REVIEW ARTICLE

PEDIATRIC ATYPICAL PROGRESSIVE ACUTE KIDNEY INJURY IN INDONESIA

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ABSTRACT

Background : In the last few months of the 2022, there has been an increase in pediatric acute kidney injury cases with high mortality in Indonesia. Atypical progressive acute kidney injury (AKI) described as duration of the development of the disease into end stage stadium occured rapidly and abruptly result in high mortality indicates more than 50% despite received dialysis treatment. The cases were dominated by previously healthy toddlers age less than five years old without comorbidities. This review presents necessary informations related to etiology, diagnosis and management of atypical progressive AKI. This review also discuss about the etiology although the spesific causes are still widely studied as well as reports of new events on the causes of AKI.

Methods : Systematic review of studies about atypical progressive acute kidney injury, the situation that is occurring at the moment in Indonesia.

Result : There are spesific operational definition for diagnosing atypical progressive AKI in children including initial symptoms cover for infection symptoms of respiratory tract and gastrointestinal system and none history of previously kidney injury which also found both hyperinflamation or hypercoagulation signs. Most children were previously health children. Spesific cause are still unknown but some children were found positive for viral and bacterial infection, SARS COV-2 antibody and also ethylene glycol intoxication as reported cases in Gambia by WHO.

Conclusion : When compared to the pediatric community AKI in general, certain variations were discovered in the atypical pogressive type of AKI, known patient features, initial symptoms, and etiology.

Keywords : Atypical progressive acute kidney injury, children, ethylene glycol.

INTRODUCTION

Acute kidney injury is a sudden decrease in kidney function that impairs the kidney's ability to perform filtration and maintain body homeostasis. This leads to changes in fluid, electrolyte, and acid-base balance as well as a rise in the nitrogen component metabolites urea and creatinine. The incidence of AKI has been reported by researchers at 26.9%. 11.6% of them developed severe AKI at stage 2 or 3 (Kidney Disease Improving Global Outcomes (KDIGO). Patients with severe AKI had a higher 28-day mortality rate than those without (11% vs. 2.5%, respectively). Pediatric atypical progressive AKI differs slightly from the general acute kidney injury in terms of the duration of disease progression and the etiology. It characterizes by a very rapid rate of progression into end stage stadium causing high mortality in children.

In Indonesia, atypical progressive AKI reports had increased in numbers since July 2022 with the cumulative cases recorded by October 18, 2022 had been reaching 206 cases scattered throughout 20 provinces in Indonesia including DKI Jakarta, East Java, West Java, Central Java, Yogyakarta, Bali, Banda Aceh, Papua, West Papua, NTT, Jambi, Kepulauan Riau, Banten, North Sumatera, South Sumatera, West Sumatera, South Sulawesi, West Kalimantan, East Kalimantan, and South Kalimantan. The ministry of health reported the latest update on November 2, 2022 showed an increase in the number of cases by 325 cases and a wider spread of cases reaching 28 provinces. The total number of death reached 178 cases which means the mortality of these cases reached 54.5% and there are 100 patients who had been declared cured (31%). The rest (14.5%) are still undergoing medical treatment at the hospital. The majority of cases occured in Jakarta (26%), West Java (12%) and Nangroe Aceh (9.5%) most of which

involved children under the age of five and more often involved males than girls.

Table 1. Age distribution of cases in Indonesia

Age	Number of cases
< 1 year old	75 (23%)
1-5 years old	169 (52%)
6-10 years old	42 (13%)
11-18 years old	39 (12%)

Understanding the harm that this condition might represent, Indonesian Pediatrician Society (IPS) considers the need for vigilance on this problem. The ministry of health with IPS always generates new reccomendation that are dynamic and subject to alter at any time in accordance with the most recent advances in scientific knowledge.

Pathophysiology of acute kidney injury

The pathophysiology of acute kidney injury involves two aspects, microvascular and tubular. In the microvascular aspect, there is increased vasoconstriction, decreased vasodilation, damage to vascular smooth muscle and endothelium, and increased leukocyte-endothelial adhesion. Whereas tubular injury causes cytoskeletal damage and loss of polarity which develops into apoptosis and necrosis in kidney cells. This process produces inflammatory mediators, which lead to a positive feedback mechanism in which oxygen delivery to the tubules decreases and leads to activation of microvascular mechanisms.

Diagnosis of atypical progressive acute kidney injury

Clinically, acute kidney injury can be classified into oliguric type and non-oliguric type. Oliguric type are more commonly found in clinical practice. Oliguria in newborns is described as diuresis of urine < 1 ml/kg/BW/hour and in children < 0.5 ml/kg/BW/hour. This definition is seen to be less precise and frequently takes longer to implement management actions. Recent advancements in the diagnosis of pediatric AKI include 1) modified RIFLE (R-renal risk, I-injury, F-failure, L-loss of kidney function, E-end stage kidney disease [ESKD]) presented as pediatric RIFLE (pRIFLE) and 2) Kidney Disease Improving Global Outcomes (KDIGO) criteria (table 2).

Table 2. pRIFLE and KDIGO criteria for AKI diagnosis

Stadium KDIGO/ pRIFLE	Creatinin		Urine Production	
	KDIGO	PRIFLE	KDIGO	PRIFLE
1 (Risk)	Creatinine increase X 1.5-1.9 OR creatinine increase ≥ 0,3 mg/dL	Creatinin increase 1.5 OR eGFR loss > 25%	<0.5 ml/kg/hour for 6-12 hours	<0.5 ml/kg/hour ≥ 8 hours
2 (Injury)	Creatinine increase X 2-2.9		<0.5 ml/kg/hour for ≥ 12 hours	<0.5 ml/kg/hour ≥ 16 hours
3 (Failure)	Creatinine increase X 3 OR creatinine increase ≥ 4 mg/dL OR eGFR < 35 ml/min/1.73 m^2		<0,3 ml/kg/hour ≥24 hour OR Anuria ≥12 jam	<0.5 ml/kg/hour ≥ 24 hour OR Anuria ≥12 hour

Those classifications are also used in diagnosing atypical progressive AKI and also become criteria for referring patients to hospitals with child dialysis facilities. The patients are indicated to be referrred to pediatric dialysis referral hospital if they are fulfilled starting at stage 1 according to KDIGO and/or starting at risk stage according to the pRIFLE criteria.

Because of the etiology, clinical condition, course of the disease are slightly different with common pediatric AKI in community, the ministry of health and IPS developed a new operational definition (table 3) for this case. A careful diagnostic approach might include a complete history taking, physical examination, blood test, and other imaging exams.

Table 3. Operational Definition for Atypical Progressive AKI

Operational definition
1. Children aged 0-18 years
2. Have a fever or a history of fever or other symptoms of infection in the last 14 days.
3. Diagnosed with acute kidney injury of unknown etiology (either pre-renal, renal, or post-renal) by the doctor in charge of the patient.
4. No previous kidney disorders or chronic kidney disease.
5. Signs of hyperinflammation and hypercoagulation are present

As a form of vigilance, IPS urges parents to always supervise for general danger signs as well as to keep observe on the quantity and color of urine (concentrated or brown) at home. If their children exhibiting symptoms of fever,

symptoms of acute respiratory infections (cough, runny nose), or symptoms of gastrointestinal infections (diarrhea, vomiting), parents are educated to monitor general danger signs and also monitor the amount and color of urine (condensed or brownish) at home. If the urine is reduced or no urine for 6-8 hours (during the day), IPS adviced parents immediately take their children to the hospital to conduct an initial examination with a kidney function test (ureum, creatinine). If the glomerular filtration rate decrease, more testing is done to confirm the diagnosis and determine any potential underlying causes and complications.

Diagnosis of the cause of atypical progressive acute kidney injury

Acute kidney injury may also be classified according to the etiology. It may be caused by prerenal, intrinsic renal, or post renal (table 4). Prerenal AKI is caused by decreased renal perfusion as a result of lower effective arterial pressure, intrinsic renal AKI is caused by kidney abnormalities or damage, and post renal AKI is caused by obstructive uropathy.

Recognizing the etiology is crucial, particularly when determining a course of therapy. Common pediatric acute kidney injury in community are mostly caused by hemodynamic problems, such as those caused by diarrhea and dehydration, shock from dengue infection, and severe congenital abnormalities of the kidneys and urinary system are the main causes of AKI in the toddler age group. While in older children and teenagers, kidney diseases such acute glomerulonephritis are the main cause of pediatric community AKI.

Table 4. The Etiology of pediatric AKI

Prerenal
Hypovolemia
- Hemorrhage
- Gastrointestinal losses
Decrease in effective vascular volume
- Sepsis (Ec systemic vasodilatation)
- Burns
- Trauma (Ec third space)
- Nephrotic syndrome (Ec hypoalbuminemia, severe edema)
Decrease cardiac output
- Heart failure
- Cardiomyopathy
- Heart surgery
Intrinsic Renal
- Vascular damage
- Glomerulus damage
- Tubulus damage
- Interstitial damage
- Congenital anomaly
Post renal
- Congenital anomaly
- Acquired (stones, clood clots)
- Tumor

Several relevant drugs and/or drug classes, may also cause AKI in children, including cancer chemotherapeutics, non-steroidal anti-inflammatory drugs, and antimicrobials. Drug-induced AKI is a significant cause of morbidity and mortality, but and potentially preventable in children. The clinicians should be aware of the risk factors and signs of AKI and use drugs judiciously in this population.

If a child is found who meets the initial symptoms (history of fever, gastrointestinal and respiratory infection symptoms) during the previous 14 days, followed by symptoms of AKI and an elevated kidney function test, patient information should be carefully recorded and documented to determine any potential underlying causes and complications. Those information including history of previous illnesses such as COVID-19 infection, COVID-19 infection in the family members, other infectious diseases, kidney disease, immune deficiency and other diseases. It is also important to record previous travel history within 14 days, COVID-19 vaccination (frequency of administration and type of vaccine) and contact history or have a pet at home.

Hospitals are expected to be able to carry out further examinations (laboratory and imaging examination) in stages according to the level of health services (public health centers/clinics or hospitals) that receive patients for the first time, consist of :

- Diagnostic aproach : complete peripheral blood count, peripheral blood morphology, kidney function (BUN/ureum, creatinine), urinalysis.
- Complication approach (including hyperinflammation and hypercoagulation) : electrolytes (sodium, potassium, chloride, calcium, phosphate), uric acid, blood gas analysis, liver function (SGOT, SGPT), inflammatory markers (CRP, procalcitonin, ferritin, IL-6, ESR, LDH), coagulopathy markers (D-dimer, fibrinogen). and imaging (including renal doppler ultrasound)
- Etiology approach : SARS CoV-2 antibodies, Leptospira serology, ASTO, nasopharyngeal and rectal smears, as well as microorganism culture examination (from sterile sites, blood, urine).

Acute kidney injury has been widely reported in patients with primary infection with COVID-19, which occurs in around 0.5 - 33.9% of people with COVID-19. The incidence of Multisystem Infammatory Syndrome in Children (MIS-C) occurs around 3.16 per 10,000 cases of COVID-19, while AKI occurs in around 25-33% of MIS-C patients.

However, there are still few literatures that explains kidney injury in MIS-C. Although children with MIS-C might have risk factors for AKI, research shows that the majority of them experience mild disease, rapid resolution, and promising outcomes. Besides primary Covid-19

infection, older age, increased inflammation, and left ventricular systolic dysfunction can be risk factors for AKI.

At the Progress Report of Atypical Progressive Acute Kidney Disorders /Acute Kidney Injuries (AKI) in November 2022, the ministry of health of the Republic Indonesia compiled information on the findings of 325 pediatric patients' examinations with atypical progressive AKI to look for the etiology. The pathogen panel for viral and bacterial examination is carried out in all Government Hospitals by the Ministry of Health. Of the 202 patients who were tested for COVID-19 PCR/antigen, only 9% were positive for COVID-19. Of the 92 patients who were tested for COVID-19 IgG, 60% were positive for IgG, and of the 71 patients who were tested for Covid-19 IgM, 83% were negative for IgM. The results were showing no consistent pattern of the disaese related to COVID-19 illness or COVID-19 vaccination.

Other pathogen test results showed that of the 32 patients, 7 patients were positive for Human Parainfluenza virus (HPIV), 6 patients were positive for Influenza A virus, 5 patients were positive for Adenovirus, 2 patients each were positive for Human Rhino Viruses (HRVs), Norovirus GII (NV GII), Influenza B, human metapnuemovirus, 1 patient was positive for Rotavirus. For bacterial pathogen examination showed 4 patients were positive for Leptospira Santarosai (examined by the metagenomic sequencing method), 2 patients were positive for Legionella Pneumophilia, and 1 patient was positive for Staphilococcus Aureus.

The pathogen examination were also detected coinfection cases with two virus detected in one patient through PCR examination, those were 1 patient was coinfected with HPIV and Adenovirus; 1 patient was coinfected with HPIV and SARS-COV2; 1 patient was coinfected with HRVs and Adenovirus, 1 patient was coinfected with HRVs and NV GII; and 1 patient was coinfected with Rotavirus and Influenza A. Considering these results that no pattern of the same causal pathogen exists.

In addition to examining the causative pathogen, the hazardous substance ethylene glycol and its derivatives that suspected might induced AKI in children were tested because 66 children in Gambia died on October 2022 from AKI induced by ethylene glycol intoxication. Ethylene glycol (EG), diethylene glycol (DEG), ethylene glycol mono-butyl ether (EGBE), ethylene glycol mono-phenyl ether (EGPE) is a toxic substance that can potentially cause atypical progressive acute kidney injury to a certain extent. They can be obtained by consuming contaminated drug syrup such as cough and antypiretic syrup. Considering the findings of the Gambia case inquiry, WHO issued a warning on 4 contaminated syrup medications worldwide. The results of these patients examination show that in the patient's blood/urine and the drugs consumed, the hazardous substance ethylene glycol and its derivatives were found positive. Of the 47 children, 34 patients were detected for ethylene glycol or its derivatives by gas cromatography and mass spectroscopy (GC-MS) method and also a kidney biopsy revealed the presence of calcium oxalate, a DEG/EG alcohol dehydrogenase byproduct. Examination and analysis determined by National Agency of Drug and Food Control based on the patient's toxicological analysis, the drugs consumed by the patient, and the WHO reference, it was highly suspected that the patients were exposed to harmful chemical compounds from the syrup they consumed.

Etylene glycol associated acute kidney injury

Often used as industrial solvents and in the production of antifreeze, dyes, and brake fluids, DEG and EG are odorless, water-soluble organic compounds having a sweetish taste. Cough and antypiretic syrup for children require harmless solvents like glycerol and propylene gylcol. These solvents also have antibacterial characteristics and serve as thickeners, preservatives, and sweeteners.

The liver converts ethylene glycol into the its toxic metabolites in the form of glycoaldehyde, glycolate, glycoxylate, and oxalate. Excess of these metabolites can inhibit cellular respiration, glucose and serotonin metabolism, protein synthesis, DNA replication, and ribosomal RNA formation. The main consequences of this occurance include central nervous system depression, cardiopulmonary arrest, and renal failure with accumulation of organic acid metabolites, particularly glycolic acid.

The minimum lethal dose for DEG/EG is estimated to range from 0.014 to 0.35 mg/kg. The intoxication process occurs in several stages include the first few hours after consumption, 4-12 hours after consumption and delay response to days and weeks. During the first few hours after consumption, there may be symptoms of changes in consciousness or behavior, gastritis with vomiting may also occur and the osmolal gap may increase. Within 4 to 12 hours, acidosis begins to occur accompanied by an elevated anion gap, hyperventilation, convulsions, unconsciousness, abnormalities in cardiac conduction, and arrhythmias. Although kidney injury is frequent, it is treatable. If untreated, the injury process and tubular system blockage continued to happend and causing calcium oxalate formation that may aggravate already existing kidney damage and lead to pulmonary and cerebral edema.

Clinical indicators that suggest etylene glycol associated acute renal injury include sudden anuria or oligouria, sudden drop of glomerular filtration rate, the possibility of intoxication exist with previous history of cough or antypiretic syrup consumption, moreover the presence of a laboratory result in accordance with the diagnostic criteria spesifically ethylene glycol plasma level > 20 mg/dL (3 mmol/L) or suspicion of EG intoxication with

the presence of at least two or more of the following
- Arterial pH > 7.3
- Bicarbonate serum < 20 mEq/L (20 mmol/L)
- osmolal gap > 10 mOsm/kg
- Presence of oxalate crystal in the urine

Health workers at Health Service Facilities temporarily did not prescribe medicines in the form of liquid/syrup preparations until an official announcement is made from the Government in accordance with the provisions of the legislation. All pharmacies temporarily did not sell over-the-counter and/or limited-free drugs in the form of syrup to the public until an official announcement is made from the Government in accordance with the provisions of the legislation.

As considerable amounts of drugs and their metabolites are exposed to glomerular, interstitial, and tubular cells, alterations in kidney structure and function typically result from drug use. Due to their function in concentrating and reabsorbing glomerular filtrate, which exposes them to significant amounts of circulating toxins, renal tubular cells are particularly susceptible to the toxic effects of medicines. Renal toxicity may be caused by changes in hemodynamics, direct harm to cells and tissue, inflammatory tissue injury, and blockage of renal excretion.

Drugs to prevent pediatric acute kidney injury

- Furosemide and bumetanide
  In order to improve urine output in critically ill patients, furosemide has been used to maintain fluid balance. Studies have shown that furosemide infusion may be used instead of boluses to improve urine output in infants undergoing cardiac surgery. In recent study, bumetanide, a newer loop diuretic, has been used in preterm infants with oliguric AKI.
- Fenoldopam
  A recent study on fenoldopam, a selective dopamine A1 receptor agonist that decreases vascular resistance and increases renal blood flow, improved urine output in neonates requiring cardiac surgery with positive fluid balance despite diuretics.
- Theophylline
  Nonspecific adenosine receptor antagonists, such as aminophylline and theophylline, may help to prevent vasoconstriction in the kidney that causing a reduction in GFR because of releasing adenosine during perinatal hypoxia in neonates. KDIGO recommends a single dose of theophylline for asphyxiated neonates since they are at risk of AKI. However, there are concerns about neurological side effects, and more so the relevance of these drugs in the era where hypothermia is a standard of care in these neonates.
- Rasburicase
  A single bolus of rasburicase (a recombinant urate oxidase enzyme) can reduced SCr, blood urea, and urine output. However, more evidence is needed for the use of this drug in the treatment of AKI in neonates and children.

Management Of Atypical Progressive AKI

If the diagnosis is according to MIS-C, it can be managed according to the MIS-C criteria with the treatment includes steroid, intravenous immunoglobulin (IVIG), anticoagulant. If there is evidence of other causes, it can be treated according to the alleged other causes. Management of atypical progressive AKI can be divided into management at hospital and dialysis at referral hospital for dialysis indicated to AKI stadium 2 KDIGO criteria or injury stadium pRIFLE. There are 14 pediatric dialysis referral hospital throughout all of Indonesia.

Intra-hospital treatment is according to the availability of infrastructure at the hospital that includes stabilizing the airway, breathing and circulation with closed monitoring for consciousness, vital signs especially blood pressure and kusmaull breath, fluid balance, diuresis during treatment. Complete laboratory examination is done that also includes examination for the etiology, complications and dialysis preparation. Maintaining fluid balance with fluid restriction might be done according to the clinical condition of the patient and according to insensible water loss (IWL) based on body surface area and the amount of urine produced by patient. Drug treatments are given according to suspected cause of renal injury. On the presumed of infectious cause, antibiotics with adjustments dosage for renal function based, among others ceftriaxone or cefoperazone is an antibiotic that is generally safe. On the presumed of DEG/EG intoxication, the antidote should be given immediately. The antidote is an alcohol dehydrogenase inhibitor with the first choice is intravenous fomepizole with alternative in the absence of IV Fomepizole is oral or intravenous ethanol. It is also essential to give cofactor treatment by giving Folic acid and supportive vitamins by giving Thiamin and Piridoxyn. Supportive and symptomatic treatment are given based on the patient's medical condition such as antihypertensive according IPS guidelines for hypertension in children and also acidosis and imbalance electrolyte correction.

During treatment, patient outcomes can be classified into two categories, that is full recovered signed with improved kidney function with eGFR >60 ml/min/1.73 m2 and/or urine output >1 ml/kg/hour and no neurological sequelae. The second is partial recovery which include patients with eGFR <60 ml/min/1.73 m2 and/or neurologic sequelae.

There are two kinds of patient outcomes that can be obtained during treatment, including full recovery with improved kidney function (eGFR >60 ml/min/1.73 m2 and/or urine output >1 ml/kg/hour) and no neurological sequelae. Patients having an eGFR of less than 60 ml/min/1.73 m2 and/or neurologic sequelae fall into the

second category, partial recovery.

The outcomes of patients can be divided into two groups throughout treatment, those who have fully recovered with improved kidney function (eGFR >60 ml/min/1.73 m2 and/or urine output >1 ml/kg/hour) and no neurological sequelae and patients within the category of partial recovery with eGFR 60 ml/min/1.73 m2 and/or neurologic sequelae.

CONCLUSION

When compared to the pediatric community AKI in general, certain variations were discovered in the atypical pogressive type of AKI, known patient features, initial symptoms, and etiology. Proper management can reduce mortality due to rapid progression of acute kidney injury in children

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CONFLICT OF INTEREST

All authors declare no competing interests.

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