. Measurement of renal size may give an indication of the chronicity of renal failure. Enlarged kidneys (standardized to patient's age and size) are suggestive of AKI due to medical renal diseases, such as acute interstitial nephritis, renal vein thrombosis, or infectious processes. Chronic kidney disease is suggested by the presence of small (for age/size) kidneys. An increase in echogenicity/echotexture may indicate chronic kidney disease in older children [79] but can be misleading in neonates [80].

Since blood flow to the kidneys is reduced but not eliminated in most cases of AKI, Doppler flow scanning may allow detection of abnormal or low renal blood flow states that can be indicative of renal artery stenosis or thrombosis [81, 82].

Nuclear Medicine Imaging in AKI

Radionuclide imaging can be employed to assess tubular function and blood flow [83] in AKI. However, significant delays in nuclide excretion by tubules can occur in both prerenal and intrinsic renal AKI, limiting its usefulness, unless blood flow is completely absent [84].

Computed Tomography (CT) in AKI

Computed tomography offers advantages when US is limited by technical issues. It is also valuable in trauma assessment when kidneys are involved [85, 86]. Non-contrast CT scans are valuable in demonstrating the renal pelvis and proximal ureter using sequential transverse sections to identify sites of ureteral obstruction. CT can also help identify primary causes of obstruction such as stones, tumors, or congenital abnormalities. Residual renal function may be identified using contrast-enhanced CT scans. In this setting, the pattern of a delayed and prolonged nephrogram may be demonstrated [87]. While technically useful, the risk of contrast nephropathy limits its usefulness as does the need for anesthesia in children for adequate studies.

Magnetic Resonance Imaging (MRI) in AKI

In recent years, magnetic resonance urography (MRU) has provided a significant advance in assessment of pediatric renal disease and AKI [87, 88]. MRU can identify collecting system morphology regardless of excretory function. It has also been utilized to effectively identify causes of postrenal AKI in terms of obstruction with a high sensitivity and specificity [89]. While both static and dynamic (gadolinium-enhanced) techniques are utilized in MRU evaluation [90], the use of gadolinium is contraindicated in patients with diminished renal function (eGFR < 30 mL/min/1.73 m^2) due to the risk of nephrogenic systemic fibrosis [91].

Renal Biopsy in AKI

Renal biopsy is considered the "gold standard" for diagnosing the underlying cause of AKI. This is especially true in pediatric patients where both prerenal and post renal causes of AKI have been excluded. Practically speaking, the benefits and risks of renal biopsy need to be carefully considered [92]. Risks include: infection, bleeding/transfusion, loss of kidney, inadequate sampling, and any anesthetic risks, depending on whether conscious sedation or general anesthesia is used. This is especially true in critical care situations where patients are already at increased risk for bleeding complications. Renal biopsy should be considered in situations where the underlying pattern of disease, in terms of history, biochemical, and imaging studies, is unclear, and the biopsy may shed light on the potential therapeutic options available. This is especially critical in the case of pediatric patients with the clinical presentation of rapidly progressive glomerulonephritis. Early diagnosis and appropriate intervention in this renal medical emergency may prevent progression from AKI to chronic kidney disease. Another important group to consider is pediatric renal transplant patients with AKI. Early biopsy diagnosis of acute rejection may direct therapeutic intervention and therefore prevent further decline in renal function [93–99].

Despite increased efforts to recognize and prevent AKI, progression to acute renal failure and loss (pRIFLE levels F and L) continues to occur with alarming frequency. The treatment of critically ill and injured children requires ready availability of renal replacement therapy (RRT) adaptable for use in children of all ages and sizes. In the following segments of this chapter, we review the three RRT modalities commonly used in pediatric patients with AKI: acute peritoneal dialysis, acute hemodialysis, and continuous renal replacement therapy.

Acute Peritoneal Dialysis

Acute peritoneal dialysis is still the modality of choice in many countries, especially in the developing world [100–102] as it is a relatively cheap form of dialysis which does not require sophisticated technical expertise or equipment. There is no necessity for highly trained dialysis or intensive care nurses to perform the procedure. Another of its major advantages over the filter-dependent procedures is that it avoids the need for vascular access, which can be a problem in infants and small children with multiple intravenous access for fluids and inotropes. It also avoids the need for blood priming in a child who is hemodynamically unstable, and large volumes of fluid can be removed slowly over a prolonged period, maintaining hemodynamic stability. Together with gradual correction of acid–base and electrolyte abnormalities, it is not associated with dialysis disequilibrium due to the relatively slower solute clearance, including nitrogenous waste products. Another advantage of acute peritoneal dialysis is the provision of calories with the use of hypertonic glucose solutions. This is important in the critically ill child where intravenous access for nutrition and maintenance of glycemia is also a problem. Moreover, in the coagulopathic child, anticoagulation can be avoided.

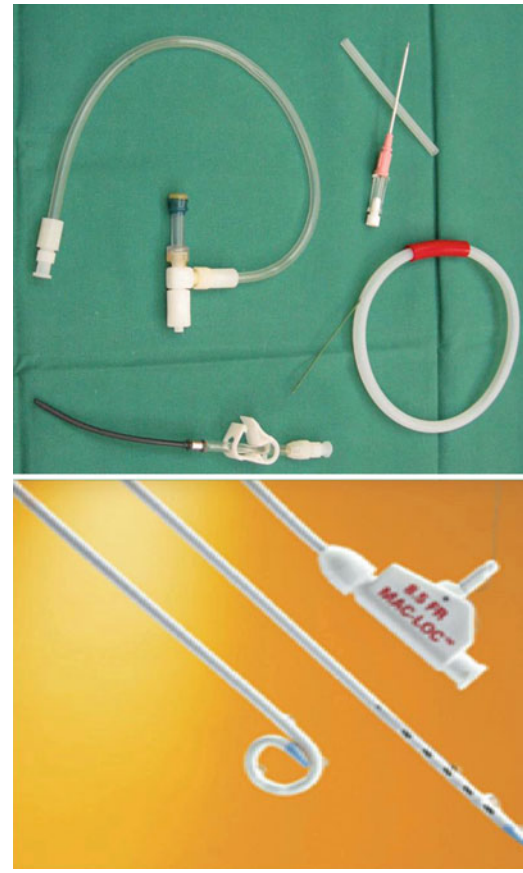

Fig. 37.2 (**a**) Peritoneal dialysis catheter using Seldinger technique for insertion. (**b**) Cook Mac-Loc Multipurpose Drainage catheter (CMMDC)

Acute Peritoneal Dialysis Catheters

Traditionally, acute peritoneal dialysis has been performed using semi-rigid stylet catheters requiring a trochar and canula method of insertion, the main advantage of which is the ease of insertion by the pediatric nephrologist without surgical intervention and general anesthesia [103]. However, this carries a high risk of perforation of viscus, especially in neonates, both at the time of insertion and with increasing dialysis duration. In order to minimize the risk of bowel perforation, infusing 10–20 mL/kg normal saline to create ascites prior to catheter insertion is useful. The incidence of peritonitis is highest with the semi-rigid catheter, particularly if it has been kept in place for longer than 72 h [103].

The newer techniques are performed with soft catheters where a Seldinger technique is utilized to insert the catheter over a guide-wire (Fig. 37.2a). This is a very useful technique, especially in infancy as it carries a minimal risk of dialysate leakage since no incision is required for the catheter insertion. Consequently, the risk of peritonitis is less and these catheters can be kept for up to 5 days without any complications [104]. Recently, another catheter, the Cook Mac-Loc Multipurpose Drainage catheter (CMMDC) (Fig. 37.2b) has been shown to be useful in infants and children, with a longer complication-free period, similar to surgically placed Tenckhoff catheter [105]. In low birth weight infants less than 1.5 kg where the length of these catheters may be excessive, a 14-gauge intravenous plastic cannula can be used as a dialysis catheter.

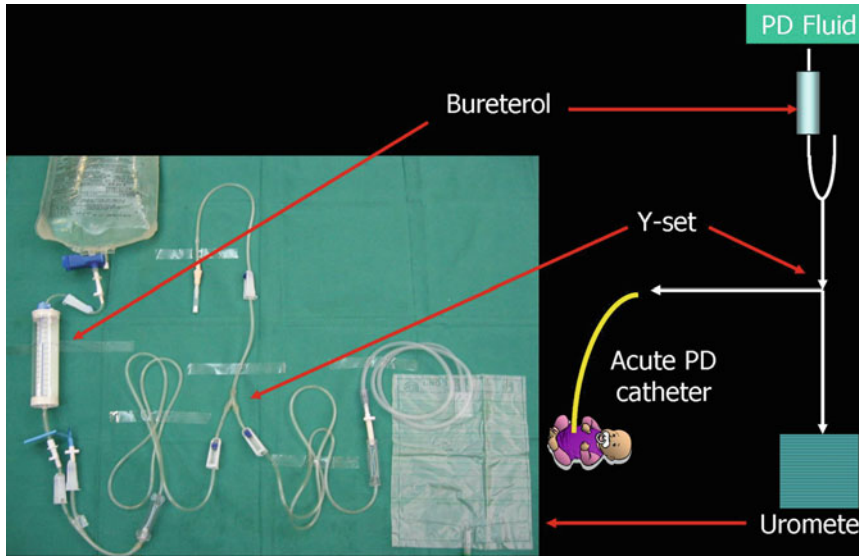

Fig. 37.3 Manual peritoneal dialysis setup for infants and young children

In high risk patients, especially those with bowel dilatation, direct surgical insertion using a single cuffed catheter to avoid perforation is safer. In fact, many cardiovascular surgeons prophylactically place a Tenckhoff catheter during cardiac surgery in infants. Some units use tunneled double cuffed permanent Tenckhoff catheters, since a good immediately functioning catheter with adequate drainage is almost assured. The main disadvantage of tunneled cuffed permanent catheters is the limitation of dialysate fill volumes in the initial week post-catheter insertion in order to avoid leakage [104]. These soft catheters pose a minimal risk to perforation of bowel or other intraperitoneal structures, and have a lower risk of peritonitis. In addition, if automated cyclers are used for the dialysis procedure, these catheters are preferable as they are associated with less technical malfunction resulting in machine alarms.

Technique of Acute Peritoneal Dialysis

Peritoneal dialysis is usually carried out manually in premature babies and small infants. Because of the small dialysate volumes involved, use of automated volumetric cyclers is often not possible due to the excessive "dead space" in the cycler tubings, resulting in poor drainage. The manual dialysis setup involves a Buretrol device, which is basically a sterile graduated cylinder, to which the dialysate bag is attached to one end, while the other end is connected to the patient's peritoneal catheter via a Y-set (Fig. 37.3). The other limb of the Y-set is connected to the drainage line, which drains into a graduated drain such as a urometer, so that the effluent volume can be accurately measured. This is very important in young infants in order to monitor the ultrafiltration closely so as to prevent fluid overload. Preassembled manual exchange systems for infants are available worldwide, but may be expensive in developing countries.

The availability of automated cyclers (Fig. 37.4) that can deliver small exchange volumes of less than 100 mL has largely supplanted the manual acute procedures in young children and infants, limiting nursing effort and repeated opening of the catheter. These cyclers automatically deliver the fill volume, which is the amount of fluid delivered to the peritoneal cavity during each dialysis cycle. After an appropriate dwell time that has been programmed into the cycler, the drain phase occurs, and the ultrafiltrate volume is computed from the difference between the

Fig. 37.4 Automated cyclers for peritoneal dialysis

drain and fill volumes at each cycle. The movement of fluid in and out of the patient is mediated either by gravity or a pump-driven system, or a combination of the two, with accurate delivery of the fill volume and measurement of drainage and ultrafiltrate volume. Another advantage of automated cyclers is the heater platform for warming the peritoneal dialysis solution before inflow into the abdomen, to prevent discomfort and promote solute transport.

Acute Peritoneal Dialysis Prescription

The dialysis prescription for acute peritoneal dialysis comprises four major components, the exchange volume, dialysate composition, individual cycle time consisting of fill, dwell, and drain, and total length of the dialysis session. For acute peritoneal dialysis, the target exchange fill volume for adequate dialysis in terms of fluid and solute clearance, without the risk of leakage, is 30 mL/kg. However, smaller initial volumes of 10 mL/kg should be used for at least 24–48 h, if there is a risk of leakage, for example if the incision is too wide or a tunneled cuffed catheter is used.

In manual dialysis, the inflow time, which is the time taken for the dialysate fill volume to flow into the peritoneal cavity by gravity, is about 10–15 min. This may be influenced by the height of the dialysate bag above the abdomen, the inflow volume and inflow resistance, such as kinking of the catheter. In automated peritoneal dialysis, dialysate is pumped into the abdomen with an inflow time of about 5 min. The dwell time is the time from the end of inflow to the beginning of the drain and should be at least 30 min, where the gradient for solute and fluid removal is optimal [106, 107]. This is followed by the drain period, which usually takes about 20–30 min. In manual dialysis, the drain occurs entirely by gravity, and therefore the drain time and volume is dependent on the vertical distance of the urometer below the abdomen. If the intraperitoneal fluid reservoir is too low, drainage may also be poor, hence increasing the fill volume may be indicated. It is important to ensure complete drainage, that is, the drain volume should exceed the fill volume, so as not to aggravate the fluid overload state and respiratory compromise, especially in infants with acute kidney injury.

Table 37.4 Peritoneal dialysis fluid composition

Content	Lactate-based (mmol/L)	Bicarbonate-based (mmol/L)
Dextrose	1.5% 2.5% 4.25%	0.0% 1.5% 2.5% 4.25%
Sodium	132	140
Chloride	96	110
Bicarbonate	0	35
Calcium	1.8	1.8
Lactate	40	0
Potassium	0	0
Magnesium	0.75	0.75

To stabilize the patient, hourly exchanges for 48–72 h are usually required, to remove the accumulated solutes and excess fluids. Subsequently, if the patient requires maintenance dialysis, the dwell times can be extended, similar to chronic peritoneal dialysis, with increasing volumes up to 40–45 mL/kg if cuffed catheters have been used. The peritoneal dialysis should be continued until the urine output improves, indicating recovering renal function.

Commercially available peritoneal dialysis solutions are usually dextrose-based, in concentrations of 1.5%, 2.5%, and 4.25% (Table 37.4). The initial dialysate composition to ensure adequate ultrafiltration is with 2.5% dextrose. In neonates where there may be a problem with hyperglycemia, it may be more appropriate to use an intermediate composition of 2.0% by mixing equal volumes of 1.5% with 2.5% dextrose infused through two Buretrols connected via the Y-set. Higher dextrose concentrations can be substituted depending on the amount of ultrafiltration needed, and the patient's hemodynamic parameters. As the standard peritoneal dialysis solutions are lactate-based, this may be a problem in patients with hepatic dysfunction and hemodynamic instability with lactic acidosis. Hence bicarbonate-based solutions which are available commercially can be used in place of the lactate-based solutions (Table 37.4), with addition of the appropriate amount of dextrose, if necessary, to obtain the desired concentration.

Following insertion of the acute peritoneal catheter, heparin should be added to the dialysate solution to prevent catheter blockage by fibrin clot. The initial dose of heparin should be 250 U/L dialysate. If the drain outflow is heavily blood-stained, this can be increased to a maximum of 1,000 U/L dialysate. The heparin is not absorbed systemically, and will therefore not be a problem in coagulopathic patients. If the patient is not on systemic antibiotics, intraperitoneal antibiotics such as cefazolin should be added prophylactically to cover for gram positive skin commensals. As patients on continuous peritoneal dialysis are at risk of developing hypokalemia, potassium should preferably be added to the intravenous fluid regimen if they are not feeding, rather than to the dialysate to avoid frequent bag changes due to changing orders. Potassium can be added to the dialysate, if the hypokalemia is severe enough such that the maximum safe concentration of potassium infusion will be exceeded.

Problems of Acute Peritoneal Dialysis

Although acute peritoneal dialysis has certain advantages over filter-dependent procedures, there are several problems that make this technique difficult especially in the small infant. Firstly, catheter problems are common such as catheter leakage into the subcutaneous tissue and hernia sites especially inguinal. Often the presence of a congenital diaphragmatic "hole" results in problematic pleural effusion. In fact, patients after cardiothoracic surgery may have a diaphragmatic pleuroperitoneal communication which results in a large pleural effusion once peritoneal dialysis is initiated. Drainage is often poor because of catheter malposition, kinking, omental wrapping, and fibrin clot. This is especially true for the relatively small bore non-cuffed peritoneal catheters in infants. Inadequate drainage may also be due to constipation. Patients may require bowel cathartics to try to improve drainage, and sometimes, even manipulation of the catheter position may be required. If a fibrin clot is suspected, flushing with heparin and in recalcitrant cases,

fibrinolytic agents such as urokinase, may be useful. Bowel perforation is a serious problem particularly with use of semi-rigid catheters, and is suspected when the peritoneal effluent is contaminated with feces or is blood-stained. Severe abdominal pain and shock may occur, and the catheter has to be removed, with bowel repair and treatment of sepsis.

Poor ultrafiltration is another concern, especially in critically ill infants due to the low fill volume with inadequate fluid reservoir intraperitoneally. Often it is not possible to increase the dwell to the desired volume, as many of these critically ill infants have acute respiratory distress syndrome, and the peritoneal fluid volume results in splinting of the diaphragm. In fact, during the inflow phase, these infants often desaturate, and require increase in the ventilatory pressures. As a result, there is poor ultrafiltration, which aggravates the fluid retention, worsening the respiratory distress. These ill patients are often hypotensive requiring multiple inotropic support. The resultant decrease in bowel perfusion due to vasoconstriction of the mesenteric vessels also contributes to the poor ultrafiltration. Additionally, there is a decrease in the osmotic gradient, because of increased absorption of glucose from the dialysate in this age group, resulting in poor ultrafiltration. There is an increased risk of peritonitis with the use of non-cuffed catheters, especially if there is leakage around the exit site. With the use of higher dialysate dextrose concentrations, hyperglycemia can be a problem, and may require insulin administration. In the severely ill child, lactic acidosis may be difficult to control due to the slower solute clearance, and may be aggravated by the lactate in the dialysate.

The slow and not very efficient removal of all types of molecules in acute peritoneal dialysis, as well as the unreliable ultrafiltration represents a considerable drawback compared to other modalities of acute dialysis especially the continuous venovenous hemodiafiltration. In fact, these problems are magnified in the young infants, especially neonates due to the small dialysate volumes involved. Hence acute peritoneal dialysis may not provide adequate clearances in the hypercatabolic patient with severe hyperkalemia, hyperphosphatemia, or inborn errors of metabolism such as hyperammonemia or organic acidemias. Therefore acute peritoneal dialysis is currently best for "uncomplicated" or medical causes of acute renal failure such as glomerular diseases, drug-induced acute tubular necrosis, ischemic acute tubular necrosis if hemodynamically stable, hemolytic-uremic syndrome, infections such as leptospirosis, and snake bites. On the other hand, absolute contraindications to peritoneal dialysis include recent abdominal surgery and necrotizing enterocolitis, common causes of acute kidney injury in neonates and infants, as well as the presence of a ventriculo-peritoneal shunt, because of the high risk of peritonitis.

Optimal Dosing in Acute Peritoneal Dialysis

The clearance of small solutes is lower with acute peritoneal dialysis over 24 h, than with a 4-hour hemodialysis session [108]. Thus the question often arises as to whether dialysis adequacy can be improved in prescribing acute peritoneal dialysis. It is increasingly recognized that the delivered dose of dialysis influences patient outcomes in acute renal failure [109–111]. In uremia, the goal therefore is to aim for maximum possible clearance to compensate for catabolic stress, utilizing continuous peritoneal exchange. As fluid overload is often the critical problem in premature infants and neonates, achieving adequate ultrafiltration reliably is also important. The obstacles to achieving this target using the conventional method of acute intermittent peritoneal dialysis include relatively poor solute clearance due to limitations in dwell volume and intermittent nature of the dwell, and the unpredictable ultrafiltration rate due to technical problems with drainage, associated hypotension requiring multiple inotropic support and increased intra-abdominal pressure. Therefore methods to increase dialysis adequacy include chronic equilibrated peritoneal dialysis, high-volume peritoneal dialysis, tidal peritoneal dialysis, and continuous flow peritoneal dialysis (Fig. 37.5) [112].

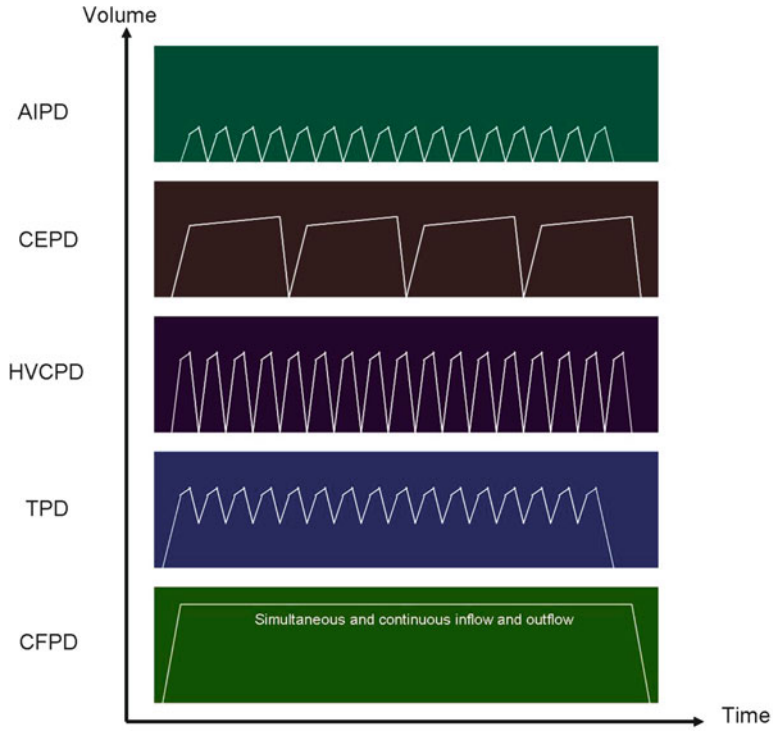

Fig. 37.5 Techniques of acute peritoneal dialysis. *AIPD* acute intermittent peritoneal dialysis. *CEPD* chronic equilibrated peritoneal dialysis. *TPD* tidal peritoneal dialysis. *HVPD* high-volume peritoneal dialysis. *CFPD* continuous flow peritoneal dialysis

Continuous Equilibrated Peritoneal Dialysis

Continuous equilibrated peritoneal dialysis is similar to continuous ambulatory peritoneal dialysis, in that it requires a larger fill volume than normally used for acute intermittent peritoneal dialysis, approximately 40–45 mL/kg or 1,200 mL/m^2, with long dwells of 2–6 h. The clearance of small molecules will probably be similar to acute intermittent peritoneal dialysis, however middle molecule clearance is possibly higher due to the long dwells.

High-Volume Continuous Peritoneal Dialysis

High-volume continuous peritoneal dialysis has been shown to provide a dialysis dose approaching that of high dose continuous renal replacement therapies or daily hemodialysis in adults. This modality of dialysis is designed to achieve high small solute clearances, and in adults involve a fill volume of 2 L, with very frequent exchanges between 18 and 24 exchanges over a 24-hour period. It is carried out through a Tenckhoff catheter, using an automated peritoneal dialysis cycler, with a prescribed Kt/Vurea of at least 0.65 per session. Studies on high-volume continuous peritoneal dialysis have demonstrated a delivered Kt/Vurea per session of approximately 0.55, and a weekly Kt/Vurea of greater than 3.0 [113]. Additionally, there was an increase in the solute reduction index over conventional acute peritoneal dialysis. Unfortunately, there is no satisfactory measure of dialysis adequacy in acute kidney injury [114]. The role of Kt/Vurea as an index of adequacy is controversial in the hypercatabolic patient with acute kidney injury, as the urea volume of distribution is variable, and exceeds total body water [115].

Tidal Peritoneal Dialysis

One method of increasing dialysis adequacy in mild-moderate hypercatabolic patients with acute kidney injury is to perform tidal peritoneal dialysis. Tidal peritoneal dialysis involves leaving a

Table 37.5 Comparison of peritoneal urea and creatinine clearances and ultrafiltration rates in continuous flow peritoneal dialysis

	Dialysate flow rate (mL/min)	Peritoneal urea clearance (mL/min)	Peritoneal creatinine clearance (mL/min)	Ultrafiltration rate (mL/min)
Raj et al. [20]: single lumen catheter with single needle device	141	26.5	24.1	3
Mineshima et al. [23]: double lumen catheter	100	14.1	No data	2.5
Cruz et al. [24]: 2 separate catheters	200	40	28	13.4
Freida et al. [25]: 2 separate catheters	100–150	21–36	13–33	2–8
Amerling et al. [26]: 2 separate catheters	200–300	25–75	No data	12–17

large volume of dialysis solution, at least 30% of the fill volume (15 mL/kg), in the peritoneal cavity throughout the dialysis session in order to optimize solute clearance. The tidal drain volume is replaced with fresh dialysate, which is the tidal fill volume. By increasing the number of tidal volumes, small solute clearance can be increased, and because of the longer duration of contact between dialysate and peritoneum, dialysis efficiency is improved further in terms of middle molecule clearance.

In a prospective cross-over study in adult patients with acute kidney injury, tidal peritoneal dialysis was able to produce higher solute clearances as shown by the clearance of creatinine, urea, potassium, and phosphate, at the expense of greater protein loss, compared to continuous low-dose equilibrating peritoneal dialysis [116]. Ultrafiltration was better in the patients receiving tidal dialysis, probably related in part to the lower dextrose absorption. With the smaller volumes required in children, tidal peritoneal dialysis is an attractive dialysis option in acute kidney injury, especially in patients who are unstable with filling and draining [117].

Continuous Flow Peritoneal Dialysis

Another novel method to improve peritoneal clearances is continuous flow peritoneal dialysis where the dialysate flow rate is increased tremendously, up to a range of 100–300 mL/min corrected for body surface area in a single pass, by synchronized inflow and outflow of sterile dialysate, or by recirculating a single large exchange through an external regenerating apparatus. Two catheters are required, one in the pelvis and one directed toward the diaphragm to achieve maximal port separation. Alternatively, an efficient dual lumen catheter with minimal intraperitoneal recirculation could be used. Kinetic studies have shown that increasing the dialysate flow rate in continuous flow peritoneal dialysis will increase peritoneal solute clearances. Higher urea clearances 2–5 times more than standard peritoneal dialysis, with peritoneal urea clearances approaching 25–60 mL/min as compared to 17 mL/min, as well as higher ultrafiltration rates of more than 10 mL/min have been achieved (Table 37.5) [118–123]. Unfortunately, it is also associated with massive protein losses.

Continuous flow peritoneal dialysis has been used to treat patients with hypercatabolic acute kidney injury, using the hemofiltration machines to deliver and even to regenerate the dialysate.

Acute Intermittent Hemodialysis

In many countries, intermittent hemodialysis is the mainstay of dialysis for acute kidney injury in older children, where it is performed in adult centers. Its main advantage is the rapid ultrafiltration and solute removal. It is therefore indicated in the emergency treatment of toxic poisonings such as lithium intoxication, severe electrolyte imbalance such as hyperkalemia, metabolic abnormalities such as hyperammonemia, tumor lysis syndrome, and acute fluid overload. In infants with severe hyperammonemia or children with lithium intoxication, hemodialysis results in rapid reduction of

the solute below toxic levels [124, 125]. Unfortunately, once hemodialysis is terminated, there is usually a rebound of the toxic solute in the serum, which can be detrimental. The patient is often continued on continuous venovenous hemodiafiltration to prevent this rebound, once the initial hemodialysis procedure is completed [125, 126].

Acute intermittent hemodialysis is suitable for hemodynamically stable patients who can tolerate rapid fluid shifts. This is a versatile modality as it allows for ultrafiltration without solute removal, as well as adjustment of the dialysate bath to treat electrolyte abnormalities such as hypernatremia. Moreover, because of the intermittent nature of the dialysis, even patients in the intensive care unit can be mobilized for other procedures. Systematic reviews in adult patients have shown that in hemodynamically stable patients, the continuous forms of renal replacement therapies do not appear to have a survival advantage over acute hemodialysis [127–129].

Vascular Access

The delivery of an adequate dialysis dose is crucial to the survival of patients with acute kidney injury, thus a good functional vascular access is an essential component for adequate renal replacement therapy. However in infants and children, vascular access may be a problem. For acute dialysis, vascular access is generally obtained through a double lumen hemodialysis catheter. This can be inserted either in the femoral, internal jugular, or subclavian veins. The former two access sites are preferred, as subclavian catheters have been associated with venous stenosis at the subclavian-internal jugular junction. In infants, the minimum catheter size for adequate blood flow is a 7-French double lumen, or 5-French single lumen where two catheters will be necessary (Table 37.6). It is preferable to use the jugular veins, as femoral access is often complicated by high intra-abdominal pressure. Alternatively, umbilical veins can be used for catheter access. Patient characteristics (coagulopathy, previous surgeries, altered local anatomy, cardiopulmonary reserve capacity), availability of insertion site in a "heavily catheterized" critically ill child, operator's skills and experience, and risk of complications may influence the choice of catheter placement. For example, a femoral vein placement is favorable for a patient on high-frequency oscillatory ventilation as this will be technically easier and has no risk of pneumothorax associated with internal jugular venous access. In patients with limited vascular access, a triple-lumen catheter is preferred if the size is appropriate. The hemodialysis catheters can be inserted at the bedside using the Seldinger technique, or by the interventional radiologists or surgeons in the case of tunneled permanent catheters.

Table 37.6 Appropriate size of hemodialysis catheters based on body weight. F: French size

Body weight (kg)	Single lumen	Double lumen (F)
Neonate	5 F	5.0–7.0
3–6		7.0
6–15		8.0
>15		9.0
15–30		10.0
>30		11.5

Dialyzers

The membrane properties of the dialyzer such as membrane thickness, pore size, and density affect dialysis efficiency, with varying clearances for small and middle molecular weight solutes. The total area of the dialyzer is important when choosing the appropriate size for the patient. Dialyzer surface area should approximate the size of the patient [130].

Another important property of the dialysis membrane is biocompatibility. Currently, two types of membranes are in use, cellulose-based and synthetic. Cellulose membranes can be broadly classified into unsubstituted such as cuprophan membranes and substituted such as cellulose acetate and cellulose diacetate. Cuprophan membranes have been reported to activate complement, accompanied by upregulation of neutrophil adhesion molecules and neutrophilic infiltration, resulting in dialysis-induced

renal injury [131–134]. However there is some controversy as to whether synthetic membranes such as the polysulfone membranes, are better than cellulose-based membranes. In earlier randomized controlled studies, adult patients with nonoliguric acute kidney injury who were using dialyzers with biocompatible membranes appeared to have better survival rates and renal recovery [135]. On the other hand, in three separate meta-analyses in adult patients with acute kidney injury, there is conflicting data as to whether synthetic membranes confer a survival benefit [136–139]. Current opinion is that the use of biocompatible synthetic membranes does not appear to confer any significant clinical advantage either in terms of mortality or recovery of renal function, except for the subgroup comparison with cuprophan membranes [138, 139].

Another consideration in the choice of dialyzers is the use of low or high flux membranes. High flux membranes have larger pores resulting in greater clearances of higher molecular weight solutes, and at the same time, carry the risk of back transport from the dialysate, of water-borne solute contaminants. In a systematic review comparing the use of high flux and low flux membranes in acute kidney injury in adults, there was no difference in the risk of mortality or dialysis dependence in survivors [139]. However, in another meta-analysis, there appeared to be a significant advantage in terms of recovery of renal function, with the use of high flux membranes [138].

High-cut-off-point membranes with a nominal cut-off point of 60 kD, have greater cytokine clearance and enhanced adsorption properties than conventional high flux dialyzers [140], and have been developed for use in septic patients with acute kidney injury [141, 142]. These membranes are made from polyamide/polyarylethersulfone, polysulfone, or cellulose triacetate. Treatment using high-cut-off-point membranes has been shown in animal models of sepsis to have beneficial effects on immune cell function and survival [143]. Preliminary clinical studies show that use of these membranes in adult patients with acute kidney injury was associated with decreased need for vasopressor therapy, with no reports of serious adverse effects [142].

Another important consideration is the use of the synthetic polyacrylonitrile (AN69) membranes which can lead to the bradykinin release syndrome [144]. Here the patient develops acute anaphylaxis associated with acute hypotension, tachycardia, and a drop in the central venous pressure. This is immediately reversible by removing the system, and can be avoided by avoiding priming with blood banked blood. Alternatively, the blood prime can be dialyzed against the bicarbonate dialysate for at least an hour prior to connection to the patient [145, 146].

Hemodialysis Prescription

All children should be dialysed using volume controlled machines and bicarbonate dialysate. Factors affecting the individual hemodialysis prescription include the extracorporeal circuit volume, the dialyzer size, blood flow rate, dialysate flow rate, ultrafiltration required, dialysate composition, anticoagulation, and length of sessions.

The total volume of the extracorporeal circuit includes the volume of the tubing, comprising both the arterial and venous lines, and the volume of the dialyzer, and should be less than 8% of the patient's blood volume calculated as 70 mL/kg for children, and 80 mL/kg for infants. If the extracorporeal blood volume exceeds 10–15% of the patient's total blood volume, a blood prime is recommended [147]. Depending on the hemodynamic status of the patient, the lines may still need to be primed with 0.9% saline or 5% albumin, even if this volume is not exceeded.

Blood flow rate depends on the size of the vascular access and is in the range of 5–7 mL/kg/min, up to a maximum of 300–400 mL/min [130]. Dialysate flow rate should be at least 1.5 times greater than the blood flow rate, in order to maximize diffusion gradients of solutes. Aim for urea clearances of 2–3 mL/kg/min; however, in order to avoid dialysis disequilibrium, urea clearances should be gradually increased over three sessions, starting at 30% of target. Ultrafiltration targets should not exceed 0.2 mL/kg/min. Other factors that must be considered are patient's ability to tolerate rapid fluid shifts, the need for vasoactive

Table 37.7 Heparinization protocol

Type of heparinization	Loading dose (U/kg)	Maintenance dose (U/kg/h)
Regular	50 (Adults: 1,500 U)	30–50 (Adults: 750 U/h)
Low-dose	>15 kg: 10–20, ≤15 kg: 5–10 (Adults: 1,000 U)	5–10 (Adults: 500 U/h)

substances to maintain blood pressure and total fluid removal goals.

Dialysate composition should be tailored based on the patient's current electrolyte status. Current hemodialysis machines use a sophisticated proportioning system to mix dialysate online from commercially available concentrates. The final concentrations of sodium, calcium, potassium, and bicarbonate can be changed according to the clinical situation.

Heparin is the most commonly used anticoagulant for intermittent hemodialysis. A loading dose of heparin may be given at the start of dialysis followed by a maintenance dose (Table 37.7). To monitor therapy, the activated partial thromboplastin time (aPTT) or activated clotting time (ACT) is used. The aPTT should be kept at 1.2–1.5 times the baseline, and the ACT between 120 and 180 s.

In coagulopathic patients, heparin-free dialysis can be performed by intermittently flushing the circuit with 0.9% saline. The filter pressure should be monitored, and dialyzer inspected for early clot formation. Unfortunately, this method not only adds to the ultrafiltration target, but also results in a decrease in the dialysis efficiency within the stipulated time period.

For patients with heparin-induced thrombocytopenia, low-molecular-weight heparins have been recommended [148]. Alternative anticoagulation protocols for patients with coagulopathies include regional anticoagulation of the circuit with a heparin-protamine protocol, regional citrate, thrombin antagonists such as hirudin and argatroban, and platelet inhibiting agents such as prostacyclin and nafamostat [149].

Problems of Acute Intermittent Hemodialysis

Hemodialysis in young children is notoriously difficult in view of the smaller blood volumes present. This problem is accentuated in the critically ill child, where inotropic support is usually required to support the systemic blood pressure. Moreover, these children often have acute respiratory distress syndrome and are hypoxemic, or they have other associated clinical problems such as congestive heart failure and cerebral edema. Therefore maintenance of an adequate blood pressure in these children is critical to alleviate tissue hypoxia.

Technical advances in the delivery of hemodialysis have dramatically reduced the propensity to cause intradialytic hypotension. The use of volume-controlled dialysis machines, biocompatible synthetic dialysis membranes, and bicarbonate-based dialysate have helped decrease the incidence of intradialytic hypotension. In adult studies, it has been demonstrated that priming the circuit with isotonic saline, discontinuing vasodilator therapy, keeping the dialysate sodium greater than 145 mmol/L and setting the dialysate temperature to below 37°C result in lesser hemodynamic instability and better outcomes [150]. Additionally, use of in-line hematocrit monitoring to minimize abrupt changes in extracellular volume is useful in young children with hemodynamic instability where large acute changes in extracellular volume are not well tolerated [151]. This method of performing intradialytic noninvasive blood volume monitoring provides an estimate of the postdialysis refilling rate (Fig. 37.6), which in turn reflects the status of the intravascular volume.

Rapid hemodialysis using dialyzers with larger surface areas, in patients with very high plasma urea concentrations may also result in the dialysis disequilibrium syndrome, characterized by neurological symptoms such as fatigue, headache, nausea, vomiting, altered consciousness, convulsions, and coma [152]. Measures to prevent the disequilibrium syndrome include decreasing the initial dialysis dose, increasing dialysate sodium concentration (143–146 mmol/L), and administration of osmotically active substances such as intravenous mannitol (0.5–1 g/kg) to prevent rapid osmolar shifts that can cause cerebral edema.

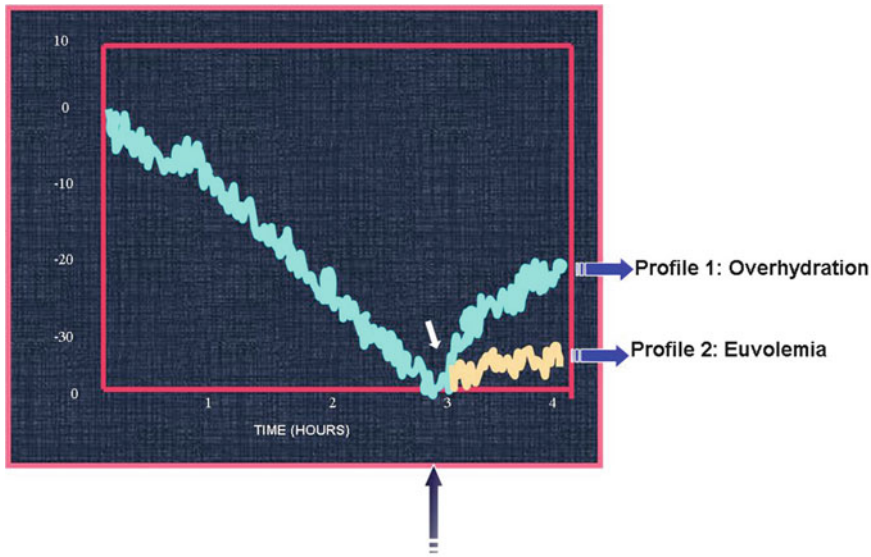

Fig. 37.6 Intradialytic noninvasive blood volume monitoring: pattern of post-dialysis refilling rate. Profile 1: overhydration. Profile 2: euvolemia

The smaller blood volumes in infants and young children place them at risk for blood loss due to clotting of the dialyzer. However, when compared to continuous renal replacement therapies, anticoagulation in intermittent hemodialysis is needed only for a limited period, or may be dispensed with altogether, whereas with continuous renal replacement therapy, there is a continuous struggle between filter coagulation and bleeding.

Infection of the catheter exit site is another potential complication in patients on hemodialysis. In the event of signs of infection such as fever, the appropriate cultures should be taken, and empiric antibiotics started.

Optimal Dosing in Acute Intermittent Hemodialysis

The prescription for acute intermittent hemodialysis comprises the dose delivered per session and the frequency of the sessions. Studies in adults have shown that in acute kidney injury, a Kt/Vurea greater than 1.2 was associated with improved survival in patients with intermediate severity of illness, but did not influence outcomes in the severely ill patients [153]. In an earlier study, daily hemodialysis was associated with a significant reduction in mortality, fewer hypotensive episodes during hemodialysis, and more rapid resolution of acute renal failure [154]. However, the delivered dialysis dose was low (Kt/Vurea of 0.94) in the patients who received intermittent dialysis, and could account for the worse outcome in this group. In contrast, the VA/NIH Acute Renal Failure Trial Network (ATN) Study did not demonstrate any difference in mortality when a more intensive dosing strategy was employed [155]. Based on these results, intermittent hemodialysis with a delivered Kt/Vurea of at least 1.2 per treatment, on alternate days, is probably sufficient for patients with acute kidney injury, unless there are indications for more intensive daily therapy, such as control of fluid volume or severe electrolyte abnormalities such as hyperkalemia or acidosis, in the smaller children.

Hybrid Therapies

A critically ill patient with severe hemodynamic instability cannot tolerate intermittent treatments carried out for 3–4 h a day and would require gentler dialysis for an extended period to improve efficiency. Since 1988, hybrid therapies which utilize the standard intermittent hemodialysis

machine technology, while providing the slower solute and fluid removal associated with continuous renal replacement therapies, have been developed for use in less stable adult patients with acute kidney injury [156, 157]. The terms for these modalities include sustained low-efficiency daily dialysis (SLEDD) or extended daily dialysis (EDD) or slow continuous dialysis (SCD) [158]. SLED is a slower dialytic modality that runs for prolonged periods using conventional dialysis machines with low blood pump speeds (200 mL/min or less) and dialysis flow rates (100–300 mL/min) for 6–12 h daily [159].

Variants such as sustained low-efficiency daily diafiltration (SLEDD-f), aimed at improving clearance of putative middle molecular inflammatory mediators of the systemic inflammatory response associated with sepsis have been developed for clinical use [160, 161]. Advantages of SLEDD-f over continuous venovenous hemodiafiltration include faster clearance of small solutes and fluid removal, whilst maintaining hemodynamic stability [162]. It allows flexible treatment schedules so that patients are accessible and can be mobilized for other medical treatments. The ability to use online production of fluid for filtrate replacement similar to the commercial hemofiltration solutions and depyrogenated saline in terms of microbial counts, endotoxin concentration, and cytokine-inducing activity, avoids the need for pre-packaged hemofiltration solutions [163, 164].

Hybrid therapies also have lesser heparin requirement and less frequent clotting. The reported incidence of clotting is 17–26% with heparin, while the reported incidence of circuit clotting without anticoagulation is 24–26% using single pass machines, and lower using batch systems [165]. This may be due to the difference in blood pump technology between the systems, with much greater leukocyte and platelet activation using the standard occlusive roller pump. Regional citrate anticoagulation in continuous venovenous hemodiafiltration is often associated with electrolyte abnormalities such as hypernatremia and metabolic alkalosis. Hybrid therapies, with the high diffusive capacity for solutes, are able to correct any alkalosis or hypernatremia, while at the same time remove the calcium chelated citrate complexes, an advantage in patients with liver failure [166].

With hybrid therapies, phosphate removal can be very extensive. Hypophosphatemia and metabolic alkalosis is easily induced in a critically ill patient, especially those on prolonged parenteral nutrition. In these instances, it may be prudent to incorporate phosphate in the dialysate solution at 0.1–0.2 mmol/kg, and reduce the dialysate bicarbonate concentration [167].

Current recommendations for hybrid therapies in adult patients state that treatment be provided at least three times per week with monitoring of the delivered dose to achieve a Kt/Vurea of at least 1.2 per treatment [167]. There is no evidence that more frequent treatment is associated with improved outcomes, unless necessitated by specific indications such as fluid overload, hyperkalemia, and hypercatabolism. In a study on adult patients comparing continuous venovenous hemofiltration with EDD, the urea reduction ratio was similar between the two groups [168]. This suggests that the effect of a 12-hour SLED is equivalent to 23 h of continuous renal replacement therapy. Many adult centers now perform nocturnal SLED so that patients may be available during the day for other diagnostic procedures, avoiding interruptions of therapy.

Continuous Renal Replacement Therapies

The most recent addition to available renal replacement therapies for the management of AKI in children is a family of continuous extracorporeal therapies now called CRRT (for continuous renal replacement therapy). This advance in the treatment of AKI offers several advantages over traditional dialysis methods when used in critically ill, unstable patients. Because CRRT is continuous, removal of solutes and modification of the volume and composition of the extracellular fluid occur gradually and evenly over time. Unstable patients who are often intolerant of the abrupt fluid volume and solute concentration changes that accompany standard hemodialysis treatments can usually be safely treated with

CRRT. The precision and stability with which fluid and electrolyte balance can be maintained using CRRT is unmatched by any currently available dialysis therapies, except perhaps one of the newer hybrid therapies discussed in the previous section. Even continuous peritoneal dialysis does not allow the control of fluid removal as can be done with CRRT, and only with CRRT can electrolytes or any formed elements of the circulation such as plasma proteins, platelets, or red blood cells be removed or added independently of changes in the volume status of the patient.

The inherent logic of the basic CRRT system is striking: a small "hemofilter" that is highly permeable to water and small solutes but impermeable to plasma proteins and the formed elements of the blood is placed in an extracorporeal circuit. As the blood perfuses the hemofilter an ultrafiltrate of plasma is removed in a manner analogous to glomerular filtration. The ultrafiltrate is concurrently replaced using a fluid with an electrolyte composition that is either similar to that of normal plasma or specifically designed to correct abnormal electrolyte concentrations in the individual patient. A portion of the ultrafiltrate can be replaced with total parenteral nutrition and other fluid therapies, and in patients with fluid overload, a portion simply is not replaced, resulting in predictable and controllable negative fluid balance.

The basic principles of CRRT are similar for adults and children. However, the application of these modalities in children requires attention to several important details unique to therapy in pediatric patients. For example, extracorporeal blood volume considerations and the need for blood circuit priming, the critical importance of nutritional support, and the use of CRRT to manage conditions unique to pediatric patients such as inborn errors of metabolism all demand a perspective different from that used to treat adult patients with CRRT. But by far the most demanding and often vexing considerations arising in pediatric CRRT are related to the need to adapt and downsize equipment and prescriptions designed for adult-size patients in order to meet the special needs of pediatric patients ranging in size and maturity from 2 kg premature neonates to 100+ kg adolescents.

Treatment with CRRT is now widely available in pediatric centers throughout the world, and in some has become the preferred method of renal replacement therapy (RRT). In this segment of Chap. 37, we review current approaches to CRRT in children, with attention to several unique aspects of pediatric CRRT that must be considered when managing the pediatric patient.

Historical Notes

The development of CRRT can be traced to the early days of maintenance hemodialysis. In the mid-1960s, Lee Henderson described a renal replacement therapy that relied solely on ultrafiltration, using membranes that were much more permeable to water and small solutes than the typical hemodialysis membranes [169]. The technique was first called "diafiltration," and later, more appropriately, "hemofiltration." Henderson showed that by pumping blood at high flow rates through an extracorporeal circuit containing a highly permeable filter, large volumes of an ultrafiltrate of plasma could be generated. This uremic fluid could be replaced concurrently with fluid that had an electrolyte composition similar to normal plasma, without the urea and other accumulated waste products. Thus, hemofiltration had many similarities with hemodialysis: both required vascular access, an extracorporeal circuit, a semipermeable membrane, and a blood pump. The difference lay in the manner in which solutes were primarily removed from the blood [170].

During any RRT in which a semipermeable membrane is used, there are two mechanisms that can be involved in the transfer of solutes: diffusion and convection. Diffusive transport is driven by solute concentration gradients that exist between blood and dialysate. Solute molecules are transferred across the membrane in the direction of lower solute concentration at a rate that is inversely proportional to molecular size and mildly influenced by molecular charge. Convective transport occurs when a solute molecule is swept through the membrane by a moving stream of ultrafiltrate, a process called "solvent drag." Convective transport is independent of

any solute concentration gradient that might be present; only the direction and force of transmembrane fluid flux are important determinants of convective transport (see also Chap. 2 (Biology of Dialysis).

During hemodialysis, solute movement across the dialysis membrane from blood to dialysate is primarily the result of diffusion, although a small amount of convective transport occurs as a result of ultrafiltration. During hemofiltration, since no dialysate is used, diffusive transport cannot occur, and solute transfer is entirely dependent on convective transport. The relative inefficiency with which small solutes are removed from the blood by convective transport when compared to diffusive transport is one of the most distinctive features of hemofiltration. For intermittent hemofiltration to serve as an alternative to the much more efficient intermittent hemodialysis, a very large volume of ultrafiltrate had to be generated and continuously and accurately replaced with a sterile, pyrogen-free and thus costly replacement fluid. As a result, intermittent hemofiltration never seriously challenged intermittent hemodialysis for preeminence as a chronic RRT [171].

The conceptualization of *continuous* hemofiltration as a treatment for acute renal failure was the contribution of a team of nephrologists in Gottingen, Germany led by Peter Kramer. In a brief German language report published in 1977, Kramer, who was familiar with the use of intermittent pumped hemofiltration in patients with acute or chronic renal failure, described a novel RRT used to treat fluid overload which he termed continuous arteriovenous hemofiltration (CAVH) [172]. In CAVH, catheters were placed in an artery and vein and were connected by relatively short, large-bore tubing to a hemofilter placed between them. An ultrafiltrate line leading from the hemofilter to a collection vessel completed the assembly. Relying solely on the cardiac function of the patient to pump blood though the hemofilter, the CAVH system was able to produce relatively large volumes of ultrafiltrate over time. An in-depth description of the circumstances that led pioneering nephrologists in Vincenza, Italy to first apply CAVH to a pediatric patient can be found in Chap. 38.

The simplicity of the CAVH system when used in children was appealing, but there were difficulties. Yet, despite the often low mean arterial pressures seen in critically ill infants and children, CAVH quickly found a place in pediatric intensive care units in North America and Europe [173–177]. Early problems with controlling ultrafiltration rates (UFR) from the surprisingly efficient adult-size hemofilters then available were addressed by using volumetric IV pumps attached to the ultrafiltrate line to regulate UFR. When it was recognized that the IV pumps were unreliable, adding downstream, weight-based urometers allowed individual titration of UFR to reflect pump performance. A better solution for infants was the development of small hemofilters (see Chap. 38).

In order to achieve predictable and more controllable ultrafiltration, and avoid the risks of long-term arterial cannulation, blood pump–driven CRRT systems were introduced in the early 1990s. Double-lumen central venous catheters could now be used as CRRT vascular access, thereby changing the name of the therapy to CVVH (continuous venovenous hemofiltration). The ongoing evolution of these technologies has resulted in more sensitive pumping systems that have increased the safety of CVVH in small patients. These and other developments have made CRRT a more attractive and viable option for critically ill children with AKI and metabolic disorders, such that CRRT is becoming the preferred method of acute therapy in many pediatric intensive care units [178].

Indications and Modality Options

In general, the indications for initiating CRRT in children and adults are similar and most often involve the treatment of AKI and fluid overload in a critically ill patient [179, 180]. CRRT can also be used to treat infants who have inborn errors of metabolism and can be readily combined with extracorporeal membrane oxygenation [181, 182]. Advantages and disadvantages of CRRT when compared with acute hemodialysis and peritoneal dialysis are summarized in Table 37.8.

Table 37.8 Comparative advantages and disadvantages of acute RRT therapies

Therapy	Advantages	Disadvantages
CRRT	Hemodynamic stability No disequilibrium syndrome Slow, gentle fluid and solute removal Increased solute removal ICU nurses can manage machines	Requires blood prime in small pts Requires vascular access Requires anticoagulation Requires patient immobilization Risks nutrient depletion Can worsen oligo-anuria Requires expensive machinery Unavailable in many emerging countries Difficult to use in tiny infants Relatively high cost
Acute HD	Rapid clearance of small solutes and toxins Rapid removal of large fluid volumes Immobilization limited to few hrs/day Widely available in developed countries	Requires blood prime in small pts Requires vascular access Requires anticoagulation Requires specialized nursing Requires expensive machinery Relatively high cost Difficult to use in tiny infants
Acute PD	Readily available throughout world No vascular access No anticoagulation required No disequilibrium syndrome Managed by ICU nurses Relatively low cost No complex machinery Can be used in tiny infants	Inefficient removal solutes, fluid Acute peritoneal access prone to leaks, obstruction Can cause respiratory compromise from abdominal distension

Because CRRT is continuous and can be conducted over days to weeks, overall solute clearance and fluid removal is easily superior to other modalities. However, this feature also has negative aspects, primarily the need to remain relatively immobilized while connected to the CRRT circuit for prolonged periods. As a result, small children typically require long-term sedation and occasionally even paralysis to prevent the small movements that can readily disrupt flow in the hypersensitive CRRT circuit.

CRRT is composed of and refers to a variety of modalities that primarily take advantage of one or both solute clearance mechanisms. In continuous venovenous hemofiltration (CVVH), blood flows through the hemofilter generating large volumes of ultrafiltrate which are replaced by introduction into the blood path of a physiologic "replacement fluid" either before (pre-dilution) or after (post-dilution) the hemofilter (see Fig. 37.7a). Clearance is thus exclusively convective. If instead of replacement fluid infused into the blood path a dialysate is infused into the hemofilter, clearance becomes primarily diffusive as in hemodialysis. Hence the name for this CRRT modality: continuous venovenous hemodialysis (CVVHD, Fig. 37.7b). When both replacement fluid and dialysate are used to combine both convective and diffusive clearances, the therapy is known as continuous venovenous hemodiafiltration (CVVHDF, Fig. 37.7c). The relative advantages of one CRRT modality over another have been debated inconclusively for a more than a decade, fueled in part in the US by the initial lack of an FDA-approved replacement fluid , leading some centers to avoid the convective therapies (CVVH and CVVHDF) altogether. Now that FDA-approved replacement fluids are readily available, proper comparative modality studies can be designed in centers offering all three modalities.

CRRT Machines

The choice of CRRT machinery for pediatric patients is based entirely on local practice and is often most influenced by cost and local experience, as well as the preferences of the adult CRRT

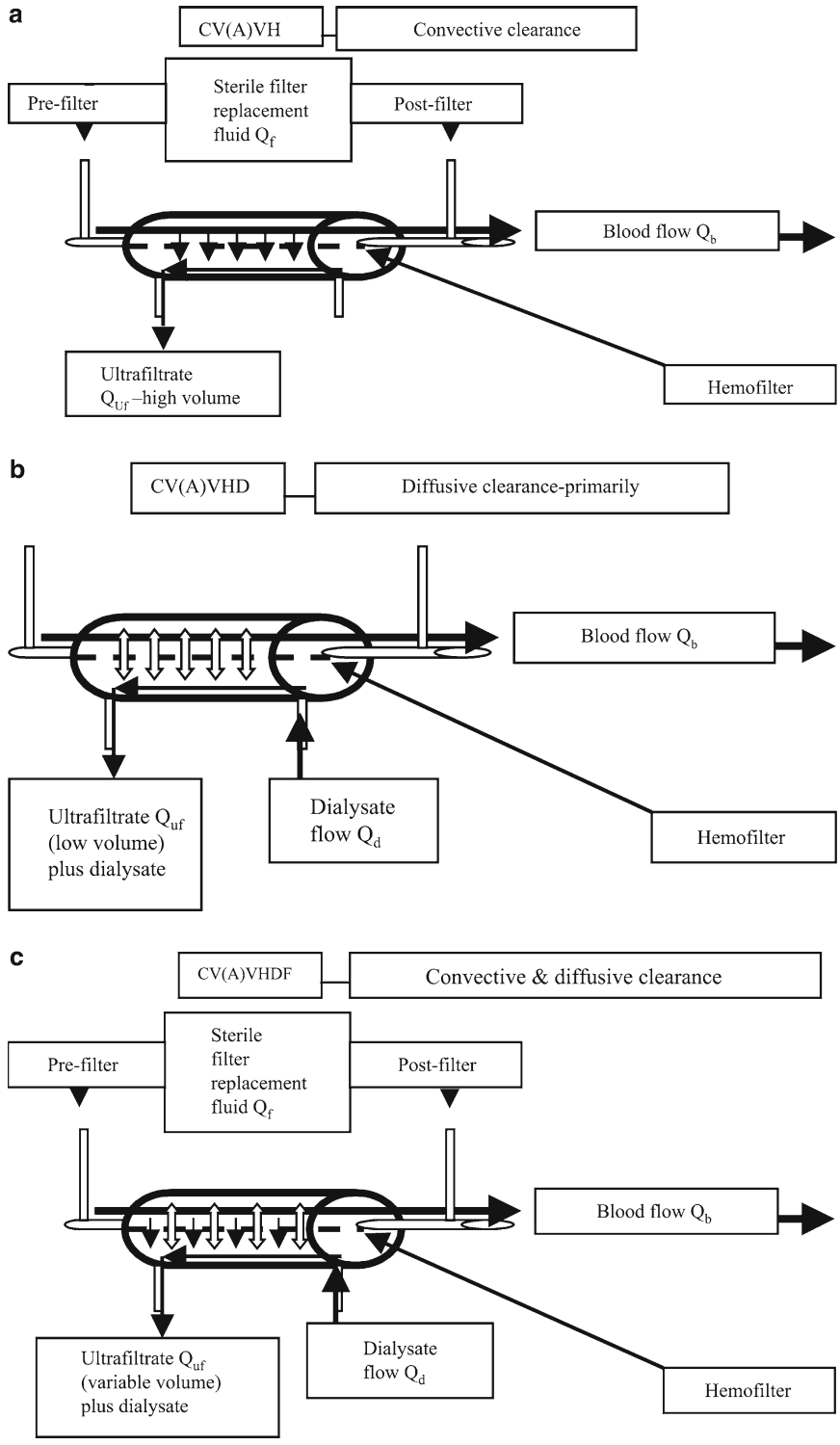

Fig. 37.7 (**a**) Diagram of a convective based (CVVH) continuous renal replacement therapy (Note use of either pre- or post-filter replacement fluid rather than dialysate). (**b**) Diagram of diffusion based (CVVHD) continuous renal replacement therapy (Note use of dialysate rather than replacement fluid. Dialysate flow is countercurrent to blood flow). (**c**) Diagram of combined convective and diffusive based (CVVHDF) continuous renal replacement therapies (Note use of both dialysate and replacement fluids)

program in settings where pediatric and adult facilities and services are combined. To date, no machine has been found superior for pediatric CRRT. In fact, no machines have been found to be particularly well suited for use in children. Fortunately, all have improved ultrafiltration controls and pumps that have reduced error rates to only a fraction of those seen in the early days of CAVH when IV pumps were used [183]. All offer blood path warming devices to minimize the risk of hypothermia and most can be run at the lower blood flow rates suitable for use in infants and small children. A detailed discussion of the various components and features of the available machines is beyond the scope of this chapter. Suffice it to say that there is no currently available optimal pediatric CRRT machine (see also Chap. 38).

Vascular Access

As with all extracorporeal therapies, the success of CRRT treatment is dependent on the quality of the vascular access. Adequate blood flow (Qb) is essential to providing optimal therapy with minimal interruption, reducing the likelihood of circuit loss due to clotting. In pediatric patients, the choice of vascular access catheter size and insertion site is critical. Table 37.6 contains a listing of available catheters suitable for use in children who are receiving either acute hemodialysis or CRRT.

In general, the right internal jugular insertion site with the tip of the double lumen catheter residing within the right atrium provides the best all around performance, especially in infants and small children. When the catheter tip resides within a central vein (e.g., the subclavian or superior or inferior vena cava) the catheter diameter can approach the diameter of the surrounding vessel. The collapse of the vessel wall against the catheter will occlude the side ports of the catheter's arterial limb causing rapid rise in access negative pressure and stoppage of flow. Femoral access can perform well and may be safer due to its relative ease of insertion. However, prolonged use often requires heavy sedation or even paralysis, as minimal flexing of the hip in an awake and moving patient will too easily crimp the catheter and result in a stoppage of flow. Many nephrologists prefer to avoid using the subclavian vein as some patients may not regain renal function and ultimately require an upper extremity arteriovenous fistula which functions poorly when there is stenosis of the subclavian vein due to its prior use for RRT (see Chap. 3(Demographics of Dialysis in Children) [Brandt chapter]).

Blood flow rates for CRRT are determined by the size of the child, the machine being used and the vascular access. Short, large bore catheters provide improved performance due to lower resistance to flow [184]. As with HD, longer, smaller bore catheters (e.g,. Broviac catheters, umbilical vessel catheters) are unsuitable for use in CRRT due to their high flow resistance.

Blood Flow Rates

With a well-functioning vascular access it is possible to adjust blood flow rate (Qb) to fit the size of the child and the clinical setting. As with pediatric HD, Qb can be prescribed initially based on body weight, but recommendations vary widely from 10 to 12 mL/kg-min in neonates to 2–4 mL/kg-min in adolescents. Higher Qb will support longer filter life by reducing the likelihood of filter fiber clotting. Higher Qb also facilitates increased patient fluid removal by providing greater filter plasma flow rates and reduces the loss of clearance efficiency from predilution mode CVVH or CVVHDF. However, not all patients will tolerate a higher Qb, especially at initiation of CRRT. In general, it is best to begin with caution and advance Qb to the targeted rate over the first 30 min as tolerated.

Solutions

As was seen in HD, the tolerability of CRRT has been greatly improved with the introduction of bicarbonate-based CRRT solutions. When solutions used lactate as the buffer, worsening lactic acidosis was common leading to hypotension and depression of cardiac function [185]. A series of comparative clinical trials of lactate- and bicarbonate-based CRRT fluids in adults [186, 187]

and children [188] have so clearly demonstrated the superiority of bicarbonate as a buffer in this setting that bicarbonate-based replacement fluid and dialysate is now the standard of care for CRRT.

Along with bicarbonate (and small amounts of lactate for stability), CRRT solutions also contain various amounts of sodium, potassium, chloride, glucose, calcium, phosphate, and magnesium. Bicarbonate-based, FDA-approved CRRT solutions are now available from several manufacturers in a dizzying array of electrolyte formulations. Most hospital pharmacies will stock only a single brand and in only a few formulations. There are clinical settings, however that call for different solutions. A key feature of CRRT, especially in small patients, is the tendency over time for the composition of the CRRT fluids to eventually determine the electrolyte composition of the patient. A fluid low in potassium, phosphorous, and magnesium may be appropriate at initiation of CRRT when concentrations of these electrolytes in AKI patients are often elevated. However, depending on the CRRT prescription, within a surprisingly short time the patient will become frankly deficient in these electrolytes which can complicate management. Thus while a "starter" fluid with reduced potassium, phosphorous, and magnesium is needed, a more physiologic fluid that adds back these electrolytes in physiologic concentrations should follow. Rather than stocking multiple formulations, some pharmacies may prefer to add potassium, phosphorous, magnesium, and even additional bicarbonate to the "starter" solutions as needed, a practice that may add risks associated with potential pharmacy errors and increase costs.

Calcium is always left out of solutions when phosphate is present ; in addition, calcium has usually but not always been left out of CRRT solutions used with citrate anticoagulation, as will be discussed below.

Hemofilter Membranes

A wide variety of hemofilter membranes have been developed for use with CRRT, none of which have been shown to be superior. However, the use of one highly biocompatible membrane, the AN-69 polyacrilonitrile membrane, has been associated in pediatric patients with the "bradykinen release phenomenon," characterized by a precipitous decline in blood pressure 5–10 min after initiating CRRT, especially when a blood prime has been used [144, 189]. Exposure of the blood to the highly negatively charged AN69 membrane co-activates pre-kallikrein and Hageman factor resulting in the release of bradykinen, a potent vasodilator. The reaction is potentiated by exposure to blood with an acid pH, which is typical of banked blood used for blood priming the circuit in infants for whom the circuit volume exceeds 10–15% of the estimated blood volume. Thus in small infants the use of a blood prime with an AN69 membrane can result in profound hypotension. Buffering the blood to physiologic pH prior to priming the circuit or infusing the blood post filter at the same rate as a saline prime have been shown to be effective in minimizing the bradykinen release syndrome, as has avoidance of the AN69 membrane [145, 190].

Anticoagulation

Activation of the clotting cascade occurs in CRRT circuits due to contact of the circulating blood with artificial surfaces. Low blood flow rates, turbulent flow, small catheters, and high hematocrits hasten this effect. Anticoagulation regimens using mixed molecular weight heparin or sodium citrate are the most commonly used in pediatric CRRT, and either can be effective. Early comparison of observed outcomes in pediatric centers showed equal filter life span with heparin and citrate, but more hemorrhagic events in the heparin group [191]. However, controlled studies are lacking, and centers tend to adopt one method or the other based on local experience and practice.

It is also possible in certain situations to use no anticoagulation, relying on periodic saline flushes of the circuit. This approach is typically considered in patients with evidence of a sustained coagulopathy due to disseminated intravascular coagulopathy or hepatic failure. However, many of these patients are receiving periodic fresh frozen plasma and platelet infusions to correct the

underlying coagulopathy that will clot a CRRT system when no anticoagulation is used. Moreover, patients with hepatic failure may have a paradoxical hypercoagulable state. An uncontrolled study has shown the no coagulation/saline flushes approach to be associated with an inferior circuit life span compared to heparin and citrate anticoagulation [191].

Heparin has been the mainstay of HD anticoagulation for decades. It is not surprising then that many pediatric CRRT programs began with and continue to rely on heparin to maintain circuit patency. Heparin is infused in the CRRT circuit pre-filter and titrated to achieve a targeted post-filter partial thromboplastin time (PTT) 1.5–2 times normal, or an activated clotting time (ACT) between 180 and 220 s. This is usually accomplished by giving an initial heparin bolus of 20–30 units/kg, followed by a continuous infusion of 10–20 units/kg h. Alternatively, the circuit may be rinsed and primed with 1–2 L of normal saline to which has been added 2,500–5,000 units/L of heparin, followed by the pre-filter heparin infusion.

As first proposed by Mehta and colleagues in San Diego in 1990, sodium citrate anticoagulation has gained wide acceptance in pediatric CRRT programs due to its ease of administration and low side effects profile compared to heparin [192]. By infusing citrate into the arterial limb of the CRRT tubing as it leaves the catheter, calcium ions are bound to the citrate, reducing available calcium and thereby greatly inhibiting coagulation within the circuit, since normal coagulation is calcium-dependent. Systemic hypocalcemia is prevented by infusing calcium chloride back into the patient at a central site away from the CRRT circuit. Thus, citrate anticoagulation achieves truly regional anticoagulation by affecting only the circuit, thereby eliminating the increased risk of bleeding seen with heparin.

The original citrate protocol proposed by Mehta and colleagues used 4% trisodium citrate, which is high in sodium (440 mEq/L) and requires pharmacy-made solutions that are hyponatremic and risk pharmacy error. Alternatively, the commercially available ACD-A (Baxter Healthcare Deerfield, IL) is now widely used in conjunction with calcium-free dialysis and replacement solutions [192]. A commonly employed approach in pediatric CRRT using ACD-A was first described by Bunchman and colleagues in 2002 [193]. A circuit ionized calcium concentration goal of 0.25–0.4 mmols/L is achieved by titrating the citrate infusion rate according to the measured post-filter ionized calcium concentration. Because available calcium in the circuit is a function of blood flow rate (Qb), the initial ACD-A rate is set to equal in mL/h 1.5–2 times the blood flow rate in mL/min. Thus for a Qb of 100 mL/min, the initial ACD-A rate is set at 150–200 mL/h. A 0.8% calcium chloride in normal saline solution is then infused to maintain the desired systemic ionized calcium concentration, usually 1.1–1.3 mmols/L. The initial CaCl2 infusion rate is usually 50–75% of the citrate infusion rate. Thus for a Qb of 100 mL/min and a citrate rate of 200 mL/h, the initial CaCl2 rate is 100–150 mL/h. Separate sliding scales are used to adjust citrate infusion rates according to the periodically measured circuit ionized calcium level and CaCl2 infusion rates according to systemic ionized calcium levels. The system often stabilizes rapidly allowing reduced frequency of monitoring after the first 4–6 h.

Adverse effects of citrate anticoagulation include metabolic alkalosis, citrate toxicity, and hyperglycemia in infants when ACD-A is used. Because citrate is metabolized by the liver to bicarbonate in a ~3:1 manner (~3 mol of bicarbonate for every mol of citrate), patients receiving citrate anticoagulation are prone to develop metabolic alkalosis. Fortunately, citrate is readily cleared by dialysis [194]. Thus, metabolic alkalosis can be forestalled by increasing the dialysate flow rate to increase citrate clearance in patients receiving CVVHD or CVVHDF. Reducing the citrate infusion rate and temporarily using normal saline (pH = 5.4) as a replacement solution can also be effective.

Citrate toxicity may be diagnosed by monitoring the ratio of the total calcium to the ionized calcium levels [195]. Citrate toxicity occurs when citrate clearance falls behind citrate delivery. Total calcium levels rise and the ratio of total calcium to systemic ionized calcium levels rises precipitously. As citrate accumulation progresses, it becomes more difficult to maintain the declining systemic ionized calcium levels within normal

ranges. Since citrate is cleared metabolically by the liver, patients with diminished liver function are at increased risk for citrate toxicity. A falling serum ionized calcium level in the face of a rising total calcium in a patient with liver dysfunction is a sure sign of citrate toxicity. Treatment often requires reducing the citrate rate after a brief period off citrate entirely. An initial citrate infusion rate of 50–70% of the usual rate is also recommended in patients with hepatic insufficiency who are at increased risk for citrate toxicity.

Nutrition

One of the most attractive features of CRRT is the ability to provide complete nutrition without risk of fluid overload. Optimization of energy and protein intake in these highly catabolic patients is potentially important to ultimate survival. However, CRRT also contributes to negative nitrogen balance through the loss of free amino acids and peptides . Studies by Maxvold and colleagues in pediatric CRRT patients have shown that nutritional prescriptions delivering the RDI for protein result in negative nitrogen balance [196]. Similar studies in adults have confirmed these observations [197]. Current nutritional recommendations for adults and children receiving CRRT include a daily intake of amino acids of 2.5–3 g/kg. Under most circumstances, a BUN of 40–60 mg/dL is a reliable indicator of adequate amino acid/protein intake.

Inborn Errors of Metabolism

The acute treatment of several inborn errors of metabolism requires the rapid removal of toxic substances, primarily ammonia, which is elevated in urea cycle defects and some organic acidemias [198, 199]. While hemodialysis is usually recommended to lower very high ammonia levels most effectively, rebound is rapid after cessation of dialysis. Many centers now begin treatment with HD and segue directly to CRRT to prevent rebound. High Qb and dialysate flow rates are recommended to maximize clearance of ammonia. Unlike too aggressive small solute clearance with HD in the setting of AKI, there is no disequilibrium syndrome associated with rapid reductions in serum ammonia levels. Highly efficient CRRT carries the increased risk of electrolyte depletion requiring the immediate use of phosphate-containing CRRT solutions.

Extracorporeal Membrane Oxygenation

The widespread use of extracorporeal membrane oxygenation (ECMO) in neonatal and pediatric critical care units along with the common occurrence of AKI in these patients with multiple organ dysfunction has led to the need to incorporate CRRT into the ECMO therapy circuit. Fortunately, this is readily accomplished. The ECMO circuit is fully heparinized obviating the need to anticoagulate the CRRT circuit. Blood flow in the ECMO circuit is often 20–30 times that required for optimal CRRT. Placement of the CRRT circuit is traditionally post- to pre-oxygenator. However, this may effectively shunt oxygenated blood away from the patient. Newer ECMO circuits with multiple access nipples allow the insertion of the CRRT circuit in an entirely pre-oxygenator location. Close collaboration between CRRT and ECMO teams is required to find the best location for the CRRT circuit and to coordinate concomitant therapy goals [182].

Plasmapheresis

CRRT can be readily combined concurrently with plasma exchange procedures without interrupting CRRT. As first described by Yorgin and associates in 2000, the placement of a three-way stopcock at both arterial and venous limbs of the CRRT circuit at the connection to the double lumen catheter allows diversion of blood through the centrifugation plasmapheresis machine [200]. At initiation of plasmapheresis, Qb on the CRRT machine must be reduced by the blood flow rate of the pheresis machine, which in turn may require reduction in CRRT replacement fluid rate.

Thermic Control

Infants and small children have large body surface area to weight ratios. In addition, a relatively large fraction of total circulating blood volume is in the extracorporeal circuit at any given time, placing these children at substantial risk for hypothermia during CRRT. In-line fluid warmers can be used, but will increase priming volume. Line warmers that can be applied to the return line offer the best results. Thermic control devices may also mask a fever in a small child.

Circuit-to-Circuit Exchange

Infants receiving prolonged CRRT may require repeated blood primes, with multiple exposures to blood-borne diseases, HLA antigen sensitization and bradykinen syndrome. After the initial blood prime, subsequent routine circuit changes can be accomplished by priming a new machine with the blood that resides in the old machine. The circuit is discontinued, the catheter flushed and locked with heparinized saline or tPA, and a saline-primed circuit on a new machine is connected to the venous line of the old circuit. Blood from the old circuit is then used to fill the new circuit, the new circuit then attached to the patient [201].

Prescription

The optimal "dose" of renal replacement therapy is not known. Studies by Ronco and colleagues of adults with AKI treated with CVVH established a total convective clearance (replacement fluid plus patient fluid removal) target of 35 mL/kg h as a threshold below which survival was significantly worse [202]. In a subset of these patients with sepsis there was a trend in favor of improved survival with total convective clearances >/= 45 mL/kg h. Recent studies by the VA/NIH Acute Renal Failure Network have shown that there was no difference in survival associated with more intensive RRT (35 mL/kg h) compared to less intensive (20 mL/kg h) therapy [155]. These studies are confounded by the use of different modalities involving different amounts of convective and diffusive solute removal. However, the thought that by attempting to push clearances ever higher outcomes would be improved seems unlikely. This is a particularly important observation in pediatric CRRT where the use of large filters in small patients allows achievement of very high clearances that can be nutritionally harmful. Despite theoretical considerations that seemed to favor high clearance targets in cytokine-driven illnesses like sepsis [203] and preliminary results in septic adults treated with very high flow CRRT [204], available evidence does not support the use of clearance targets above 20–35 mL/kg h. For pediatric patients, this translates to 2–3 L/1.73 m^2 h, rates that are reasonably easy to achieve.

A representative prescription for pediatric CRRT would include a blood flow rate of 4–6 mL/kg/min and a dialysate or replacement fluid rate (or the sum of both in the case of CVVHDF) of at least 2,000–3,000 mL/1.73 m^2 h.

Outcome

Survival of pediatric patients treated with CRRT has been reported in single center studies to vary widely by disease and modality [205–207]. Recent evidence points to the degree of fluid overload as an independent determinant of outcome in pediatric patients treated with CRRT. Goldstein and colleagues first showed this effect in a single center study [205] that has been confirmed by a large multicenter study from the prospective pediatric CRRT (ppCRRT) registry [208]. Patient survival was inversely correlated with percent fluid overload at initiation of CRRT; survivors had a mean fluid overload of 14.2% while in non-survivors mean fluid overload was 25.4%, a difference that was highly significant and independent of diagnosis or severity of illness [205]. Further analysis of the ppCRRT Registry data has established 20% fluid overload as the threshold above which mortality of pediatric patients receiving CRRT is four times that of patients with less than 10% fluid overload at

initiation of CRRT [208]. These data suggest that earlier initiation of measures to control fluid accumulation, including CRRT, may improve survival.

Conclusion

AKI is frequently seen in the pediatric population, often associated with high risk of mortality or long-term morbidity. Recent advances in the understanding of the pathophysiology of AKI have pointed to newer diagnostic and therapeutic strategies that focus on early recognition and treatment. Exciting developments in technology have made renal replacement therapies more accessible and more easily applied in the pediatric setting. Yet despite these advances mortality rates among children who suffer AKI remain disturbingly high. Hopefully, future developments will bring about improved outcomes for the majority of children afflicted with AKI.

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