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By the mid 2000s, the old term acute renal failure (ARF) was widened and superseded by the more inclusive concept of acute kidney injury (AKI).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.
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 depleting the blood from toxic and waste products. Fluid retention, and accumulation in the blood of products normally found in the urine (urea), 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 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
recovered normal or previous renal function. 4–6% patients need dialysis during AKI [17], a number that grows up to 13% among ICU patients [6].

Besides immediate consequences, medium and long-term morbimortality is also increased after AKI. Up to 7.5% of patients need dialysis for life [41]. But in those patients with low renal function prior to AKI (< 44 mL/min), 40–60% never come off dialysis [25]. An association has been established linking AKI with higher odds of progressing to chronic kidney disease [10,32]. This relation is especially strong for severe AKI cases, for repeated AKI episodes, and for AKI patients with handicapped renal function before the AKI episode [70,3,12,28,2]. But transient AKI [8,15,73,9,47], mild AKI [52] and even subclinical AKI [26] are also associated to higher incidence of chronic kidney disease (CKD) and worse mediate and long term outcome. An extrapolation by [40] from a study performed by [77] concluded that AKI-induced CKD accounted for 3% of the annual incidence of end-stage renal disease. AKI patients have higher incidence of cardiovascular events and higher mortality [55,21].

Direct AKI-associated cost poses 1% of the overall health expenditure [38], and 5% of total hospital expenditure [13,75]. AKI cost derives from extended hospital stay, closer monitoring and dialysis application. Nearly 50% of patients hospitalized with uncomplicated ARF require some type of post-hospital care, of whom 27% undergo extended facility care, while 22% receive home health care [23]. AKI cost approximately $10 billion annually in the USA by the 2000 s [14], and $1.02 billion in England by the 2010s [38]. In 2003, it was estimated in the USA that a 0.3 mg/dL increment in plasma creatinine originated an extra cost of $8902 per patient, whereas an increment of 2.0 mg/dL cost an additional $33,162 [13]. In the early 2000s, also in the USA, data compiled from 23 hospitals estimated direct cost for uncomplicated AKI of $26,000 [22]. In cardiac surgery patients, total post-operative cost was increased by over $18,000 by AKI (double the cost of patients not undergoing AKI) [16]. In major surgery patients, AKI increased costs by approximately $16,000 [31]. The disparity of these numbers clearly indicates that further studies with homogenization in computing criteria and target population are needed to more accurately estimate both direct and indirect AKI costs and the determinants of cost.

3. A wider concept of AKI

AKI diagnosis based on plasma creatinine poses important clinical limitations. These limitations derive from the late capacity of creatinine to detect reduced filtration. It is necessary that about 60–70% of the total normal renal function be void for plasma creatinine to increase [50,45]. When this happens, very significant damage has already occurred. Late sensitivity of plasma creatinine results from high renal functional reserve and increased tubular secretion of creatinine. Renal functional reserve provides functional compensation initially, whereby remaining nephrons carry out additional filtration to compensate for damage nephrons [61]. Renal functional reserve works through modulation of glomerular hemodynamics. Extra filtration is achieved by single nephrons mainly by dilating the afferent arteriole and letting single nephrons blood flow and glomerular capillary pressure to increase, which in turn augment glomerular filtration rate. When damage progresses over the maximal compensating capacity of functional reserve, total filtration and excretion decline. However, plasma creatinine does not start to increase yet. When filtration starts to drop, less creatinine is cleared from the blood by glomerular filtration, and thus more creatinine reaches the peritubular capillaries. In this situation, tubular secretion of creatinine increases, and mostly compensates for the loss of filtration, resulting in preserved creatinine excretion [49,19,65]. Only after the buffering capacity of secretion is saturated, further decline in filtration is translated into abnormal accumulation of creatinine in the blood (Fig. 1).

The late capacity of creatinine to detect AKI questions the concept of AKI itself, because by that time a large renal damage has occurred. In addition, mild parenchymal injury may not give ever rise to renal dysfunction [56,48,20]. However, unnoticed renal damage is clinically important for several reasons: (i) it may lead to CKD, especially upon repeated (maybe unnoticed) episodes [55,21]; (ii) it may make kidneys more sensitive to AKI; and (iii) patients might have higher risk of future cardiovascular diseases [55,21].

The preceding situations describe a clinically orphan condition, as they do not fit within the internationally accepted definitions of AKI. This condition is considered today as “subclinical AKI”, referring to renal structural and functional alterations not resulting in increments of plasma creatinine, which needs to be addressed, classified, and introduced in the conceptual and functional definitions of AKI [56,20] (Fig. 1). However, from a conceptual point of view, there is no clear pathophysiological event that differentiates subclinical and clinical AKI as independent clinical entities. Both are graded steps of a continuous pathological process [74]. During this continuum, different pathophysiological events arise, involving functional or structural alterations (or both), compromising or not glomerular filtration, giving rise to increments in plasma creatinine or not, affecting different parts of the nephrons, or not, etc.

Because there are no available treatments for AKI other than supportive dialysis [44,78], the earliest possible diagnosis is critical [44,34] to withdraw potential causes and implement preventive or ameliorative measures [60,63,40]. A new generation of plasma and, mainly, urinary biomarkers has been developed in the last 15 years that have been associated to renal parenchymal injury, independently of renal function status [74,20]. Two among these new markers stand out for their level of preclinical and clinical validation, the amount of literature produced, and their initial arrival to clinical use. Their clinical use inception is due to the existence of clinically useful and validated measuring techniques. These two markers are neutrophil gelatinase-associated lipocalin (NGAL) [63,48,27], and kidney injury molecule 1 (KIM-1) [5]. Because their renal tissue and urinary levels increase rapidly in association to injury, they have been shown to detect AKI at the subclinical stage (i.e. normal plasma creatinine). Accordingly, some authors have already proposed that AKI definitions and diagnosis should be based also on the presence of this type of markers, and not only on plasma creatinine [56,20].

4. AKI is a multi etiopathogenic syndrome

Many circumstances and renal insults have been identified that lead to AKI, which has been traditionally classified in three types, namely pre-renal, renal and post-renal [35,72]. In pre-renal AKI, the commonest form of AKI, altered renal hemodynamics underlies the reduced filtration as a result of: (i) diminished renal blood flow beyond the control exerted by autoregulation; (ii) imbalanced afferent and efferent arteriole contractility leading to reduction of intraglomerular pressure. Pre-renal AKI is caused by severe hypertension (e.g. from surgical or traumatic blood loss, burns and mild sepsis), dehydration (as from vomiting, diarrhea, bleeding or hypovolemia), heart failure, liver failure, narrowing of renal arteries, renal microangiopathy, exposure to vasoactive drugs and toxins, and others. Renal or intrinsic AKI occurs when the primary cause of AKI is parenchymal (mostly tubular) damage, as caused by drugs, toxins, ischemia, sepsis, etc. Finally,
“post-renal AKI” occurs by obliteration of the urinary ways, mainly the ureters, as by trauma, lithiasis, tumors or congenital alterations (Fig. 2).

This is more an academic, pathophysiological classification than a description of many, if not most, cases of AKI, in which regardless of whether initiated by a pre-renal, renal or post-renal insult, a mixed phenotype suddenly arises. The very term of pre-renal AKI has been recently criticized [43] because: (1) In primarily pre-renal AKI some parenchymal injury eventually occurs; (2) Fluid-responsiveness is not always associated to (and not to all) pre-renal cases; and even some pre-renal etiologies –nephrotic, hepatorenal and cardiorenal syndromes- require fluid restriction; (3) Reversibility does not imply absence of damage; (4) Damage biomarkers can be found elevated in pre-renal AKI, even in transient cases and with conserved fractional excretion of sodium (FENa). The Acute Dialysis Quality Initiative (ADQI) consortium proposes to re-classify AKI according to functional and tissue damage criteria [43]. A new etiopathogenic concept has enrooted in many experts in the field, who consider AKI a continuous process through which different molecular, cell and tissue events and mechanisms progressively enroll into and develop the specific pathophysiological scenario of each individual case [74,20,43]. In some instances, or at determined time points of AKI evolution, different scenarios can occur, depending on the participating mechanisms. These scenarios include cases of (1) renal tissue damage with no renal dysfunction; (2) renal tissue integrity with significant renal dysfunction; and (3) renal tissue damage with renal dysfunction [20].

5. Acute tubular necrosis: a term for revision

Acute tubular necrosis (ATN) is a term used in the literature since the 1940–50s [18] to define a medical condition involving the death of tubular epithelial cells. The term comprised, at least partially, other hitherto used terms also mostly referring to renal tubular damage, such as “acute tubular nephrosis” and “lower nephron nephrosis”, as differentiated from inflammatory nephritis [1]. The conditions and syndromes behind these terms were rather vague about the type of histological findings, and they were stuffed with clinical symptomatic, functional and etiologic concepts. The emergence of the term ATN paralleled the origin of the term ARF, which was coined in 1951 [64]. Since then, both terms have been used in association, as ATN was a pattern frequently seen in ARF patients.

The term ATN was already in use when the only form of cell death known was necrosis; that is, before the discovery of apoptosis as a distinct mode of cell demise in the late 1960s and early 1970s (the term was proposed in [37]). In those days, a clear conceptual link was established between the concept of tissue
necrosis (as in ATN) and that of cell necrosis, which was evaluated at the histological level by the presence of karyolysis (nuclear fading after chromatin dissolution by endonucleases), pyknosis (nuclear shrinkage) or karyorrhexis (nuclear fragmentation) [7]; or by more evident alterations such as luminal debris, hyaline casts or epithelial derangement. Progressive discovery of other modes of cell death, including anoikis, autophagic death, necroptosis, pyrroptosis, entosis [24], but very especially apoptosis, disrupted the conceptual link between ATN and cell necrosis. Despite this digression, the term ATN implicitly incorporated all other forms of cell death different from necrosis. Still, unfounded assumptions and semantic confusions between ATN and cell necrosis are rife in the literature.

More recently, ATN has been interpreted in a wider sense that encompasses renal parenchymal alterations not necessarily involving widespread tubular cell death and injury [29,58]. This is because the severe histological findings traditionally associated with the term ATN (mostly in animal models) are more rarely observed in the kidneys from AKI patients [30]. In most human cases, only mild or no tubular derangement is detected during AKI, even in those cases with profound renal dysfunction ([58,29,30]; as early described as in [7]). Although a note of caution must be interposed in this latter consideration, clearly the term ATN is decontextualized [57,30]. The note of caution must be set because in human biopsies: (i) small amount of material is examined, and renal injury is usually focal; and (ii) biopsies are taken at heterogeneous time-points during pathophysiologically heterogeneous and evolving AKI episodes, in which the capacity of the kidneys to repair damaged nephrons must also be considered. Another important difference between experimental animal and human AKI is that severe injury to distal nephron segments is common in the former, whereas a similar extent of injury has not been clearly documented in human material [57]. Urinary biomarkers may, in the near future, help to make a global evaluation of kidney status. Biomarkers found in the urine might contain information on the undergoing pathophysiological events of the kidneys as a whole, as a complement to the focal information provided by biopsies. In addition, whereas biopsies are only rarely performed, the biochemical analysis of the urine for specific biomarkers can be achieved in an easy and bloodless manner.
Apart from glomerular and interstitial nephritis, the rest of intrinsic AKI syndromes are mostly ascribed to ATN. Because the semantic field of ATN comprises a wide range of mixed histological and functional patterns, and because the different scenarios have distinct clinical consideration, outcome and appropriate handling, a revision, classification and stratification of ATN appears clearly necessary. And this is not only at the semantic level, but because the semantic classification has important clinical consequences. The range of different ATN patterns spans from significant renal dysfunction (from intrinsic origin) with no gross morphological alterations, or parenchymal injury with no functional consequences, to cases with both parenchymal injury and dysfunction. Even more, some of these different scenarios may consecutively appear during the same AKI episode, with variable severity and prognosis [20]. What then is the logic and utility of the word “necrosis” in ATN? What then can be exactly referred to as ATN? Do all forms of renal functional alterations from parenchymal origin, involving or not tissue or cell damage, constitute ATN? Only tubular ones? If not all alterations different from nephritis are ATN, what are they? What are those that do not fit within the ATN boundaries, wherever these are set? Specifically, how will functional alterations leading to AKI in the absence of tissue injury be classified and named?

If tissue injury became a boundary set to discern ATN from non-nephritis, non-ATN forms of intrinsic AKI, or to discern subclasses or levels of ATN, how will “tissue injury” be defined? Will tissue injury necessarily imply cell death? Where is the boundary that determines “cell damage” and “tissue damage”? At the molecular level (not compromising cell death)? At the, say, cell membrane transporter level altering a specific cell function, altering or not a key renal function? At the cell viability level? At histological alterations, involving or not cell death? Which ones? e.g., is tubular dilation a pattern qualifying for ATN? And tubular epithelial cell vacuolation? Polarity loss? Brush border loss? Does ATN occur only when parenchymal alterations cause or contribute to decreased glomerular filtration, uremia and azotemia. If so, do frank tubular alterations (wherever the threshold be set to be so considered) not giving rise to azotemia (i.e. increased plasma creatinine) not qualify for ATN? (Fig. 3) Because, significant tissue damage can occur without paralleled increment in plasma creatinine.

Even the mode of cell death may make a pathophysiological difference in ATN, although this has not been thoroughly studied. The gross histological pattern of ATN caused mainly by apoptosis of tubule epithelial cells, might not differ substantially from the pattern of ATN caused mainly by necrosis of the same cells. However, the pathophysiological evolution and outcome of the associated ARF might differ to a yet undetermined extent. This is because the growing knowledge on the phenotypic and molecular differences between cell necrosis and apoptosis led to the
realization that apoptosis and necrosis elicit a different response from the organism. Specifically, whereas necrosis triggers a strong inflammatory response, apoptosis does not. Whereas necrosis is characterized by cell membrane disruption and release of cytoplasmic content, cell membrane integrity is preserved in apoptosis. In parallel with better cell death understanding, it was also increasingly realized that in processes in many cell types, cell death modes and their role in AKI pathophysiology have been poorly investigated.

6. Conclusions

A thorough reconsideration and appropriate reclassification of ATN and intrinsic AKI need to be addressed through a international consensus initiative. The new definitions and classification must consider key pathophysiological patterns and mechanisms in their relation with clinically relevant events, outcomes and endpoints; so that they are useful for etiological and pathophysiological diagnosis, patient stratification, and appropriate personalized handling and prognosis estimation.

7. Executive summary

- Acute kidney injury (AKI) defines a syndrome of acutely impaired renal function leading to azotemia or reduced urinary output. Realization that subclinical AKI (i.e., renal tissue damage with no renal dysfunction) has health consequences, invites to widening the concept of AKI itself.

- The most common form of AKI is pre-renal AKI, in which the primary alterations leading to AKI are renal hypoperfusion or glomerular hemodynamic imbalance. In renal or intrinsic AKI, the primary cause affects the renal structures. Hitherto, to main types of intrinsic AKI have been defined, namely acute tubular necrosis (ATN) and nephritis. Distinct AKI types pose different risks for patients and are associated to different outcomes.

- ATN is an old term coined when only one form of cell death was known (i.e., necrosis). ATN defined a syndrome of tubular damage involving epithelial cell death. Today, the term ATN has lost meaning partially, as it has incorporated not only other forms of tubular cell death, but also syndromes of tubular origin with little or no tubular destruction.

- Accordingly, redefinition of ATN and, if appropriate, reclassification of intrinsic AKI subtypes appear timely and necessary to better profile AKI cases according to their underlying pathophysiological events, to better stratify and handle patients in a personalized way, and to more precisely estimate prognosis.

Conflict of interest statement

The authors declare no conflict of interest.

Ethical statement

No ethical issues apply.

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