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Unveiling Current Controversies in Acute Kidney Injury

John A. Kellum[a] · Claudio Ronco[b] · Jean-Louis Vincent[c]

[a]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, USA, [b]Department of Nephrology, Dialysis & Transplantation, International Renal Research Institute Vicenza, S. Bortolo Hospital, Vicenza, Italy, [c]Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium

Acute kidney injury (AKI) is a deadly and incompletely understood disorder in which sudden impairment of kidney function occurs secondary to one or more of a variety of underlying conditions. Mortality associated with AKI is very high and treatment is unsatisfactory. The condition primarily affects acutely ill and injured patients and disproportionably affects the elderly. Many of those that survive have permanent kidney failure and other long-term morbidities, which may include cardiovascular disease and immune dysfunction. While the term 'acute kidney injury' dates back to the early 20th century, when it was used in reference to acute mercury poisoning, it has only recently been applied to describe impaired kidney function in the setting of critical illness. In 2002, during an Acute Dialysis Quality Initiative (ADQI) conference held in Vicenza, AKI was defined using the now widely accepted consensus criteria known as RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease). AKI replaced the term acute renal failure in part because of the recognition that acute impairment in renal function, even when relatively mild and far less than frank failure, was associated with worse clinical outcomes. Criteria for AKI were therefore set at small changes in serum creatinine or urine output. Thanks to consensus criteria for AKI, we now know that this condition is very common, occurring in as many as two thirds of ICU patients and about 2,100 per million population, and is associated with dramatic reductions in survival – as much as a 3- to 8-fold decrement at hospital discharge compared to controls without AKI.

With the increasing body of information about AKI, it becomes more and more evident that we need to find an answer to some crucial questions, e.g. 'What are exactly the so-called pre-renal syndromes?', 'Do we know in detail

the pathogenesis of AKI?', 'Are critically ill patients dying *of* or *with* AKI?', and 'What is the most appropriate management of AKI?'.

It seems that classic distinctions such as 'prerenal and 'renal' AKI may be questionable today or at least they should be scrutinized with a critical approach.

For example, if the prerenal state is very transient and/or mild, and when it occurs in the setting of normal baseline renal function, it may appear to be well tolerated. However, emerging evidence suggests that the prerenal state is precarious. First, it may potentiate renal toxicity from radiocontrast or other nephrotoxins. Second, renal impairment may lead to volume overload, acid-base and electrolyte imbalance, immune dysfunction, coagulation abnormalities, abnormal drug elimination, and direct effects on the function of various organs. Indeed renal impairment results in multiple organ failure. Finally, when severe or prolonged, or perhaps even when mild and transient but in an already compromised kidney, the prerenal state can lead to direct kidney damage.

Several other areas of controversy exist in the field of AKI. One important area concerns our understanding of the pathogenesis of AKI. Epidemiologic evidence suggests that AKI is not a single disease, but a syndrome comprised of multiple, often coexisting, etiologies. The most common forms of AKI appear to be nonischemic and arise in settings such as sepsis and heart failure. Early AKI may be purely functional and reversible, but it soon gives way to tissue injury and a complex array of vascular, metabolic and inflammatory changes. Furthermore, the kidney may be an innocent bystander injured by the very toxins that it filters from the blood in the setting of remote tissue injury and infection. Cytokines, free radicals and other damage-associated molecular patterns may initiate AKI. These same triggers may also lead to so-called 'maladaptive repair' mechanisms that can cause further damage particularly in the most susceptible patients such as the elderly and those with chronic kidney disease. On the other hand, the concept of acute tubular necrosis as the main pathogenetic picture in AKI seems to be questioned by the common findings that renal blood flow may not be reduced, at least in sepsis, and other types of cell damage may occur. The concomitant presence of inflammation seems to be a requirement to initiate and extend tissue damage and to activate multiple organ crosstalk responsible for the high morbidity and mortality associated with AKI.

Studies conducted in animals and humans have displayed their limits to elucidate all complex mechanisms involved in this disorder. Therapies that work in specific experimental models may have little or no efficacy when translated into the clinical realm where overlapping etiologies is the rule. There may be no simple solution for the complex problem that is AKI. Instead it may be possible to develop a suite of therapies to attenuate the many different inciting factors and to produce effective countermeasures that facilitate resolution of injury and promote recovery of function. Novel biomarkers for early detection of AKI and for predicting the course of disease in humans are being developed and, thus, we will soon have better ways to apply the right therapies to the right patients.

An interesting distinction is made today between renal replacement and renal support. Hemodialysis and hemofiltration are being delivered earlier and to more severely ill patients than ever before. In several cases this is done with the intent to support specific clinical conditions rather than to replace lost function of the kidney. There is some evidence that survival for patients with AKI is improving, though it is still quite poor in the most critically ill. Renal support may well be the bridge to recovery, but innovation is lagging – we have seen little change in the way we provide support over the last 3 decades. If we are to expect better outcomes, we will need to develop better therapies.

Increased hemofiltration volumes and new technologies such as higher cut-off membranes, plasma filtration and adsorption, and new sorbent devices are potential solutions to improve renal support. Technologies for extracorporeal removal of larger microbial toxins such as endotoxin are also becoming available. Finally, it must be recognized that AKI is usually part of multiorgan failure syndrome and extracorporeal support may also target fluid overload and heart failure, extracorporeal CO_2 removal for combined kidney and lung support, albumin dialysis for liver support, and other techniques unified under the umbrella of MOST (multiple organ support therapy). Such therapies aim to improve organ function and decrease the severity of organ damage.

In spite of significant advances, new challenges are also appearing in the clinical arena. We need to better understand why AKI occurs and to develop new methods to treat it. We need to improve outcomes and find ways to mitigate organ damage and stimulate organ recovery. The interesting and growing cooperation among specialists of different disciplines may well be the key to moving to a more holistic approach for the patient suffering from AKI. The process has begun and it is our responsibility to maintain it over the years to come.

Claudio Ronco
Department of Nephrology, Dialysis & Transplantation
International Renal Research Institute Vicenza
S. Bortolo Hospital, Viale Rodolfi, 37, 36100 Vicenza, Italy
Tel. +39 444 75 38 69, E-mail: cronco@goldnet.it