RANDOX

ACUTE KIDNEY INJURY
&
ANTIMICROBIAL STEWARDSHIP

INTRODUCTION

Acute Kidney Injury (AKI), a sudden loss of kidney function, poses a significant challenge in healthcare. This condition disrupts the kidneys' ability to filter waste from the blood, leading to a build-up of waste products and imbalances in electrolytes. Certain antibiotics, which are essential in treating various infections, can trigger AKI, thereby adding complexity to the healthcare scenario. Amidst this daunting health challenge, Antimicrobial Stewardship (AMS) emerges as a key strategy. Here, we will explore the key features of AKI and AMS, underlining the importance of responsible antimicrobial use in this context. Finally, we will delve into classical testing for AKI and the novel solutions Randox provides for diagnosing this potentially fatal condition.

ACUTE KIDNEY INJURY

Acute kidney injury, previously known as acute kidney failure, is the often reversible, sudden reduction of kidney function and glomerular filtration rate (GFR)[1]. The GFR is the process in which waste products are filtered from the blood. The normal GFR process is shown in Figure 1.

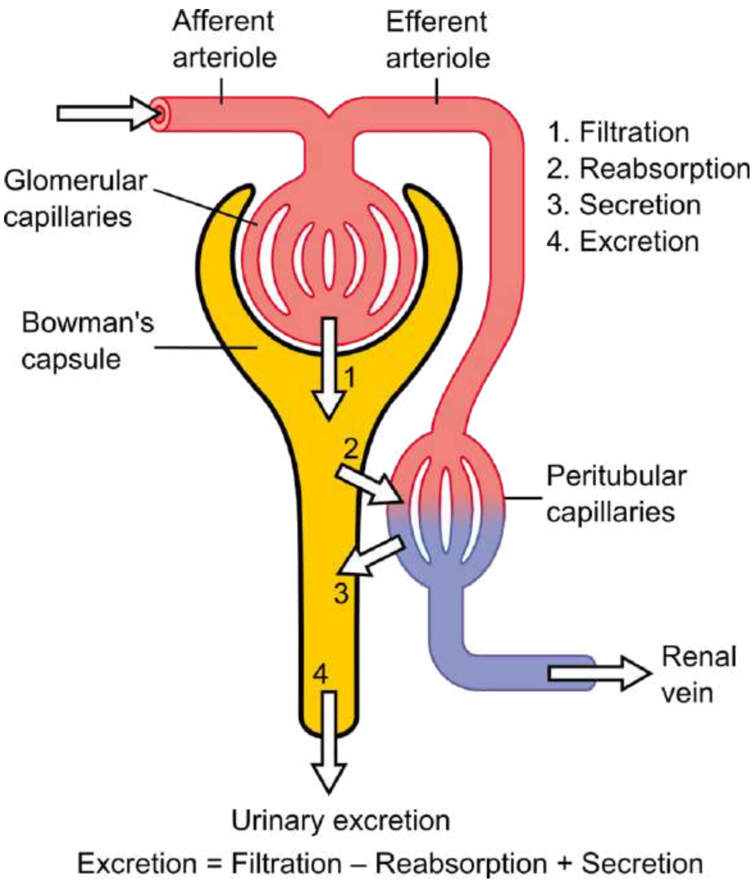

Figure 1. *This diagram shows the process of ultrafiltration in the kidney. Blood enters the glomerulus through the afferent arteriole. Blood pressure in the glomerulus is high, causing water and dissolved substances to filter out the blood in the glomerular capillaries, across the Bowman's capsule and into the renal tubules. The resulting fluid is called the glomerular filtrate. This filtrate then undergoes further modification through reabsorption and secretion, before finally being excreted as urine.*

The reduction in kidney function of AKI results in an aggregation of water and minerals such as sodium and other metabolic products, which manifests as a reduction in urine output and a variety of electrolyte imbalances.

It is a common condition, displayed by up to 7% of hospital admissions and up to 30% of Intensive Care Unit admissions. Despite its widespread prevalence, there remains no definitive clinical definition for AKI, however, several criteria have been proposed in the literature which have been detailed in Table 1.

Table 1. *Clinical Definitions of AKI*

CRITERIA	DESCRIPTION
RIFLE	**Risk, Injury, Failure, Loss, End-stage:** Each category is defined by specific criteria based on the GFR and urine output. Proposed in 2004, RIFLE assessed patients over 7 days to determine their status. RIFLE classes are associated with increased lengths of hospital stay, renal replacement therapy and renal function recovery[2].
AKIN	**Acute Kidney Injury Network:** Proposed in 2007, AKIN is a modified version of RIFLE which is used to define and stratify the severity of AKI. Compared with RIFLE, AKIN assess patients over 48 hours and does not assess GFR[3].
KDIGO	**Kidney Disease:** Improving Global Outcomes: A global, nonprofit organisation dedicated to improving the care and outcomes of kidney disease patients. The KDIGO guidelines are the most recent and classify chronic kidney disease (CKD) based on cause, GFR category, and albuminuria category, abbreviated as CGA. The guidelines also provide recommendations for the identification and prognosis of CKD, the management of progression and complications of CKD, and the management of blood pressure in CKD[4].

KDIGO is the most used guideline for AKI and CKD. According to KDIGO, AKI is defined as the presence of any of the following[4,5]:

1. An increase in Serum Creatinine (SCr) by 0.3mg/dl or more within 48 hours.
2. An increase in SCr 1.5x or more from baseline within the last 7 days.
3. Urine volume less than 0.5ml/kg/h for at least 6 hours.

Aetiology

Differential pressure between the glomerulus and Bowman space is the driving force for glomerular filtration[1]. This pressure gradient is subject to the combined resistances of the afferent (to the glomerulus) and efferent (away from the glomerulus) vascular supplies to the kidney[6]. During normal kidney function, these resistances are balanced, allowing GFR to carry out its normal functions. For example, efferent resistance is increased to reduce the blood flow out of the kidney, increasing pressure in the kidneys and decreasing GFR and vice versa[1]. However, in AKI, the reduction in renal blood flow and GFR has a pathological cause. The pathophysiology of AKI can be categorised as prerenal, intrinsic renal, or postrenal.

Pre-renal AKI

Pre-renal AKI is caused by reduced afferent blood flow or, in other words, increased afferent resistance. While tubular and glomerular functions generally remain intact, pre-renal AKI may be caused by systemic hypoperfusion (decreased blood flow) or selective hypoperfusion to the kidney, caused by renal artery stenosis or aortic dissection[7]. Pre-renal AKI can occur through the following mechanisms:

1. Hypovolemia - can occur due to various factors such as prolonged immersion, and cold diuresis, but more commonly blood loss due to trauma or haemorrhage. Hypovolemia can lead to a decrease in renal blood flow and GFR and progression of AKI. The mechanism of hypovolemia in AKI involves a decrease in the volume of blood circulating in the body, leading to a decrease in renal perfusion pressure. This can result in ischemic injury to the kidneys, which can lead to AKI[7].
2. Hypotension from decreased cardiac output – a result of cardiogenic shock, massive pulmonary embolism, acute coronary syndrome and more[7].
3. Hypotension from systemic vasodilation – typically a result of septic shock, anaphylaxis, or anaesthesia[7].
4. Renal vasoconstriction – Can be caused by drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), iodinated contrast or hepatorenal syndrome[8].
5. Glomerular efferent arteriolar vasodilation – Caused by drugs such as ACE inhibitors and angiotensin receptor blockers[9].

Pre-renal AKI characterises kidney injury which has not yet reached the kidneys; however, prolonged, or untreated prerenal AKI is likely to progress to renal AKI.

Intrinsic Renal AKI

Renal AKI describes the conditions which affect the glomerulus or tubule, for example, acute tubular necrosis and acute interstitial nephritis[1]. This collection of conditions is associated with vasoconstrictor expression in renal afferent pathways. The mechanisms responsible for renal AKI are detailed below:

1. Acute tubular necrosis – cell damage caused by a decrease in renal blood flow and oxygen delivery to tubular cells[10]. May be caused by prerenal injury, intravascular haemolysis or drugs including aminoglycosides and vancomycin[1].
2. Acute interstitial nephritis - characterised by inflammation of the interstitial tissue of the kidney and a common cause of AKI, accounting for up to 20% of cases[11]. Caused by infection, autoimmune disorders, and drugs such as β-lactam antibiotics, penicillin, NSAIDs and proton pump inhibitors[1].
3. Glomerulonephritis - Inflammation of the glomeruli of the kidney's accounts for 10% of AKIs in adults[12]. May be caused by anti-glomerular basement membrane disease or IgA nephropathy[1].
4. Intratubular Obstruction - The blockage of the renal tubules by various substances, leads to a decrease in urine output and an increase in intratubular pressure. This can be caused by toxins, tumour lysis syndrome or because of monoclonal gammopathy in multiple myeloma[1].

Post-renal AKI

Post-renal AKI usually results from an obstruction in the filtration system. Causes of obstruction include kidney stones, tumours, or blood clots, commonly in the bladder outlet. Obstruction affecting one side might not invariably lead to acute kidney injury, especially when the impediment develops slowly, such as with tumour growth. This is because the unaffected kidney might be able to adjust and make up for the compromised functionality[7].

Symptoms, Diagnosis & Treatment

In many cases, the only sign of AKI is decreased urine output. However, when other symptoms present, they may include fatigue, nausea, vomiting or confusion[13]. For an accurate diagnosis, a thorough review of the patient's medical history is required along with a physical examination to determine the primary cause of the condition. As detailed in the clinical criteria discussed previously, serum creatinine levels are typically used to aid the diagnosis of AKI. This and other biomarkers associated with AKI are investigated later in this guide.

The treatment and management of AKI is determined by the underlying cause of the condition. In less severe cases, measures are taken to maintain the correct levels of fluid, electrolytes, and blood pressure. When required, nutritional support will also be provided. The most severe cases of AKI may require dialysis to make up for the reduced kidney function[14].

Complications

Electrolyte Imbalance
Electrolytes help to regulate heart and neurological function, fluid balance, oxygen delivery, acid-base balance, and much more. Cardiac arrhythmias, seizures and muscle weakness can result from an imbalance in sodium, calcium, or potassium[15].

Fluid Overload
Swelling, hypertension and shortness of breath can result from excess fluid. Several observational studies have shown a direct correlation between fluid overload and mortality in critically ill patients with AKI[16,17].

Metabolic Acidosis
Metabolic acidosis can occur in both AKI and CKD. In AKI, metabolic acidosis can result from the overproduction of organic acids such as ketones or lactic acid, or it may reflect bicarbonate wasting and impaired renal acidification. This can result in fatigue, confusion, shortness of breath and more[18].

Chronic Kidney Disease
The risk of developing CKD after AKI is high, with one meta-analysis showing that adults with AKI are at a 9-fold higher risk of developing CKD[19].

End Stage Renal Disease
End-stage renal disease (ESRD) is a severe form of CKD that can develop after AKI. ESRD is characterised by a significant loss of kidney function, requiring renal replacement therapy such as dialysis or kidney transplantation to sustain life. The development of ESRD after AKI is associated with a high risk of morbidity and mortality, and it is estimated that up to 50% of patients with ESRD have a history of AKI[20].

Biomarkers

SCr is used to assess individuals for AKI, as shown in the KDIGO guidelines discussed previously. Creatinine is a useful diagnostic tool for renal conditions, capable of assessing kidney health, GFR and muscular dystrophy. However, abnormal levels of SCr do not present until a large proportion of the renal mass is damaged. The kidneys have a remarkable ability to compensate for reduced function meaning a substantial loss of function or GFR is required to alter SCr levels. This provides a challenge for early detection of AKI[21].

Novel biomarkers associated with AKI can be analysed through molecular testing. These new methods can provide a fast and accurate assessment of an individual's kidney health, at a much earlier stage than SCr quantification.

KIM-1

Kidney Injury Molecule-1 (KIM-1) is a protein expressed in the proximal tubules of the kidney which is upregulated in response to kidney injury. This protein plays a role in the phagocytosis of apoptotic cells and in the repair of injured cells. KIM-1 is a sensitive and specific diagnostic marker for AKI, providing analysis much earlier in the condition than SCr[1].

NGAL

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein expressed in multiple types of cells, including those of the kidney. They play an important role in the regulation of iron metabolism and in preventing bacterial growth. In AKI, NGAL is upregulated; however, the mechanism for this is not fully understood. Nonetheless, NGAL provides another sensitive biomarker for the detection and monitoring of AKI[1].

Clusterin

Clusterin is involved in the regulation of apoptosis and the maintenance of cell survival. Like NGAL, the mechanisms of Clusterin upregulation are not fully understood. However, Clusterin upregulation in response to AKI provides an additional, sensitive biomarker for AKI.

Cystatin C

Cystatin C is constantly produced by all nucleated cells. It is filtered in the glomerulus and undergoes reabsorption and catabolism but is not secreted by the tubules. It is retained in the blood and is, therefore, a biomarker for GFR. Although there is no clinically defined cut-off value for the use of Cystatin C, it is an extremely sensitive marker for AKI, detecting injury up to 2 stages earlier than SCr[1].

ANTIMICROBIAL STEWARDSHIP

Antimicrobial Stewardship (AMS) is a coordinated approach aimed at promoting the appropriate use of antibiotics to combat antimicrobial resistance (AMR). AMR is defined as the ability of microorganisms to resist the effects of antimicrobial drugs, rendering them ineffective[22]. AMS programs are designed to optimize antimicrobial use, reduce the development of AMR, and improve patient outcomes. These programs involve a range of strategies, including education and training, guidelines and protocols, antimicrobial use monitoring and feedback, and antimicrobial formulary management. By promoting the appropriate use of antibiotics, AMS programs can help to preserve the effectiveness of existing antimicrobial agents and slow the development of AMR[22].

Antibiotics Commonly Implicated in AKI

Various antibiotics are associated with the progression of AKI due to their nephrotoxicity. This nephrotoxicity can cause severe damage to the kidneys resulting in AKI. Some of these antibiotics are discussed below.

Polymyxins

Polymyxins are a class of antibiotics effective against Gram-negative bacteria, commonly used as a treatment against multidrug-resistant (MDR) organisms[23]. Examples of this class of antibiotics include Polymyxin B and colistin, which are used as the final therapeutic option to treat many MDR infections. Whilst effective against bacteria when all else fails, this class of antibiotics is associated with high nephrotoxicity and an increased risk of developing AKI[24]. The mechanism of this nephrotoxicity is not fully elucidated, although, it is proposed that it is due to damage caused to the cellular membrane of the proximal tubule cells due to the detergent activity of these antibiotics[24]. Alternative suggestions state it is the accumulation of the antibiotic which causes damage to the mitochondria and ultimately induces AKI[24].

Aminoglycosides

Aminoglycosides are a class of antibiotics that are particularly potent against members of the Enterobacteriaceae family and have been associated with nephrotoxicity. They exert their antibiotic action through the inhibition of protein synthesis and are effective agents against MDR infections[25]. Aminoglycosides are considerably nephrotoxic, possibly inducing unreversible kidney damage, with the risk of AKI estimated to be between 5-25%[24]. The proposed mechanism for this nephrotoxicity is an accumulation of the drug in the proximal tubule cells, resulting in apoptosis and acute tubular necrosis due to the disruption of phospholipid metabolism. Some additional risk factors for aminoglycoside-associated AKI include diabetes, hypotension, advanced age, liver disease, hypoalbuminemia, multiple daily doses, and accumulative dosage[24].

Vancomycin

Vancomycin is an antibiotic commonly used to treat suspected and confirmed cases of Methicillin-Resistant Staphylococcus aureus (MRSA) infection as well as other Gram-positive bacterial infections. This antibiotic functions by inhibiting transpeptidation by binding to the D-alanyl-D-alanine residues of the bacterial cell wall[24]. Like the other antibiotics discussed, the mechanism of nephrotoxicity has not been fully elucidated, although several pathways have been proposed. Vancomycin is associated with an increased risk of developing AKI when compared with other antibiotics with an odds ratio of 2.45 and therapy lasting longer than 7 days has been shown to increase risk from approximately 6% to 21%[24].

RANDOX RENAL INJURY DETECTION

Due to the well-documented poor sensitivity and specificity of SCr for the detection of AKI, several biomarkers have been proposed to replace this method of AKI diagnosis. Novel methods for early detection of AKI, monitoring of drug toxicity and identifying those at increased risk of CKD have been developed in recent years. Using the patented Biochip Technology, the Randox Acute Kidney Injury (AKI) array, available on the Evidence Investigator, simultaneously tests for four novel biomarkers (KIM-1, NGAL, Clusterin, Cystatin C) delivering an early diagnosis and monitoring of treatment efficacy. Multiplex testing better captures reduced renal function, as each biomarker reflects different mechanisms that result in similar injury outputs, allowing for a more accurate picture of the underlying cause of AKI. Along with being able to identify AKI at a much earlier stage, this array provides an accurate and sensitive solution for the diagnosis and monitoring of AKI.

CONCLUSIONS

Acute kidney injury can be diagnosed by assessing the glomerular filtration rate. The reduction of renal function results in an aggregation of metabolic products causing a reduction in urine output and a variety of metabolic imbalances. AKI can be categorised as prerenal, intrinsic renal or postrenal with each having distinct pathological mechanisms. The diagnosis of AKI, according to KDIGO, requires the evaluation of serum creatinine levels, however, this method is associated with poor sensitivity and specificity. Novel biomarkers and methods have been introduced which boast improved sensitivity and specificity. The Randox AKI Array can determine the underlying cause of AKI, aiding not only in diagnosis but also in ensuring the correct therapeutic strategy is implemented. This array displays superior sensitivity and specificity compared with serum creatinine quantification, providing a faster, more accurate approach to AKI diagnosis.

Antibiotics are used to treat many different infections. However, their indiscriminate use throughout their history has led to the development of antimicrobial resistance, limiting the options available to clinicians. Many of the antibiotics used to treat multidrug-resistant infections have been shown to display nephrotoxic effects, potentially initiating AKI. Antimicrobial stewardship is crucial in the fight against antimicrobial resistance. In addition, the dosage of these antibiotics should be strictly controlled and patients who are administered them should be closely monitored to ensure their kidney functions and glomerular filtration rate is maintained.

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