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The assessment of acute kidney injury in critically ill patients

Sebastjan Bevc [a,c,*], Robert Ekart [b,c], Radovan Hojs [a,c]

[a] Clinic for Internal Medicine, Department of Nephrology, University Medical Centre Maribor, Maribor, Slovenia
[b] Department of Dialysis, University Medical Centre Maribor, Maribor, Slovenia
[c] Faculty of Medicine, University of Maribor, Maribor, Slovenia

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ABSTRACT

Acute kidney injury (AKI) is common in critically ill patients and is associated with high morbidity and mortality. The availability of several biomarkers of kidney injury offers new tools for its early recognition and management. The early identification of high-risk patients provides an opportunity to develop strategies for the prevention, early diagnosis and treatment of AKI. Despite progress in critical care medicine over the past decade, the treatment strategies for AKI in critically ill patients, such as when to start renal replacement therapy, remain controversial. A recently proposed risk prediction score for AKI, based on routinely available clinical variables, presents a new means of identifying patients at high risk of AKI.

1. Pathophysiology and pathologic features of acute kidney injury

The etiologies of acute kidney injury (AKI) can be summarized into three main causes: ischemia, hypoxia and nephrotoxicity. The mechanisms involved in the pathophysiology of AKI and their repair are complex. The kidney is susceptible to ischemia and toxins, resulting in vasoconstriction, endothelial damage and activation of inflammatory processes. This susceptibility arises in part from the vascular-tubular relationships in the outer medulla of the kidney, where the partial pressure of oxygen is low, thus making the outer medulla more vulnerable to a decreased renal blood flow (RBF), renal hypoperfusion and the resulting decreased glomerular filtration rate (GFR) [1–3]. In response to this condition the kidney maximally concentrates urine and avidly reabsorbs sodium in order to maintain or increase intravascular volume and normalize renal perfusion. However, a prolonged decrease in renal perfusion can result in irreversible ischemic damage, leading to ischemic AKI or acute tubular necrosis (ATN), the most severe form of AKI. ATN is characterized by injury of the tubular cells, mainly in distal regions of the proximal tubule and the thick ascending limb of Henle's loop [2]. According to the pathophysiological process of AKI five well-characterized phases of ischemic ATN have been identified: pre-renal, initiation, extension, maintenance and recovery phase [4–6].

The pre-renal phase occurs first, when RBF decreases but cellular integrity is still maintained.

In the initiation phase there is a decrease in GFR caused by a decrease in net ultrafiltration pressure. Ischemia causes the depletion of high-energy molecules, inhibition of active sodium transport and the formation of reactive oxygen species. This results in alterations in the cytoskeletal structure with the loss of cell polarity and the tight junctions between cells and the loss of the attachment of cells to the basement membrane. The accumulation of detached cells and necrotic debris in the lumen of the tubule contributes to occlusion and "back-leak" of filtrate. If RBF is restored early all this damage can be repaired.

In the third extension phase morphological and functional changes occur in the vascular endothelial cells and the renal tubular epithelium, resulting in the recruitment of circulating inflammatory cells (e.g., neutrophils, lymphocytes, macrophages) and the expression of adhesion molecules and chemokines. AKI induces the production of inflammatory mediators by endothelial and tubular cells, contributing to the recruitment of leukocytes. Proximal tubule cells produce cytokines and interferons. Some of them are also released into the tubular lumen and can be used as early biomarkers of kidney damage.

The fourth maintenance phase is when oliguria and uremic complications usually occur. It typically lasts 1–2 weeks and is when GFR is stabilized at its lowest level. It is thought that GFR is kept low by dysregulation of the release of vasoactive mediators from endothelial cells, the congestion of medullary blood vessels, and damage by reactive oxygen species and inflammatory mediators produced by leukocytes and renal cells after reperfusion. During this phase, cells undergo repair, migration, apoptosis and proliferation to reestablish and maintain cellular and tubule integrity.

The fifth, or recovery phase, is characterized by the repair and regeneration of tubular epithelium and an increase in GFR. Cell differentiation

* Corresponding author at: Clinic for Internal Medicine, Department of Nephrology, University Medical Centre Maribor, Ljubljanska 5, 2000 Maribor, Slovenia.
E-mail addresses: sebastjan.bevc@ukc-mb.si (S. Bevc), robert.ekart2@guest.arnes.si (R. Ekart), radovan.hojs@ukc-mb.si (R. Hojs).

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continues, epithelial polarity is reestablished and normal cellular and organ function returns. Surviving cells undergo a process of de-differentiation and migration to enter the cell cycle and repopulate the basement membrane and regenerate damaged epithelium. At the same time there is a parallel process to clear the accumulation of tubular cells. The successful recovery from AKI depends on these repair processes, which may be compromised in the elderly and/or chronic kidney disease patients [3–6]. Recovery takes 1–2 weeks after renal perfusion returns to normal, and requires the repair and regeneration of tubular cells [4]. The recovery phase may be complicated by a diuretic stage caused by the failure of the cells of the proximal tubule to reabsorb water and solutes [7].

The pathologic features of ischemic ATN are focal lesions of necrotic tubular epithelium, with detachment of cells from the basement membrane and occlusion of the tubular lumen by composite cylinders (casts), Tamm-Horsfall protein and pigments. The accumulation of leukocytes is frequently observed in the vasa recta but the morphological characteristics of the glomeruli and vasculature are usually normal. Necrosis is most serious in the proximal tubule and the thick ascending limb of Henle's loop. After exposure to nephrotoxic agents, morphological changes tend to be more prominent in the proximal tubules [4].

Although a common condition in the critically ill, our understanding of the pathophysiology of AKI during sepsis is limited, mainly because of a scarcity of histological studies and an inability to measure renal microcirculatory flow. AKI during sepsis is associated with renal hypoperfusion and diminished oxygen transport, but once a hyperdynamic state occurs RBF is found to be normal or increased, with no significant histological evidence of tubular necrosis. Therefore, factors other than ischemia may be involved in the genesis of AKI in sepsis, including apoptosis, glomerular and medullary microcirculatory disorders, cell changes in response to the characteristic pro-inflammatory cascade of sepsis, oxidative stress, mitochondrial dysfunction and damage induced by mechanical ventilation [1–6].

2. Defining acute kidney injury

AKI occurs frequently (range 20 to 70% depend on diagnostic settings) in hospitalized critically ill patients and those admitted to intensive care units (ICU). It is associated with a high morbidity, mortality (around 50% of those who requiring renal replacement therapy (RRT)) and costs [7–10]. In recent years, standardized diagnostic and staging criteria for AKI have contributed to an improved understanding of its incidence and course in ICU patients. However, there is wide variation in how promptly AKI is recognized and managed, and in its outcomes [11–13]. Several sensitive and specific urine and serum biomarkers of kidney injury have emerged for the detection of AKI in an attempt to diagnose it earlier [9–19]. Whereas some of these biomarkers seem to work in well-controlled conditions and restricted populations, their performance decreases in mixed or more complex populations, and the confidence intervals for sensitivity and specificity become wide [7,9,10]. Today, biomarkers can be accepted as functional markers (e.g., serum creatinine, serum cystatin C, urine output), or damage markers (e.g., kidney injury molecule-1 (Kim-1), neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases-2 (TIMP2) and IGF-binding protein-7 (IGFBP7)). Measuring them in combination improves diagnostic categorization and permits more guided interventions [20,21]. Some studies have demonstrated that changes in the levels of kidney damage markers prior to the clinical onset of AKI are important for the identification of the mechanistic pathway of AKI, and essential for development of effective future therapeutic interventions. However, at the present time, biomarkers still lack sufficient validity to impact clinical decision making and further studies in this field are needed. The negative predictive values of AKI biomarkers seem to be much greater than their positive predictive values, suggesting they may be more useful in identifying patients who will not develop clinical AKI, rather than identifying those who will. Moreover, the predictive values of biomarkers are highly dependent on the incidence of AKI in the patient population being studied [22].

Over the last few years several initiatives have been made to harmonize the definition of AKI and bring the problem of AKI to the attention of non-nephrologists and other clinicians [23–25], and the principles of RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease), AKIN (Acute Kidney Injury Network) and KDIGO (Kidney Disease Improving Global Outcomes) have been widely adopted into clinical practice. However, the boundaries of the diagnostic criteria, especially in relation to the baseline value of creatinine, are constantly changing [23–27]. For clinicians, AKI is the reduction in GFR, when usually the kidney has already been damaged substantially. For the experimental physiologist, on the other hand, harm to even a few tubular cells as evidenced by biomarkers is enough to establish the diagnosis. AKI is a multifaceted condition, in terms of severity, underlying disease and circumstances, and sequence of events. By creating stages of AKI, RIFLE, AKIN and KDIGO have tried to address this problem, and these stages have all been shown to correlate with outcome [28]. However, in order to define a change in serum creatinine, a baseline value is needed, changing the problem of definition of AKI into a problem of defining a baseline value of serum creatinine, which might lead to different classifications [29]. In addition to the difference between a baseline and a second value, the kinetics of the further evolution of serum creatinine must also be taken into account. The current definitions of RIFLE, AKIN and KDIGO do not consider the kinetics of serum creatinine, or the duration of its increase. The distinction between renal and pre-renal failure can only be made by evaluating fluid responsiveness or the effect of increasing renal perfusion, not by a definition based on single changes from baseline in serum creatinine or a biomarker [30]. For example, if a patient with normal kidney function becomes acutely dehydrated his serum creatinine might be several folds his baseline value, but will decrease rapidly with rehydration. Therefore, in such a patient fluid responsiveness and a rise in urinary outputs are the best prognostic indicators [31]. On the other hand, in critically ill septic patients declining urinary output despite fluid loading is often the first sign of impending AKI, but the serum creatinine will only rise slowly initially. With RIFLE relative risk rather than predictive value is used to indicate the increase in risk for a certain outcome when serum creatinine changes. Using these definitions to guide therapy could potentially harmful treatment that patients will not benefit from because they do not have AKI in the first place. Moreover, it is not certain whether changes in serum creatinine and/or urinary output have the same impact in a patient on a ward, or with sepsis, or after different surgery procedures, adding to the multifaceted aspects of AKI and its management.

There are numerous risk factors associated with poor outcomes from AKI, which include older age, heart failure, liver failure, chronic kidney disease, anemia and exposures to nephrotoxic agents such as antibiotics, non-steroidal anti-inflammatory drugs and contrast media. Furthermore infections, sepsis, shock, need for mechanical ventilation and surgery also increase the risk developing AKI [10]. It is increasingly recognized that ICU treatment may be required for both community-acquired and hospital-acquired AKI. Hospital-acquired AKI is associated with a worse prognosis and is often iatrogenic in nature [32].

3. Treatment of acute kidney injury

In all critically ill patients volume replacement is crucial to hypovolemia management and optimal therapy. It prevents the development of multiple organ and kidney failure by assuring stable circulatory parameters and organ perfusion while reducing excessive interstitial fluid overload [33]. The choice of fluid is still a subject of discussion. Most crystalloids consist of a non-physiological mixture of electrolytes, so the patients who have large amounts of saline infused can get hyperchloremic acidosis [34]. Colloids have been shown to have some benefits with respect to crystalloids for correcting intravascular volume deficits and for improving systemic and microcirculatory hemodynamics.

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