Shifting Paradigms in Acute Kidney Injury

W. De Corte, I. De Laet, and E.A.J. Hoste

Introduction

Acute kidney injury (AKI) is a frequent finding in critically ill patients and associated with adverse outcomes, such as increased length of stay, end-stage-renal disease (ESRD) and mortality [1, 2]. Approximately 50 % of ICU patients have AKI as defined by the sensitive RIFLE definition, and 5–15 % of ICU patients are treated with renal replacement therapy (RRT). Several new concepts, encompassing practically all aspects of AKI from diagnosis to treatment and outcome, have evolved over the last few years. This overview describes the most important new insights on AKI, based on recent research and consensus reports.

Expanding the Scope of AKI

Towards a Consensus Definition

Over the last years, the emphasis in 'acute kidney disease' has shifted from total failure of kidney function, to less severely impaired kidney function, leading to the concept of 'AKI', a grading system describing different levels of acute kidney dysfunction. More recently, a new entity, "subclinical AKI", has been introduced [3].

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The term 'acute renal failure' was introduced in the 1950s by Homer W. Smith [1]. This terminology was widely used and resulted in over 35 different definitions of acute renal failure in the medical literature [4]. The Acute Dialysis Quality Initiative (ADQI), a group of experts in the field of nephrology and intensive care, recognized the need for a standard definition of kidney failure. They introduced the Risk, Injury, Failure, Loss and End stage renal failure (RIFLE) classification, a grading system for increasing degrees of severity of AKI [4], emphasizing the importance of a small decline in kidney function. This RIFLE classification was later modified by the Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) groups [5, 6]. This allowed for the terminology 'AKI' to cover the whole range from mild impairment of renal function to the need for RRT [5].

Using these new definitions, it became clear that the incidence of AKI is high in critically ill patients, ranging from 16 % to 67 % depending on the baseline characteristics of the study population [7–9]. The increased sensitivity of the AKI definition is related to relevant clinical outcomes. Other, less sensitive definitions, such as the American Society of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) definition (rise in serum creatinine greater than 2 mg/dl or the acute need for RRT) cannot take into account the risk associated with mild AKI. Bihorac et al. showed, in a large study including over 27,000 patients, that the ACS-NSIQIP definition of postoperative AKI does not detect 93 % of RIFLE-AKI patients. Nevertheless, these patients account for 80 % of the 90-day mortality [10]. The new definitions of AKI have allowed and will continue to allow a much more realistic evaluation of the true incidence, risks and costs of AKI in different patient populations.

The Changing Face of AKI

Change in ICU case-mix and the concept of frailty

The aging society in developed countries is resulting in a change in case-mix of ICU admissions. Patients >65 years of age now account for approximately 50 % of all ICU admissions and for 60 % of all ICU days [11]. Elderly patients often have impaired cardiac, pulmonary, metabolic and renal function prior to their ICU admission. Increasing age and comorbidity are associated with adverse outcomes. Single point serum creatinine measurement on admission in these patients may underestimate the degree of kidney dysfunction, as decreased muscle mass in these patients leads to decreased creatinine generation and lower serum concentrations.

Together with the admission of this geriatric population came the concept of frailty, initially introduced by the geriatricians. Frailty describes a multidimensional syndrome of loss of physiological reserve that gives rise to the accumulation of deficits and increased risk of vulnerability to adverse events. Frailty has been associated with worse outcomes. In ICU patients, the concept of frailty is quite new and was only recently described [12]. To date, there is no consensus definition of frailty. One of the most widely used descriptions to measure frailty is the defini-

tion proposed by Fried et al. [13]. The Clinical Frailty Scale (CFS) a simple and validated seven-point judgment-based tool may be applicable in ICU patients [14]. These frail patients with moderate organ function requiring ICU care for extended periods of time form a new challenge for modern ICU care. As a consequence, the concept of frailty should be considered when studying outcomes in the critically ill population suffering from AKI.

Increasing Incidence of AKI

Interestingly, AKI has been increasingly diagnosed in ICU patients over the past decades. Data from the Australian and New Zealand Intensive Care Society (ANZICS) showed an annual increase of 2.8 % from 1996 to 2005 [15]. Similarly, in the USA, a > 20-fold increase in the incidence of AKI has been observed over the past 30 years [16]. It remains uncertain whether this last finding is the reflection of a true increase in the incidence of AKI or if this is the result of more adequate recording of AKI diagnoses. AKI defined by the need for RRT is diagnosed in approximately 5–10 % of critically ill patients [17, 18].

Organ Crosstalk

Patients with severe AKI mostly suffer from multiple organ dysfunction. Extrarenal organ dysfunction most probably contributes to the high mortality rates in these patients.

In AKI patients there is strong evidence of an 'adverse organ crosstalk' between damaged kidneys and other organ systems such as heart, lung, liver, intestinal tract and brain [19].

Ischemic AKI activates several inflammatory cascades initiating distant organ dysfunction. Of special interest is the crosstalk between the kidney and the heart. Several studies have demonstrated the bidirectional communication and feedback between these organs. Recently the ADQI proposed a consensus definition of cardiorenal syndromes (CRS) [20]. CRS were classified into five subtypes based on the original organ dysfunction. Three subtypes are most interesting to the intensivist. CRS type 1, the acute cardiorenal syndrome, is characterized by an acute deterioration in cardiac function leading to AKI. CRS type 3, also known as the acute renocardiac syndrome, is characterized by AKI leading to cardiac injury and/or failure. Both syndromes are associated with adverse outcomes. Finally, type 5 CRS occurs when a systemic disease, such as sepsis, leads to both kidney and heart dysfunction. Preventive and therapeutic strategies in CRS are derived from the management of the individual cardiac and renal dysfunctions. Therefore, the ADQI workgroup advises a multidisciplinary approach combining cardiology, nephrology and critical care medicine. Combining the knowledge from these competencies may contribute to new insights in a better understanding of this complex pathology and better research, but may also facilitate well-designed studies in the field of CRS and organ crosstalk. Future studies should not only focus on the complex pathophysiologic mechanisms of the complex entity of organ crosstalk in AKI, but should also evaluate possible preventive and therapeutic strategies.

Patients are dying of AKI

In the past, AKI was often considered a surrogate marker for severity of illness. In critically ill patients, AKI often develops in the course of another disease, e. g., sepsis or trauma. Patient mortality was considered a consequence of this underlying disease. In other words, the statement that patients died with AKI and not from AKI was widely accepted. However, epidemiologic data have made it clear that AKI is an independent risk factor for mortality. A whole range of clinical complications of AKI, such as volume overload, electrolyte abnormalities, acidosis, and inadequate drug dosing, may help explain the increased morbidity and mortality in AKI. This facet was already realized for patients treated with RRT, but several more recent studies have demonstrated a correlation between small decreases in kidney function and short-term mortality [2, 21]. These findings suggest that AKI is not a benign syndrome and that patients actually die from AKI, rather than with AKI [22].

Diagnosis and Prevention of AKI

Novel renal biomarkers and the concept of subclinical AKI

The above mentioned paradigm shifts emphasize the need for early recognition of AKI and highlight the importance of early interventions to prevent AKI or to halt the evolution towards severe kidney dysfunction.

Measurements of serum creatinine and its derived calculations of glomerular filtration rate (GFR) have served as the gold standard for the diagnosis of AKI for decades. Even small increases in serum creatinine of ≥ 0.3 mg/dl in hospitalized patients have been associated with an increased risk of death [23]. However, measurement of serum creatinine carries some important limitations. Most importantly, it is a late marker of kidney injury. Changes in serum creatinine reflect alterations in kidney *function* [3]. They do not provide any information concerning kidney *damage*. Unfortunately, functional changes only present after significant kidney damage has taken place. This is in stark contrast to, for example, the management of myocardial ischemia. Patients with myocardial ischemia suffer from chest pain and sensitive and early biomarkers of myocardial ischemia, such as troponin I, are available allowing physicians to intervene early in the course of the disease. The lack of sensitive and specific renal biomarkers has hampered the development of specific interventions to prevent or treat AKI [24].

Until very recently, diagnosis of AKI was based on alterations in GFR, reflected by changes in serum creatinine or urine output, but the absence of clinically manifest AKI does not necessarily mean that the kidney is undamaged. Given the important functional reserve, renal impairment becomes evident only when more than 50 % of the renal mass is compromised. So, the diagnosis of AKI was usually made when GFR had been impaired for at least 24–48 hours after the initial damage had occurred [3].

Very recently, new renal biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin (IL)-18, kidney injury molecule 1 (KIM 1), and the combination of insulin-like growth factor-binding protein 7 (IGFBP-7) and

tissue inhibitor of metalloproteinases-2 (TIMP-2) have been introduced [25]. These biomarkers are produced in the kidney itself, making them 'early' indicators of kidney damage. As they are produced even before a decrease in GMR is noticed, an early diagnosis of AKI is made possible [26].

This development has led to concepts like 'subclinical AKI' and 'renal angina', which are biomarker-guided and describe the clinical condition characterized by positive biomarker and negative creatinine findings. Goldstein and Chawla recently suggested that these biomarkers could therefore act as the "renal troponin I" and proposed a framework of AKI based on risk factor assessment, in analogy with the cardiovascular literature [24]. In this framework, intensivists should be aware of the possibility of renal angina in patients at risk for AKI (advanced age, diabetes, liver failure, congestive heart failure, chronic kidney disease [CKD] and cardiopulmonary bypass [CPB]). Further extensive investigation for early signs of AKI should be performed in these patients if signs of oliguria, volume overload or small increases in serum creatinine develop [26]. Measurement of renal biomarkers, urine microscopy and more frequent serum creatinine measurements are advised in this very specific population. This concept has a high negative predictive value. Patients without renal angina have a very low risk of developing AKI (Fig. 1). However, when renal angina is suspected, interventions to prevent further kidney damage are applied earlier in the course of the disease and may, therefore, be more successful. In this respect, modern technologies, such as the use of a real-time electronic alert device, can be of additional help [27].

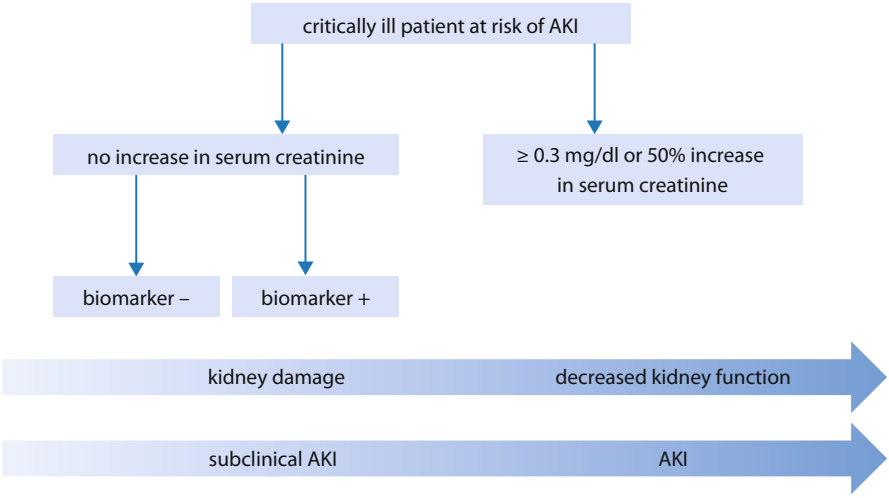

Fig. 1 Biomarker-guided AKI continuum. Serum creatinine is assessed in patients at risk of acute kidney injury (AKI). If there is no significant increase in serum creatinine, renal biomarkers are assessed. A positive biomarker without a significant increase in serum creatinine is suggestive of kidney damage, depicting a subclinical form of AKI. Subclinical AKI can lead to AKI, which is associated with decreased kidney function and, therefore, a significant increase in serum creatinine

At present, the exact role of AKI biomarkers is uncertain. Initial data suggesting high sensitivity and specificity of NGAL for early diagnosis of AKI could not be replicated in other settings. Recently the KDIGO group formulated clinical practice guidelines for prevention and treatment of AKI, advising the maintenance of renal perfusion, the avoidance of nephrotoxic drugs and correction of underlying processes or diseases [6]. Several observational but also interventional studies have demonstrated that early intervention indeed results in a lower incidence of severe AKI [28], but it is uncertain whether earlier diagnosis of AKI using new renal biomarkers can impact on the timing and results of AKI prevention.

Pathophysiology

AKI in critically ill patients is a syndrome with a multifactorial etiology, typically occurring with multiple hits. It is, therefore, probably also a very heterogeneous disease. This concept is not new, but we are now more aware of this. A few decades ago, AKI was considered the consequence of decreased kidney perfusion and ischemia with resulting acute tubular necrosis. However, acute tubular necrosis is seldom found, and markedly decreased renal perfusion could not be demonstrated in animal models of sepsis [29]. On the other hand, decreased microvascular perfusion secondary to inflammation, diffuse intravascular coagulation, tissue edema, vascular shunts in the kidney, and also glomerular changes are probably responsible for decreased kidney function in sepsis. In addition, other pathophysiologic mechanisms, such as increased intra-abdominal pressure (resulting in abdominal hypertension and abdominal compartment syndrome), drug toxicity, and increased venous pressure may contribute to damage and decreased kidney function [30]. Finally, other causes of AKI such as tubulo-interstitial nephritis or glomerulonephritis may play a bigger role than previously thought.

Timing of initiation of RRT

Although RRT has been in use for more than half a decade, many aspects of this therapy remain controversial. The timing of initiation of RRT is a very contentious issue. Over time, there has been a trend towards earlier initiation of RRT. Historically, AKI was considered a problem of uremia and RRT a means of treating uremic symptoms. The world's first successful artificial kidney was presented in 1942 by Willem Johan Kolff as "a new way of treating uremia". As uremic symptoms occur only late in the course of AKI, RRT was also initiated very late and basically considered a life-saving rescue treatment.

This urea-driven approach stood for several decades. Over time, helped by technological advances and more widely available dialysis equipment, early initiation of RRT and its possible positive impact on outcome started to appeal to many. Several – mostly retrospective – studies were published searching for the optimal serum urea threshold for initiation of RRT. Even recently, during the Vancouver meeting in 2006, the AKIN working group considered a blood urea nitrogen (BUN) concentration > 76 mg/dl as a relative indication and a BUN > 100 mg/dl an absolute indication for the initiation of RRT. However, recent retrospective studies showed that serum urea cut-offs at time of initiation of RRT have no predictive

value for mortality in ICU patients with AKI [31]. Since the introduction of the AKI definitions that emphasize the importance of less severe stages of AKI and their impact on mortality [4–6, 21], the idea of early initiation of RRT has remained intact, even though the notion of urea-guided initiation of RRT should probably be abandoned.

Based on a meta-analysis of 23 heterogeneous and mostly retrospective studies, Seabra et al. suggested that early initiation of RRT was associated with better outcome [32]. More recently, Karvellas and colleagues updated these findings in a meta-analysis. They made no firm conclusions on the concept of timing of RRT because of absence of a consensus definition of 'early RRT' and the lack of well-designed studies [33].

However, we can make several comments related to this topic of 'early initiation of RRT'. In today's ICU, there is not only a change in case-mix with older patients with more comorbidities, but there is also a change in attitude towards initiation of RRT that leads to a possible 'inclusion bias' in studies on RRT. Patients, who were previously excluded from RRT because of advanced age and severe comorbidity, have more often been included in more recent studies. The general lack of established criteria for the initiation of RRT further complicates the issue. Hopefully, the recently introduced AKI biomarkers could be used in future guidelines for timing of RRT. For now, we argue that there is an urgent need for a consensus definition on what 'early' and 'late' timing of initiation of RRT mean in order to improve study comparability.

Outcomes in AKI: Shift of Focus

Mortality as an Endpoint

Until recently, studies of AKI in ICU patients focused on conventionally accepted short-term outcomes, such as mortality at day 30, or at ICU and hospital discharge. However, these endpoints may underestimate the true burden of kidney disease. In modern-day ICU care, we should aim for more relevant endpoints, such as long-term mortality (90 days, 6 months, one-year).

Initially, studies focused on long-term mortality were mostly performed in patients with AKI defined by treatment with RRT. The RENAL study reported a 44.7 % mortality rate three months after initiation of RRT [34]. Bagshaw and co-workers described a 1-year mortality of 63.8 % in a population-based study [35]. Korkeila et al. reported 65 % mortality at 5 years in a mixed Finnish ICU population with AKI without pre-existing renal failure [36]. Ahlström and colleagues confirmed these findings in a cross-sectional cohort study on patients from a mixed ICU and dialysis unit with a 5 years mortality of 70 % [37].

However, assessing long-term mortality based on 'AKI defined by RIFLE criteria' highlights the stepwise adverse long-term mortality associated with different stages of AKI. Coca et al. demonstrated in a systematic review and meta-analysis of 49 studies that even mild and rapidly reversible forms of AKI are associated with

worse short and long-term outcomes [38]. Very recently, in a large retrospective study including more than 15,000 ICU patients with no history of end-stage renal disease (ESRD), Fuchs and co-workers described the strong relationship between AKI and mortality. Patients with AKIN 3 had 61 % higher mortality risk 2 years from ICU discharge compared with patients without AKI [39].

Composite Endpoints

In the cardiovascular literature, composite endpoints, such as major adverse cardiac events (MACE) are widely used. Ideally, these 'pooled' endpoints have a higher incidence than each of their components, reducing required sample size and increasing statistical efficiency. However, the use of composite endpoints in clinical trials can easily be biased, because component endpoints may be selected to ensure statistic significance [40]. Therefore, pooled endpoints have to be well defined and meticulously constructed.

A renal composite endpoint, major adverse kidney events (MAKE), was recently introduced as a concept. However, there is no standard definition for MAKE. This composite endpoint might include death, need for RRT, renal hospitalization within 90 days, persistent decline in kidney function and progression of underlying chronic kidney disease [41].

Renal Recovery

Until recently, it was widely accepted that most patients surviving AKI fully recover renal function [42]. However, because of the increasing focus on long-term outcomes, several studies have investigated the link between AKI, CKD and ESRD [43, 44]. Incomplete recovery after AKI is associated with tubulo-interstitial fibrosis and inflammation. These processes give rise to irreversible loss of functional kidney mass and may eventually lead to ESRD. Despite the lack of a standard definition, the term 'renal recovery' is widely used and is usually interpreted as independency of RRT [45]. Chertow et al. nicely demonstrated that 33 % of patients surviving AKI treated with RRT were still on RRT after one year [46]. Schiffl and Fischer reported that maximal improvement or normalization of renal function took place within the first year [47]. Bell et al. reported, in a 7-year follow-up trial, that 14 % of patients surviving AKI treated with continuous RRT remained on chronic dialysis indefinitely [48]. Interestingly, these and other observational studies suggest that renal recovery is less marked in patients treated with intermittent RRT compared to continuous RRT.

One can argue that 'renal recovery' should encompass more than just independence from RRT. It is well known that patients suffering from an episode of acute-on-chronic kidney disease have an increased risk of progression towards ESRD [43]. Given the fact that CKD stage is associated with a proportionally higher risk of developing new episodes of AKI [49], these patients may eventually

be trapped in a downward spiral as their renal functional reserve progressively reduces. Moreover, AKI in patients without preexisting CKD can also cause ESRD directly, depicting the mutual relationship between AKI and CKD. Interestingly, the progression to CKD is facilitated by the frequency of AKI episodes and the severity of AKI [44]. Very recently, Pannu et al. demonstrated, in a retrospective analysis on more than 190,000 patients, that incomplete renal recovery within 90 days of AKI was associated with a higher risk for ESRD [50]. In addition, there is growing evidence that lesser forms of AKI (not requiring RRT) are associated with worse long-term renal outcomes. Even subclinical AKI may result in worse long-term outcomes. With regard to these data and taking into account the social and economic impact of chronic dialysis, some investigators suggest that hospital survivors of severe AKI should be followed by a nephrologist after discharge to prevent undiagnosed CKD in these patients [42].

Quality of Life

The importance of long-term outcomes cannot be overestimated and were recently highlighted in a systematic review on the topic of renal recovery by Bell [51]. This author demonstrated that patients surviving AKI but in need of chronic dialysis have worse quality of life compared to patients without the need for chronic dialysis. Naturally, mortality remains a decisive endpoint, but it is not the only relevant clinical endpoint beyond hospital discharge. For example, failure of renal recovery leading to dialysis dependency is associated with substantial health care costs, but also affects quality of life [52]. Several studies describe health-related quality of life (HRQOL) in patients recovering from AKI. Commonly used HRQOL assessments in critically ill patients include the Short Form-36 (SF-36), the Nottingham Health Profile (NHP) and the European Quality of Life score (EQ-5D). Although most patients who recovered from AKI reported a lower HRQOL than the general population, for the greater part they felt satisfied with their health status; in most patients, quality-of-life after AKI is perceived as acceptable and good [36, 37].

Future Perspectives and Conclusions

The incidence of AKI has increased over the past decades and this condition is becoming a major public health problem. The introduction of a standardized consensus definition for kidney dysfunction and the awareness that even small increases in serum creatinine are associated with adverse outcomes have expanded the scope of AKI and broadened its horizons with the inclusion of less-severely ill AKI patients. At the same time, the concept of organ crosstalk and the increasing numbers of frail elderly patients with co-existing comorbidities have complicated the issue.

At present, we can only speculate as to why even small increases in serum creatinine lead to adverse outcomes. Plausible causes are volume overload, inflammation, adverse effects on other organs and inadequate clearance of potentially toxic waste

products of metabolism [1]. The recent introduction of AKI biomarkers may clarify these processes; however, they have limitations. There is currently no single ideal AKI biomarker available, but it is probably naïve to aim for this 'ideal' AKI biomarker that would be suitable in all types of AKI. The question rises whether all AKI is equal? Perhaps we should differentiate several types of AKI, each with their specific AKI biomarker, according to specific populations (e. g., cardiac surgery patients, general ICU patients). These AKI biomarkers may reveal AKI at an early stage, so specific preventive and therapeutic interventions may be implemented halting further decline in kidney function.

Ideally, biomarkers will also help us predict need for RRT, renal recovery, and long-term outcome. New concepts of subclinical AKI and renal angina have been introduced through the use of novel renal biomarkers. These new discoveries may offer new targeting points for preventive interventions and therapeutic strategies. In this way, intensivists may be able to act earlier in the course of AKI, preventing further kidney damage and halting the downward spiral of AKI, thereby preventing the progression to ESRD. Given the increasing incidence of AKI and the burden on health economics, future studies will have to address the most appropriate implementation of strategies preventing and eventually treating AKI. These future interventions can only be successfully studied and implemented if endpoints are optimized with focus on composite endpoints or long-term outcomes.

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