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Acute kidney injury in the critically ill patient

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A B S T R A C T

The stage at which acute kidney injury (AKI) is detected is dependent upon the definition used. More recently it has been demonstrated that even relatively small increments of serum creatinine portend a worse outcome. This has prompted the development of new definitions based on small rises in serum creatinine or decreases in urine output. Acute kidney injury on the intensive care unit (ICU) is usually multifactorial secondary to hypovolaemia and sepsis resulting in hypoperfusion of the kidneys. In patients with good baseline kidney function the condition is generally reversible if the patient regains health. However it has been recognised that kidney function does not always completely recover. An episode of AKI may represent an antecedent to the development of chronic kidney disease (CKD), and patients who already have CKD are at risk of AKI and further loss of function. Preventative measures should therefore be instituted as soon as possible in patients identified to be at risk of developing AKI. The cornerstone of treatment for patients who develop AKI remains renal replacement therapy (RRT). Ultimately it is hoped that the development of new biomarkers may enable earlier detection of patients at risk of developing AKI.

1. Definitions of acute kidney injury

Acute kidney injury (AKI), previously referred to as acute renal failure, has traditionally been recognised as a rapid decline in kidney function from hours to days with the failure to regulate fluid, electrolyte and acid base balance. In previous years more than 35 different definitions have been used to define AKI in the literature. This has hampered the ability to characterise the true incidence of the disease, assess its impact and make any significant progress with clinical and scientific research. The proposals for a universal definition and classification system for AKI is the result of a collaborative effort by both nephrologists and intensive care specialists through the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN).[1,2] In 2002 the ADQI proposed the term AKI to represent the entire spectrum of ARF, preferring the term injury to failure, as it was felt this more accurately reflects the earlier degrees of injury that may occur prior to failure of kidney function. Simultaneously the ADQI proposed the RIFLE staging system (Table 1), which includes three levels of progressive kidney dysfunction, Risk, Injury and Failure and two outcomes, Loss of function and End stage kidney disease. Categorisation into a particular stage is dependent upon rises in serum creatinine from baseline values within a one week time interval or reductions in urine output. The staging criteria (serum creatinine or urine output) selected is that which translates to the higher stage of AKI.

Subsequent studies demonstrated relatively small increments in serum creatinine were associated with a significant increase in length of hospital stay and patient mortality.[3,4] This prompted proposals for further refinements to the definition and classification system by the AKIN in 2005.[2] The Acute Kidney Injury Network modified the RIFLE staging system to produce an interim staging system to allow additional data to be gathered and research initiatives to be proposed (Table 1). The modifications included using a smaller change in serum creatinine >26.4 μmol/L to define the presence of AKI thereby attempting to increase the sensitivity of the criteria. This change is based on the work from Chertow et al.[1] that found that patients in a large urban hospital who experienced an increase in serum creatinine of just 0.3 mg/dl (26.4 μmol/L) had a 70% higher multivariable adjusted odds of death compared to patients with little or no change in serum creatinine. Further changes included the introduction of a time interval of 48 h and between serum creatinine values and classifying any patient that received RRT as stage 3 AKI. The 48-hour time interval was based upon data demonstrating a poor outcome was associated with with small rises in serum creatinine occurring within 24 to 48 h.[5] The AKIN group also proposed that the diagnostic criteria could not be applied until the patient's volume status had been optimised and

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urinary tract obstruction had been excluded. This has led to a certain degree of debate as to whether pre-renal and obstructive aetiologies should be included or excluded from the staging criteria.

There are inherent difficulties with both of the newly proposed definitions as they rely on changes in either serum creatinine or urine output both of which are recognised as relatively poor biomarkers. Serum creatinine does not accurately reflect the true glomerular filtration rate (GFR) in a patient who is not in steady state. In the early stages of severe AKI the serum creatinine may not be significantly elevated despite a marked reduction in GFR due to there being insufficient time for the creatinine to accumulate. Once a patient has commenced on RRT serum creatinine becomes less useful as a marker of kidney injury as it is removed. The accurate measurement of urine output is generally confined to patients with urinary catheters and is modified by the use of diuretics. It must also be remembered that AKI can be oliguric (<400 mls/24 h) or non-oliguric so that serum creatinine rises can occur despite an adequate urine output. Another contentious issue is the definition of baseline serum creatinine and what value to accept when calculating the stage of AKI. Some studies have used the Modification of Diet in Renal Diseases (MDRD) equation to calculate a baseline serum creatinine assuming a lower limit of normal baseline GFR 75 ml/min when a true baseline value has not been available.[6] A recent publication has compared AKIN staging using known baseline serum creatinine values versus estimation of the baseline serum creatinine using the MDRD equation.[7] The study concluded that estimation of the baseline serum creatinine using the MDRD equation when the premorbid serum creatinine was unavailable appeared to perform reasonably well for determining the RIFLE staging only if the premorbid GFR was near-normal. However this was not the case in patients with suspected CKD.

2. Epidemiology of acute kidney injury on the ICU

The incidence of AKI on the ICU has been more clearly characterised due to established data collection systems such as the Intensive Care National Audit and Research Centre (ICNARC) in the UK and has been estimated at 25–30%. To date over 20 different studies using the RIFLE staging system have demonstrated a wide ranging incidence of AKI in the ICU dependent upon the population case mix.[8] Further studies have compared the AKIN staging system with the RIFLE staging system in critically ill patients on the ICU demonstrating little difference between the systems in overall incidence and outcomes of AKI.[6]

3. Aetiology of AKI on the ICU

The aetiology of AKI is best considered divided into three main categories, pre-renal, intrinsic and post-renal AKI (Fig. 1). This allows the clinician to systematically consider the cause of the injury for the purposes of diagnosis and management. The frequency of aetiology will depend upon the cohort studied.

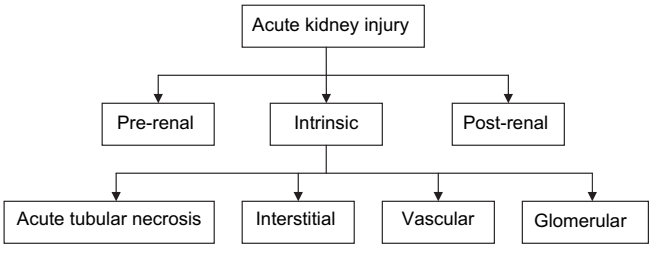

Fig. 1. Aetiology of acute kidney injury.

Outside of the ICU the percentage of patients with AKI is generally recognized as, pre-renal AKI 55–60%, intrinsic AKI 35–40% and post-renal AKI < 5%.[9] In contrast the majority of critically ill patients with multiorgan failure on the ICU will have potentially reversible intrinsic AKI secondary to kidney hypoperfusion (ischaemia) and/or sepsis.

Pre-renal and ischaemic AKI may be considered as two extremes of a spectrum of injury that is the result of hypoperfusion of the kidneys. In pre-renal AKI there is a reduction in glomerular filtration rate (GFR) without overt tubule cell injury. Restoration of adequate kidney perfusion will result in rapid recovery of GFR. However if the hypoperfusion is sustained tubule cell injury occurs resulting in acute tubular necrosis (ATN) from which recovery will be delayed. It is important to consider in each patient whether there is a defined cause of the AKI that can explain the patient's clinical presentation. If the aetiology of the AKI cannot be obviously identified as being secondary to a defined insult such as hypoperfusion, sepsis or nephrotoxins then a more esoteric aetiology should be considered prompting discussion with the renal team.

4. Pathophysiology of AKI on the ICU

The pathophysiology of AKI will be dependent upon the underlying aetiology for which there are many different causes. For the purposes of this article only acute tubular necrosis (ATN) secondary to kidney hypoperfusion will be considered. Acute tubular necrosis is strictly a histopathological diagnosis and is often used interchangeably with ischaemic AKI. Significant kidney hypoperfusion results in the preferential shunting of blood away from the already relatively ischaemic environment of the outer medulla.[10] It is therefore the proximal tubules and medullary thick ascending limbs of the distal tubules which lie in the outer medulla that sustain most ischaemic injury. The resultant depletion of ATP leads to tubule epithelial cell injury.

Paradoxically kidney biopsy studies have sometimes failed to demonstrate frank tubule cell necrosis despite marked kidney dysfunction. There have been a number of proposed mechanisms to explain the marked reduction in GFR in this setting. These include a decrease in the filtration pressure in the glomerulus secondary to afferent arteriolar vasoconstriction and sublethal cell injury resulting in tubule cell dysfunction. Continuing ischaemia results in further ATP depletion and marked tubular cell necrosis. At the cellular level there is disruption of tubule tight cell junctions leading to loss of tubule epithelial cells resulting in proximal tubular obstruction, and back leak of glomerular filtrate across denuded basement membrane. Recovery of kidney function is possible on restoration of perfusion and repletion of ATP levels. The recovery involves tubule cell proliferation and differentiation which can take up to six weeks to complete.[11]

An area of increased interest is the distant organ effects of AKI. As previously described patients who developed even small increases in serum creatinine have been demonstrated to have an increased mortality. Patients who develop AKI are at an increased risk of, sepsis, respiratory failure, haemorrhage and central nervous system (CNS) dysfunction. It has been proposed that AKI is a multisystemic condition that results in distant organ dysfunction. Experimental data has demonstrated that isolated ischaemic AKI results in an increase in circulating cytokines, chemokines and activated leucocytes resulting in cell infiltration of a number of different organ systems including the lungs, heart and CNS.[12–14]

5. Clinical presentation and diagnosis of AKI

Early differentiation of recoverable AKI secondary to kidney hypoperfusion and ATN from CKD or other causes of AKI that