DOI- 10.21304/2018.0502.00377

Symposium

Prevention of Acute Renal Injury and Drug Modification

Amita Kaul*, Sachin Shah**

*Consultant PICU, **Chief Consultant and Director, Surya Mother and Child Superspecialty hospital, Pune, India

Received: 21-Feb-18/Accepted: 12-Mar-18/Published online: 30-Apr-18

ABSTRACT

Acute kidney injury (AKI) causes increased morbidity in critically ill children and damage to the kidney affects survival. The incidence of AKI in pediatrics is significant and despite alarming data, therapeutic interventions have failed to effect a meaningful difference in outcomes. In this review, we will discuss prevention of AKI in paediatrics, drug modification, need for risk stratification and staging which would help to recognise at risk children.

Key words: prerenal, fluid overload, diuretics, RRT prerenal, fluid overload, diuretics, RRT

Introduction:

Acute kidney injury (AKI) is defined as the abrupt loss of kidney function that results in reduction in glomerular filtration rate (GFR) leading to retention of urea and other nitrogenous waste products, and fluid overload and dyselectrolytemia. The term acute renal failure (ARF) has been replaced by AKI, as it more clearly describes renal dysfunction as a continuum rather than a discrete finding of failed kidney function. Pediatric AKI presents with a wide range of clinical manifestations from a minimal elevation in serum creatinine to anuric renal failure, arises from multiple causes, and occurs in a variety of clinical settings.

Epidemiology:

AKI is an independent risk factor for mortality, with a high odds ratios of 4.8. It independently increases length of stay, ventilator days and cost of treatment.[1] The mortality rate is lower among children who develop AKI outside ICU setting, with reports ranging from 1.5 to 9.5%.[2] In a study of close to 4000 critically ill children, AKI increased mortality and lengthened intensive care stay four-fold .AKI increases mortality with multi-organ failure, hematopoietic stem cell or solid organ transplant, extra-corporeal membrane oxygenation (ECMO), or ARDS anywhere from 10-57.1%.[3] AKI commonly effects kids following cardiopulmonary bypass. For these children, even a small creatinine rise of ≥25% is a significant risk factor for AKI. Severe AKI, defined as receiving renal replacement therapy in children, is associated with a mortality rate between 30 and 50 percent. About 40-50% of pediatric patients who suffered AKI when followed up after 3-5 years, showed signs of chronic renal insufficiency, implying that sub-lethal insult permanently alters the renal bed.[4] Collectively, these studies strongly suggest that AKI represents a serious burden to the pediatric patient population.

Correspondence:
Dr. Sachin Shah MD, DM, Chief Consultant and Director, Surya Mother and Child Superspecialty hospital, Pune, India. Phone:+919850566196, Email: sshahdoc@gmail.com

Risk Factor Assessment:

Significant risk factors associated with AKI are:

- Thrombocytopenia
- DIC
- Hypoxemia
- Hypotension
- Need for invasive ventilation
- Need for vasoactive drugs
- Use of nephrotoxic drugs
- Sepsis
- MODS
- Stem cell transplantation

It has been recommended that any children with above risk factors should be monitored for development of AKI.

Prevention Of Acute Kidney Injury:

General measures to prevent AKI include:

- Preload optimization
- Early detection of fluid overload and treating it with diuretics and renal replacement therapy.
- Drug modification
- Early nutrition

Preload Optimization :

Fluid administration in the conditions mentioned have successfully prevented AKI:

Prerenal AKI due to hypovolemia

In children with a history and physical findings consistent with hypovolemia, administration of an intravenous (IV) fluid bolus with normal saline (10 to 20 mL/kg over 30 minutes) may prevent more severe intrinsic AKI. If required the bolus can be repeated twice or thrice, until urine output is re-established. Fluid challenge is contraindicated in patients with obvious volume overload or heart failure. Each time a fluid bolus is administered one should watch out for warning signs of overdose.

At-risk patients for AKI

Volume expansion with IV normal saline has been effective in preventing AKI in patients at risk for AKI with the following conditions:

- Hemoglobinuria and myoglobinuria
- Administration of potential nephrotoxins including:-Aminoglycosides,Amphotericin, Radiocontrast media, Cisplatin,-IV administration of Acyclovir, Tumor lysis syndrome
- Surgical procedures, in which there is a reduction in the intravascular volume during either the intraoperative or postoperative period.

With the restoration of intravascular volume if the urine output does not increase and renal function fails to improve, it is recommended to catheterize the bladder to confirm anuria. At this point, other forms of invasive monitoring, such as measuring central venous pressure, and bedside ultrasound may be required to adequately assess the child's fluid status and help guide further therapy.

Fluid overload :

Acute kidney injury can be assessed by fluid overload. Decrease in renal function and oliguria will lead to fluid overload and fluid overload per se would contribute to renal dysfunction. It has been observed in various studies that fluid overload progressively worsens the outcome. Fluid balance is independent risk factor for mortality. Several observational studies have demonstrated a correlation between fluid overload and mortality in critically ill patients with acute respiratory distress syndrome, acute lung injury, sepsis, and AKI. Bouchard et al., have shown that patients with fluid overload defined as an increase in body weight of over 10 % had considerably more respiratory failure, need of mechanical ventilation, and more sepsis.[8]

Lungs are one of the organs in which undesirable effects of fluid overload are most evident, which can lead to acute pulmonary edema or acute respiratory distress syndrome. [9] Several studies have substantiated that positive fluid balance is associated with poorer respiratory outcomes. In one of these studies, septic shock patients with acute lung injury who received conservative fluid management after initial fluid resuscitation had lower mortality.[10] Patients randomized to the conservative fluid strategy had lower cumulative fluid balance, improved oxygenation index and lung injury score, increased number of ventilator-free days, and reduction in the length of ICU stay. It is worth to mention that the conservative fluid management strategy did not increase the incidence or prevalence of shock during the study or the need for renal replacement therapies.[11]

It is important in such patients to calculate fluid overload percentage which helps guide the management.

It is calculated as:

FLUID OVERLOAD = [(Fluids in – Fluid out)/Admission weight] X100

Example: for a 10kg child, if in 24 hours he receives 1500ml of IVfluids and his urine output is 1000ml,

then 1500-1000 = 500/10 x 100= 50% is his fluid overload percent.

In the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry Group,[12] mortality rates for patients who developed fluid overload greater than 20 percent, between 10 and 20 percent, and less than 10 percent were 66, 43, and 29 percent, respectively. It was shown in the study that for each 1 percent increase in severity of fluid overload mortality increased by 3 percent.

Treatment of Fluid Overload :

Diuretics. Reducing fluid overload with diuresis can limit the use of renal replacement therapy but has not been proven to improve outcomes from AKI. The use

of diuretics in adults with AKI has been associated with an increased risk of death and has shown no benefit in recovery of kidney function.[13] Using diuretics to convert oliguric AKI into non-oliguric AKI does not reduce the mortality.

A trial of Furosemide may be attempted to induce a diuresis and convert AKI from an oliguric to a nonoliguric form, thereby simplifying fluid and nutritional management. However, loop diuretic therapy does not significantly alter the natural course of AKI. The diuretic probably increases the urine output in the still functioning nephrons and have no effect on the non-functioning one, as a result it doesn't change the course of renal failure even though child may start passing urine.

If a trial of furosemide is used, it should be given as a single high-dose bolus (2 to 5 mg/kg/dose) to children in the early stages of oliguric AKI with hypervolemia (ie, oliguria of less than 24 hours' duration). If the diuretic bolus is effective, a continuous infusion of furosemide (0.1 to 0.3 mg/kg per hour) may be started. Furosemide should be promptly discontinued if the bolus doses do not augment the urine output within two hours of bolus administration. There is higher risk of renal toxicity and ototoxicity from furosemide use due to potential elevated serum levels. Care should also be taken to avoid hypotension from overuse of diuretic therapy as this might result in further kidney injury and, in some cases, increase mortality. Loop diuretics should be given for a short length of time for volume control in responsive patients and not to be used as prolonged therapy for established AKI.

Renal Replacement therapy.

RRT should be considered for critically-ill children with AKI in following conditions:

1. When fluid overload exceeds 10 percent with multiorgan failure, oliguric despite diuretic therapy, or child requires large volumes of fluids (nutrition, blood products, or fluid overload).
2. Serious and potentially life-threatening complications due to fluid overload such as pulmonary edema, heart failure, and hypertension that is refractory to pharmacologic therapy
3. Uremia defined as a BUN between 80 to 100 mg/dL
4. Hyperkalemia (serum or plasma potassium >6.5 mEq/L) unresponsive to nondialytic therapy

RRT modalities include hemodialysis (HD), peritoneal dialysis (PD), and continuous RRT (CRRT). The RRT choice depends on the clinical status of the patient, the expertise of the clinician, and the availability of appropriate resources.

HD requires central vascular access, specialized equipment and technical personnel, anticoagulation (except in patients with coagulopathy), and the ability to tolerate a large extracorporeal volume. Hemodialysis when used for AKI rapidly corrects imbalances in fluid, electrolyte, and acid-base status.

The advantages of PD include ease of performance and no requirement for specialized equipment, personnel, or systemic anticoagulation. Peritoneal dialysis is frequently the therapy of choice in neonates and small infants. The regular bedside PD can be done just for 3-5 days. The insertion of CAPD catheter has to be done by a surgeon under anaesthesia and is a costly affair.

CRRT is especially useful in patients with multiorgan dysfunction and hemodynamic instability and, since it allows continuous management of fluid overload without significant fluid shifts that may occur with HD. Disadvantages of CRRT are vascular access, requirement of technical expertise, vigilance over hemodynamic and coagulation parameters. The cost of disposables per session in a private setup may ranges between Rs. 25,000 and 30,000.[14]

Drug modification in AKI

1. Avoid use of nephrotoxic drugs as they may worsen the injury and delay recovery of function.
2. Dosing adjustment of renally excreted drugs – Doses of renally excreted medications will require adjustment to avoid toxic accumulation of drugs and their metabolites and to prevent worsening of AKI. When AKI is first recognised, creatinine clearance of the child should be calculated. If AKI is in an early stage and Cr is rising, assume GFR to be <10 mL/min/1.73 m^2 and adjust the doses of drugs having renal excretion accordingly. Dose reductions are necessary when GFR falls below 50 mL/min per 1.73 m^2. Medication dosing should be re-evaluated regularly throughout the child's

illness and readjustments should be made as warranted if renal function improves or declines.

3. Example: Meropenem a routinely used antibiotics for gram negative sepsis. Usual dose being 200mg thrice a day for a 10 kg child. (20mg/kg/dose).If the creatinine is 5mg/dl eGFR of the child is 9ml/min and creatinine clearance is 6ml/min the dose would be 50% of usual dose and given once in 24 hours: 100mg once a day. GFR calculations are better marker of kidney function and drug doses is based on creatinine clearance.[15]
4. In addition, drug levels should be routinely monitored for medications for which therapeutic monitoring is available (eg,vancomycin, aminoglycosides ,enoxaparin and digoxin).
5. Drugs aggravating hyperkalemia like spironolactone should be stopped. Betablockers and digoxin both can inhibit sodium potassium ATPase pumps which can pump potassium inside the cells. These drugs renders patient resistant to insulin/glucose infusion used for treatment of hyperkalemia.
6. Avoiding aminoglycosides if possible and using single-daily dosing with therapeutic drug monitoring.
7. Acyclovir causes crystal nephropathy hence prior hydration is important before drug administration. Amphotericin B can cause renal vasoconstriction, it is advised to hydrate the child well before administrating it. Using liposomal amphotericin or azoles and/or echinocandins for fungal and parasitic infections is advised in a child with AKI.

Nutrition :

AKI is associated with marked catabolism, and aggressive nutritional support is the key to enhance the recovery process. A child with AKI will need not only the normal maintenance requirements but also the supplemental calories to tackle the catabolic needs. The enteral route is preferred over the parenteral route for nutritional support. Enteral feeding restores immune responses, promotes gut mucosal integrity, prevents gut atrophy, reduces the risk of nosocomial infection, and is more cost-effective. TPN should be considered only if enteral feeding cannot be established after five to seven days in the PICU or if the child is severely malnourished.

Drugs to enhance the renal perfusion in AKI :

The use of renal vasodilators to increase renal perfusion has not been associated with improved outcomes. Adult studies of so-called "renal-dose", or low dose dopamine have failed to show benefit and may actually be harmful.[18] A meta-analysis of dopamine use in adults showed that in 24 studies, dopamine did not prevent the onset of acute kidney failure, or the need for dialysis and mortality. In children as well renal dose dopamine did not show any improvement in the outcome. Further, low dose dopamine may increase the ischemic injury to the myocardium by increasing myocardial oxygen consumption and also increases the risk of tachyarrhythmias.[16]

Fenoldopam: is a potent, short-acting, selective dopamine A-1 receptor agonist that increases renal blood flow and decreases systemic vascular resistance.[17] Data are limited in the use of this agent in children at risk for AKI.

- In a small single center retrospective study of 13 critically-ill children receiving fenoldopam, a significant increase in urine output and a reduction in blood urea nitrogen (BUN) within 24 hours were noted.[18]
- In a small, 1 prospective, single-center randomized, double-blind, controlled trial of 80 children undergoing cardiac surgery requiring cardiopulmonary bypass, patients who received fenoldopam compared with those treated with placebo. The treatment with high-dose fenoldopam during CPB in pediatric patients significantly decreased urinary levels of NGAL and Cystatin C and reduced the use of diuretics and vasodilators during CPB.[19]

Neither low-dose dopamine nor fenoldopam have been tested in a large prospective cohort pediatric study and cannot be recommended for prevention or management of AKI outside of the context of a clinical trial.

Conclusion

AKI in children is associated with increased mortality and morbidity. Prevention of AKI is important to reduce the long term consequences. It is imperative to monitor children with risk factors. Early and

regular assessment using the staging criteria and daily assessment of fluid overload status should be performed. Interventions to prevent AKI include judicious use of intravenous fluids, avoiding and modifying doses of nephrotoxic drugs.

Source of Funding - Nil

Conflict of Interest - Ni

References

1. Hoste EA, De Waele JJ. Acute kidney injury in the intensive care unit: it's the gene, stupid. Crit Care Med 2008;36:3266–67.
2. Sutherland SM, Ji J, Sheikhi FH, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. Clin J Am Soc Nephrol 2013; 8:1661
3. Zappitelli M. Epidemiology and diagnosis of acute kidney injury. Semin Nephrol 2008;28:436-46.
4. Askenazi DJ, Feig DI, Graham NM, et al. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. Kidney Int 2006;69:184-89.
5. Khwaja A. KDIGO clinical practice guidelines for acute kidney injuryNephron Clin Pract 2012;120(4):c179-84.
6. Mishra J, Dent C, Tarabishi R. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-38.
7. Hirsch R, Dent C, Pfriem H, et al. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatr Nephrol 2007;22:2089-95.
8. Bouchard J, Mehta RL. Fluid balance issues in the critically ill patient. Contrib Nephrol 2010;164:69-78.
9. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med 2004;351(2):159-69.
10. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest 2009;136(1):102-9.
11. Mehta RL, Kellum JA, Shah SV. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
12. Sutherland SM, Zappitelli M, Alexander SR. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis 2010; 55:316.
13. Uchino S, Doig GS, Bellomo R. Diuretics and mortality in acute renal failure. Crit Care Med 2004;32:1669-77.
14. Walters S, Porter C, Brophy PD. Dialysis and pediatric acute kidney injury: choice of renal support modality. Pediatr Nephrol 2009; 24:37.
15. Perazella MA. Drug use and nephrotoxicity in the intensive care unit. Kidney Int 2012; 81:1172.
16. Bellomo R, Chapman M, Finfer S. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356:2139-43.
17. Ranucci M, Soro G, Barzaghi N. Fenoldopam prophylaxis of postoperative acute renal failure in high-risk cardiac surgery patients. Ann Thorac Surg 2004; 78:1332.
18. Moffett BS, Mott AR, Nelson DP. Renal effects of fenoldopam in critically ill pediatric patients: A retrospective review. Pediatr Crit Care Med 2008; 9:403.
19. Ricci Z, Luciano R, Favia I. High-dose fenoldopam reduces postoperative neutrophil gelatinase-associated lipocaline and cystatin C levels in pediatric cardiac surgery. Crit Care 2011; 15:R160.

How to cite this article:
Kaul A, Shah S. Prevention of Acute Renal Injury and Drug Modification. J Pediatr Crit Care 2018;5(2):69-73

How to cite this URL:
Kaul A, Shah S. Prevention of Acute Renal Injury and Drug Modification. J Pediatr Crit Care 2018;5(2):69-73.
Available from: http://jpcc.in/userfiles/2018/0502-jpcc-mar-apr-2018/JPCC05020012.html