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Review article

Acute tubular necrosis: An old term in search for a new meaning within the evolving concept of acute kidney injury

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ABSTRACT

By the mid 2000s, the old term acute renal failure (ARF) was widened and superseded by the more inclusive concept of acute kidney injury (AKI). Whereas ARF referred to patients acutely needing dialysis to preserve life, AKI comprised all patients whose plasma creatinine concentration increased, or whose renal output decreased abruptly. This conceptual change primed clinical consideration, and stratification and handling criteria for a broader range of patients, hitherto not considered as such. A similar circumstance now lurks on the concept of acute tubular necrosis (ATN). ATN is the most common histo-functional pattern of a subtype of AKI, namely intrinsic AKI. In intrinsic AKI, the primary cause of AKI is posed by alterations in the renal parenchyma; as opposed to: (i) pre-renal AKI, in which the primary cause is a deficit of renal blood flow resulting from decreased perfusion pressure or glomerular hemodynamic alterations; and (ii) post-renal AKI, derived from obstruction of the urinary ways. The concept behind ATN has also evolved spontaneously, and without appropriate conceptual reconsideration, along with the evolution of AKI and the increasing knowledge of cell death modes. From the pristine concept of tubule cell necrotic death, ATN now even comprises syndromes and patterns involving sub-lethal alterations in tubule cells. This spontaneous evolution has blurred the conceptual boundaries of ATN and, most importantly, by doing so it has also nulled important stratification criteria, which are crucial for patient outcome. Prognosis of patients with mild, sub-lethal functional alterations may differ substantially from that of patients with extensive tissue destruction. Cataloging the whole range between both extremes under a unique ATN concept abrogates effective classification and care. By the mid 2010s, an international consensus redefinition of ATN with a severity scale, in which grades are associated to specific histo-functional alterations, seems timely and appropriate. Thereon, diagnostic criteria to discriminate ATN grades and handling recommendations must follow.

Focal points:

- Benchside
  The term ATN has evolved spontaneously out of its initial semantic field in parallel to widening pathophysiological knowledge. Redefinition and sub-classification of ATN is necessary, which will refine histopathological studies in animal models and their translation to corresponding human conditions.
- Bedside
  An updated definition of ATN will help to more appropriately, more specifically and individually stratify patients, and apply personalized handling according to their pathophysiological process.
- Industry
  Translation of new ATN definition and sub-classification criteria into new and specific diagnostic tools is expected to broaden the market in the field and to provide new business opportunities.

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- Government
  Sub-classification of ATN and development of specific diagnostic technologies may enable implementation of new standardized diagnostic protocols for AKI in public and private health systems, as appropriate.
- Regulatory
  Refinement of regulatory issues on nephrotoxicity on drug development may benefit from ATN redefinition and sub-classification, especially upon identification of ATN subtype markers.

Contents

1. Acute kidney injury: an evolving term

Acute kidney injury (AKI) is a syndrome in which renal excretory function becomes suddenly handicapped. In this situation, the kidneys become incapable of effectively achieving hydroelectrolytic balance and depurating the blood from toxic and waste products. Fluid retention, and accumulation in the blood of products normally found in the urine (uremia), and especially of nitrogen-containing metabolic products, such as urea and creatinine (azotemia), lead to dysfunction of other organs, including the heart, lungs, liver and brain. Excessive fluid retention and high levels of azotemia are acutely and rapidly incompatible with life, and dialysis becomes mandatory. In all cases, the central pathophysiological event underlying the handicapped renal excretory function is a sudden reduction in glomerular filtration rate.

AKI is a rather recent term adopted in 2004 by the Acute Dialysis Quality Initiative group, and generally accepted subsequently, to substitute for the old term “acute renal failure” (ARF) [71]. ARF defined a state of renal dysfunction needing dialysis. Renal functional alterations not needing dialysis were considered of little clinical significance, as in most cases, renal dysfunction was spontaneously transitory, or reversed to normal function upon withdrawal of the cause, with no apparent sequelae. However, realization was increasingly gained on that even mild cases of renal dysfunction had short-, medium- and long-term consequences for health and survival. This knowledge prompted the redefinition of a wider range of clinically important circumstances related to renal damage and dysfunction, under the new term AKI. Definitions of AKI presently used are not conceptual definitions but mostly functional definitions that rely on increments in plasma creatinine, a waste product from the muscle metabolism that accumulates in the blood when filtration decreases. According to international consensus definitions [66,20,71], no AKI takes place until plasma creatinine concentration becomes elevated, as reflected by the three most used AKI severity scales worldwide (i.e. RIFLE/pRIFLE, AKIN and KDIGO; [68,71]).

2. Clinical and economic impact of AKI

The clinical consideration bestowed to AKI has evolved during the last 6 or 7 decades. By the 1950s, ARF was considered a very serious condition. From the widening AKI concept, consideration to the immediate danger and risk posed by non dialysis-requiring AKI episodes has been low. However, we have recently started to learn that AKI has important immediate consequences for health, with dramatic statistics, notably in determined patient groups, and considerable associated costs. In the last decades, increasing realization and consolidation that not only mild AKI episodes, but also subclinical AKI have important consequences for health in the medium and long term, has turned up the awareness on the seriousness of AKI over a wider casuistic.

AKI epidemiology has bold numbers obtained from data in the hospital medium. However, the number might be even higher to an undetermined extent, because AKI may also occur in the primary care setting, where, except for severe cases, might go largely unnoticed. About 1–2% of hospital admissions are related to AKI, and 2–7% of hospitalized patients develop AKI [4,36,76,38]. However, a recent study showed that, in the world, in-hospital incidence of AKI is close to 1 in every 5 adults, and 1 in every 3 children [67]. Importantly, AKI incidence grows at a yearly rate of 10% [44,62], due in part to population growth and increase in the incidence of AKI-precipitating factors. The incidence of dialysis-requiring AKI grows at a similar rate [33]. Overall worldwide, AKI has a mortality of 23.9% in adults, and 13.8% in children [67].

AKI is a disproportionate problem in the Intensive Care Units (ICUs). In this setting, incidence is as high as 30–50% of cases [20,68], and the associated mortality has remained rather constant for decades at dismally 50–80% of cases [46,4,36,76]. In other reports, AKI incidence in the ICU is lower (1–25%), which indicates that incidence is variable among populations, circumstances and studies, and, importantly, it differs depending on the AKI-defining criteria [6]. Critically ill patients with multiorgan failure are most susceptible to AKI-induced havoc. A fraction of AKI patients never