AKI after pediatric cardiac surgery for congenital heart diseases—recent developments in diagnostic criteria and early diagnosis by biomarkers-

Yuichiro Toda¹* and Kentaro Sugimoto²

Abstract

**Background:** Acute kidney injury (AKI) after cardiac surgery in children with congenital heart disease is a common complication. AKI is also associated with high morbidity and mortality. The Kidney Diseases Improving Global Outcomes (KDIGO) criteria for AKI classification are now widely used for the definition of AKI. It is noteworthy that a statement about children was added to the criteria. Many studies aimed at finding useful biomarkers are now being performed by using these criteria. Clinicians should be aware of the recent progress in understanding AKI in children.

**Main contents:** Unlike adult patients, young age is one of the major risk factors for AKI in pediatric cardiac surgery. The mechanism of the development of AKI in children might be different from that in adults because the surgical procedure and CPB technique in pediatric patients are greatly different from those in adult patients. There are many biomarkers for early detection of AKI, and some of them are widely used in hospitals. One of the major benefits of such biomarkers is the rapidness of expression for detecting increases in their expression levels. Neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C, and albumin have been investigated in some studies, and the usefulness of these biomarkers for detection of AKI and diagnosis of disease severity has been shown.

Although there are many interventions for preventing and treating AKI after cardiac surgery in children, there is still no specific effective treatment. Peritoneal dialysis is effective for only maintaining a negative fluid balance early after cardiac surgery. The long-term prognosis of AKI is an issue of interest. Although mortality and morbidity of AKI in the acute phase of disease remain high, the long-term condition in pediatric patients is relatively acceptable unlike in adults.

**Conclusions:** KDIGO criteria are advocated as a diagnostic tool for common perception. Early recognition and intervention for AKI can be achieved by using several biomarkers. Further studies are needed to establish effective treatment for AKI.

**Keywords:** Acute kidney injury, Children, Cardiac surgery, Cardiopulmonary bypass, Biomarker, Urinary albumin, NGAL

* Correspondence: ytoda-pccs@umin.ac.jp
¹Department of Anesthesiology and Intensive Care Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki-shi, Okayama 701-0192, Japan
²Full list of author information is available at the end of the article

© The Author(s). 2017 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background

Acute kidney injury (AKI) is a common comorbidity after cardiac surgery in adults [1] and children. Previously reported incidences of AKI in children after cardiac surgery have varied widely [2–4]. It has been shown that many children in whom AKI occurs have prolonged mechanical ventilation and prolonged intensive care unit stay [5, 6]. Although various criteria have been used for the diagnosis of AKI, the Kidney Disease Improving Global Outcomes (KDIGO) classification has recently been introduced as a standard diagnostic tool. Many children suffer from AKI after cardiac surgery, but there is still no specific effective treatment for AKI. The precise mechanism by which AKI develops after cardiac surgery is still not known. Early diagnostic tools such as urine and serum biomarkers have not been established, and there is still no specific treatment for preventing or curing AKI. Here, we describe transition of criteria used for diagnosis of AKI, available biomarkers, and treatment for pediatric patients after cardiac surgery.

Mechanism of the development of AKI after cardiac surgery in children

The precise mechanism by which AKI develops after cardiac surgery is not clear because many factors are involved. The factors involved in the development of AKI include 5 large categories: preoperative, cardiopulmonary bypass (CPB), postoperative, inflammatory, and neuroendocrine factors [7]. Since kidney function in newborns is extremely limited, younger age as a risk factor for AKI is one of the differences from adults. Many adults with heart diseases have vascular changes such as arterial sclerosis, whereas microemboli during CPB is less common in pediatric patients due to the rarity of vascular diseases. Besides, the degree of inflammatory and neuroendocrine responses is considered to be much larger in children than in adults since pediatric CPB results in extensive hemodilution. Moreover, children with congenital heart disease often have various systemic to pulmonary shunts. This may make it difficult for surgeons to maintain a bloodless surgical field, often resulting in prolonged CPB time and/or intentionally decreased CPB flow.

AKI definition

Criteria for diagnosis of AKI such as AKIN [8] and RIFLE [9] criteria have recently been proposed. The RIFLE criteria have also been modified to a pediatric version [10] using Schwartz formulae [11]. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) classification was advocated as AKI definitions in adults and children [12]. The main difference from pediatric RIFLE is the degree of creatinine change as a diagnostic tool, and an optional statement is added for pediatric AKI in stage 3 (Table 1). There is no designation about which formula should be used to calculate estimated glomerular filtration rate (GFR). However, it has been validated in a pediatric population, and higher stages have been shown to be associated with poor prognosis [13, 14].

Epidemiology and risk factors

In children who underwent cardiac surgery for congenital heart diseases, the reported incidences of AKI by the pRIFLE criteria ranged from 20 to 64.6% [2, 15–17]. The reported incidences of AKI by the KDIGO classification ranged from 29 to 86% [3, 4, 18]. Possible reasons for the difference in incidences are differences in patient characteristics (age, heart disease, cardiac status), surgeon’s skill, CPB technique, management of anesthesia, and postoperative care practices. As shown in Table 2, there appears to be a higher incidence of AKI in a younger age group, whereas adults of advanced age have a higher risk of AKI.

There are many risk factors of AKI after pediatric cardiac surgery for congenital heart diseases: low body weight, young age, cyanosis, previous cardiac surgical procedure, risk adjustment in congenital heart surgery—version 1 (RACHS-1) score, univentricular anatomy, preoperative pulmonary hypertension and congestive heart failure, preoperative inotrope and captopril use, preoperative PICU admission, preoperative mechanical ventilation, calendar year (era), and study site [19]. Ruf et al. reasonably showed that low blood pressure in the first 24 h postoperatively was a risk factor [16]. There have been many studies with no detailed hemodynamic data including blood pressure as factors determining kidney perfusion. The study by Ruf et al. re-highlighted the importance of hemodynamics for the risk of AKI.

Biomarkers

Diagnosis and severity of AKI are determined by serum creatinine and urine output. However, serum creatinine and urine output are not timely markers. The usefulness of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin-C, liver type fatty acid-binding protein (L-FABP), and interleukin (IL)-18 as markers has been shown in many studies. NGAL is the most promising marker for detecting AKI at an early phase of disease. Proteomic analysis showed that NGAL was one of the most highly induced proteins in injured distal nephron segments after ischemic or nephrotoxic AKI in animal models [20–22]. In urine that was harvested 2 h after initiation of CPB in pediatric cardiac surgery, it was found that urinary NGAL was significantly increased in children with AKI defined by serum creatinine, and the area under the curve (AUC) for detecting AKI was as high as 0.90–0.99 [23–26]. Unfortunately, measurement of new biomarkers such as NGAL, KIM-1, cystatin-C, L-FABP, and IL-18 are still expensive for them.
to be used as routine measurements. Furthermore, measurements must be done outside the hospital and it usually takes a few days to obtain results. Urine albumin is an old but promising biomarker in this field, and several studies have reaffirmed its importance. Urine albumin can be measured in a general hospital at low cost and the results are promptly available. Generally, in the normal kidney, a small amount of serum albumin goes through the glomerular filter, and almost all of the albumin in the tubule is reabsorbed. Concomitant occurrence of an increase in albumin leakage from the glomerulus and a decrease in albumin reabsorption in the tubule results in albuminuria. It has been reported as additional mechanism that the albumin gene was induced at the renal cortex [27]. AKI can be detected earlier by urinary albumin than by serum creatinine because albumin expression occurs as early as that of NGAL or KIM-1. The diagnostic utility of urine albumin for prediction of AKI after pediatric cardiac surgery is shown in Fig. 1. The AUC for detecting AKI by urine albumin ranges 0.57 to 0.76 [15, 28–30]. These differences are justified by the wide variation of the normal range for urine albumin even in healthy individuals. The normal value of urine albumin in children varies widely depending on age [31, 32], gender [33], weight [34], and race [35]. It was shown that urine albumin corrected by urine creatinine in infants was three times higher than that in adolescents in healthy children [36]. Although a large cohort study in Europe showed that there was no difference in urine albumin levels among all age groups, urine albumin corrected by urine creatinine was higher in a younger age group [31]. There is the same problem for other biomarkers, even NGAL (which is the most extensively investigated biomarker) [37, 38]. In healthy children, approximately 50% of urine protein, mostly Tamm-Horsfall protein (uromodulin), is excreted from the tubular epithelium. Tubular proteinuria is non-reabsorption of freely filtered low-molecular-weight proteins. Albu-
minuria is one of major glomerular proteinuria across the glomerular capillary wall [39].

When a kidney has been damaged, urine NGAL is mainly induced from the tubule, and urine albumin is mainly induced from glomerulus. The mechanism of the development of AKI after cardiac surgery is multifactorial. The participation of both tubular and glomerular damage is one of important mechanisms for development of AKI. In order to detect AKI early and precisely, the combination of multiple AKI biomarkers should be used. Cystatin C is not bound to plasma proteins and is freely filtered by the glomerulus. Cystatin C is reabsorbed and degraded in the renal proximal tubule by the endocytic receptor megalin [40]. Unlike creatinine, cystatin C is not secreted into urine by the tubule, and its appearance in urine therefore indicates its filtration at the glomerulus and reduced uptake by the damaged proximal tubules [41]. The appearance of urinary cystatin C reflects a decrease in GFR. The feasibility of using a combination of cystatin C (functional biomarker) and NGAL (tubular biomarker) after pediatric cardiac surgery has been reported [42]. In that study, the use of combination of

| Stage | Serum creatinine | Urine output |
|-------|-----------------|--------------|
| 1     | 1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase | <0.5 ml/kg/h for 6–12 h |
| 2     | 2.0–2.9 times baseline | <0.5 ml/kg/h for 212 h |
| 3     | 3.0 times baseline or increase in serum creatinine to ≥4.0 mg/dl (≥2353.6 μmol/l) or initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m² | <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h |

Reference [12]
NGAL and cystatin C improved diagnostic precision after cardiac surgery in children.

Management and treatment
There is still no effective specific therapy for AKI after pediatric cardiac surgery. From a physiological point of view, a reasonable intervention is maintenance of appropriate circulation and avoidance of nephrotoxic agents. In the following, issues about peritoneal dialysis (PD), aminophylline, and hydroxyethyl starch (HES) after pediatric cardiac surgery are described.

PD
Pediatric cardiac surgery causes electrolyte disorder, acidosis, and fluid overload that are refractory to standard postoperative care. When infants or neonates are in condition of AKI, starting peritoneal dialysis (PD), aminophylline, and hydroxyethyl starch (HES) after pediatric cardiac surgery are described.

Aminophylline
Theophylline is recommended as class 2B. A single dose of theophylline may be given in neonates with severe perinatal asphyxia, who are at high risk of AKI in the KDIGO AKI practice guidelines [12]. Both theophylline and aminophylline are xanthine derivatives and have a strong diuretic effect. Axelrod et al. showed no effectiveness of prophylactic peritoneal dialysis catheter placement in 22 neonates in a randomized controlled trial. There were no differences between their PDC+ group and PDC− group in mean time to first postoperative negative fluid balance, time to achieve lactate ≤2 mmol/L, maximum vasoactive-inotrope scores on postoperative days 2 to 5, time to sternal closure, time to first extubation, modified clinical outcome score, and hospital length of stay [44]. Sanchez-de-Toledo et al. showed the effectiveness of early initiation of renal replacement therapy (RRT) after pediatric heart surgery in 480 patients in a single-center retrospective study. RRT techniques were used in 32 patients (6.6%), with 25 patients (78%) receiving peritoneal dialysis (PD) and 7 patients (22%) receiving continuous RRT (CRRT). Patients who received PD within the first 24 postoperative hours had lower mortality than did those in whom PD was initiated later [4/16 (25%) vs. 4/9 (44.4%)] [45]. Sasser et al. showed the effectiveness of prophylactic peritoneal dialysis following cardiopulmonary bypass in 52 children in a prospective before-and-after nonrandomized cohort study. Median net fluid balance was more negative in the prophylactic PD group at 24 h (−24 vs. +18 mL/kg) and at 48 h (−88 vs. −46 mL/kg). The prophylactic PD group had less fluid intake and lower inotrope score at 24 h and earlier sternal closure [46]. With regard to the timing for discontinuation of PD, Riley et al. showed in a prospective randomized controlled study that PD continuation for a further 24 h was not effective in 20 infants under 90 days old. Although the group with PD continuation for a further 24 h had lower mean urine output, median levels of AKI biomarkers did not differ significantly between the groups [47]. Prophylactic peritoneal dialysis catheter placement and early initiation of PD may be effective, but more prospective randomized studies are needed.
was administered every 6 h for 72 h in the ICU. There was no significant difference between the incidences of AKI in the aminophylline group and placebo group [48]. Onder et al. showed that the intraoperative usage of aminophylline was more effective than furosemide in reversal of oliguria in the early postoperative period in a single-center, historical control, retrospective cohort study for 200 children after pediatric cardiac surgery. There was no significant difference between the incidences of AKI during a period of 48 h in the aminophylline group and furosemide group [49]. Their study indicates that the effectiveness of aminophylline is limited.

HES
Hydroxyethyl starch (HES) has been used for cheaper and safer volume replacement fluids than albumin solution. However, one of the problems for HES infusion is the possibility of development of renal injury by interstitial proliferation, macrophage infiltraton, and tubular damage [50]. In 7000 adult ICU patients, the use of 6% HES 130/0.4 was associated with a higher incidence of the requirement for RRT [51]. However, a correction was recently made for adverse events in the journal, and an editor in BMJ was concerned the reliability of data [52, 53]. There is a limited information on HES infusion in pediatric patients after cardiac surgery. Van Der Linden et al. showed that the effectiveness of 6% HES 130/0.4 was equal to that of 5% albumin for kidney injury in 61 cardiac surgery children in a randomized, controlled, parallel-group, double-blinded trial. HES and 5% albumin were used for intraoperative volume replacement including priming of the extracorporeal circuitry. Urinary renal biomarkers (α1-microglobulin, β-N-acetylglucosaminidase, NGAL, and albumin) increased in all patients after surgery but without significant differences between the HES group and 5% albumin group [54]. Van Der Linden et al. also showed in a retrospective propensity-matched study that the effectiveness of 6% HES 130/0.4 was equal to that of 4% albumin for kidney injury in 1495 cardiac surgery children with CPB [55]. In that study, there was no difference between the groups in the incidence of postoperative renal failure requiring renal replacement therapy. Akkucuk et al. showed that HES usage as CPB priming solution did not have a negative effect on renal function compared with Ringer’s lactate in 24 cardiac surgery children with CPB in a prospective, randomized study. From CPB initiation to 48 h postoperatively, there were no differences between the groups in cystatin C, β2-microglobulin, fractional excretion of sodium (FENa), urine albumin/creatinine ratio, creatinine clearance, and urine output [56].

Conclusions
Frequent incidences of AKI after pediatric cardiac surgery are recognized. Morbidity and mortality rates in patients with AKI are high for both children and adults. The KDIGO criteria are useful for diagnosing AKI, even in children. Biomarkers for AKI including NGAL, cystatin C, and albumin have become available, and they will enable early and timely intervention. However, only PD seems to be an effective treatment at the current stage. The long-term outcome in children with AKI might be different from that in adults.

Abbreviations
AKI: Acute kidney injury; AKIN: Acute kidney injury network; AUC: Area under curve; CPB: Cardiopulmonary bypass; CRRT: Continuous renal replacement therapy; eCCl: Estimated creatinine clearance; eGFR: Estimated glomerular filtration rate; HES: Hydroxyethyl starch; KDIGO: Kidney Diseases Improving Global Outcomes; KIM-1: Kidney injury molecule-1; L-FABP: Liver fatty acid-binding protein; LMW: Low molecular weight; NGAL: Neutrophil gelatinase-associated lipocalin; PD: Peritoneal dialysis; RIFLE: Risk, injury, failure, loss, end stage kidney disease; UO: Urine output.

Acknowledgements
Not applicable.

Funding
There is no funding for the current article and for this submission.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.
Authors' contributions
YT is responsible for writing and adjusting the manuscript. KS contributed to writing a draft version of the manuscript. Both authors read and approved the final manuscript.

Authors' information
The authors are the authors of reference 15.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1Department of Anesthesiology and Intensive Care Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki-shi, Okayama 701-0192, Japan.
2Department of Anesthesiology and Resuscitology, Okayama University Medical School, Okayama, Japan.

Received: 24 April 2017 Accepted: 6 July 2017
Published online: 20 July 2017

References
1. Bastin AJ, Ostermann M, Slack AJ, Diller GP, Finney SJ, Evans TW. Acute kidney injury after cardiac surgery according to risk/injury/failure/loss/end-stage, acute kidney injury network, and kidney disease: improving global outcomes classifications. J Crit Care. 2013;28:389–96.
2. Gil-Ruiz Gil-Esparza MA, Alcaraz Romero AJ, Romero Otero A, Gil Villanueva N, Sanavía Moran E, Rodríguez Sanchez de la Blanca A, Lorente Romero J, Bellon Cano JM. Prognostic relevance of early AKI according to pRIFLE criteria in children undergoing cardiac surgery. Pediatr Nephrol. 2014;29:265–72.
3. J. Le DL, Toth R, Cserep Z, Alexander SI, Breuer T, Sapi E, Szatmari A, Szekely E, Gal J. Szekely A. A comparison of the systems for the identification of postoperative acute kidney injury in pediatric cardiac patients. Ann Thorac Surg. 2014;97:1020–10.
4. Park SK, Hur M, Kim E, Kim WH, Park JK, Kim Y, Yang JH, Jun TG, Kim CS. Risk factors for acute kidney injury after congenital cardiac surgery in infants and children: a retrospective observational study. PLoS One. 2016;11:e0166228.
5. Taylor MS, Carmona T, Thagalajaran MR, Westgate L, Ferguson MA, del Nido PJ, Rajagopal SM. Mild postoperative acute kidney injury and outcomes after surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2013;146:456–52.
6. Toth R, Breuer T, Cserep Z, Lex D, Fazelek S, Sapi E, Szatmari A, Gal J, Szekely A. Acute kidney injury is associated with higher morbidity and resource utilization in pediatric patients undergoing heart surgery. Ann Thorac Surg. 2012;93:984–90.
7. Bellomo R, Aurierma S, Fabbi A, D'Oonofrio A, Katz N, McCullough PA, Ricci Z, Shaw A, Ronco C. The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). Int J Artif Organs. 2008;31:166–78.
8. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
9. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative w. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204–12.
10. Aiknan-Arikian A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71:1028–35.
11. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34:571–90.
12. The Kidney Diseases Improving Global Outcomes (KDIGO) Working Group. Definition and classification of acute kidney injury. Kidney Int. 2012;Suppl 2:19–36.
13. Sutherland SM, Byrne JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol. 2015;10:554–61.
14. Selevko DT, Connell TJ, Heung M, Troost JP, Ehrmann BJ, Lombel RM, Blatt NB, Luckritz K, Heiber S, Gajarski R, Kenshaw DB, Stanley TP, Gipson DS. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. Intensive Care Med. 2014;40:1481–8.
15. Sugimoto K, Toda Y, Iwasaki T, Shimizu K, Kanazawa T, Muto N, Kawase H, Morimatsu H, Morita K, Maeshima Y, Mor K, Sano S. Urinary albumin levels predict development of acute kidney injury after pediatric cardiac surgery: a prospective observational study. J Cardiothorac Vasc Anesth. 2016;30:64–4.

Ruf B, Bonelli V, Balling G, Horer J, Nagdyman N, Braun SL, Ewert P, Reiter K. Intraoperative renal near-infrared spectroscopy indicates developing acute kidney injury in infants undergoing cardiac surgery with cardiopulmonary bypass: a case-control study. Crit Care. 2015;19:27.
16. Meersch M, Schmidt C, Van Aken H, Rossaint J, Gorlich D, Stege D, Malec E, Januszewska K, Zarbock A. Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery. PLoS One. 2014;9:e108856.
17. Hazle MA, Gajarski RJ, Ayagari R, Yu S, Abraham A, Donohoe J, Blatt NB. Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. J Thorac Cardiovasc Surg. 2013;146:661–7. e1
18. Zappitelli M. Preoperative prediction of acute kidney injury—from clinical scores to biomarkers. Pediatr Nephrol. 2013;28:1173–82.
19. Mishra J, Ma Q, Prada A, Mitrofies MM, Zahedi K, Lang J, Barash J, Devrashian P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol. 2003;14:2543–4.
20. Mishra J, Mori K, Ma Q, Kelly C, Barash J, Devrashian P. Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. Am J Nephrol. 2004;24:137–15.
21. Mori K, Lee HT, Roaporoto D, Drexler R, Foster K, Yang J, Schmidt-Ott KM, Chen X, Li JY, Weiss S, Mishra J, Cheema FH, Markowitz G, Suganami T, Sawai K, Mukomaya M, Kunis C, D’Avati V, Devrashian P, Barash J. Endocytic delivery of lipocalin-siderophore-ion-complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest. 2005;115:610–21.
22. Mishra J, Dent C, Tarabishi R, Mitrofies MM, Ma Q, Kelly C, Ruff SM, Zaheki K, Shao M, Bean J, Mori K, Barash J, Devrashian P, Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;365:1231–8.
23. Bennett M, Dent CL, Ma Q, Dastrala S, Greiner F, Workman R, Syed H, Ali S, Barash J, Devrashian P. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. J Clin Am Soc Nephrol. 2008;36:665–73.
24. Krawczeski CD, Woo JG, Wang Y, Bennett MR, Ma Q, Devrashian P, Neutrophil gelatinase-associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. J Pediatr. 2011;158:1009–15. e1
25. Krawczeski CD, Goldstein SL, Woo JG, Wang Y, Pyathaneee N, Ma Q, Bennett M, Devrashian P, Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. J Am Coll Cardiol. 2011;58:2901–9.
26. Ware LB, Johnson AC, Zager RA. Renal cortical albumin gene induction and urinary albumin excretion in response to acute kidney injury. Am J Physiol Renal Physiol. 2011;300:F628–8.
27. Zheng J, Xiao Y, Yao Y, Xu G, Li C, Zhang Q, Li H, Han L. Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. Pediatr Cardiol. 2013;34:880–6.
28. Zappitelli M, Coca SG, Garg AX, Krawczeski CD, Thiessen Heather P, Sint K, Li S, Parkh CR, Devrashian P, Consortium T-A. The association of albumin/creatinine ratio with postoperative AKI in children undergoing cardiac surgery. Clin J Am Soc Nephrol. 2012;7:1761–72.
29. Devrashian P, Krawczeski CD, Nguyen MT, Kathman T, Wang Z, Parkh CR. Proteomic identification of early biomarkers of acute kidney injury after cardiac surgery in children. Am J Kidney Dis. 2010;56:632–42.
30. Sanchez-Bayle M, Rodriguez-Cimadevilla C, Asencio C, Ruiz-Jarabo C, Baena J, Arnaiz P, Villa S, Cocho P. Urinary albumin excretion in Spanish children. Nino Jesus Group Pediatr Nephrol. 1995;9:428–30.
32. Rademacher ER, Sinaiko AR. Albuminuria in children. Curr Opin Nephrol Hypertens. 2009;18:246–51.
33. Davies AG, Postlethwaite RJ, Price DA, Burn JL, Houton CA, Fielding BA. Urinary albumin excretion in school children. Arch Dis Child. 1984;59:255–30.
34. Skinner AM, Addison GM, Price DA. Changes in the urinary excretion of creatinine, albumin and N-acetyl-beta-D-glucosaminidase with increasing age and maturity in healthy schoolchildren. Eur J Pediatr. 1996;155:556–602.
35. Hanefold CD, Pollock JS, Harshfield GA. Racial differences in microalbumin excretion in healthy adolescents. Hypertension. 2008;51:334–8.
36. Kwak BO, Lee ST, Chung S, Kim KS. Microalbuminuria in normal Korean children. Jyonsei Med J. 2011;52:476–81.
37. Bennett MR, Nehus E, Haffner C, Ma Q, Devarajan P. Pediatric reference ranges for acute kidney injury biomarkers. Pediatr Nephrol. 2015;30:577–85.
38. McWilliam SJ, Antoine DJ, Sabbisetti V, Pearce RE, Jorgensen AL, Lin Y, Leeder JS, Bonventre JV, Smyth RL, Pirmohamed M. Reference intervals for urinary renal injury biomarkers KIM-1 and NGAL in healthy children. Biomark Med. 2014;8:1189–97.
39. Haraldsson B, Nystrom J, Deen WM. Properties of the glomerular barrier and mechanisms of proteinuria. Physiol Rev. 2008;88:451–87.
40. Kaseda R, Iino N, Hosoyama M, Takeda T, Hosaka K, Kobayashi A, Yamamoto K, Suzuki A, Kasi A, Suzuki Y, Geyjo F, Saito A. Megalin-mediated endocytosis of cystatin C in proximal tubule cells. Biochem Biophys Res Commun. 2007;357:1130–4.
41. Vannassenhove J, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 2013;28:254–73.
42. Basu RK, Wong HR, Krawczeski CD, Wheeler DS, Manning PB, Chawla LS, Devapriam P, Goldstein SL. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. J Am Coll Cardiol. 2014;64:2753–62.
43. Kiviartowski DM, Menon S, Krawczeski CD, Goldstein SL, Morales DL, Phillips A, Manning PB, Eghtesady P, Wang Y, Nelson DP, Cooper DS. Improved outcomes with peritoneal dialysis catheter placement after cardiopulmonary bypass in infants. J Thorac Cardiovasc Surg. 2015;149:230–4.
44. Ryden L, Sartipy U, Evans M, Holmman MI. Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease. Circulation. 2014;130:2005–11.
45. Cooper DS, Claes D, Goldstein SL, Bennett MR, Ma Q, Devarajan P, Krawczeski CD. Follow-Up renal assessment of injury long-term after acute kidney injury (FRAIL-AKI). Clin J Am Soc Nephrol. 2016;11:21–9.
46. Atkins SC, Williamson K, Davidson M, Donahue RS. Long-term mortality associated with acute kidney injury in children following congenital cardiac surgery. Pediatr Anesth. 2014;24:919–26.
47. Mel E, Davidovits M, Dagan O. Long-term follow-up evaluation of renal function in patients treated with peritoneal dialysis after cardiac surgery for correction of congenital anomalies. J Thorac Cardiovasc Surg. 2014;147:451–5.