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The Causes of Acute Kidney Injury in Critically Ill Children Who Needs Renal Replacement Therapy

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ABSTRACT

Background: Acute kidney injury (AKI) is the result of various causes and is associated with significant morbidity and mortality as well as long-term renal sequelae in pediatric patients. **Objectives:** The aim of the study is to determine the causes of AKI in pediatric patients who needed renal replacement therapy (RRT) and were admitted to the Pediatric and Neonatal Intensive Care Unit (PICU and NICU) at the Pediatric Clinic, University Clinical Center Sarajevo (UCCS). **Methods:** Our research included 81 children with AKI who needed RRT. We used the Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI. Severe acute kidney injury was defined as stage 2 or 3 of AKI when plasma creatinine level ≥2 times the baseline level or urine output <0.5 ml per kilogram of body weight per hour for ≥12 hours. Other laboratory findings and imaging tests were made depending on their primary disease that led to the AKI and its complications. **Results:** Our research analyzed 81 children with AKI who needed RRT 38 girls and 43 boys ages from birth to 18 years. Mean age of presentation was 6.28 years. Male female ratio in this study was 1.1:1. Non-olyguric AKI was diagnosed in 12 (14.8%) of children with AKI, while the rest 69 (85.2%) had the olyguric type. Patients with AKI were analyzed after a rough division on prerenal in 57 (70.4%) children, intrarenal in 23 (28.4%) and post-renal in 1 (1.2%) patient. **Conclusion:** As the AKI plays a key role in the mortality and morbidity in pediatric patients, especially in infants, it is important to recognise and treatment on time different etiologies of this serious condition. Some causes of AKI in our country can be prevented by better organization of primary and secondary health care, which would also reduce mortality and morbidity from AKI.

Keywords: acute kidney injury, causes, intensive care unit, early detection, survival.

1. BACKGROUND

Acute kidney injury (previously called acute renal failure) is a very common complication in hospitalized patients. Unfortunately, an estimate of renal function based on serum creatinine (SCr), urea and diuretic levels is poorly sensitive and specific for recording early changes in renal function especially in pediatric AKI (1). Until know standardized definitions for pediatric AKI include the Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease (pRIFLE), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) are most commonly used (1, 2). 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 setting due to various reasons (3). Since there is no standard definition of AKI or reliable biomarkers it is not possible to detect AKI in time which is the main reason for the delay with adequate therapy.

Many patients with AKI have a mixed etiology where sepsis, ischemia, and nephrotoxicity go hand in hand in a single patient, complicating disease recognition and treatment. In general AKI occurs in 2% to 5% of hospitalized adults, and in children, the incidence is slightly lower, except in the neonatal period, where it is varies from 8% to 60% (4-6). Among the neonate subgroup, the largest retrospective study in the neonatal population, known as Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN), was performed in 2017. This study included more than 2,000 newborns in four different countries admitted to the neonatal ICU before 14 days of life. AKI was seen in 30% of all newborns and with a higher incidence in extreme preterm birth infants and children who are ventilated and are on

inotropes (7). The reason for this is the immaturity of the mechanism of autoregulation of blood flow through the kidney in newborn. Also, it is common in pediatric intensive care units (PICUs) with incidence of 10% to 35% (8). Recent studies have shown that the incidence of AKI in hospitalized patients is increasing and that the causes have changed from primary renal disease to multifactorial causes in the state of multiorgan failure (9). AKI, also is a risk factor for hypertension and chronic kidney disease (CKD) in the long term (13).

Some forms of AKI can be managed conservatively, but severe cases require some of the dialysis techniques. Scientific and technological advances during the second half of the 20th century and in two decades in 21st century enabled the development of dialysis techniques and their application in children. At the Pediatric Clinic of the UCCS, a dialysis began just before the war in 1992 in Bosnia and Herzegovina. After a 5-years of break during the war, peritoneal dialysis (PD) continued, and hemodialysis (HD) was performed at the UCCS Clinic of Hemodialysis until 2009, and after that at the Pediatric Clinic UCCS (10). Indications for RRT include fluid overload, severe hyperkalemia, metabolic acidosis, and severe uremia. The optimal timing of RRT initiation remains controversial until now. RRT modalities for AKI have begun with peritoneal dialysis and hemodialysis, and are now expanding to continuous renal replacement therapy (CRRT) (11). Each modality has advantages and disadvantages. Peritoneal dialysis can be used in small children such as preterm infants, but removes fluid and waste slowly and unpredictably. Hemodialysis removes toxins rapidly, but is dangerous for small children and hemodynamically unstable patients. In Bosnia and Herzegovina, peritoneal dialysis is preferred only in very small children with acute renal failure, but for the other children we use hemodialysis.

2. OBJECTIVE

The aim of the study is to determine the causes of AKI in pediatric patients who needed renal replacement therapy (RRT) and were admitted to the Pediatric and Neonatal Intensive Care Unit (PICU and NICU) at the Pediatric Clinic, University Clinical Center Sarajevo (UCCS).

3. MATERIALS AND METHODS

This was a clinical, retrospective, descriptive study, based on data from patient medical records which included all 81 children who required some of the dialysis techniques due to definition of stage 2 and 3 AKI at the PICU and NICU on the Pediatric Clinic UCCS from 1 January 2006 and 1 October 2021. We used the KDIGO criteria to define AKI. Severe acute kidney injury was defined as stage 2 or 3 AKI when plasma creatinine level ≥2 times the baseline level or urine output <0.5 ml per kilogram of body weight per hour for ≥12 hours, because these stages have been associated with increased mortality in studies involving children (1). The estimated GFR was calculated with the use of the original Schwartz formula (12). All AKI patients in this study were examined clinically along with detailed and accurate history, physical examination, and laboratory studies like 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 same cases we did creatine phosphokinase (if rhabdomyolysis is suspected), urine for eosinophils (if patient is receiving a medication with potential to cause interstitial nephritis), stool for enteropathogenic *Escherichia coli* (if HUS is suspected). Anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-streptolysin O titer (ASO), complement component C3 and C4 level, anti-nuclear cytoplasmic antibody (ANCA), anti-glomerular basement membrane antibody (if patient has history, signs and symptoms consistent with a glomerulonephritis), 24-hour urine for calcium, oxalate, citrate, cratinine, uric acid (in patients with confirmed nephrolithiasis), electrocardiogram, chest X-ray and ultrasonography of abdomen. Other special investigations like echocardiography, electroencephalography, abdominal computed tomography scan (if trauma or abdominal mass is suspected), spiral computed tomography scan (if nephrolithiasis is suspected) and kidney biopsy were performed whenever necessary. The researches were conducted at the different Clinics on the UCCS. We did some kinds of dialysis, peritoneal dialysis with the stay-safe system, and since March 2009 we started different types of hemodialysis on the Multifiltrate Acute Therapy.

Statistical analysis

Categorical data are presented as counts and percentages and were analyzed with the chi-square test and Fisher's exact test, as appropriate. The value of < 0.05 was taken as statistically significant. Analyses were conducted with the use of MedCalc v 12.7, and Microsoft Excel 2010.

4. RESULTS

The age of patients who were on dialysis for AKI was from 12 days to 17 years and 2 months, and the gender ratio was 43 (53.1%) males and 38 (46.9%) females ($\chi 2=0.0548$; $p=0.815$; $p>0.05$) without statistically significance. AKI was present in 42 (51.9%) infants and in 39 (48.1%) children after one years of age ($\chi 2=0.00598$; $p=0.9383$; $p>0.05$;) without statistically significance (Figure 1).

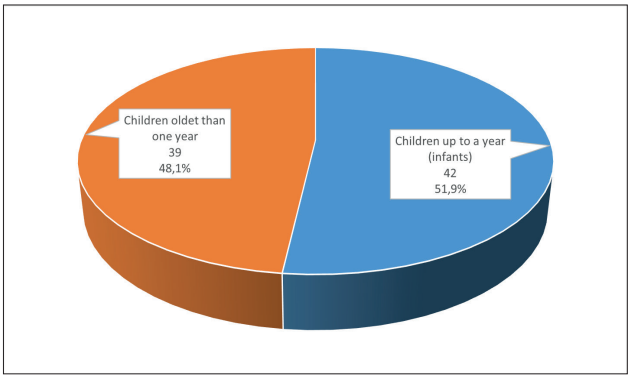

Figure 1. The age of children with acute kidney injury

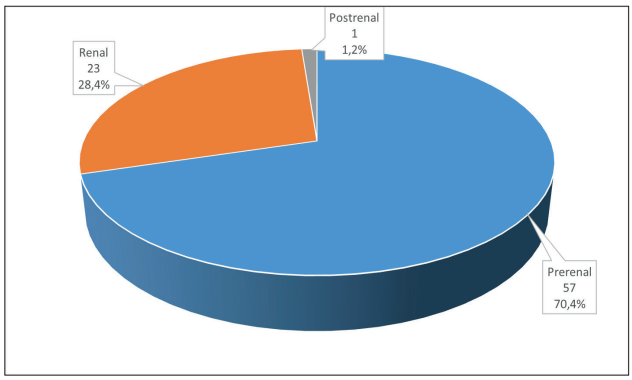

Figure 2. Causes of acute kidney injury

The prerenal causes of AKI were present in 57 (70.4%) patients, renal 23 (28.4%), and postrenal in 1 child (1.2%), a statistically significant difference, dominated by prerenal causes of AKI ($\chi 2=6.703$; $p=0.0096$; $p<0.05$) (Figure 2).

5. DISCUSSION

On the Pediatric Clinic of the UCCS in 1998, the Pediatric and Neonatal Intensive Care Unit were established for intensive treatment of infants and young children. This contributed to admit the most difficult patients almost from all Bosnia and Herzegovina at the Pediatric Clinic. In addition to patients with severe internist diseases, a large percentage of surgical patients, especially those following surgery of complex heart anomalies, and severe infectious diseases and malignancy are treated at the PICU and NICU. In most developed countries in the intensive care units of children, the proportion of surgical patients is around 50%.

In the period from 1 January 2006 to 1 October 2021 there were 81 patients, 43 (53.1%) boys and 38 (46.9%) girls with AKI at the PICU and NICU of the Pediatric Clinic UCCS who were needed some of dialysis modality. As in our study, in most studies, the incidence of boys with AKI is higher in relation to girls. So, in one multicentric study in United States of America 56.4% (13), in Norway 53% (14), in Belgium 50.8% (15) and in Nigeria 68.6% were males (16).

Mean age of AKI presentation in our examination was 6.28 years. It is similar as in Norway 6.0 years, and Belgium 6.1 years, while in Nigeria was 4.8 years (14, 15, 16). For many years the diagnosis and management of AKI was based on the 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 renal cellular damage and hence intrinsic renal disease (4).

In our study, the most common causes were prerenal in 57 (70.4%) patients. The main causes of AKI in Africa and Asia are of prerenal origin, due to dehydration, which is often caused by gastroenteritis and infections. This is in favor of underdeveloped states with poorly developed preventive medicine (16-18). In a multicenter study in the world's most populous country China, published in 2013, acute glomerulonephritis was the major cause of AKI in the study population, followed by severe dehydration (19). On the contrary, in Europe, the most common cause of AKI is renal, especially, haemolytic-uraemic syndrome (HUS) and glomerulonephritis (20, 21).

Etiology of AKI	No. of cases	Percentage of total cases
Hemolytic-uremic syndrome (HUS)	10	25.6%
Systemic diseases with macrophage activation syndrome (MAS)	3	7.7%
Glomerulonephritis	3	7.7%
Tumors	3	7.7%
Meningococcal disease	3	7.7%
Leucosis	2	5.2%
*Diseases that were represented as just one case of AKI	15	38.4%
Total		

Table 1. Etiological factors of AKI among children older than one years of age. * Diseases that were represented as just one case of AKI, respectively: 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 perforated of ventriculus, case of sepsis after surgery of volvulus in children 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 our study in the newborn and infant AKI was caused by a combination of cardiac insufficiency caused by complex heart defects which were operable or inoperable (Tetralogia Fallot, transposition of large blood vessels, hypoplastic heart, and others), prenatal asphyxia, respiratory distress syndrome, sepsis, congenital anomalies of other organs, lower gestational age, use of inotropic agent and prolonged mechanical ventilation which directly threatened their life, and in 3 cases hemolytic-uremic syndrome.

The pathophysiology of septic-AKI is very complex and involves inflammation, oxidative stress microvascular dysfunction and amplification of injury via secretion of cytokines by tubular cells. Several studies have demonstrated that, there may be genetic risk factors for AKI in some newborns and children. Polymorphism of the angiotensin-converting enzyme (ACE) gene , tumor necrosis factor alpha, interleukin 1b, 6 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 (22). In the study, Martin-Ancel and Fernandez and colleagues incidence of AKI in infants ranged between 8% and 24% respectively, and AKI was particularly common in infants, who had heart surgery (23, 24). Newborns with severe asphyxia and extremely-low-birth weight have a higher

incidence of AKI compared to those with moderate asphyxia and normal birth weight (25).

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 (26). The incidence of neonatal AKI varies from 2.5% to 17.6% (4, 27) in NICU patients, and could reach up to 40% in very-low-birth-weight (VLBW, BW<1500 gms.) and to 60% in extremely-low-birth-weight (ELBW, BW<1000 gms.) infants with a low score of Apgar test, open ductus arteriosus, and maternal antibiotics and non-steroidal anti-inflammatory drugs during pregnancy (6, 25).

We had one patient with hyperammonemia. Hyperammonemia in the newborn (in all term infants with ammonia> 200 micromoles / L) is a life-threatening condition. It is caused by a genetic defect of a certain enzyme that is crucial for the development of a normal metabolic pathway. Discovering the true cause of hyperammonemia is important for treatment that is individual to each patient and depends on which enzyme defect is involved, prognosis, and genetic counseling (28).

It is paradoxical, but the fact is that the incidence of AKI in preterm infants and newborns has increased with the development of neonatal intensive care worldwide. The reason for this is aggressive therapeutic procedures, transportation services, and an aggressive surgical approach to seriously ill children.

In children over the first year of life in 10 cases the cause was hemolytic-uremic syndrome (HUS) associated with diarrhea, the increase of which has been observed in recent years at our Clinic. Enterohemorrhagic *Escherichia coli*-induced HUS is a common cause of AKI in children and leads to significant morbidity and mortality and long-term complications (29).

In 3 cases, the cause of AKI was systemic disease in combination with macrophage activation syndrome, in 3 cases glomerulonephritis (two of them had AKI due to nephrotoxicity of the calcineurin inhibitor in the case of focal and segmental glomerulosclerosis, and in one case it was a severe form of Henoch–Schönlein – nephritis - HSPN), three cases of tumor (ovarian cancer, retinoblastoma and lymphoma, which quickly led to multiorgan failure and death). In 40 to 50 percent of patients with Henoch-Schönlein purpura, the most serious consequence is kidney disease, which very rarely results in death (30).

Three children had meningococcal disease, which is the leading infectious cause of death in early childhood. The mortality rate now ranges from 2-11% due to circulatory collapse (31). Most patients with fulminant meningococcal sepsis require dialysis. One child with acute lymphoblastic leukemia (ALL) and one with acute myeloid leukemia (AML) associated with sepsis quickly ended in death. Children with acute lymphocytic leukemia and B-lymphoma are at the highest risk of developing AKI due to uric acid-induced nephropathy and / or tumor lysis syndrome causing extreme hyperphosphatemia and precipitation of phosphate crystals (32). Rasburicase is a recombinant form of urate oxidase that catalyzes uric acid to allantoin, and has been shown to be most effective than Allopurinol in the prevention of AKI in pediatric patients with tumor lysis syndrome (33).

The incidence of drug-induced acute liver failure is increasing due to the large and uncontrolled use of drugs. In our one case, anesthetic drug 2,6-diisopropylphenol (propofol), was reason for AKI and acute liver failure. Propofol infusion syndrome (PRIS) is a rare but potentially lethal side effect of propofol. In the medical literature, various causes of unfavorable outcome are cited such as: unexplained metabolic acidosis, rhabdomyolysis, hyperkalaemia, hepatomegaly, renal failure, hyperlipidaemia, arrhythmia, and changes on electrocardiograph and rapidly progressive cardiac failure (34). The cause of AKI was one case of poisoning with non-steroidal antiinflammatory drugs (NSAIDs). The renal risks of NSAIDs are less well quantified than gastrointestinal and cardiac risks (35). The results of Sabaté and his colleagues from Spain indicated that paracetamol in therapeutic dosages may be considered in the causality assessment in non-alcoholic patients with acute liver injury (ALI) (36).

We had one patient with an hydatid cyst on the liver and lungs who was treated surgically. Inactivation of the scolex with scolicides (silver nitrate) prior to opening or removing the cyst is strongly recommende to prevent recurrence but it is responsible to significant complications including renal and liver failure (37).

Severe sepsis is the most common etiology of ARDS, and patients with sepsis-induced ARDS have higher case fatality rates than patients with other risk factors of ARDS (38).

Varicella often has mild clinical course and complications are rare. Severe and disseminated varicella infection with organ dysfunction can also be seen among diabetics and immunocompromised patients (39). Unfortunately, our 3-year-old patient who was immunocompromised developed a malignant hemorrhagic disease called hemorrhagic chicken pox syndrome whose etiology is unknown and this led to a fatal outcome (40).

MELAS is a rare genetic, multisystem and progressive neurodegenerative disorder. The causes of death in our 16-year-old patient was stroke episode and number of organs involved (poliserositis). Multivariate analysis showed that age at first symptoms was a major independent predictor of mortality: patients with first symptoms before 6 months had a highly increased risk of mortality (41).

We had one case of congenital anomalies of the urinary system associated with complications of ventriculoperitoneal shunt due to hydrocephalus in a child with myelomeningocele of the lumbo-sacral region associated with sepsis which ended in a lethal outcome. One patient had interstitial nephritis of unknown etiology which had a positive response to hemodialysis.

We had one unusual case of viral haemorrhagic fever with Hantavirus Pulmonary Syndrome (HPS) in boys aged 11.5 years. It has dominated the respiratory symptomatology with the development of respiratory insufficiency, which required mechanical ventilation,

and because of AKI he was on HD. With proper therapy, complete recovery followed. Otherwise, the HPS mortality rate in North America is greater than 35% (42). AKI is not an isolated event but occurs secondarily due to multiorgan dysfunction caused by a pro-inflammatory mechanisms the so-called cytokine storm.

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 hemolytic uremic syndrome, GN, and primary renal diseases have been replaced by sepsis, critically ill status, congenital heart disease, postsurgical, postransplantation, and oncological illness. It is normal that the prognosis of AKI is highly dependent on the underlying etiology of the AKI. Mortality rate is much higher in a children who have AKI as a component of multisystem failure. In the past it has been thought that such patients are at a low risk for late complications, but several recent studies have demonstrated that chronic kidney disease can evolve from AKI (9). From that reason such children need long-term follow-up of their renal function.

In our study 39 (48.1%) patients died, and the death was due to the nature of the primary disease and multiple organ failure syndrome. The highest number of mortality was found in children in the first year of life, of whom 22 (56.4%), and 17 (43.6%) were children of older age. This relationship is understandable, because AKI in very young babies has a bad prognosis and usually reflects disorders of several organic systems.

6. CONCLUSION

As the AKI plays a key role in the mortality and morbidity in pediatric patients, especially in infants, it is important to recognize and treatment on time different etiologies of this serious condition. Some causes of AKI in our country can be prevented by better organization of primary and secondary health care, which would also reduce mortality and morbidity from AKI. Improved understanding of the pathophysiology of AKI and the detection of new and better biomarkers that will help to detect AKI on time are a prerequisite for the developing of successful therapeutic strategies for the treatment of AKI.

- **Patient Consent Form**: All participants (parents of the children) were informed about subject of the study.
- **Authors contribution**: All authors were involved in all steps of preparation this article. Final proofreading was made by the first author.
- **Conflicts of interest**: There are no conflicts of interest.
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