Clinical Consequences of Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) can no longer be considered a surrogate marker for severity of illness. Recent epidemiologic data demonstrate the association of AKI and mortality. Even small decreases of kidney function are associated with increased mortality. Several clinical consequences of AKI may explain the association of AKI and mortality. Decreased free water clearance leading to volume overload contributes to morbidity and mortality, but also to deterioration of kidney function. Acid-base disorders and electrolyte abnormalities interfere with normal functioning of many processes in the body. Critically ill patients have an increased prevalence of infection. Infection and antimicrobial therapy can be the cause of AKI, but infection can also be a consequence of AKI. Finally, inadequate antimicrobial dosing probably plays an important role in the morbidity and mortality of AKI. These findings have led to a paradigm shift: patients die *because of* AKI rather than *with* AKI.

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In the past, acute kidney injury (AKI) was considered a surrogate marker for severity of illness, and patient mortality was considered a consequence of the underlying disease [1]. Especially in intensive care unit (ICU) patients, AKI develops as a consequence of another disease, e.g. sepsis, cardiogenic shock or trauma, which in a certain number of patients will lead to mortality. However, there is an abundance of epidemiologic data that demonstrates that AKI itself also contributes to higher mortality. This is the case for the most severe form of AKI, where patients are treated with renal replacement therapy (RRT) [2–6]. Small decreases of kidney function are also associated with increased short-term mortality (hospital and 28-day). This has been demonstrated in various settings such as contrast-induced AKI, in patients who underwent cardiac surgery,

Fig. 1. Patients are dying of AKI and not with AKI. The interaction between the etiology of AKI and the consequences of AKI, and the impact on morbidity and mortality.

in hospitalized patients and in ICU patients [7–12]. When AKI is classified according to the newly developed sensitive RIFLE or AKI classification, all studies have demonstrated an association with hospital mortality [5, 13–15]. Other outcomes, such as length of hospital stay, readmission rate, development of end-stage kidney disease and long-term (1–10 years) mortality, are also affected by severe and less severe episodes of AKI during ICU stay [16–21].

In this overview we will discuss the clinical consequences of AKI that may explain the association of AKI and mortality (fig. 1).

Morbidity Caused by Acute Kidney Injury

Fluid Overload

Fluid resuscitation is one of the cornerstones for treatment of ICU patients with an episode of oliguria or developing AKI. The majority of AKI patients, especially those with severe AKI, will have decreased (free) water clearance. This will lead to accumulation of water, and several observational studies found that this is associated with worse outcome [22–24]. It is difficult to delineate whether fluid overload is only a surrogate marker of severity of illness or if it is in itself the cause of increased morbidity and mortality. Some arguments are in favor of the latter. Fluid overload may lead to a series of minor and major complications that may influence outcome. It may result in a broad range of complications

such as development of tissue edema, ascites and eventually intra-abdominal hypertension and abdominal compartment syndrome, pleural effusion, and pulmonary edema [25]. An elegant prospective study demonstrated the untoward effects of increased total body water on patients who underwent colorectal surgery and who were randomized to a restrictive and a normal perioperative fluid regimen [26]. Patients who were randomized to the restrictive fluid regimen had significantly less complications, in particular cardiopulmonary complications, and better tissue healing.

Despite the fact that many AKI patients are already fluid overloaded, the majority of these patients receive fluid boluses in order to restore effective arterial blood volume and restore prerenal AKI. However, fluid overload may not only contribute to extra morbidity, but may also contribute to deterioration of kidney function. Especially in cardiac patients, increased central venous pressure and right ventricular failure is associated with the development of AKI [27–29]. Additionally, in acute respiratory distress syndrome, randomization to a restrictive fluid therapy regimen resulted in less need for RRT (10 vs. 14%, $p = 0.06$) [30]. Another mechanism by which fluid overload may lead to AKI is through the development of intra-abdominal hypertension, abdominal compartment syndrome, decreased thoracic and abdominal wall compliance, retroperitoneal edema, and ascites [25, 31, 32].

Inflammation and ‘Organ Crosstalk’

AKI is characterized by a profound inflammatory reaction in the kidneys and in the systemic circulation. This systemic inflammatory response leads to dysfunction of other organs. Animal experiments have demonstrated that AKI leads to gene activation of proinflammatory and anti-inflammatory mediators in the lung, which results in acute respiratory distress syndrome with exudation of albumin in the alveoli, changes of aquaporins and sodium channels, and infiltration of neutrophils [33–40]. Acid-base disorders, which are commonly seen in AKI, also play a role in this inflammatory reaction. Hyperchloremic acidosis is associated with an increased interleukin (IL)-6/IL-10 ratio with a resulting proinflammatory effect, while lactic acidosis decreases both IL-6 and IL-10 resulting in an anti-inflammatory status [41–43]. More extensive discussions on this topic can be found in other chapters of this issue of *Contributions to Nephrology*.

Acidosis

The kidneys play an important role in acid-base homeostasis. Metabolic acidosis is the result of accumulation of anions such as chloride, phosphate and

other anions that are not routinely measured [44, 45]. Acidosis occurs in up to one third of the patients who are initiated on RRT [46], interferes with normal functioning of many processes in the body, and leads to hemodynamic instability by decreased cardiac output and vasodilatation. Decreased density of β -receptors at the cell surface of the myocardium, interference with intracellular calcium handling, increased nitric oxide production and interference with the inflammatory response are the mechanisms that most likely play a role in this [41, 42, 47–49]. Further, different etiology of acidosis is associated with different systemic effects [41–43]. Moderate hyperchloremic acidosis is associated with increased nitric oxide production, leading to vasodilatation, while in lactic acidosis there is a gradual decline in nitric oxide production.

Electrolyte Abnormalities

The kidney also regulates electrolyte homeostasis. Up to one third of the patients with severe AKI will develop dilution hyponatremia by decreased free water clearance [50, 51]. Hyponatremia is associated with severe complications, such as cerebral edema, and worse outcomes [52, 53]. Furthermore, between 6.1% and one third of the patients who are initiated on RRT develop hyperkalemia, a condition that is associated with arrhythmias and death [46, 50].

Infection

Infection and antimicrobial therapy for infection play a central role in the course of AKI [54]. ICU patients with AKI have an increased prevalence of infection [54–58]. Infection and antimicrobial therapy may be the cause of AKI, but infection may also be a result of AKI. In a series at our center, we found that 80.2% of ICU patients who had AKI and who were treated with RRT were also treated for infection [55]. 37.5% of the patients even had two or more episodes of infection. Almost half of these infections started just before initiation of RRT, 40% during RRT and approximately 10% in the period immediately after discontinuation of RRT. Several factors may play a role in this interplay between infection, antimicrobial therapy and AKI.

Inadequate Antimicrobial Therapy

Adequate prescription of antimicrobial therapy is a challenge in ICU patients. The volume of distribution, metabolization and clearance can have important variations among patients and also within the same patient in different time

periods of ICU stay. This may result in underdosing and overdosing of antimicrobials when standard antimicrobial dosing schedules are used.

Correct dosing is even more difficult in AKI patients. A first issue is correct evaluation of kidney function. Formulas that are used for assessment of kidney function in patients with chronic kidney disease, such as the Cockcroft-Gault and MDRD equations, were validated in non-ICU patients with moderate chronic kidney disease and are based on serum creatinine and variables such as age, body weight and gender. These equations are not adequate for assessment of kidney function in ICU patients [59, 60].

Kidney function is best assessed by measurement of urinary creatinine clearance, i.e. $(\text{urine volume} \times \text{urine creatinine concentration}) / (\text{time in minutes} \times \text{serum creatinine concentration})$. This calculation requires exact timing and measurement of urine volume, and a stable kidney function during the measurement period. As this condition is seldom met in patients with AKI, one can shorten the measurement period to, for example, 2 or 4 h or use the mean of serum creatinine concentration measured just before and after the measurement period [60].

Another issue that precludes correct dosing of antimicrobial therapy in ICU patients who have AKI is that dosing schedules for antimicrobial therapy are mostly based on data from patients with chronic kidney disease. These are not necessarily useful in ICU patients with AKI and a comparable degree of GFR. Serum concentration can be lower in ICU patients with increased volume of distribution, decreased gastrointestinal absorption, increased GFR during treatment, or RRT. Examples of factors that may increase serum concentrations are decreased albumin concentration, decreased kidney function and periods without RRT.

In patients treated with RRT, dosing schedules are available. But variables such as dialysis blood flow, dialysate flow, ultrafiltration rate, administration of pre- or postdilution, and filter characteristics may vary from center to center and have an impact on dialysis dose and clearance.

Inadequate Metabolic and Nutritional Support

ICU patients with AKI are usually in a catabolic state, and treatment with RRT leads to additional losses of amino acids and proteins. Loss of phosphorus in continuous RRT can lead to prolonged time on mechanical ventilation [61]. Further, the concentration of trace elements can be lower as a result of acute phase reaction, losses of fluids and removal by RRT. Finally, water-soluble vitamins such as vitamin C, thiamine and folic acid are removed by RRT [62].

At present, the data on the effects of nutritional interventions and different RRT modalities on nutritional status, and blood concentrations of trace elements and vitamins in ICU patients with AKI are insufficient. Given the data

that we do know, and given the vast evidence on the importance of nutritional status and nutritional interventions in chronic hemodialysis patients and in ICU patients in general, this aspect of care needs further exploration.

Conclusion

Current epidemiologic findings demonstrate the strong association between AKI and short-term and long-term mortality. A whole range of clinical complications of AKI help to explain this. Factors that may help explain increased morbidity and mortality in AKI patients are a consequence of decreased kidney function such as volume overload, acidosis and electrolyte abnormalities. AKI may also impact on other organs, as in organ crosstalk between kidneys and lungs. AKI patients have an increased incidence of infection. Infection may impact on mortality, but also, inadequate antimicrobial therapy may play an important role. Current dosing recommendations for antimicrobials are mostly inadequate for ICU patients who have AKI, and adequate dosing is therefore a topic that needs further study. Finally, nutritional support is an underemphasized aspect of care for AKI patients in the ICU. Especially in AKI patients treated with RRT, we need more data on nutrition and supplementation of trace elements and vitamins.

The paradigm shift that patients die of, rather than with AKI, emphasizes the need for early recognition of AKI or clinical circumstances that eventually can lead to the development of AKI. RIFLE and AKIN criteria can be useful tools for intensivists in the early identification and management of AKI. The prevention of AKI in critically ill patients cannot be overemphasized. Adequate fluid therapy, the correction of acid-base disorders and electrolyte imbalances, the early recognition of infections, and adequate dosing of antimicrobial therapy are key issues in the management of AKI and in reducing its additional mortality in critically ill patients.

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