INTRODUCTION

Acute kidney injury (AKI) is the new consensus term for acute renal failure. It refers to a clinical syndrome characterized by a rapid (hours to days) decrease in renal excretory function, with the accumulation of products of nitrogen metabolism such as creatinine and urea and other clinically unmeasured waste products. Other common clinical and laboratory manifestations include decreased urine output (not always present), accumulation of metabolic acids, and increased potassium and phosphate concentrations.[1]

During the past decade, this acute loss of kidney function, previously referred to as acute renal failure, has been the subject of significant re-examination, with increased recognition of the importance of relatively small changes in kidney function on both short- and longer term clinical outcomes.[2-6]

This has resulted in the change in terminology from acute renal failure, for which the focus generally was limited to the most severe episodes with complete or nearcomplete loss of kidney function, to the current terminology of AKI, with increased focus on smaller decrements in kidney function. [7-9]

AKI may develop in a wide variety of settings, including in ambulatory outpatients, hospitalized patients, and, in particular, critically ill patients, for whom AKI represents a common complication of both underlying disease and treatment.AKI is associated with substantial morbidity and mortality. For example, severe AKI occurs in 5% of critically ill patients and is associated with mortality rates of 40%-70%.[10-12]

Definition and Classification of AKI

Our understanding of the epidemiology of AKI and interpretation of results across clinical trials has been hindered by the prior absence of a broadly accepted clinical definition, with more than 30 operational definitions of AKI used in published studies. [13] During the past decade, there has been a considerable effort to forge a consensus definition. The first attempt at developing a consensus definition, known as the RIFLE criteria, was developed by the Acute Dialysis Quality Initiative (ADQI) in 2002. (Appendix 1). [14]

AKI was defined based on a > 50% increase in serum creatinine level occurring over 1-7 days or the presence of oliguria for more than 6 hours. The AKIN criteria added an absolute increase in serum creatinine level of 0.3 mg/dL and reduced the timeframe for the increase in serum creatinine level to 48 hours. [14]

The KDIGO Work Group (Kidney Disease: Improving Global Outcomes) harmonized these 2 definitions, keeping the absolute increase in serum creatinine level of ≥ 0.3 mg/dL within 48 hours from the AKIN definition, but returning to the 7-day timeframe for the ≥ 50% increase in serum creatinine level. [15]

The successive stages of a serum creatinine–based AKI definition reflect a tradeoff between sensitivity and specificity. At low stages, sensitivity is high (ie, almost every patient with true AKI is identified), but specificity is low (ie, many patients without trueAKI are misidentified as having AKI). As part of the decision to

recommend a cutoff value based on a biomarker such as serum creatinine or physiologic variable such as urine output, the implications of the cutoff need to be carefully considered. [16]

Inclusion of urine output into the definition of AKI

Both RIFLE and AKIN included duration of oliguria in their definitions and staging criteria (Appendix 1).[14] Several criticisms have been offered of these urine output criteria, many of which are acknowledged by the KDIGO AKI Guideline Work Group but deserve further mention. Only a small number of studies have examined the urine output criteria for AKI and correlated them with adverse clinical outcomes, in contrast to the numerous studies that have focused on the serum creatinine criteria. The studies that have evaluated the urine output component of the criteria have found poor calibration between these criteria and the serum creatinine criteria.[18] Specifically, when assessed, there was poor prognostic correlation between the briefer durations of oliguria and small changes in serum creatinine level.

Second, oliguria may be an appropriate response to volume depletion and hence reflect under-resuscitation rather than injury to the kidney, which is implicit in the term "AKI." Therefore even demonstrating an association between oliguria and adverse clinical outcomes is insufficient to justify its incorporation into the definition of AKI. [17]

Third, the use of a weight-based definition for AKI limits its use in the obese due to the nonlinear relationship between body weight and urine output. Under the current definition, urine output of 40 mL/h in a 90-kg patient for 12 hours would lead to classification as stage 2 AKI. [17]

Fourth, diuretic administration has been shown to change RIFLE classification by urine output criteria, as would be expected when a definition is based on a physiologic variable that can be manipulated pharmacologically. [18]

Finally, the use of oliguria in a definition of AKI may promote its use in clinical practice as a surrogate end point. We know from several studies that pharmacologic agents that can increase urine output independent of augmentation of kidney function, such as loop diuretics or dopamine, may not be helpful and may even be harmful in some settings.While the inclusion of these criteria in the AKI guideline may have the beneficial effect of encouraging more rigorous documentation of urine output and overall fluid balance in settings outside the operating room and critical care units, there are also risks of unintended consequences with defining transient oliguria as AKI. In particular, we believe that current data are inadequate to support the reliance on oliguria as a surrogate end point in clinical trials or in performance metrics. [19,20]

Use of small changes in serum creatinine to define AKI

The inclusion of a small absolute change in serum creatinine level in the AKIN definition of AKI was based on the demonstration by Chertow et al. that minor fluctuations in serum creatinine concentration were strongly associated with adverse outcomes in a retrospective analysis of data from individuals hospitalized at a single medical center. Although the association remained, albeit attenuated, after multivariable adjustment, only administrative data were available for construction of the multivariable models, and residual confounding may have been present. Small

changes in serum creatinine level have also been identified to be of prognostic importance in subsequent studies. Even a 0.1-mg/dL increase in serum creatinine level appears to be associated with increased risk compared to no change in serum creatinine level. Whether these small changes in serum creatinine level reflect clinically meaningful fluctuations in kidney function that are causally linked to adverse outcomes or are merely a marker of underlying vascular disease or diminished renal reserve, which could be the actual mediators of the adverse outcomes, remains unresolved. Furthermore, an implicit assumption underlying the incorporation of small changes in serum creatinine concentration into the definition of AKI is that GFR in an individual is constant over time and not subject to physiologic fluctuation. In addition, biological fluctuation in serum creatinine level may also result from variations in diet, creatinine generation, tubular secretion, medications, and variability in sodium and volume homeostasis that are within the physiologic range. Such fluctuation in serum creatinine concentration is more prominent in individuals with decreased renal reserve or overt CKD. For all these reasons, an absolute change in serum creatinine level of 0.3 mg/dL may represent a relatively inconsequential change in GFR in patients with underlying CKD and not reflect superimposed acute pathology, Whether novel biomarkers of tubular injury may enhance risk stratification of patients with small changes in serum creatinine level is a question that requires further investigation and may lead to further refinement of AKI staging. [21]

The independent role of duration of AKI

Several recent studies have suggested that duration of AKI may be a more important predictor of outcomes than the magnitude of change in serum creatinine level. For example, in one study, even a transient elevation in creatinine level (<3 days) was associated with increased risk of death, and the risk of mortality was greater in patients with prolonged duration of AKI. [22]

After adjustment for duration of AKI, staging was no longer predictive of adverse outcomes. Unfortunately, this important dimension can only be assessed retrospectively and cannot be included in prospective staging criteria; however, consideration should be given to including an assessment of duration of AKI in future criteria designed for epidemiologic studies.

In addition to defining and staging AKI, the KDIGO guideline introduces the new term acute kidney disease (AKD), defined as AKI, or GFR _60 mL/min/1.73 m^2 for less than 3 months, or a decrease in GFR by _35% or an increase in serum creatinine level by >50% for less than 3 months, or structural kidney damage of less than 3 months' duration. While we understand the nosological rationale for developing terminology to describe patients with kidney disease that does not meet the criteria for either AKI or CKD, we have concern that the introduction of this terminology may confuse clinicians and inappropriately divert attention away from diagnostic considerations. While CKD encompasses a number of pathophysiologically and histopathologically distinct diseases, arguably the majority of patients with CKD have diseases such as hypertensive nephrosclerosis and diabetic nephrosclerosis, for which treatment approaches are similar.[15]

However, in the acute setting, distinctions between causes of disease have greater consequence. To lump the broad range of conditions that result in acute and subacute kidney disease, ranging from acute tubular necrosis to obstructive uropathy, atheroembolic disease, and rapidly progressive glomerulonephritis, into the single umbrella term of AKD runs the risk of promoting diagnostic laziness among clinicians who would have a convenient name to apply rather than an abnormal laboratory value to investigate. We would have welcomed a more in-depth discussion of what specific kidney diseases are likely to segregate to AKD as opposed to AKI or CKD and how the introduction of a new term was thought by the authors to help in clinical practice. While AKD may be a useful construct in epidemiologic studies, we believe the use of this term should be discouraged in clinical practice.

In contrast to our reservations regarding the introduction of the AKD terminology, we strongly concur with the KDIGO recommendations that the cause of AKI should be determined whenever possible and that patients with AKI should be evaluated promptly to determine the cause, with special attention to reversible causes. However, our Work Group had several concerns regarding several of the other recommendations related to the evaluation and general management of patients with and at risk of AKI. Specifically, our Work Group has concerns regarding the recommendation to manage patients with AKI according to the stage and cause. We believe that the stage-based management recommendations are not adequately evidence based. These recommendations implicitly assume homogeneity within each AKI stage and successive increases in severity across stages. As a result of the lack of correlation between serum creatinine level and GFR in the acute setting, a patient's serum creatinine level may increase, resulting in apparent progression in AKI stage, despite improvement in GFR. Clearly no guideline can accommodate all the subtleties of clinical practice or substitute for clinical judgment, but the recommendations for management overall were relatively nonspecific and unlikely to help in daily clinical practice. We are especially concerned that the development of clinical action plans based on AKI stage may result in inappropriate protocolization of care. While recommendations such as discontinuation of nephrotoxic agents when possible and ensuring volume status and perfusion pressure in high-risk patients or patients with AKI, waiting until stage 2 AKI to check for changes in drug dosing implies that this need not be done earlier, while the recommendations for considering initiation of RRT and intensive care unit admission in stage 2 AKI seem premature. Overall, we thought that the extreme heterogeneity of AKI and its lack of consistent mapping to stages 1, 2, and 3 make the proposed stage-based management of AKI clinically unhelpful and inapplicable to many patients. [23]

Acute kidney injury is a common and important diagnostic and therapeutic challenge for clinicians. [24] Incidence varies between definitions and populations, from more than 5000 cases per million people per year for non-dialysis-requiring acute kidney injury, to 295 cases per million people per year for dialysis requiring disease. [25] The disorder has a frequency of 1-9% in hospital inpatients and is especially common in critically ill patients, in whom the prevalence of acute kidney injury is greater than 40% at admission to the intensive-care unit if sepsis is present. Occurrence is more than 36% on the day after admission to an intensive-care unit, and prevalence is greater than 60% during intensive-care-unit admission. [26]

Some causes of acute kidney injury are particularly prevalent in some geographical settings. For example, cases associated with hypovolaemia secondary to diarrhea are frequent in developing countries, whereas open heart surgery is a common cause in developed countries. Furthermore, within a particular country, specific disorders are common in the community, whereas others arise only in hospitals. Thus, any diagnostic approach to the cause or trigger of acute kidney injury must take into account the local context and epidemiology. [27]

Neurohormonal mechanisms

Sympathetic system activation and neurohormonal responses unique to the kidney are activated in acute kidney injury.The renin–angiotensin–aldosterone system, renal sympathetic system, [28] and tubulo glomerular feedback system are activated. Knowledge of these changes has led to schemata of how acute kidney injury can be precipitated in human beings (figure 1).

These frameworks show that, in situations such as sepsis, infection leads to induction of nitric oxide synthase and nitric-oxide-mediated vasodilation, which in turn causes arterial under filling and baroreceptor activation. These circulatory changes trigger activation of the sympathetic system, which induces increased renin–angiotensin–aldosterone activity and renal vasoconstriction.[29]

Simultaneously, arginine vasopressin is released and contributes to water retention.[29]

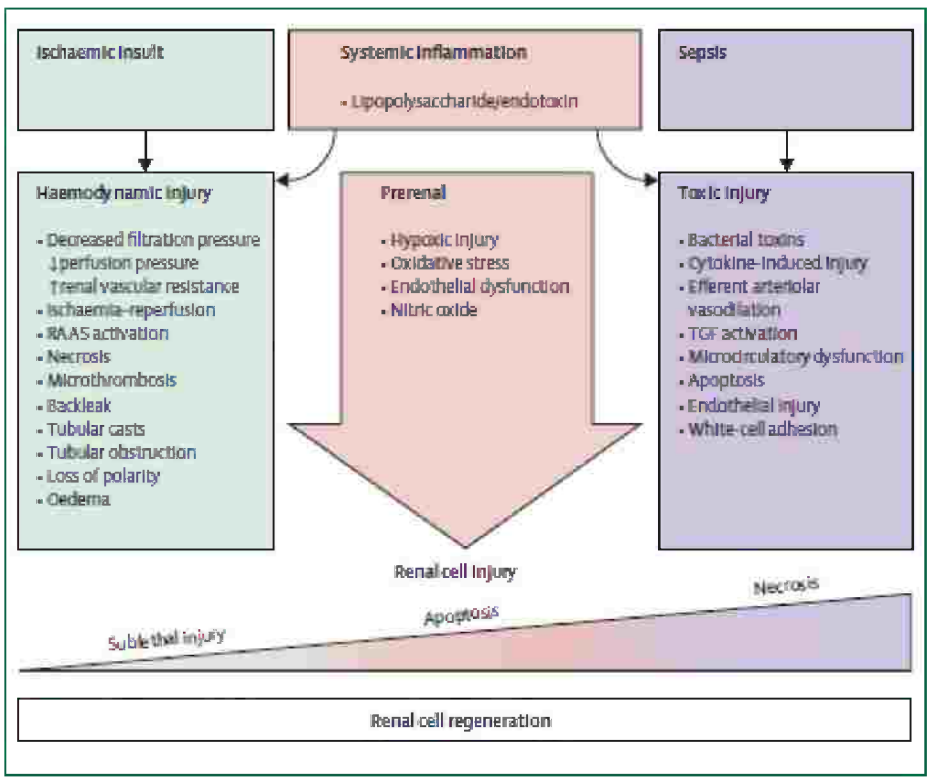

Figure (1): Key potential pathways implicated in pathogenesis of acute kidney injury due to ischemia or sepsis

Causes of acute kidney injury

AKI can result from decreased renal perfusion not severe enough to cause cellular injury; an ischemic, toxic, or obstructive injury of the renal tubule; a tubulointerstitial process with inflammation and edema; or a primary reduction in the filtering capacity of the glomerulus. If renal tubular and glomerular function is intact, but solute clearance is limited by factors compromising renal perfusion, the injury is termed *prerenal azotemia*. If renal dysfunction is related to obstruction of the urinary outflow tract, it is termed *postrenal azotemia*. AKI due to a primary intrarenal cause is called *intrinsic renal injury* or *renal azotemia*. Prerenal azotemic and intrinsic renal injury due to ischemia and nephrotoxins are responsible for most episodes of AKI. [30]

Renal blood flow is approximately 1200 mL/min and constitutes 20% of cardiac output. Given this apparently generous perfusion, it may seem surprising that the kidneys are so susceptible to hemodynamic insults. The majority of this perfusion (80%-90%), however, is to the renal cortex, where glomerular filtration occurs. The medulla is designed to concentrate and dilute urine. During urine concentration, the high osmotic gradient required for reabsorption of water is associated with a low rate of blood flow. In fact, oxygen tension in the outer medulla in the region of the metabolically active thick ascending limb of Henle is only around 10 mm Hg. This combination of low blood flow and oxygen tension in a metabolically active environment makes the kidneys very susceptible to ischemic injury. [31]

Risk factors for developing Acute kidney injury.[32]

- Age > 65 years
- Infection on admission
- Cardiovascular failure
- Cirrhosis
- Respiratory failure
- Chronic heart failure
- Lymphoma or leukemia

Prerenal Causes

Prerenal azotemia is a consequence of reduction in renal perfusion without cellular injury. As such, this is a reversible process if the underlying cause is corrected. It may be secondary to decreased blood volume, as occurs with vomiting, dehydration, and hemorrhage, or it may be due to a reduction in the effective arterial blood volume, as in congestive heart failure and cirrhosis. Further, the administration of medications that interfere with the normal autoregulatory ability of the kidney can contribute to prerenal azotemia. In settings of diminished renal perfusion, administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or angiotensin-converting enzyme (ACE) inhibitors can precipitate overt prerenal azotemia. [33]

During prerenal azotemia, the renin-angiotensin-aldosterone system becomes activated secondary to a decrease in renal blood flow accompanied by increased activity of the adrenergic nervous system. Increased levels of angiotensin II and adrenergic activation serve to increase the proximal reabsorption of sodium, whereas aldosterone increases sodium reabsorption in the distal tubule. Together these actions

decrease urine sodium concentration to less than 20 mmol/L and fractional excretion of sodium (F_ENa) to less than 1%.[34]

Prerenal azotemia accounts for approximately 70% of community acquired cases of AKI and 40% of hospital-acquired cases. Therefore, prerenal causes should be excluded in all cases of AKI. Therapy of prerenal AKI involves reversing the underlying cause, such as volume replacement or discontinuation of offending agents.[35]

Postrenal Causes

Postrenal AKI occurs when there is bilateral (or unilateral in the case of a single kidney) obstruction of urine flow. Intratubular pressure increases and in turn decreases net glomerular filtration pressure.

Obstruction of urine flow is a relatively uncommon cause of AKI and is more common in the community than in the intensive care unit (ICU). Several series have placed the incidence of postrenal AKI at 3% to 25% of all cases of AKI. Postrenal AKI can be divided into renal and extrarenal causes. Extrarenal causes include prostatic disease, pelvic malignancy, and retroperitoneal disorders. Intrarenal causes include crystal deposition, as occurs in ethylene glycol ingestion, or uric acid nephropathy in tumor lysis syndrome. Cast formation and tubular obstruction also occur in light-chain diseases such as multiple myeloma.[36]

Postrenal causes of AKI should be evaluated with renal ultrasonography and measurement of postvoid residual urine in the bladder (>50 mL is abnormal). It is important to rule out these causes rapidly, because the potential for renal recovery is inversely related to the duration of obstruction.[36]

Intrinsic acute renal failure

Intrinsic acute renal failure can be categorized anatomically, according to the site of the lesion: vascular, glomerular, or tubulointerstitial.

Acute tubular necrosis

The most common cause of intrinsic AKI in hospitalized patients is acute tubular necrosis (ATN). ATN is caused by ischemia, nephrotoxins, or a combination of both, and accounts for approximately 85% to 90% of intrinsic ARF cases.[37] Ischemic ATN is commonly seen in patients with sepsis or severe cardiac failure, or postoperative patients, particularly after cardiac and aortic surgeries. Massive trauma or cardiac arrest are other causes of ATN. Prerenal failure can result in ischemic ATN if renal hypoperfusion is severe and not reversed by timely therapy. Although improving renal perfusion may reverse prerenal ARF (by definition), and diminish ischemic contributions to the pathogenesis of ATN, it is quite conceivable that in many cases ATN develops despite appropriate resuscitation and adequate renal perfusion (Figure 2). Zager has shown in an endotoxemic rat model of septic ARF that paired combinations of insults (renal cross clamp, systemic endotoxin, aminoglycoside, and temperature elevation) cause azotemia and renal pathologic findings of ATN, but these insults individually cause no renal dysfunction or injury.[38]

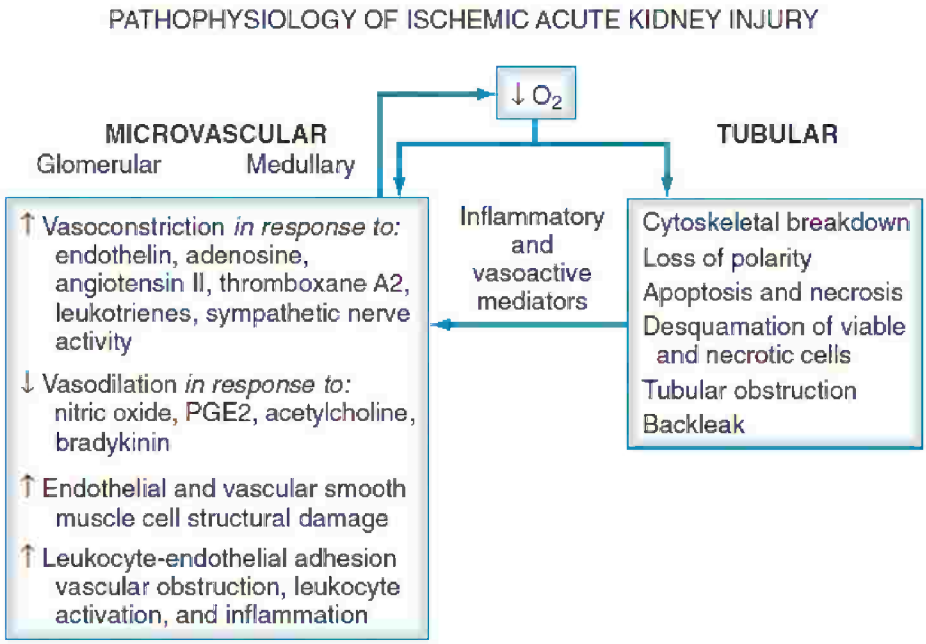

Figure (2): pathophysiology of ischemic of acute kidney injury

We suspect that this synergistic injury model accurately reflects the pathogenesis of much AKI in the ICU. Positive pressure mechanical ventilation alters renal perfusion and function through a variety of mechanisms, both hemodynamic and inflammatory. [39] Other experimental data have shown that endotoxin, tumor necrosis factor, and numerous other inflammatory mediators are directly cytotoxic to renal endothelial and tubular cells. [40]

Cellular mediators that play a role in the pathogenesis of ATN include calcium, reactive oxygen species, phospholipases, proteases, adhesion molecules, and nitric oxide (NO). [41]

ATN has several phases: prerenal, initiation, extension, maintenance, and repair. [42] It is not intuitive that renal tubular injury should cause decreased glomerular filtration and ARF. A decrease in glomerular ultrafiltration coefficient has been shown in several animal models of ARF, but this is a minor contributor to the observed decrement in GFR. [43,44] The pathophysiologic mechanisms that explain the reduction of GFR in ATN are hemodynamic abnormalities, tubular obstruction, and tubular backleakage of glomerular filtrate (Figure 3). [45] Renal vasoconstriction is seen in ARF [46] caused by activation of tubuloglomerular feedback; increased distal chloride delivery past injured tubular segments is sensed by the macula densa, causing vasoconstriction of the corresponding afferent arteriole. This reversible, functional mechanism seems to be the major cause of decreased GFR in ATN, and is in part protective. Severe hypovolemia would rapidly result if injured tubules failed to reabsorb the bulk of filtered sodium and water; thus the term (acute renal success) has been used to describe the development of decreased GFR in the presence of tubular necrosis. [46]

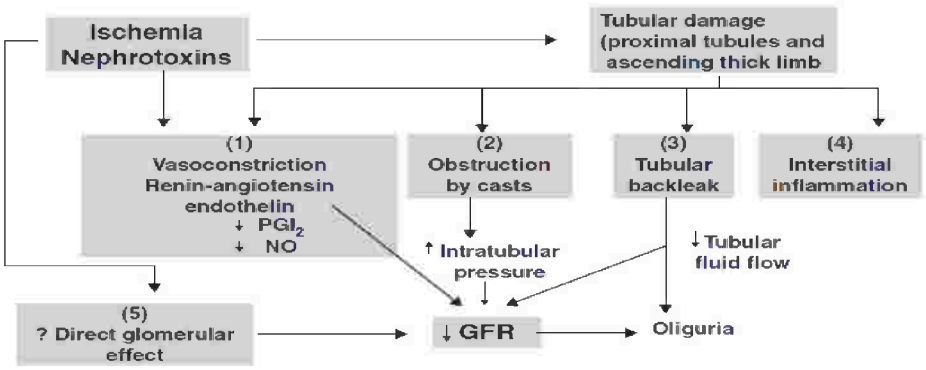

Figure (3): The pathophysiologic mechanisms of reduction of GFR in ATN

Furthermore, reabsorption of filtered sodium accounts for the bulk of renal oxygen consumption; continued glomerular filtration of sodium in ATN may aggravate hypoxic damage to sub lethally injured tubules. The phenomenon of medullary hypoxia plays an important role in the pathogenesis of ATN. Low medullary blood flow is required for urinary concentration. [47]

Reabsorption of sodium chloride by the medullary thick ascending limb of the loop of Henle (mTAL) is the major determinant of medullary oxygen consumption, resulting in a hypoxic environment under normal circumstances. [43,44] mTAL is vulnerable to ischemic injury if increased oxygen requirement is associated with decreased oxygen delivery. In addition, the inflammatory mechanisms that dominate as ATN progresses from initiation to extension and maintenance phases of ATN result in medullary congestion and hypoperfusion.[48]

The tubular factors that are also involved in the reduction of GFR in ARF are tubular obstruction and tubular backleakage. Necrotic cell debris incorporated into casts causes obstruction of proximal and distal tubules and has been shown to play a significant role in experimental AKI. Backleakage of tubular fluid across denuded basement membranes and injured proximal tubule cells has been demonstrated in several experimental models of ARF. Subsequently it has been shown that tubular back leakage and intratubular obstruction are important factors contributing to the reduction of GFR in human ischemic AKI. [49]

Nephrotoxic injury is the second major cause of ATN. Nephrotoxic ATN is caused by drugs (aminoglycosides, cisplatin, amphotericin, and chemotherapy), radiocontrast agents, heme pigments (myoglobin and hemoglobin), and myeloma light chain proteins. ARF due to aminoglycosides and radiocontrast agents accounts for most cases of nephrotoxic ATN.[50]

Diagnosis of AKI

The diagnosis of AKI using the AKIN (Acute Kidney Injury Network) or RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria is currently limited as SCr and UOP can only indirectly reflect that kidney damage has occurred. These criteria, by definition, are retrospective in nature and require at least 6 h to several days, thus inherently delaying the clinical diagnosis of AKI [51,52]. The UOP criteria for AKI

diagnosis (<0.5 ml/kg/h for >6 h) are hindered by limited sensitivity when diuretics are administered, reduced specificity in the presence of dehydration, and lack of practicality in measurement when an indwelling urinary catheter is not present. [53]

Limitations of sCr and the Need for Novel AKI Biomarkers

To date, sCr has typically been used for AKI diagnosis. However, there are several limitations to its use as an AKI biomarker. First, its release varies with age, gender, diet, muscle mass, drugs, and vigorous exercise. Second, tubular secretion accounts for 10–40% of SCr clearance, which could mask a decrease in glomerular filtration rate (GFR). Third, SCr becomes abnormal when more than 50% of GFR has been lost. Therefore, there is a delay between injury and the subsequent rise in SCr and it might require up to 24 h before sufficient increase becomes detectable. It is assumed that the biological damage in cellular or molecular level precedes the clinical spectrum of AKI. For instance, the injured tubular cells secrete various molecules many hours before the functional decline which is evident by sCr increase. However, so far the lack of an early AKI biomarker has hampered the development of preventive strategies against AKI. [54]

These limitations have contributed to the in ability to successfully characterize various aspects of the disease, consistently identify individuals at risk, and translate promising preclinical therapeutic strategies into successful treatments.

Over the last few years, several new markers have been developed to identify kidney injury, such as NGAL, KIM-1, IL-18 and L-FABP, among others. Besides known filtration function markers such as SCr and cystatin C, there are filtered proteins that are increased due to glomerular injury (e.g. albumin), not reabsorbed at the tubular level due to tubular injury (albumin, cystatin C), markers that are released from damaged cells (α-glutathione S-transferase (GST), π-GST, collagen IV), or up regulated in response to cellular/tissue injury (NGAL, KIM-1, L-FABP, and IL-18). The availability of these new markers of 'kidney damage' affords a new opportunity to identify patients with AKI in addition to changes in SCr, glomerular filtration rate (GFR) or UOP. As discussed in the introductory paper in this series, the combination of simultaneous assessment of a functional and damage markers can help stratify patients into 4 subgroups: no marker change, functional alone, damage alone, or change in both functional and damage markers. [55]

This categorization permits identification of a new category of patients who may have 'subclinical' AKI, i.e. an increase in damage markers without a simultaneous loss of kidney function (fig. 4, upper right quadrant). In these conditions, e.g. nephrotoxic drug exposure, loss of function may not develop at all or be seen at some time interval after detection of renal injury. Although direct evidence is sparse, it appears that these patients are at higher risk for adverse outcomes including need for RRT and mortality, than patients without an increase in damage biomarker levels. [56]

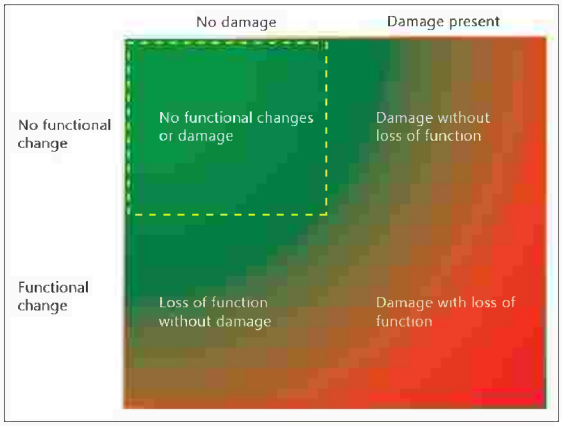

Figure (4) New spectrum of AKI based on combination of functional and damage biomarkers.

As illustrated, the combination of functional and damage biomarkers allows the clinician to differentiate a normal state of kidney function from abnormal to diagnose AKI. The current criteria for diagnosis include the lower two quadrants. This new spectrum enables the recognition of four subgroups of patients according to their AKI state. Patients negative for functional and kidney damage markers are considered to have no AKI (upper left quadrant). The ability to detect a state of damage alone (right upper quadrant) allows an expanded criteria for diagnosis of AKI. This may represent a 'subclinical' state in which loss of function might develop several days after detection of kidney damage or not at all, however, still associated with impaired outcomes. The bottom left quadrant indicates a dynamic change in renal filtration of SCr but without detectable kidney damage that may be physiologic such as seen in patients with dehydration. The right lower quadrant represents patients with functional and damage criteria of AKI associated with the worst prognosis. It is expected that the process is dynamic and patients will move from one phase to another during the course of their illness. Currently, there is limited information on what thresholds will be applicable for each of the damage biomarkers for the best diagnostic and staging criteria based on damage criteria alone. This will need to be defined in future studies. [57]

Urinary angiotensinogen

In recent years, the role of the intrarenal RAS in the pathophysiology of renal injury has become a focus of interest to researchers. Considerable attention has been paid to the significance of the local/tissue RAS in different tissues, including the brain, heart, adrenal glands, vasculature and kidneys. [58] Urinary angiotensin II is unstable and, therefore, cannot be used as a reliable marker of intrarenal RAS activity in clinical studies. Experimental studies have demonstrated that angiotensinogen (AGT) levels in renal tissues reflect the activity of the intrarenal RAS. [59]

Katsurada et al. [60] recently developed a sandwich enzyme-linked immunosorbent assay (ELISA) system to directly measure urinary human AGT levels. Urinary AGT levels have been shown to be highly correlated with intrarenal AGT and angiotensin II levels. Consequently, urinary AGT concentration has been suggested as a reliable Marker for intrarenal RAS activity.

Angiotensinogen is the principal substrate of renin, and a major driver of activation of the renin-angiotensin system (RAS). Animal studies have suggested a role for the RAS in the molecular mechanisms of AKI. It has been observed that angiotensin II increases and angiotensin, the molecular counterbalance of angiotensin II decreases in kidney tissue following ischemia reperfusion injury in rats. [61,62]

The biology of intrarenal angiotensinogen is highly intriguing. In this respect, data from animal models have been essential to guide interpretation of human urinary studies. Angiotensinogen is synthesized primarily in cells of the proximal tubule and is secreted from the apical surface into the lumen, where it is converted first to angiotensin (Ang) I and then Ang II by tubular renin and angiotensin-converting enzyme (ACE), respectively. Indeed, the kidney contains all components of the RAS, and intrarenal Ang II formation can occur via several pathways, leading to interstitial concentrations of Ang II that far exceed circulating levels, particularly in the vicinity of the proximal tubule. Circulating Ang II is also taken up by cells via an AT1 receptor-dependent mechanism, increasing kidney content. After angiotensinogen enters the proximal tubular lumen, it may spillover to distal nephron segments. In the collecting duct, luminal angiotensinogen can be converted to Ang I and Ang II by local renin and ACE, before appearing in the final urine.[63]

The activation of the intrarenal RAS contributes significantly to hypertension and CKD progression, via inappropriate elevation of Ang II levels and stimulation of kidney AT1 receptors. The activation of AT1 receptors is associated with enhanced intrarenal vasoconstriction and sodium and water retention, as well as adverse non-hemodynamic effects that culminate in tubulointerstitial fibrosis and glomerulosclerosis. The role of proximal tubular angiotensinogen in these pathways appears to be paramount. In support of this role, intrarenal expression of angiotensinogen substantially increases in animal models of hypertension and CKD. [64,65] In a series of elegant experiments performed by Chan and colleagues [66,67], transgenic mice with overexpression of proximal tubular angiotensinogen develop hypertension, albuminuria and tubulointerstitial injury and are more susceptible to diabetes-induced tubular cell apoptosis. Adverse renal endpoints in these mice are prevented by the blockade of the RAS, or by the inhibition of reactive oxygen species generation, which occurs independent of blood pressure lowering. Thus, these studies support a vital role for intrarenal angiotensinogen-stimulated production of Ang II in the pathogenesis of progressive renal injury. [68,69]

In order to put the brakes on proximal tubular angiotensinogen synthesis in CKD, it would therefore seem important to understand how the system is regulated, and here the story becomes even more interesting. In rats chronically infused with Ang II, proximal tubular expression of angiotensinogen paradoxically 'increases', as does collecting duct renin activity. As a result, angiotensinogen spillover into the distal nephron occurs, with increased urinary excretion. This phenomenon, referred to by Navar and colleagues, as intrarenal angiotensinogen 'augmentation', appears to occur as a direct consequence of Ang II-mediated AT1 receptor activation in tubular cells. Indeed, rats infused with Ang II generate increased tubular Ang II in a feed-forward fashion, which serves to exacerbate hypertension and renal injury. [70,71]

Urinary angiotensinogen levels directly reflect intrarenal RAS activity, supporting its candidacy as a biomarker. Thus, the amount of urinary angiotensinogen derived from increased glomerular permeability, as occurs in the setting of generalized proteinuria, seems quite limited. [70] Not surprisingly, with the recent development of a sensitive sandwich enzyme-linked immunosorbent assay (ELISA) for human angiotensinogen,[71] the effect of hypertension or kidney disorders on urinary angiotensinogen levels has been the subject of several investigations. In a cross-sectional study involving 70 hypertensive and 36 normotensive subjects, Kobori et al. [72] showed that urinary angiotensinogen levels were positively correlated with systolic and diastolic blood pressures. In hypertensive subjects, RAS blockade attenuated the increase in urinary angiotensinogen. Increased urinary excretion of angiotensinogen has also been reported in humans with CKD due to diabetic nephropathy,[73] membranous nephropathy,[73] renal transplantation,[74] chronic glomerulonephritis from a variety of causes[75,76] and IgA nephritis. In the case of IgA nephritis, urinary angiotensinogen levels correlate with renal tissue angiotensinogen gene expression, supporting a link to activation of the intrarenal RAS. Although these reports have been highly informative, patient numbers have been small, CKD studies were performed largely in Asian subjects and adjustment for multiple potential confounding variables has not been consistent. Thus, the applicability of these initial observations to other populations with CKD is unclear.[77,78]Angiotensin II can contribute to renal injury through pro-inflammatory effects mediated by the nuclear factor-κB (NF-κB) pathway, and it has been demonstrated that inhibition of angiotensin converting enzyme and the angiotensin II type 1 receptor with captopril and losartan, respectively, reduce renal inflammation and mitigate the severity of AKI in rats subjected to renal ischemia reperfusion injury. [79,80] Interestingly, intrarenal angiotensin II concentration strongly correlates with urinary angiotensinogen concentration , but is not correlated with plasma angiotensinogen. [81] Our findings are suggestive of a role of the RAS in modulating the severity of AKI, a notion which is supported by a recent study in which an association was reported between severity of tubular atrophy and urinary angiotensinogen among individuals with chronic kidney disease. [82]

Sepsis and severe sepsis

Sepsis with acute organ dysfunction (severe sepsis) is common and frequently fatal and represents a significant health care burden. The incidence and associated mortality and morbidity rates of severe sepsis are commonly underestimated. [83]

This is a function of a number of factors. Severe sepsis is not generally reported as a primary diagnosis. For example, although steps are underway to address this issue, the most recent edition of the International Classification of Diseases, Ninth Revision, Clinical Modification lacks a diagnostic code for severe sepsis. Instead, severe sepsis is often coded as a complication of another disorder (e.g., cancer or pneumonia). Several recent publications have evaluated the epidemiology of severe sepsis in the United States. [84]

They have estimated that the annual incidence of severe sepsis in the United States is in the range of 240 to 300 cases per 100,000 population. Further, in 2003, there were approximately 750,000 cases of sepsis in the United States. Reported mortality rates in patients with severe sepsis range from28%to50%or higher. Thus, in the United States , at least 700 to 1300 patients die daily from severe sepsis. [85]

In a study by Angus et al.[83] of the patients who developed severe sepsis, nearly 66% were older than 65 years. This population also accounted for more than 75% of the overall health care costs of the disease. The incidence of severe sepsis is anticipated to increase approximately 1.5% per year until at least 2050.This increase is due to a number of factors, including age shifts in the population, prevalence of more critically ill patients (e.g., transplant recipients), and increases in the numbers of invasive diagnostic procedures and monitoring techniques. This predicted increase has significant implications for the critical care community because it has been estimated that by 2020 there will be a 22% shortfall of available intensivists hours to meet this demand. [86]

Definition

Sepsis is defined as infection plus systemic manifestations of infection (Scheme 1)[88]. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. The threshold for this dysfunction has varied somewhat from one severe sepsis research study to another. An example of typical thresholds identification of severe sepsis is shown in Scheme 2 . [87,88] Sepsis induced hypotension is defined as a systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure < 70 mm Hg or a SBP decrease < 40 mm Hg or < 2 SD below normal for age in the absence of other causes of hypotension. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation.

Sepsis induced tissue hypoperfusion is defined as either septic shock, an elevated lactate, or oliguria.

Scheme 1. Diagnostic criteria for sepsis [87]

Infection, documented or suspected, and some of the following:

General variables

- Fever (>38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min or >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
- Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables

- Leukocytosis (WBC count >12,000mm^3)
- Leukopenia (WBC count <4000mm^3)
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

Hemodynamic variables

Arterial hypotension (SBP <90 mm Hg; MAP <70 mm Hg; or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)

Organ dysfunction variables

- Arterial hypoxemia (PaO2/FIO2 <300)
- Acute oliguria (urine output <0.5 mL/Kg hr or 45 mmol/L for at least 2 hrs, despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dL or 44.2 mmol/L
- Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000mL)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)

Tissue perfusion variables

- Hyperlactatemia (>upper limit of lab normal)
- Decreased capillary refill or mottling

Scheme 2. [87,88]

Severe sepsis = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)

- Sepsis-induced hypotension
- Lactate greater than the upper limits of normal laboratory results
- Urine output <0.5 mL/kg hr for >2 hrs, despite adequate fluid resuscitation
- ALI with PaO2/FIO2 < 250 in the absence of pneumonia as infection source
- ALI with PaO2/FIO2 < 200 in the presence of pneumonia as infection source
- Creatinine >2.0 mg/dL (176.8 mmol/L)
- Bilirubin >2 mg/dL (34.2 mmol/L)
- Platelet count <100,000 /mL
- Coagulopathy (INR >1.5)

Septic Acute Kidney Injury

Acute kidney injury (AKI) is one of the most feared complications in septic critically ill patients because it further worsens prognosis and increases cost of care. In addition, sepsis and septic shock are the dominant causes of AKI, accounting for nearly 50 % of episodes of AKI. [89]

The incidence of acute kidney injury proportionally rises with the severity of sepsis, occurring in 19 % of patients with sepsis, 23 % patients with severe sepsis and 51 % patients with septic shock. [90,91]

Of note, even a slight decline in renal functions results in higher morbidity and mortality highlighting the potentially important role of the kidney dysfunction during the natural history of critical illness. The above mentioned reasons increase the urgent need to improve our understanding of its pathophysiology and to develop new treatment. There is now emerging evidence that the pathogenesis of septic AKI involves distinct mechanisms as compared to non-septic causes of AKI. Therefore, the purpose of this brief review is to discuss the most recent advances in the understanding of the pathogenesis of sepsis-induced AKI. [92]

Pathophysiology of septic AKI

In general, the pathophysiology of sepsis involves a multitude of systemic and cellular processes as well as mediators. In most cases, AKI develops as a part of multiple organ dysfunction syndrome (MODS) sharing many common pathophysiological mechanisms that are also involved in the dysfunction of other organs. [90]

However, the nephron is highly organized structure and may, therefore, have unique response to injury. Indeed, within the kidney there are multiple levels at which significanly different changes might occur. These include alterations in renal blood flow, glomerular and peritubular microcirculation, tubular cell function and structure as well as derangements in cellular bioenergetics and renal proteome. It is important to note that much of our insights into the pathophysiology of septic AKI have been derived from experimental studies. Therefore, one should consider the available evidence still as hypothesis generating rather than confirmatory. [93]

Renal hemodynamics in sepsis: new paradigms

Whereas systemic hemodynamic changes in sepsis are well defined, the behavior of renal blood flow in human sepsis is not clearly understood, in particular due to the lack of reliable methods allowing continuous renal blood flow measurement. Undoubtedly, hypovolemia caused by increased venous capacitance and venous pooling, increased vascular permeability with fluid leak into the tissue interstitium and hypotension resulting from septic vasoplegia are the dominant hemodynamically-mediated and, therefore, potentially reversible causes of septic AKI. However, if renal hypoperfusion persists and compensatory kidney reserve is exhausted or absent, AKI progresses from "pre-renal" state to established structural tubular injury. Unfortunately, not every drop in renal perfusion pressure is clinically visible and renal hypoperfusion might occur even in the absence of marked hypotension, especially in high risk patients with chronically disturbed intrarenal autoregulatory mechanisms [94]

While human data on renal hemodynamics in sepsis are scarce and unreliable, recent comprehensive review of the available experimental evidence showed that renal blood flow reported in these studies is highly variable. [95]

It has to be stressed, however, that majority of studies reporting a reduction in renal blood flow were derived from heterogeneous, usually short-term and mostly hypodynamic models characterized by a reduced cardiac output, which clearly limits the inference that could be drawn. In fact, cardiac output appears to be the dominant predictor of renal blood flow. This has been demonstrated in a study by Australian research group in a sheep sepsis model, in which hyperdynamic and normotensive circulation was accompanied by significant renal vasodilatation and increased renal artery blood flow. [96,97]

Renal venous congestion: an underestimated factor?

Not only renal inflow but also renal outflow, if impeded, might be involved in septic AKI. The renal venous congestion has been increasingly recognized as key mechanism driving AKI in decompensated heart failure patients. [98,99]

In the case of sepsis, aggressive fluid resuscitation in the terrain of severe capillary leak might lead to the development of tissue edema and abdominal hypertension. It is well recognized that the kidney is especially vulnerable to the increased intraabdominal pressure and tissue edema, [100] In this context, we observed gradually and significantly increased renal venous pressure during progressive porcine sepsis resulting in reduced renal perfusion pressure despite clinically acceptable mean arterial pressure (70 mm Hg) Hence, it is plausible to speculate that renal venous congestion (i.e. congestive kidney disease) might be unrecognized factor contributing to the fall in glomerular filtration in septic AKI. [101]

Renal glomerular injury in sepsis

There is widely held concept of a fall in transcapillary hydraulic pressure due to afferent arteriolar vasoconstriction leading to the reduction in glomerular filtration rate (GFR) in sepsis [90,94] This concept is based on studies from the eighties showing that the afferent arteriole is primarily affected by a preglomerular vasoconstriction resulting in a decrease in cortical flow and reduced GFR in rats challenged with large endotoxin bolus[104] However, the absolute lack of data from humans and experimental models of hyperdynamic, well resuscitated sepsis questions the robustness of this paradigm. Although it seems reasonable to argue that changes in the intraglomerular hemodynamics are likely involved in the deterioration of glomerular filtration, at least at early stages, the exact response of both afferent and efferent arterioles in the course of sepsis is completely unknown. Interestingly, significant renal vasodilatation, increased renal artery blood flow and reduced glomerular filtration with preserved tubular functions observed in the above mentioned large animal studies offer a provocative hypothesis: decreased rather than increased glomerular vascular resistance affecting both the afferent and efferent arterioles, with the effect predominating on the latter vessels, might explain the fall in glomerular filtration, and the opposite changes in intraglomerular circulation might account for the restoration of glomerular filtration. [96,97]

The lack of effectiveness or even worse outcome in clinical trials investigating various vasodilators in septic AKI, [103,19] and, conversely, less severe kidney dysfunction with higher urine output achieved by vasopressin-mediated action on efferent arteriole in a porcine model of fecal peritonitis induced septic shock fit well with the above hypothesis.[104]

The latter experimental observation has recently been supported by a post hoc analysis of a randomized, controlled trial in which septic patients at risk for AKI (risk category according to RIFLE criteria) treated with vasopressin were less likely to progress to renal failure than their noradrenaline-treated counterparts, [105] Collectively, an imbalance in intraglomerular vasomotor control and yet undefined disharmony of glomerular vascular balancing mediators may represent a form of vasomotor nephropathy as a primary cause of early, "functional" AKI, preceding an intrinsic renal structural injury.[106,107]

Not only impaired glomerular hemodynamic auto regulation, but also inflammatory changes affecting glomerular microvasculature may facilitate septic AKI. Although the human data are very scarce and reporting only mild structural alterations of the glomerulus,[108] experimental studies revealed leukocyte infiltration in the glomerular capillaries, apoptotic death of glomerular endothelial cells as well as formation of microvascular thrombosis. [109,110]