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EARLY EDUCATION OF ACUTE KIDNEY INJURY AND PRE-RENAL PROBLEMS IN ANAPHYLACTIC SHOCK PATIENTS

Putu Nindya Ayu Ningrum Subadra*)1
Intern doctor in RSD Wangaya Denpasar; nindyaningrum98@gmail.com
*)*Corresponding author; E-mail addresses:* nindyaningrum98@gmail.com

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Abstract. Acute kidney injury (AKI) may manifest in patients experiencing anaphylactic shock. Arterial hypotension significantly contributes to the pre-renal etiology of AKI. The condition of anaphylactic shock is a life-threatening situation that requires immediate intervention. The decrease in perfusion to the renal organs in patients with acute anaphylactic shock can lead to the development of acute kidney injury (AKI). This is characterized by an increase in the Urine (U) and Creatinine (Cr) ratio (>20:1) and is reversible if promptly managed through fluid resuscitation, which results in a decrease in serum creatinine levels. Anaphylactic shock can lead to the occurrence of pre-renal acute kidney injury (AKI), which can be reversible if promptly addressed.

INTRODUCTION

Anaphylaxis is one of the allergic conditions that manifests rapidly after allergen exposure and can be life-threatening. Anaphylactic shock is characterized by a drop in blood pressure and circulatory collapse, making it an emergency situation that requires prompt and appropriate intervention (Sudoyo et al., 2016). Anaphylactic shock is relatively uncommon, with an estimated prevalence of 0.05-2%, and epidemiological data indicate that 2 to 20% of cases result in fatal anaphylaxis (Tringgini et al., 2008). Acute kidney injury (AKI) can manifest in patients experiencing anaphylactic shock. Arterial hypotension significantly contributes to the pre-renal etiology of AKI, leading to ischemic renal lesions and eventual renal failure. Acute kidney injury, previously referred to as acute renal failure (ARF), refers to a sudden and often reversible decrease in kidney function, as measured by glomerular filtration rate (GFR). Initially, after a renal insult, blood urea nitrogen (BUN) or creatinine levels may remain within the normal range. A reduction in urine output might be the sole indicator of acute kidney injury.

All patient in setting of emergency room, who had symptom of anuria for more than six hours, consideration should be given to the possibility of an acute kidney injury and required prompt treatment. The best initial workup study should be done as soon as possible. As clinician we must be aware of acute condition of kidney disease and find the underlying causes of the disease to prevent the replacement therapy procedure. Even most of cases of AKI is reversible, but delayed therapy can result in permanent kidney damage (Xu Gang et al., 2014).

Recently published National UK guidelines on AKI put emphasis on early identification of AKI and prompt investigation of patients; therefore, increasing the awareness of AKI among non-nephrologists may help to improve outcomes. Non nephrologist doctor have to aware and have an enough education and collaborated with technologies and resources in health care services (Basile et al., 2012). The report of a case of anaphylactic shock with pre-renal AKI manifestation. This case is being presented due to the occurrence of anaphylactic shock with renal complications, leading to AKI, a condition that is not frequently reported. This situation can be life-threatening, and inadequate management may result in permanent kidney damage.

METHOD

This research was carried out using the observation method towards patient suffering from kidney disorders. After the data were collected, they were analyzed and presented in the form of table. The results of data analysis were then described and supported by appropriate ways to overcome the disease. The case was a 46-year-old male presented to the emergency department of Wangaya District General Hospital with complaints of weakness and shortness of breath. He had developed a widespread reddish rash accompanied by itching one day prior after taking Sodium Diclofenac for muscle pain and discomfort. Six hours before arrival, the patient experienced difficulty breathing and swallowing. He also reported not having urinated for more than 12 hours. He felt nauseous and vomited twice at home. There was no history of allergies, systemic diseases such as hypertension, diabetes, or kidney disorders.

Upon physical examination, his blood pressure was 80/50 mmHg, heart rate 127 beats per minute, respiratory rate 22 breaths per minute, body temperature 37°C, and oxygen saturation was 97% in room air. He was fully conscious and oriented, with a Glasgow Coma Scale (GCS) score of E4M6V5. Chest examination revealed minimal wheezing in the right lung field, while cardiac examination was within normal limits. Abdominal examination did not reveal any abnormalities. His extremities felt cold, and capillary refill time was prolonged (>2 seconds). A urinary catheter was inserted, but no urine production was observed in the emergency department. Complete blood count showed hemoglobin of 14.2 g/dL, hematocrit of 40.6%, platelet count of 233,000/µL, and white blood cell count of 10.87 × 10^3/µL. Serial renal function tests were conducted every 48 hours: on the first day, urea was 135 mg/dL, creatinine was 4.4 mg/dL; on the second test, urea was 139 mg/dL, and creatinine was 1.8 mg/dL; on the third test, urea was 82 mg/dL, and creatinine was 0.8 mg/dL. Electrolyte levels were within normal limits: serum sodium 139 mmol/L, potassium 3.8 mmol/L, and chloride 95 mmol/L. Urinalysis results were normal. Liver function tests were within normal limits, with SGOT at 38 U/L and SGPT at 31 U/L. Peripheral blood smear showed normochromic, normocytic erythrocytes with leukocytosis showing a left shift suggestive of leukemic reaction. Chest X-ray revealed a cardiothoracic ratio (CTR) of less than 50% and minimal pleural effusion. Urology ultrasound examination showed normal findings.

Based on the provided data, the patient was suspected to have acute kidney injury (AKI) with a pre-renal etiology due to anaphylactic shock triggered by the consumption of Sodium Diclofenac. During treatment, the patient received 1.5 liters of 0.9% NaCl fluid as a loading dose, dopamine at 3 mcg/kg/min titrated according to hemodynamics, followed by maintenance therapy with 20 drops per minute of Ringer's Lactate solution, 40 mg of intravenous esomeprazole every 12 hours, and 62.5 mg of intravenous methylprednisolone every 12 hours. Topical therapy included desoximethasone cream and gentamycin cream.

The patient responded well to treatment, improving his condition. He responded to vasoconstrictor therapy, resulting in a urine output of 800 cc every 6 hours. His shortness of breath diminished, and the rash on his body began to improve.

RESULTS AND DISCUSSION

Acute Kidney Injury (AKI) is the term that has recently replaced the term ARF. AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). Classification of AKI includes pre-renal AKI, acute post-renal obstructive nephropathy and intrinsic acute kidney diseases. Of these, only 'intrinsic' AKI represents true kidney disease, while pre-renal and post-renal AKI are the consequence of extra-renal diseases leading to the decreased glomerular filtration rate (GFR). If these pre- and/or post-renal conditions persist, they will eventually evolve to renal cellular damage and hence intrinsic renal disease. The current diagnostic approach of AKI is based on an acute decrease of GFR, as reflected by an acute rise in sCr levels and/or a decline in urine output over a given time interval.

Tabel 1. RIFLE Criteria for Classification and Staging AKI and the Modifications Proposed by the AKIN Network - Modified from References

RIFLE criteria for classification/staging AKI			AKIN criteria for classification/staging AKI		
Stage	GFR criteria	Urine output criteria	Stage	Serum Creatinine criteria	Urine output criteria
Risk	1.5fold increase in sCr or >25% decrease in GFR	UO < 0.5mL/kg/h for 6h	Stage 1	Absolute increase in sCr ≥ 0.3 mg/dL (≥26.5 μmol/L) or ≥ 1.5 to 2.0 fold from baseline	UO < 0.5mL/kg/h for 6h
Injury	2.0fold increase in sCr or >50% decrease in GFR	UO < 0.5mL/kg/h for 12h	Stage 2	Increase in sCR> 2.0 to 3.0 fold from baseline	UO < 0.5mL/kg/h for 12h
Failure	3.0fold increase in sCr or >75% decrease in GFR or sCr>4.0 mg/dL with an acute increase of 0.5 mg/dL	UO < 0.3mL/kg/h for 24h or anuria for 12 h	Stage 3	Increase in sCr > 3fold from baseline or increase of sCr to ≥4.0 mg/dL (≥ 354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L)	UO < 0.3mL/kg/h for 24h or anuria for 12h
Loss	Complete loss of kidney function for > 4 weeks				
ESKD	End stage kidney disease for > 3 months				

ESKD=end stage kidney disease, AKI=acute kidney injury, GFR=glomerular filtration rate, sCr= serum creatinine, UO=urinary output

In pre-renal AKI, renal hypoperfusion leads to a decreased GFR (without damage to the renal parenchyma), as an adaptive response to various extra-renal insults (Basile et al., 2012). It is known that maintaining a normal GFR is dependent on adequate renal perfusion. The kidneys receive up to 25% of cardiac output and thus any failure of the systematic circulating blood volume or isolated failure of the intra-renal circulation can have a profound impact on renal perfusion. The pathophysiology of AKI is multifactorial and complex. The most common cause of AKI is ischaemia, which can occur for a number of reasons. When delivery of oxygen and metabolic substrates becomes inadequate, the resulting cellular injury leads to organ dysfunction. The kidney is highly susceptible to injury related to ischaemia, resulting in vasoconstriction, endothelial injury, and activation inflammatory processes. Following the reduction in effective kidney perfusion, the epithelial cells are unable to maintain adequate intracellular ATP for essential processes (Sharfuddin & Molitoris, 2011). This ATP-depletion leads to cell injury and if it is severe enough can lead to cell death by necrosis or apoptosis. During an ischaemic insult all segments of the nephrons can be affected but proximal tubular cells are the most commonly injured. In addition, the nephron's natural function is to filter, concentrate and reabsorb many substances from tubular lumen, and the concentration of these substances may reach toxic levels for the surrounding epithelial cells (Bonventre, J.V. (2010).

Table 2. Causes of Acute Kidney Injury.

Category	**Abnormality**	**Possible causes**
Prerenal	Hypovolaemia	Haemorrhage Volume depletion Renal fluid loss (over-diuresis) Third space (burns, peritonitis, muscle trauma)
	Impaired cardiac function	Congestive heart failure Acute myocardial infarction Massive pulmonary embolism
	Systemic vasodilatation	Anti-hypertensive medications Gram negative bacteraemia Cirrhosis Anaphylaxis
	Increased vascular resistance	Anaesthesia Surgery Hepatorenal syndrome NSAID medications Drugs that cause renal vasoconstriction (i.e. cyclosporine)

Category	Abnormality	Possible causes
Instrinsic	Tubular	Renal ischaemia (shock, complications of surgery, haemorrhage, trauma, bacteraemia, pancreatitis, pregnancy) Nephrotoxic drugs (antibiotics, antineoplastic drugs, contrast media, organic solvents, anaesthetic drugs, heavy metals) Endogenous toxins (myoglobin, haemoglobin, uric acid)
	Glomerular	Acute post-infectious glomerulonephritis Lupus nephritis IgA glomerulonephritis Infective endocarditis Goodpasture syndrome Wegener disease
	Interstitium	Infections (bacterial, viral) Medications (antibiotics, diuretics, NSAIDs, and many more drugs)
	Vascular	Large vessels (bilateral renal artery stenosis, bilateral renal vein thrombosis) Small vessels (vasculitis, malignant hypertension, atherosclerotic or thrombotic emboli, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura)
Postrenal	Extrarenal obstruction	Prostate hypertrophy Improperly placed catheter Bladder, prostate or cervical cancer Retroperitoneal fibrosis
	Intrarenal obstruction	Nephrolithiasis Blood clots Papillary necrosis

In this case, anuria persisted for 12 hours, followed by an increase in serum urea and creatinine levels, with values of 135 mg/dL for urea and 4.4 mg/dL for creatinine. The patient's baseline Urine/Creatinine (Ur/Cr) ratio is unknown. However, there is no history of chronic conditions such as hypertension, diabetes, or cardiac and renal diseases. Laboratory findings showed a normal hemoglobin level of 14.2 g/dL, ruling out the possibility of chronic kidney disease. According to the RIFLE criteria, the patient falls under the "Failure" category due to 12 hours of anuria. The abrupt decline in kidney function is attributed to decreased renal perfusion caused by shock, evidenced by hemodynamic

impairment such as hypotension and increased capillary refill time (CRT). The patient's shock condition is a result of an anaphylactic reaction.

The diagnosis of anaphylaxis is established based on the clinical symptoms that occur immediately after exposure to allergens or other triggering factors. The Sampson criteria for diagnosing anaphylaxis include: first, an acute onset (within minutes to a few hours) involving skin and mucosal tissues, with at least one respiratory or cardiovascular symptom such as decreased blood pressure, collapse, syncope, or incontinence. Second, clinical manifestations occur in two or more organs shortly after exposure. Third, there is an immediate drop in blood pressure after exposure, with a systolic pressure less than 90 mmHg or a reduction of over 30% from the patient's baseline blood pressure immediately after allergen exposure, without any other apparent cause of shock. Symptoms during anaphylaxis vary, with manifestations affecting various target organs, including the skin and mucous membranes, respiratory, cardiovascular, gastrointestinal, and other systems (Dewi et al., 2019 & Triggiani, 2008).

Anaphylaxis is a type 1 hypersensitivity reaction mediated by IgE that occurs immediately after a patient is exposed to allergens or other triggering factors. It is an emergency condition and can be life-threatening. Anaphylactic shock is characterized by a decrease in blood pressure and circulatory collapse, leading to organ dysfunction. The root cause of anaphylaxis is the massive release of biochemical mediators from mast cells and basophils. Mast cell activation is primarily triggered by the crosslinking of antigens with IgE bound to FcεRI receptors on cell membranes. However, other membrane receptors can also activate mast cells or enhance IgE activation. The binding between IgE antibodies and these receptors triggers cellular degranulation, releasing mediators. The mediators released by mast cells and basophils include histamine, tryptase, chymase, carboxypeptidase A, and lipid mediators like cysteinyl leukotriene C4, Prostaglandin D2, and platelet-activating factor (PAF). These mediators are released within minutes. Cytokines such as tumor necrosis factor (TNF-α), interleukin-4 (IL-4), IL-6, and IL-13 are released several hours or days after mast cell activation. The effector phase corresponds to the clinical impact on organ shock due to the release of these mediators (Matuszkiewicz-Rowińska & Małyszko, 2020). The multiple activation pathways allow for immunologic (e.g. IgE mediated) and/or non-immunologic activation (e.g. drug directly interacting with receptors). Some antigens may mediate effects via several mechanisms simultaneously (e.g. vespid venom, NSAIDs, opiates). In non-IgE mediated anaphylaxis, symptoms can occur on first exposure to an antigen as prior exposure and sensitization is not required (Brown, 2009).

The inflammatory mediators released during anaphylactic reactions trigger vasodilation and increased permeability of blood vessel walls. This can cause both direct and indirect changes in the cardiovascular system. Vasodilation leads to a decrease in systemic vascular resistance (SVR), resulting in lowered blood pressure. Increased vascular permeability leads to fluid extravasation into the interstitial space. Due to vasodilation, there is a decrease in preload in patients, resulting in decreased cardiac output (CO). As a compensatory response to reduced cardiac volume, tachycardia occurs (Stephen & Shravan, 2019). The reduction in CO also results in decreased perfusion to various organs, including the kidneys, leading to a sudden decline in glomerular filtration rate (GFR) and acute kidney injury (AKI). In situations of hypotension or inadequate systemic perfusion, baroreceptors in arteries and receptors in the heart detect these changes and increase sympathetic tone. The sensed decrease in perfusion by afferent arterioles prompts an increase in renin secretion and antidiuretic hormone secretion. Reduced perfusion to the kidneys can lead to AKI, characterized by elevated serum

creatinine levels and reduced urine production, in accordance with the KDIGO diagnostic criteria (Sharfuddin & Molitoris, 2011).

As a clinician, it is essential to understand how prerenal kidney failure differs from other causes of AKI. To make this distinction, many tests must be obtained. The reported gold standard in differentiating prerenal from other causes of AKI is responsiveness to fluid administration. When a sufficient amount of fluid is given to correct for volume depletion, then the serum creatinine should trend down to baseline within 24 to 72 hours. In the case, there was an improvement in the patient's kidney function following fluid therapy, evidenced by a decrease in serum urea and creatinine levels. Additionally, the assessment of the Blood Urea Nitrogen (BUN) to creatinine ratio is crucial. In cases of prerenal disease, this ratio is typically higher than 20:1. In the patient, the urea to creatinine ratio was measured as 30.7:1 (Macedo & Mehta, 2009). Intrinsic kidney abnormalities were ruled out based on a normal urinalysis and a urology ultrasound imaging examination aimed at assessing kidney structure, which showed results within normal limits. In cases of pre-renal problems, urinalysis results should generally be normal. An exception to this rule could occur if there's an underlying or additional renal condition. Occasionally, the presence of hyaline or granular casts might be observed as well (Perazella et al., 2008).

The management of pre-renal kidney failure is dependent on the stage of AKI, underlying etiology, and the setting where it is identified. In the emergency department or the hospital setting, the mainstay of treatment of pre-renal AKI is isotonic fluid administration. It is both therapeutic and diagnostic. A downtrend in creatinine after administration of isotonic fluids is the gold standard in diagnosis. The degree of volume resuscitation depends on the degree of volume depletion caused by the underlying condition (Perazella et al., 2008).

A thorough history and physical exam should be coupled with investigations to find out the cause of AKI, and the management should be directed towards that cause. In patient who present with anaphylactic shock, it should be remove the causative agent. According to the European Academy of Allergy and Clinical Immunology most recent guidelines, assessment using the ABCD (Airway, Breathing, Circulation, Disability and Exposure) approach should promptly applied to patients with anaphylaxis. Cardiopulmonary resuscitation should be immediately instituted if cardiorespiratory arrest occurs (Perazella et al, 2008). Treatment with intramuscular epinephrine is recommended as a first-line intervention before other approaches. The use of epinephrine is the first and most effective measure to be taken in the management of the anaphylaxis treatment. A dose of 0.5 mg has to be injected into the vastus lateralis of the thigh and this injection may be repeated every 5 to 15 minutes if systemic symptoms persist. The intramuscular route is preferable to the intravenous one (if used, apply adrenaline at a concentration of 1:1.000). As soon as is feasible, adjust the inspired oxygen concentration to achieve an oxygen saturation of 94 – 98% (in patients at risk of hypercapnic respiratory failure, consider a target range of 88 – 92%). Observe signs of respiratory failure or laryngeal stridor, which may arise due to airway edema and, if they are observed, perform an orotracheal intubation. Corticosteroids should be started aiming at preventing a late anaphylaxis reaction and should be maintained for 5 days in conjunction with antihistamines, particularly in patients with asthma and biphasic reactions (Muraro et al, 2014).

CONCLUSION

The condition of anaphylactic shock is a life-threatening condition characterized by arterial hypotension, which leads to complications in decrease renal perfusion, potentially causing acute kidney injury (AKI). This is marked by an increase in serum creatinine levels and a

decrease in urine production. If promptly managed with resuscitation fluids, this condition can be reversible. However, if ischemia in the kidney tissue has already occurred, it can lead to irreversible kidney damage.

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