ORIGINAL ARTICLE

Outcomes of acute kidney injury in critically ill children who need renal replacement therapy

Danka Pokrajac, Admir Hadžimuratović, Ismeta Kalkan, Emina Hadžimuratović, Verica Mišanović, Duško Anić, Aida Mustajbegović-Pripoljac

Paediatric Clinic, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To determine an outcome of acute kidney injury (AKI) in critically ill children (CIC) who needed renal replacement therapy (RRT) and were admitted to the Paediatric and Neonatal Intensive Care Unit (PICU and NICU) at the Paediatric Clinic, University Clinical Centre Sarajevo (UCCS).

Methods The research included 81 children with AKI. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI was used. Other laboratory findings and imaging tests were made depending on children's primary disease that led to the AKI.

Results Among 81 children with AKI, 38 were girls and 43 boys. A total of 39 (48.1%) patients died; the death was due to the nature of the primary disease and multiple organ failure syndromes. Out of the total of 81 patients the highest mortality rate was found in children in the first year of life, 22 (56.4%), while 17 (43.6%) patients died after the first year of life.

Conclusion Without an accurate diagnosis at the right time, due to the lack of adequate biomarkers for AKI screening, the heterogeneity of AKI, comorbidities often lead to unfavourable outcomes of the disease, among CIC, especially in infants with low birth weight and extreme immaturity. Some causes of AKI are preventable and can be reduced by a better organization of primary and secondary health care.

Key words: dialysis, morbidity, mortality

Corresponding author:
Danka Pokrajac
Paediatric Clinic,
University Clinical Centre Sarajevo
Patriotske lige 81, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 566 445;
Fax: +387 33 566 525;
E-mail: dankapokrajac@hotmail.com
ORCID ID: https://orcid.org/0000-0002-5998-5620

Original submission:
19 November 2022;
Revised submission:
12 December 2022;
Accepted:
17 December 2022
doi: 10.17392/1562-22

Med Glas (Zenica) 2023; 20(1): 63-70

INTRODUCTION

Acute kidney injury (AKI) is the result of various causes and is associated with significant morbidity and mortality (1). AKI is a very common complication in hospitalized patients (2). Unfortunately, an estimate of renal function based on serum creatinine, urea, and diuresis is poorly sensitive and specific for recording early changes in renal function especially, in paediatric AKI (3). Until now standardized definitions for paediatric AKI have included the Paediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease (pRIFLE), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO), which are most commonly used (3,4). From time to time, researchers have discovered several proteins that could be used as potential early biomarkers of AKI. They have not yet been fully used in clinical settings due to various reasons (5). Since there is no standard definition of AKI or reliable biomarkers, it is not possible to detect AKI on time, which is the main reason for a delay with adequate therapy and consequently a high mortality rate (6).

In general, AKI occurs in 2% to 5% of hospitalized adults and in the neonatal period in the Neonatal Intensive Care Unit (NICU) varies from 8% to 60% (7-9). Also, AKI is common in Paediatric Intensive Care Units (PICUs) with the prevalence of 10% to 35% (10).

Some forms of AKI can be managed conservatively, but severe patients require some dialysis techniques or renal replacement therapy (RRT) (11,12). RRT was indicated for specific situations, like electrolyte imbalances, anuria, refractory acidosis, fluid overload, uremic organ involvement (pericarditis, encephalopathy, neuropathy, myopathy), progressive severe dysnatremia, malignant hyperthermia and removal of endogenous toxins (e.g. ammonia)/exogenous toxins (i.e., poisons), and it was not dependent on the class of AKI (12). The optimal timing of RRT initiation remains controversial until now (13).

We decided to examine the outcome of AKI in critically ill children who needed RRT in Bosnia and Herzegovina (B&H) because of its relatively high prevalence and association with a poor outcome. Our internal annual data from the Paediatric Clinic show that every year acute kidney injury affects up to 12.0% of all hospitalized and up to 60.0% intensive care unit patients. In our Clinic, only in B&H, all dialysis techniques in children have been performed since 2006 by paediatric nephrologists, which we consider to be great success, because only paediatric nephrologists can understand the etiology, pathology, pathophysiology, diagnosis and treatment of AKI in children. A few years ago, the use of dialysis techniques was started in the University Clinical Hospital in Mostar (B&H) by paediatric nephrologists. There is a lot of research on this topic in the world, especially in high-income countries, where most articles on this issue come from, but they are quite uneven and as such are difficult to compare (2,4,7). Also, follow-up studies evaluating the relationship between children's AKI and long-term outcome are generally rare. The awareness that geographical, ethnic and other specific factors of each country have an influence on the etiology of AKI is important for the treatment of these patients. In addition, B&H has a poor disease prevention program, primarily immunization programs, which was the reason why some infectious diseases were the cause of severe forms of AKI and even deaths. Unfortunately, in the developing countries, in rural regions, the etiological factors remain as dehydration, sepsis, and haemolytic uremic syndrome (11). Also, in these countries, there is a problem of a lack of technical and economic support in performing different RRT modalities and other sophisticated diagnostic and therapeutic procedures necessary for the treatment of critically ill children in intensive care units (12). These have been among the important reasons for high mortality rate in these patients for decades.

Recent studies on the paediatric epidemiology of AKI, more clearly defining newer biomarkers and newer criteria for risk stratification of children admitted to intensive care units, are very promising. There is also new research on machines made specifically for smaller children with smaller extracorporeal volumes (13). It should always be remembered that the best is the individual approach to each patient.

The aim of the study was to determine the outcome of acute kidney injury in critically ill children (CIC) who needed renal replacement therapy and were admitted to the Paediatric and Neonatal Intensive Care Unit at the Paediatric Clinic, University Clinical Centre Sarajevo (UCCS).

Patients and methods

Patients and study design

This retrospective descriptive study based on data from patients' medical records included all 81 children who required some of the dialysis techniques due to definition of stage 2 and 3 AKI at the Paediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at the Paediatric Clinic, University Clinical Centre Sarajevo (UCCS) between 1 January 2006 and 1 October 2021. The KDIGO criteria to define AKI were used (14). Severe acute kidney injury was defined as stage 2 or 3 AKI at the plasma creatinine level ≥2 times the baseline level or urine output <0.5 mL per kilogram of body weight per hour for ≥12 hours (3).

Methods

The estimated glomerular filtration rate was calculated with the use of the original Schwartz formula (15). All AKI patients had detailed history, physical examination and laboratory data: serum levels of urea, creatinine, serum electrolyte, acid-base balance, uric acid, cholesterol, triglycerides, proteinogram, C - reactive protein, complete blood count, urinalysis with microscopy, urine culture, urinary electrolytes, creatinine and urea nitrogen. In some cases creatine phosphokinase was determined (if rhabdomyolysis was suspected), eosinophils count in urine sample (if the patient was receiving a medication with the potential to cause interstitial nephritis), stool sample for enteropathogenic *Escherichia coli* (if the haemolytic uremic syndrome was suspected). Anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-streptolysin O titre, complement component C3 and C4 level, anti-nuclear cytoplasmic antibody, anti-glomerular basement membrane antibody (if the patient had history, signs and symptoms consistent with glomerulonephritis), 24-hour urine for calcium, oxalate, citrate, creatinine, uric acid (in patients with confirmed nephrolithiasis), electrocardiogram, chest X-ray and ultrasonography of abdomen. Other special investigations, echocardiography, electroencephalography, abdominal computed tomography scan (if trauma or abdominal mass was suspected), spiral computed tomography scan (if nephrolithiasis was suspected), and kidney biopsy, performed when it was necessary.

The research was conducted at different Clinics of the UCCS. Peritoneal dialysis with the stay-safe system, and different types of haemodialysis on the device Multifiltrate Acute Therapy are available at the Clinic. Haemodialysis with peritoneal dialysis was combined where it was necessary.

Statistical analysis

Categorical data are presented as counts and percentages and were analysed with the $\chi 2$ test and Fisher's exact test, as appropriate. The $p<0.05$ was taken as statistically significant.

RESULTS

The age of patients who were on dialysis for AKI was from 12 days to 17 years and 2 months; the mean age of AKI presentation was 6.28 years. Gender was represented with 43 (53.1%) males and 38 (46.9%) females (p=0.815). AKI was presented in 42 (51.9%) infants and in 39 (48.1%) children after the first year of age (p=0.9383).

The prerenal causes of AKI were noticed in 57 (70.4%) patients, renal in 23 (28.4%), and postrenal in one child (1.2%), with predominance of prerenal causes of AKI (p=0.0096).

The causes of AKI were different depending on the age of the children (Table 1).

Table 1. Etiological factors of acute kidney injury (AKI) among children older than one year of age

Etiology	No (%) of children
Haemolytic-uremic syndrome (HUS)	10 (25.6)
Systemic diseases with macrophage activation syndrome (MAS)	3 (7.7)
Glomerulonephritis	3 (7.7)
Tumours	3 (7.7)
Meningococcal disease	3 (7.7)
Leucosis	2 (5.2)
Diseases represented as just one case of AKI*	15 (38.4)
Total	**39 (100.0)**

*drug-induced AKI with propofol, non-steroidal anti-inflammatory drug, acute liver injury induced by paracetamol, hepatitis unknown cause, after surgery of hydatid cyst of lung and liver, tubulointerstitial nephritis, sepsis in child with severe anomalies of urinary system with myelomeningocele and hydrocephalus, case of sepsis after unusual, unexplained and accidental perforation of ventriculus, case of sepsis after surgery of volvulus in child with West syndrome, Hantavirus pulmonary syndrome (HPS), Salmonellosis and dehydration, septic shock and acute respiratory distress syndrome (ARDS), varicella and disseminated intravascular coagulation (DIC), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome and neonatal hyperammonemic encephalopathy.

In children over the first year of life in 10 cases the cause was haemolytic-uremic syndrome (HUS) associated with diarrhoea. Three cases

each were the cause of AKI: systemic disease in combination with macrophage activation syndrome, glomerulonephritis (two of them had AKI due to nephrotoxicity of the calcineurin inhibitor in case of focal and segmental glomerulosclerosis, and in one case it was a severe form of Henoch–Schönlein – nephritis -HSPN), tumour (*ovarian cancer, retinoblastoma and* lymphoma), which quickly led to leukaemia (ALL) and one with acute myeloid leukaemia (AML) associated with sepsis quickly ended in death.

Among children older than one year of age interesting and rare diseases that were represented as a single case of AKI were found in 15 (38.46%) out of the total of 39 children (Table 1).

A total of 39 (48.1%) patients died, and the death was caused by the nature of their primary disease and multisystem failure syndrome (Tables 2, 3). The highest number of deaths was noticed in children in the first year of life, 22 (56.4%), compared to 17 (43.6%) after the first year of life (p=0.7298).

Table 2. Primary etiological causes of death in infants with acute kidney injury (AKI)

Cause of death	No (%) of children
Congenital heart diseases	7 (31.9)
Perinatal asphyxia + respiratory distress syndrome	6 (27.3)
Sepsis in Premature Babies	4 (18.2)
Multiple congenital anomalies	3 (13.6)
Neonatal hyperammonemic encephalopathy	1 (4.5)
Coagulopathy and hepatic dysfunction (cause was unknown)	1 (4.5)
Total	**22 (100.0)**

Table 3. Etiological causes of death after the first year of life with acute kidney injury (AKI)

Causes of death	No (%) of children
Tumours	3 (17.6)
Meningococcal disease	2 (11.7)
Congenital heart disease	2 (11.7)
Diseases represented as a single case of AKI*	10 (59.0)
Total	**17 (100.0)**

*systemic diseases with macrophage activation syndrome, glomerulonephritis in Henoch-Schönlein purpura, leucosis , acute liver injury induced by paracetamol, sepsis in a child with severe anomalies of urinary system with myelomeningocele and hydrocephalus , case of sepsis after unusual, unexplained and accidental perforated of ventriculus, case of sepsis after surgery of volvulus in a child with West syndrome, varicella and DIC, MELAS syndrome and neonatal hyperammonemia encephalopathy.

The primary etiological causes of death from AKI were different depending on the age of the children (Table 2, 3). In infants causes of death included congenital heart disease, perinatal asphyxia with respiratory distress syndrome, sepsis in premature babies, multiple congenital anomalies, neonatal hyperammonemia encephalopathy, coagulopathy and hepatic dysfunction (a cause was unknown). Etiological causes of death after the first year of life were: tumours (*ovarian cancer, retinoblastoma and* lymphoma), meningococcal disease, congenital heart disease. It should be mentioned that we noted among children older than one year of age interesting and rare diseases that were represented as a single case of death in children with AKI (Table 3).

Out of the total of 81 patients with AKI, 39 (48.1%) fully recovered, two (2.5%) children had chronic kidney disease (CKD), one (1.3%) child had a transplantation due to the end-stage renal disease, and 39 (48.1%) patients died during the acute phase (Table 4).

Table 4. Overall outcome in acute kidney injury (AKI) in children

Outcomes	No (%) of children
Complete recovery	39 (48.1)
Partial recovery (chronic renal disease)	2 (2.5)
Renal replacement therapy (RRT)	1 (1.3)
Death	39 (48.1)
Total	**81 (100.0)**

DISCUSSION

In the Paediatric Clinic of the UCCS in 1998, the Paediatric and Neonatal Intensive Care Unit were established for intensive treatment of infants and older children. This contributed to admitting the most difficult patients almost from all B&H. In addition to patients with severe internal diseases, a large percentage of surgical patients (38.27%), especially those following complex heart anomalies surgery (54.84%) and severe infectious diseases and malignancy are treated at the PICU and NICU. In most developed countries in the intensive care units (ICUs) for children, the proportion of surgical patients is around 50% (16).

Scientific and technological advances during the second half of the 20th century and in two decades in the 21st century enabled the development of dialysis techniques and their good application in children (17). At the Paediatric Clinic of the UCCS, dialysis began just before the war in 1992 in B&H; after a 5-year break during the war, peritoneal dialysis continued, and haemodialysis has been performed since 2009 (18).

Each modality of RRT has advantages and disadvantages. Peritoneal dialysis can be used in

small children such as premature babies, because it seems to be a feasible procedure without major complications. Haemodialysis removes fluid and toxins rapidly, but it is dangerous for small children and hemodynamically unstable patients (19). Mortality in patients requiring renal replacement is high, up to 66% (20,21).

As in our study, in most studies the AKI prevalence in boys is higher in relation to girls. The males prevalence of 56.4% in the USA (22), 53% in Norway (23), 50.8% in Belgium (24), 57.9% in Germany (25) and 68.6% in Nigeria (26) was noticed. The mean age of children with AKI presentation in our study was 6.28 years similarly to Norway (6.0 years) and Belgium (6.1 years), while in Nigeria it was 4.8 years (23-26).

For many years the diagnosis and management of AKI was based on the inadequate concept of classification to three main categories: prerenal, intrinsic (renal) and postrenal. If these pre- and/or post-renal conditions persist, they will eventually evolve to into renal cellular damage and hence intrinsic renal disease (7).

A large proportion of prerenal causes of AKI occurs in underdeveloped countries with poorly developed prevention (26-28). In our study, a large percentage of prerenal causes of AKI was the result of multifactorial causes in the state of multiorgan failure due to severe primary diseases, especially in newborns and infants. Many patients with AKI have a mixed etiology where sepsis, severe infections, various post-operative conditions of congenital anomalies, especially heart defects in newborns, malignancy, chronic kidney, heart, liver or gastrointestinal disease, use of inotropes, aminoglycosides and other multiple nephrotoxic drugs and ischemia, in a single patient, complicating primary disease recognition and treatment (29). Our results from this field of paediatric nephrology observed changes in the pathology of comorbidity of AKI in critically ill children, which is of great importance for further investigations and management of these patients. Studies have found that the causes of AKI have changed dramatically in the last few decades. It has been noted that earlier causes of AKI in hospitalized children, such as haemolytic uremic syndrome, glomerulonephritis, and primary renal diseases, have been replaced by sepsis, critically basic serious illness status, congenital heart disease (7, 30-32), postsurgical, postransplantation, and oncological illness. This was also the case in our study, especially in children younger than one year of age.

In various studies, the prevalence of newborns with AKI in the intensive care unit is high, even up to 60% (33). The reason for this high span of AKI in newborns resulted from non-uniformity of the examined parameters in the studies that investigate this issue. It must not be forgotten that in newborns, the mechanism of autoregulation of blood flow through the kidney is still immature, and consequently any agent can damage this precise mechanism and lead to AKI (34).

The AKI frequently occurs in children under the age of one year (35). In our study of newborns and infants with AKI, death was caused by a combination of cardiac insufficiency caused by complex heart defects, which were operable or inoperable in the first place, which were complicated by other usual unfavourable factors in the ICU. It should also be kept in mind that AKI patients who need RRT and are on mechanical ventilation, with mixed etiology require a significantly longer stay in the ICU and after that standard hospital therapy and care, which represents a great burden for the health system (4,9,13,31).

Newborns with severe asphyxia, a low score of the Apgar test, open ductus arteriosus, and whose mothers used antibiotics and non-steroidal anti-inflammatory drugs during pregnancy and very-low-birthweight (<1500g), could reach AKI up to 40% and to 60% in extremely low birthweight (<1000g) compared to those with moderate asphyxia and normal birth weight (9,36). These patients are extremely susceptible to sepsis. The pathophysiology of sepsis in AKI patients is very complex and involves inflammation, oxidative stress microvascular dysfunction and amplification of injury via secretion of cytokines by tubular cells, as well as the application of many diagnostic and therapeutic procedures (37). AKI is a clinically relevant immunocompromised state (38).

The pathophysiology of hypoxia/ischemia-induced AKI is not well understood. The kidney is a vascular organ so it is highly susceptible to injury related to ischaemia, resulting in vasoconstriction, endothelial injury, and activation of inflammatory processes (31).

Each acute kidney injury in the period of active nephrogenesis before 34 weeks of the gestation leads to decreased number of nephrons and subsequent glomerulomegaly (30).

These facts are the reason for the high mortality rate in newborns and infants.

Several studies have demonstrated that genetic risk factors are involved in AKI in some newborns and children (39). Polymorphism of the angiotensin-converting enzyme gene, tumour necrosis factor alpha, interleukin 1b, 6, 8 and 10 genes were investigated to determine if polymorphisms of these genes would lead to a more intense inflammatory response and predispose newborns to AKI (40,41).

Bosnia and Herzegovina is a country with a small population. For this reason, the results of our study are limited in the involved number of critically ill children with AKI who required renal replacement therapy. According to etiological factors of AKI obtained from this research, B&H is between developed and developing countries. We have found interesting and rare individual cases that led to AKI and even fatal outcomes (38.46). These patients, who had primary serious life-limiting diseases, were immunocompromised, and some of them had drug-induced AKI. It is understandable that despite all procedures, which are applied in intensive care unit and RRT in this group of patients, mortality was very high, even 66.67% (10).

The prevalence of AKI and mortality rate in preterm infants and newborns has increased despite numerous improvements in ICU and the use of renal replacement therapy worldwide. The reason for this are aggressive therapeutic procedures, especially surgical, increased use of RRT, mechanical ventilation, longer stays in the ICU, hypoalbuminemia, and transportation services to seriously ill children (42). Published mortality rates for such patients in the USA, Belgium, Nigeria, Argentina and Brazil range from 11% to 46% (7, 24, 26, 43, 44). In our study a high percentage of mortality is quite expected considering the treatment of the most severe cases in intensive care units. Children who have AKI as a component of multisystem failure have a much higher mortality rate, which was the case especially in children under one year of age.

In our research of all surviving children, only one patient had developed end-stage renal disease and after one period of haemodialysis, kidney transplantation was performed. In two patients there was chronic kidney disease, hypertension and permanent tubular dysfunction, which requires careful monitoring and therapeutic and dietary measures. In a Belgian study 15% of children died, while 16.1% developed CKD (24). Previously it was thought that such patients were at a low risk for late complications (45), but several recent studies have demonstrated that CKD can evolve from AKI (20, 23). For this reason such children need long-term follow-up of their renal function.

In our opinion, describing the epidemiological and etiological aspects of this serious condition in Bosnia and Herzegovina makes an important contribution to evaluating the national relevance and burden on the healthcare system since it is the most expensive medical service.

In conclusion, the heterogeneity of AKI casemix, comorbid factors, and the complex nature of the pathophysiology of AKI, without accurate diagnosis at the right time, due to the lack of reliable biomarkers for AKI screening, do not allow for early detection of AKI, leading to delays in the induction of treatment until the renal injury is well advanced. Timely recognition of patients at risk or with possible acute kidney injury is essential for early intervention to minimize further damage and improve outcomes, especially in infants, in case of low birth weight and extreme immaturity. Some causes of AKI are preventable, and it should be possible to reduce mortality and morbidity by better organization of primary and secondary healthcare. In addition, an optimal paediatric dialysis program should provide all dialysis modalities for all children and well-trained healthcare personnel. We are fortunate that at the Paediatric Clinic, University Clinical Centre Sarajevo, we can provide all modalities of dialysis techniques to critically ill children with AKI in intensive care units.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Bhojani S, Stojanovic J, Melhem N, Maxwell H, Houtman P, Hall A, Singh C, Hayes W, Lennon R, Sinha MD, Milford DV. The incidence of paediatric acute kidney injury identified using an AKI e-alert algorithm in six English hospitals. Front Pediatr 2020; 8:29.
2. Parikh RV, Tan TC, Salyer AS, Auron A, Kim PS, Ku E, Go AS. Community-based epidemiology of hospitalized acute kidney injury. Pediatrics 2020; 146 (3):e20192821.
3. Sutherland SM, Byrnes 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.
4. Sethi SK, Bunchman T, Chakraborty R , Raina R. Pediatric acute kidney injury: new advances in the last decade. Kidney Res Clin Pract 2021; 40:40–51.
5. Beker BM, Corleto MG, Fieiras C, Musso CG. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. Int Urol Nephrol 2018; 50:705-13.
6. Yoon SY, Kim JS, Jeong KH, Kim SK. Acute kidney injury: biomarker-guided diagnosis and management. Medicina 2022; 58:340.
7. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 2017; 376:11-20.
8. Chowdhary V, Vajpeyajula R, Jain M, Maqsood S, Raina R, Kumar D, Mhanna MJ. Comparison of different definitions of acute kidney injury in extremely low birth weight infants. Clin Exp Nephrol 2018; 22:117-25.
9. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, Chishti AS, Woroniecki R, Mammen C, Swanson JR, Sridhar S, Wong CS, Kupferman JC, Griffin RL, Askenazi DJ. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health 2017; 1:184-94.
10. Kavaz A, Ozçakar ZB, Kendirli T, Oztürk BB, Ekim M, Yalçinkaya F. Acute kidney injury in a paediatric intensive care unit: comparison of the pRIFLE and AKIN criteria. Acta Paediatr 2012; 101:e126–e9.
11. Annigeri RA, Ostermann M, Tolwani A, Vazquez-Rangel A, Ponce D, Bagga A, Ravindra C, Mhta LR. Renal support for acute kidney injury in the developing world. Kidney Int Rep 2017; 2:559–78.
12. Kluwer W. Dialysis therapies in acute kidney injury for children. Indian J Nephrol 2020; 30:579-86.
13. Valdenebro M, Martín-Rodríguez L, Tarragón B, Sánchez-Briales P, Portolés J. Renal replacement therapy in critically ill patients with acute kidney injury: 2020 nephrologist's perspective. Nefrologia 2021; 41:102–14.
14. Levi TM, de Souza SP, de Magalhães JG, de Carvalho MS, Cunha AL, de Oliveira Dantas JG, Cruz MG, Guimarães YLM, Cruz CMS. Comparison of the RIFLE, AKIN and KDIGO criteria to predict mortality in critically ill patients. Rev Bras Ter Intensiva 2013; 25:290–6.
15. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976; 58:259-63.
16. Restrepo JM, Mondragon MV, Forero-Delgadillo JM, Lasso RE, Zemanate E, Bravo Y, Castillo GE, Tetay S, Cabal N, Calvache JA. Acute renal failure in children. Multicenter prospective cohort study in medium-complexity intensive care units from the Colombian southeast. PLoS One 2020; 15:e0235976.
17. Tang YS, Tsai YC, Chen TW, Li SY. Artificial kidney engineering: the development of dialysis membranes for blood purification. Membranes 2022; 12:177
18. Miličić-Pokrajac D. Pedijatrijski RRT pacijenti u Bosni i Hercegovini (Pediatric RRT patients in Bosnia and Herzegovina). In: Resić H, Mešić E. Nadomještanje bubrežne funkcije u Bosni i Hercegovini 2001-2014. (Replacement kidney function in Bosnia and Herzegovina 2001-2014) [in Bosnian]. Sarajevo: Štamparija Fojnica, 2015: 79-87.
19. Raina R, Lam S, Raheja H, Krishnappa V, Hothi D, Davenport A, Chand D, Kapur G, Schaefer F, Sethi SK, McCulloch M, Bagga A, Bunchman T, Warady BA. Pediatric intradialytic hypotension: recommendations from the Pediatric Continuous Renal Replacement Therapy (PCRRT) Workgroup. Pediatr Nephrol 2019; 34:925-41.
20. Cho MH. Pediatric acute kidney injury: focusing on diagnosis and management. Child Kidney Dis 2020; 24:19-26.
21. Naik S, Sharma J, Yengkom R, Kalrao V, Mulay A. Acute kidney injury in critically ill children: risk factors and outcomes- Indian J Crit Care Med 2014; 18:129-33.
22. Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, Ling XB. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. Clin J Am Soc Nephrol 2013; 8:1661-9.
23. Jenssen GR, Hovland E, Bangstad HJ, *Nygård* K, Vold L, Bjerre A. The incidence and aetiology of acute kidney injury in children in Norway between 1999 and 2008. Acta Pædiatrica 2014; 103:1192–7.
24. Keenswijk W, Vanmassenhove J, Raes A, Dhont E, Vande Walle J. Epidemiology and outcome od acute kidney injury in children, a single center study. Acta Clinica Belgica 2017; 72:405-12.
25. Marzuillo P, Baldascino M, Guarino S, Perrotta S, Miraglia Del Giudice E, Nunziata F. Acute kidney injury in children hospitalized for acute gastroenteritis: prevalence and risk factors. Pediatr Nephrol 2021; 36:1627-35.
26. Esezobor CI, Ladapo TA, Osinaike B, Lesi FE. Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. PLoS One 2012; 7:e51229.
27. Vachvanichsanong P, Dissaneewate P, Lim A, McNeil E. Childhood acute renal failure: 22-year experience in a university hospital in southern Thailand. Pediatrics 2006; 118:e786–91.
28. Bhattacharya M, Dhingra D, Mantan M, Upare S, Sethi GR. Acute renal failure in children in a tertiary care center. Saudi J Kidney Dis Transpl 2013; 24: 413–7.

29. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev 2016; 37:85-98.
30. Stritzke A , Sumesh Thomas S , Amin H , Fusch C, Lodha A. Renal consequences of preterm birth. Mol and Cell Pediatr 2017; 4:2.
31. Gaut JP, Liapis H. Acute kidney injury pathology and pathophysiology: a retrospective review. Clin Kidney J 2021; 14:526 –36.
32. Ricci Z, Raggi V, Marinari E, Vallesi L, Di Chiara L, Rizzo C, Gist KM. Acute kidney injury in pediatric cardiac intensive care children: not all admissions are equal: a retrospective study. Cardiothorac Vasc Anesth 2022; 36:699-706.
33. Ibiebele I, Algert CS, Bowen JR, Christine, Roberts CL. Pediatric admissions that include intensive care: a population-based study. BMC Health Serv Res 2018 ;18:264.
34. Post EH, Vincent JL. Renal autoregulation and blood pressure management in circulatory shock. Crit Care 2018; 22: 81.
35. Coleman C, Tambay Perez A, Selewski DT, Steflik HJ. Neonatal acute kidney injury. Front Pediatr 2022; 10:842544.
36. Lee CC, Chan OW, Lai MY,Hsu KH,Wu TW,Lim WH,Wang YC, Incidence and outcomes of acute kidney injury in extremely-low-birth-weight infants. PLoS One 2017;12:e0187764.
37. Manrique-Caballero CL, Del Rio-Pertuz G, Gomez H. Sepsis-associated acute kidney injury. Crit Care Clin 2021; 37:279–301.
38. Formeck CL, Joyce EL, Fuhrman DY, Kellum JA. Association of acute kidney injury with subsequent sepsis in critically ill children. Pediatr Crit Care Med 2021; 22:e58-e66.
39. Vilander LM, Kaunisto MA, Pettilä V. Genetic predisposition to acute kidney injury – a systematic review. BMC Nephrol 2015; 16:197.
40. Vasarhelyi B, Toth-Heyn P, Treszl A, Tulassay T. Genetic polymorphism and risk for acute renal failure in preterm infants. Pediatr Nephrol 2005; 20:132–5.
41. Kadi FA, Yuniati T, Sribudiani Y, Rachmadi D. The association of rs187238, rs19465518 and rs1946519 IL-8 polymorphisms with acute kidney injury in preterm infants. BioMedicine 2021; 11:43-50.
42. Leghrouz B, Kaddourah A. Impact of acute kidney injury on critically ill children and neonates. Front Pediatr 2021; 26:9:635631.
43. Martin SM, M.D. Balestracci A, Aprea V, Bolasell C, Wainsztein R, Debaisi G, Rosón G. Acute kidney injury in critically ill children: incidence and risk factors for mortality. Arch Argent Pediatr 2013; 111:412-7.
44. Riyuzoa MC, Silveira LV, Macedoa CS, Fioretto JR. Predictive factors of mortality in pediatric patients with acute renal injury associated with sepsis. J Pediatr (Rio J) 2017; 93:28.
45. Rifkin DE, Coca SG, Kalantar-Zadeh K. Does AKI truly lead to CKD? JASN 2012; 23:979-84.