Review Article

# Acute kidney injury after pediatric cardiac surgery

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## ABSTRACT

Acute kidney injury is a common complication after pediatric cardiac surgery. The definition, staging, risk factors, biomarkers and management of acute kidney injury in children is detailed in the following review article.

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**Key words:** Acute; Cardiac; Injury; Kidney; Pediatric; Surgery

## INTRODUCTION

The term "acute kidney injury (AKI)" was introduced in recent past to replace the earlier term of acute kidney failure or acute renal failure. It was proposed to encompass all forms of insults to the kidney in the broad term of "AKI," including those which were at risk. The incidence of AKI after pediatric cardiac surgery is between 9.6% and 52%.[1-7]

AKI is defined as an increase in serum creatinine more than 50%. However, there are two different classifications based on serum creatinine levels and urine output to describe AKI in children in current clinical practice – the pediatric risk, injury, failure, loss, end-stage (pRIFLE),[8] and AKI Network (AKIN)[9] criteria.

Clinicians have debated the use of one criteria over another. Many researchers have used AKIN criteria with some modifications as per their settings. Blinder *et al*. explained that the 48 h window and smaller absolute increase in the serum creatinine, as described in the AKIN criteria, would be more appropriate for postoperative AKI.[4]

Cystatin C has also been used by researchers to evaluate AKI after contrast agent use and pediatric cardiac surgery. Zappitelli *et al*. proposed the use of cystatin C instead of creatinine to diagnose AKI. They concurred that cystatin C, like creatinine, is also filtered through glomerulus.[7] The serum concentrations of cystatin C are not affected by muscle mass or gender, although corticosteroids, and thyroid disease may affect its levels. They replaced creatinine in AKIN criteria by cystatin C and found that the incidence of AKI as defined by creatinine was more than double of AKI defined by cystatin C. There was an agreement between Stage 2 (and 3) AKI, between creatinine and cystatin AKI. There was a significant difference in the incidence of Stage 1 AKI between creatinine and cystatin groups because the increase in cystatin C was late. The time to the first diagnosis of AKI was 2 days versus 1 day for creatinine AKI and cystatin AKI, respectively. The cystatin AKI was more strongly associated with kidney injury molecule 1 (KIM 1) and interleukin 18 (IL-18) compared with creatinine AKI. In spite of all observations and studies of

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**Pediatric modified RIFLE criteria[8]**

| | Estimated creatinine clearance | Urine output |
|---|---|---|
| Risk | eCCl decrease by 25% | <0.5 ml/kg/h for 8 h |
| 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 $m^2$ | <0.5 ml/kg/h for 24 h or anuric for 12 h |
| Loss of function | Persistent failure >4 weeks | |
| End stage | End stage renal disease (persistent failure >3 months) | |

eCCL: Estimated creatinine clearance

**Pediatric modified Acute Kidney Injury Network Criteria[9]**

| AKIN stage | Urinary output criteria | Serum creatinine criteria |
|---|---|---|
| I | <0.5 ml/kg/h in 8 h | Increase in serum creatinine level by ≥0.3 mg/dl or increase to 150-200% of reference value in 48 h |
| II | <0.5 ml/kg/h in 16 h | Increase of serum creatinine level to 200-300% of reference value in 48 h |
| III | <0.3 ml/kg/h in 24 h or anuria for 16 h | Increase of serum creatinine level to >300% of reference value or serum creatinine level ≥4.0 mg/dl with acute rise of ≥0.5 mg/dl in 48 h |

alternative biomarkers serum creatinine prevails as the most commonly used molecule to diagnose and stage AKI.

## IMPACT OF ACUTE KIDNEY INJURY

It has been repeatedly proven that AKI is an independent predictor of morbidity and mortality in children who undergo surgery for congenital heart diseases with cardiopulmonary bypass. Severe AKI has been associated with longer duration of mechanical ventilation, inotropic support, Intensive Care Unit (ICU) stay, and hospital stay.[4,5] Stage III AKI is also associated with systemic ventricular dysfunction at hospital discharge. AKI can cause left ventricular dysfunction as a result of interorgan "cross talk" that may be mediated by cytokines and chemokines, a phenomenon known as Cardiorenal syndrome.[10] Piggott *et al*. studied neonates after cardiac surgery and found that AKI and early fluid overload (>15% increase in fluid content of body) were associated with increased mortality. Children having fluid overload of >30% had 100% mortality.[6]

## RISK FACTORS [TABLE 1]

Blinder *et al*. studied 430 infants of <3 months age who underwent pediatric cardiac surgery. They used AKIN criteria and on multivariate analysis found age (median 7 days), functional single ventricle status, higher baseline serum creatinine, higher risk adjustment for congenital heart surgery 1 (RACHS 1) category, CPB of use, and its duration as risk factors for AKI.

Piggott *et al*. studied neonates aged 6–29 days who underwent cardiac surgery for congenital heart disease. They also used AKIN criteria to stage AKI. Risk factors included small kidneys by preoperative renal ultrasound, preoperative aminoglycoside exposure, selective cerebral perfusion, CPB duration, and RACHS 1 category.

Preoperative small kidneys as risk factor for AKI was studied by Carmody *et al*.[11] They found that kidney volume <17 $cm^3$ in neonates was associated with higher peak postoperative creatinine and greater risk of AKI after surgery for congenital heart disease. Functional single ventricle was also a risk factor for AKI in neonates.

Sethi *et al*. studied 208 children (age <18 years) who underwent surgery on CPB for congenital heart disease.[5] The risk factors for AKI were age (<12 months), CPB duration, prolonged ventilation, low cardiac output syndrome, sepsis, and hematological complication (platelet count <80,000/$mm^3$ or decrease in count by 50% from the highest value recorded over last 48 h).

## BIOMARKERS [TABLE 1]

Apart from creatinine and cystatin C, other biomarkers have been well-studied and associated with AKI. Urine and plasma neutrophil gelatinase-associated lipocalcin (NGAL), brain natriuretic peptide (BNP), IL 6 and 18, KIM 1, liver fatty acid binding protein, and homovanillic acid sulfate (HVA $SO_4$).[7,12-17]

### Neutrophil gelatinase-associated lipocalin

NGAL is a protein secreted in urine and produced in renal tubules in response to ischemic injury to kidneys. It may predict patients who are at risk to develop AKI.[13] Alcaraz *et al*. studied 106 children and found

**Table 1: Risk factors and Biomarkers for Acute Kidney injury after Pediatric Cardiac Surgery**

| Risk factors | Biomarkers |
|---|---|
| Age | Serum creatinine |
| Functional single ventricle | Serum cystatin C |
| Higher baseline serum creatinine | Serum NGAL |
| Higher risk adjustment for congenital heart surgery 1 category | Urine NGAL |
| CPB use | Interleukin 6 |
| CPB duration | Interleukin 18 |
| Small kidneys (by preoperative ultrasonography) | Kidney injury molecule 1 |
| Preoperative aminoglycoside exposure | Liver fatty acid binding protein |
| Selective cerebral perfusion | Homovanillic acid sulfate |
| Prolonged ventilation | |
| Low cardiac output syndrome | |
| Sepsis | |
| Platelet count <80,000/mm$^3$ | |

NGAL: Neurophilgelatinase associated lipocalcin, CPB:Cardiopulmonary bypass

no association of NGAL with AKI when staged as per pRIFLE criteria.[14] Urine NGAL/creatinine ratios at 15 h postcardiac surgery were higher in patients who were in the category of pRIFLE I (injury) or pRIFLE F (failure) than with pRIFLE R (risk). Urine NGAL (U NGAL) at 1 and 3 h postoperatively were independent predictors of postoperative AKI but did not categorized the severity of AKI. U NGAL does not differentiate between prerenal and sustained kidney injury. However, U NGAL may be able to differentiate between acute and chronic kidney disease.[18]

U NGAL in the first 3 postoperative hours could predict patient outcomes, duration of mechanical ventilation, ICU, and hospital stays.[12,14,15] A cut-off value of 50–100 pg/ml, 3 h after renal insult (post-CPB) is recommended to initiate renal protection interventions. Mishra *et al*. observed that a cut-off value of 50 pg/ml at 2 h post-CPB was found to be an independent predictor of AKI.[19] Plasma and urine NGAL have been shown to peak within 6 h of ICU arrival compared to serum creatinine levels which peaked at 24–48 h.[20] The first postoperative urine IL-18 and NGAL levels have been associated with severe AKI.[12]

### Interleukin 6 and 18

Miklaszewska observed that serum IL6 levels more than 185 pg/ml, at 2 h post-CPB, increased the risk of AKI by 3 times.[16] Furthermore, that increase in level of soluble IL 6 by 100 pg/ml increased the chance of AKI development by 70%.

Low levels of IL18 2 h postsurgery were associated with a negative predictive value of 91% for AKI in infants of <6 months age.

### Brain natriuretic peptide

The increase in BNP and NT-pro-BNP has been associated with heart failure, ventricular dysfunction, and poor outcomes. Hornik *et al*. studied 277 children between 1 month and 18 years of age and found that serum BNP levels were not associated with increased incidence of AKI.[21]

### Homovanillic acid sulfate

Beger *et al*. identified a potential marker of AKI in the form of HVA $SO_4$ which appears in the circulation as early as 4 h postsurgery.[17] They found that patients who subsequently developed AKI, the level of HVA $SO_4$ had become twice at 4 h postsurgery and 4 times at 12 postsurgery. HVA $SO_4$ is a major end product of dopamine metabolism. They postulated that the increase release of dopamine in autocrine/paracrine manner following an insult may cause an increase in HVA $SO_4$. HVA $SO_4$ may be used as a complementary marker to NGAL and IL 18 after pediatric cardiac surgery.

### Investigations

Following investigations in the postoperative period aid in the diagnosis and management of AKI.

- Inflammatory markers: Total leukocyte count, increased the percentage of polymorphonuclear neutrophil, elevated erythrocyte sedimentation rate, an increase in serum procalcitonin levels, and a decrease platelet count indicates a systemic inflammatory response the cause of which may be an infection, organ ischemia, or cardiopulmonary bypass-induced
- Hemoglobin: A low hemoglobin concentration aggravates hypoxic injury in an under-perfused or injured kidney due to a decrease in oxygen delivery. Therefore, hemoglobin should be increased so as to achieve an optimal oxygen delivery of >300 ml/min/m$^2$
- Liver function tests: Increased liver enzymes (serum glutamic-oxaloacetic transaminase/serum glutamic pyruvic transaminase), bilirubin, alkaline phosphatase, and decreased albumin levels indicate liver failure. If the AKI follows liver failure, it may indicate a hepatorenal syndrome
- Renal function test: Serum creatinine and blood

urea nitrogen (BUN) levels help in diagnosing AKI, differentiating between prerenal and renal failure and monitor the progress with the initiation of treatment. A BUN/creatinine ratio of >20:1 and urine osmolarity of more than 500 mosmol/L indicate prerenal failure. Fractional excretion of sodium ($FENa^+$) also differentiates between prerenal and renal failure. A value of <1% indicates prerenal and >3% renal kidney injury. However, it may not be a reliable index in patients receiving diuretic therapy

$FENa^+ = 100 \times$ ([urinary sodium × serum creatinine]/[serum sodium × urine creatinine])

- Serum electrolytes: Hyponatremia in patients with AKI is due to hypervolemia. Therefore, sodium levels may be normalized by losing excessive body water. Serum potassium levels may increase and should be strictly monitored. They may also indicate improving or deteriorating kidney function
- Urine: Routine examination may reveal proteinuria or free hemoglobin (hemolysis). The presence of leukocytes and pus cells on microscopy suggest infection. The presence of free hemoglobin and red blood cells in urine indicates pigment nephropathy. A peripheral blood smear is valuable to rule out schistocytes. Urine culture can be done to confirm infection
- Chest X–ray: A chest X-ray depicts changes secondary to low cardiac output (cardiomegaly, pulmonary edema, pleural effusion, and signs of pulmonary artery hypertension) and infection (consolidation) or it may establish lung collapse or pneumothorax as causes of hypoxia
- Echocardiography helps to evaluate ventricular function and rule out low cardiac output
- Ultrasonography (USG): USG lung confirms the findings of chest X-ray such as pleural effusion (or hemothorax), collapse, and consolidation of the lung USG abdomen evaluates kidney abnormalities (single kidney, horseshoe kidney, pelvic kidney, and malformed kidney), obstruction to urinary tract and renal artery stenosis (Doppler of renal artery). A new onset loss of corticomedullary differentiation in the postoperative period on USG signifies acute tubular necrosis
- Kidney biopsy to establish specific diagnosis, for example, rapidly progressive glomerulonephritis; nonresolving acute glomerulonephritis; interstitial nephritis; acute tubular necrosis; or hemolytic uremic syndrome >2–3 weeks; acute renal failure without any cause.

## MANAGEMENT

### General management

- Maintain cardiac output: Cardiac output depends on preload, afterload, heart rate, contractility, and rhythm of the heart. Therefore, each of the above factors should be optimized. Inodilators especially may help in improving cardiac output after surgery
- Fluid: Avoid potassium-containing solutions. Isotonic saline may be used as a replacement. Insensible fluid loss of 300–400 $ml/m^2$/day should be included when calculating fluid balance. A fluid intake, at least, equal to urine output + insensible losses should be given per day
- Electrolytes: Serum sodium and potassium should be maintained within normal levels. Hyponatremia in after AKI is mostly due to fluid retention rather than low intake, therefore, fluid restriction may improve sodium levels in children after cardiac surgery

Hyperkalemia may occur after AKI and should be corrected as:[22]

**Management of Hyperkalemia**

| Action | Mechanism | Onset | Duration |
|---|---|---|---|
| Plasma $K^+$: 5.0-6.0 mEq/L | | | |
| Furosemide 1 mg/kg | Removes $K^+$ | 10 min | End of diuresis |
| Sodium bicarbonate 1 mEq/kg | Shifts K into cells | 10 min | 1-2 h |
| Nebulize with salbutamol | Shifts K into cells | 5-15 min | 1-2 h |
| Plasma $K^+$: >6.0 mEq/L | | | |
| Calcium gluconate 10% 0.5 ml/kg | Antagonizes $K^+$ | 1-3 min | 30 min |
| Glucose insulin<br>Insulin 0.05 U/kg f/b 0.05 U/kg/h + glucose 0.5 g/kg/h for 2 h | Shifts K into cells | 30 min | 4-6 h |
| Calcium polystyrene sulfonate<br>15 ml for adults with juice or dextrose | Binds potassium in intestine and then excreted through feces | 1-2 h | |
| Prepare to start PD or heart failure | Removes $K^+$ | As soon as dialysis | Duration of dialysis |

PD: Peritoneal dialysis

- Nutrition: For neonates and infants expressed breast milk should be given through enteral route. These children who have undergone cardiac surgery are in a catabolic state and, therefore, protein intake should be kept in the range of 0.6–1.0 g/kg/day.[23] For older children, formula renal feeds may be administered

as per fluid restrictions. Calorie intake should be initially 50–60% of daily recommended intake and may be increased subsequently to 60–80%

- Drugs: Avoid nephrotoxic antibiotics, sedatives, analgesics, and anticonvulsants or reduce dose as per creatinine clearance.

### Implications of acute kidney injury on common drugs used in the postoperative period after pediatric cardiac surgery

| Class | Dose reduction not required | Dose reduction required |
|---|---|---|
| Antimicrobial | Cefoperazone | Cefepime |
| | Ceftriaxone | Ceftazidime |
| | Clindamycin | Cefotaxime |
| | Linezolid | Clarithromycin |
| | Tigecycline | Daptomycin |
| | | Imipenem |
| | | Meropenem |
| | | Ciprofloxacin |
| | | Levofloxacin |
| | | Cefoperazone-Sulbactam |
| | | Vancomycin |
| | | Teicoplanin[a] |
| | | Piperacillin-tazobactam |
| | | Aminoglycosides |
| | | Colistin |
| | | Metronidazole[b] |
| Antifungal | Oral voriconazole[c] | Fluconazole |
| | Oral itraconazole[d] | Amphotericin B |
| Antivirals | | Acyclovir |
| | | Ganciclovir |
| | | Valganciclovir |
| Anticonvulsant | | Phenytoin[e] |
| | | Levetiracetam |
| | | Phenobarbitone |
| | | Sodium valproate |
| Analgesic | Ketamine | Morphine |
| | | Fentanyl[f] |
| | | Tramadol |
| | | NSAIDs |
| Sedative | Propofol[g] | Midazolam[h] |
| | Dexmedetomidine[i] | Lorazepam |
| Proton pump inhibitor | Pantoprazole | |
| H2 antihistaminic | | Ranitidine |
| Cardiac medications | Amiodarone | Digoxin[j] |
| | Esmolol | |

[a]Teicoplanin has better renal profile than vancomycin, [b]Dose only modified when creatinine clearance <10 ml/min, [c]Intravenous voriconazole is contraindicated in renal dysfunction because the carrier sulfobutylether B cyclodextrin gets accumulated, [d]Intravenous itraconazole is contraindicated in renal failure, [e]No oral loading dose in renal dysfunction, [f]Fentanyl is the preferred opioid in renal dysfunction asmetabolites are nontoxic, [g]Not recommended for use in pediatric ICU sedation; [h]When creatinine clearance <10 ml/min 50% reduction in dose, [i]Not FDA approved for pediatric ICU sedation; [j]measure levels to prevent toxicity. ICU: Intensive Care Unit, NSAIDs: Nonsteroidal anti-inflammatory drugs

Diuretics: Loop diuretics are routinely used after cardiac surgery to prevent and treat early fluid overload. It has been proven that early fluid overload (>15%) is an independent adverse prognostic marker after cardiac surgery in children.[24] Loop diuretics, in comparison to other classes of diuretics, may increase urine output even in low cardiac output states hence used commonly after cardiac surgery. Loop diuretics have been associated with metabolic alkalosis, neurohumoral activation, systemic vasoconstriction, electrolyte disturbances, impairment of renal function, and worse clinical outcomes.

Most common loop diuretic in postoperative use is furosemide. Furosemide may be used up to a maximum dose of 2–3 mg/kg/day. The routinely used dose is 1 mg/kg/day divided over three doses daily. A convenient way of administering furosemide is once a day dosing.[25] Although this practice ensures greater compliance, it is not advantageous from pharmacological point of view. Once daily dosing ensures therapeutic levels for an only short period, with excess output during that duration, and increases "sodium avidity" for rest of the period. Frequent intermittent dosing prevents this rebound increase in sodium levels and is preferable. A continuous infusion of furosemide is even more beneficial in terms of less fluid alterations, decrease total dose of furosemide per day and reversal of resistance to intermittent boluses of furosemide. Van der Vorst *et al*. observed that high dose intravenous furosemide is well-tolerated, safe and effective in reducing volume overload in hemodynamically unstable infants after CPB surgery.[26]

Ricci *et al*. compared infusions of high dose furosemide with ethacrynic acid and found that both diuretics were safe in terms of renal function, ethacrynic acid was associated with higher incidence of metabolic alkalosis.[27] Ethacrynic acid is also more ototoxic compared to furosemide.

## RENAL REPLACEMENT THERAPY

The types of renal replacement therapy (RRT) used are:

1. Intermittent hemodialysis (IHD)
2. Continuous renal replacement therapies (CRRT)
    a. Continuous venovenous hemofiltration (CVVH)
    b. Continuous venovenous hemodialysis
    c. Continuous venovenous hemodiafiltration (HDF)
    d. Slow continuous ultrafiltration
    e. Continuous arteriovenous hemofiltration

3. Hybrid therapies, for example, sustained low-efficiency dialysis (SLED)
4. Peritoneal dialysis (PD).

RRT uses membrane filters and extracorporeal circuits to filter blood of toxins and metabolites. Inside a nephron, the smallest functioning unit of the kidney, renal blood passes through the glomerulus and is filtered by it. The filterate passes through different tubules where certain compounds are added to filterate before being excreted through the collecting duct. Similarly, in hemofiltration, the blood flow is directed toward a semipermeable membrane (glomerulus) where it is filtered, and the effluent is discarded. Before the purified blood re-enters, the body replacement fluid is added, a process similar to tubular secretion in the nephron.

Vascular access may be achieved from jugular or femoral vessels. Subclavian vein should be avoided because of the risk of thrombosis. The vascular catheter should be $\leq 1/3^{rd}$ of the vein diameter to minimize vessel thrombosis. Arteriovenous fistulas are created to achieve higher flows, in comparison to vascular catheters.[28]

The principle of dialysis and hemofiltration are different. Dialysis is based on diffusion, in which molecules in higher concentration on one side of a semipermeable membrane passively cross to other side of the membrane where the concentration is low. Hemofiltration is based on convection where a high transmembrane pressure is generated on one side of a semipermeable membrane (with the help of a pump) so that there is a net movement of solution across membrane (limited by the pore size and transmembrane pressure). Therefore, the solute is filtered because of the "solvent drag" thus generated. There is a rapid decrease in the solute diffusion coefficients compared to sieving coefficients with an increase in the molecular size. Therefore, dialysis is more suitable for smaller molecules (urea, creatinine) and hemofiltration may remove mid-size and larger molecules like β2 microglobulin.

The timing of RRT depends on many factors such as fluid overload, azotemia, and pH, hyperkalemia. Biomarkers such as serum creatinine, cystatin C, NGAL, IL 6, and HVA $SO_4$ can predict and relate to the severity of AKI. Therefore, optimal time to initiate RRT should be based on clinical and biological markers.

An improvement in the creatinine clearance up to a level of 20ml/min may act as an endpoint to stop CRRT.[29]

In children who are hemodynamically unstable CRRT is better than IHD. Children who are stable and no longer require intensive care IHD is better. The flow rates of both dialysate and blood are much higher in IHD compared to CRRT, hence the instability. Moreover, the dialysate flow is higher than blood flow in IHD whereas in CRRT it is lower than blood flow. The degree of hemodynamic stability with SLED and CRRT is quite similar.

A therapy which combines both dialysis and hemofiltration is known as HDF. HDF is defined as a blood purification therapy combining diffusive and convective solute transport using a high flux membrane characterized by an ultrafiltration coefficient >20 ml/h/mmHg/$m^2$ and a sieving coefficient for β2 microglobulin >0.6. Convective transport is achieved by an effective convection volume of at least 20% of total blood volume processed. Appropriate fluid balance is maintained by external infusion of a sterile, nonpyrogenic solution into patient's blood.[30] The types of HDF are listed in Table 2.

Postdilution HDF is the most efficient mode of HDF as solute concentration is maximum but suffers from drawback of hemoconcentration and clogging of membrane. Predilution HDF is less efficient compared to the former but can achieve ultrafiltration rates up to 100%. In children, a blood flow of 5–8 ml/kg/min or 150–249 ml/min/$m^2$ body surface area is recommended during HDF.

### Peritoneal dialysis

Peritoneum acts as a natural semipermeable membrane during PD. A PD catheter is placed between the abdominal wall and peritoneum. The dialysate fluid is administered through the same catheter inside the cavity and after some time is drained through the same catheter. Therefore, the cycles are defined in terms of in time (during which the dialysate is infused inside the

**Table 2: Modes of controlled hemodiafiltration**

| Mode | Definition |
|---|---|
| Post-dilution hemodiafiltration | Ultrafiltration followed by infusion of replacement fluid |
| Pre-dilution hemodiafiltration | Infusion of replacement fluid followed by ultrafiltration |
| Mid-dilution hemodiafiltration | Infusion of replacement fluid at the mid-point of ultrafiltration (post-dilution followed by pre-dilution) |
| Mixed-dilution hemodiafiltration | Infusion of replacement fluid before and after ultrafiltration (pre-dilution followed by post-dilution) |

cavity), dwell time (the period during which actually diffusion takes place), and drainage time (time given for the effluent to come out). The cycles are usually done 2–3 hourly and dosing of dialysate is about 20 ml/kg/cycle. Dextrose may be added to dialysis fluid to achieve higher osmolarity. Peritoneum is permeable to albumin and, therefore, there is a risk of hypoalbuminemia. If albumin loss is to be prevented then the cycles are commenced more frequently (hourly) with less dwell time. Albumin being a larger molecule in comparison to urea and creatinine has lower diffusion coefficient and takes time to diffuse, therefore, is preserved with frequent cycling.

Metabolic complications such as loss of proteins, catecholamines, and phosphate may occur after RRT. Hypophosphatemia is associated with respiratory and cardiac depression and immune dysfunction.

### Anticoagulation during renal replacement therapy

#### *Unfractionated heparin*

Unfractionated heparin (UFH) is administered as an infusion during RRT, and the effect is monitored by activated partial thromboplastin time (aPTT). The aPTT should be maintained about 1.5 times the control. At this low level of anticoagulation, activated coagulation time is relatively insensitive. A dose of 20–50 U/kg/h is sufficient to maintain anticoagulation. The half-life of unfractionated heparin is 90 min and is prolonged up to 3 h in renal failure due to accumulation of smaller fragments.[31]

#### *Low molecular weight heparin*

Low molecular weight heparin is eliminated by CRRT. However, compared to UFH it has low incidence of heparin-induced thrombocytopenia, less platelet activation, and no metabolic side effects. Anti-Xa levels should be maintained in a range of 0.25–0.35 U/ml to increase the filter life.

#### *Regional citrate anticoagulation*

Local anticoagulation may be achieved by infusing sodium citrate into the blood before it reaches the extracorporeal circuit. Citrate chelates the calcium ion and prevents coagulation. An ionic calcium concentration <0.35 mmol/L is usually sufficient for regional anticoagulation which can be achieved by citrate doses of 4–6 mmol/L in blood. Citrate is converted to bicarbonate in liver. In children with liver dysfunction, this conversion may not take place, and citrate toxicity may occur. A ratio of total calcium to ionic calcium ≥2.5 is suggestive of citrate toxicity.

#### *Direct thrombin inhibitors*

Bivalirudin may be used in a dose of 0.05–0.5 mg/kg bolus followed by 0.03–0.2 mg/kg/h to maintain an aPTT of 1.5 (2.5) times of control. The half-life of bivalirudin is 25 min in patients with normal renal function. The dose needs to be reduced during RRT. Argatroban is another thrombin inhibitor which is metabolized by liver and may be used with renal dysfunction. The dose of argatroban is 100 micg/kg followed by 0.1–0.5 micg/kg/min to maintain an aPTT of 1.5 times of control. Anti IIa levels may also be used for monitoring.

In summary, the incidence of AKI after pediatric cardiac surgery is high. Prompt recognition and management of AKI improves the prognosis of the patient. Treatment of the cause is of utmost importance along with supportive RRT, which should be customized for each patient.

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### Conflicts of interest

There are no conflicts of interest.

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