CRITICAL CARE

COMMENTARY

Controversies in acute kidney injury: the 2011 Brussels Roundtable

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Abstract

The recent advent of consensus definitions for acute kidney injury (AKI) has led to improvement in epidemiology of this complex disease and facilitated the development of new diagnostic makers and new therapies. However, important new challenges are also apparent. We still do not really understand why AKI occurs and urgently need to develop new therapies to treat it. Progress in this area will require new ideas and thinking outside the conventional box. By confronting some of the most significant controversies in the field of AKI we seek to develop new concepts that will ultimately yield new results.

A mysterious disorder is killing more than half a million patients around the world each year. This disorder is associated with sudden onset of profound impairment of kidney function and its exact cause is unclear and treatment is unsatisfactory. The condition primarily affects acutely ill and injured patients and disproportionably affects the elderly. Many of those that survive remain with permanent kidney failure.

The term acute kidney injury (AKI) was coined by William MacNider in 1918 in reference to acute mercury poisoning, but only became a preferred term since 2004 when it was defined using widely accepted consensus criteria known as Risk-Injury-Failure-Loss-End stage kidney disease (RIFLE) [1]. 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 (only an increase in serum creatinine of 0.3 mg/dl or 6 hours of oliguria), is associated with worse clinical outcomes. Criteria for AKI were therefore set at small changes in serum creatinine or urine output, and when these criteria were applied to intensive care [2], hospital or even population-based [3] cohorts two observations were made. First, AKI is common, occurring in as many as two-thirds of ICU patients [2] and about 2,100 per million population [3], and is associated with dramatic reductions in survival [2-3].

As more information becomes available on this illness, it is clear that much of what we think we know is questionable. For example, dehydration causes the kidney to concentrate the urine but when dehydration is extreme, our kidneys can no longer excrete the solute load produced by our bodies and we develop biochemical evidence of impaired kidney function. We refer to this state as pre-renal because it is produced by abnormalities 'upstream' of the kidney. A similar situation arises when there is insufficient circulating blood volume due to hemorrhage or when the heart fails to deliver adequate cardiac output. Indeed, even a thrombosis of the renal artery would be classified as pre-renal. When the pre-renal state is very transient and/or mild, and when it is occurring in the setting of normal baseline renal function, it may appear to be well tolerated. However, emerging evidence suggests that the pre-renal 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 [4]. 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 pre-renal state can lead to direct kidney damage.

Another area of controversy concerns our understanding of the pathogenesis of AKI [4]. Epidemiologic evidence suggests that AKI is not a single disease but a syndrome comprising multiple, often coexisting etiologies [5]. The most common forms of AKI appear to be non-ischemic [6,7] and arise in settings such as sepsis and heart failure. Early AKI may be purely functional and reversible but soon gives way to tissue injury and a

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complex array of vascular, metabolic and inflammatory changes. Furthermore, the kidney may be an innocent bystander injured by the 'toxic waste' that it filters from the blood in the setting of remote tissue injury and infection. Cytokines, free radicals, microvesicles and other damage-associated molecular patterns may initiate AKI, and 'maladaptive repair' mechanisms [8] may cause further damage, particularly in the most susceptible patients, such as the elderly and those with chronic kidney disease.

Such a multifaceted disease process has been difficult to study both in animals and in humans. 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 'magic bullet' for AKI. Instead, it may be possible to develop a 'magic shield' 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 we will thus soon have better ways to apply the right therapies to the right patients.

Finally, we have learned a great deal about renal support. Though our recent trials have been negative, they have been successful and they have generated important hypotheses about patient selection and timing of initiation. Renal replacement therapy is being delivered earlier and to more severely ill patients than ever before. There is some evidence that survival for patients with AKI is improving, though it is still quite poor in critically ill patients. 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 past three decades. If we are to expect better outcomes, we will need to develop better therapies.

Advanced technologies in the forms of increased hemofiltration volumes, higher cutoff membranes, plasma filtration and adsorption 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 a multi-organ 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) [9]. Such therapies aim to improve organ function and decrease severity of organ damage.

In summary, the advances in AKI epidemiology that have been seen in the past decade have opened new vistas that we can explore for new diagnostic makers and new therapies. However, new challenges are also apparent. We need to better understand why AKI occurs and to develop new paradigms to treat it. Business as usual will result in the usual outcomes and as survival from other forms of vital organ failure improve [10], AKI has lagged behind. It's time we took up the challenge to set a new course. The 2011 Brussels Roundtable seeks to begin this process.

Abbreviations

AKI, acute kidney injury.

Competing interests

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References

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup: **Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group.** *Crit Care* 2004, **8:**R204-212.
2. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: **RIFLE criteria for acute kidney injury is associated with hospital mortality in critical ill patients: a cohort analysis.** *Crit Care* 2006, **10:**R73.
3. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod A: **Incidence and outcomes in acute kidney injury: a comprehensive population-based study.** *J Am Soc Nephrol* 2007, **18:**1292-1298.
4. Murugan R, Kellum JA: **Acute kidney injury: what's the prognosis?** *Nat Rev Nephrol* 2011 [Epub ahead of print].
5. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: **Acute renal failure in critically ill patients: a multinational, multicenter study.** *JAMA* 2005, **294:**813-818.
6. Langenberg C, Wan L, Egi M, May CN, Bellomo R: **Renal blood flow in experimental septic acute renal failure.** *Kidney Int* 2006, **69:**1996-2002.
7. Ricci Z, Polito A, Polito A, Ronco C: **The implications and management of septic acute kidney injury.** *Nat Rev Nephrol* 2011 [Epub ahead of print].
8. Bonventre JV: **Pathophysiology of AKI: injury and normal and abnormal repair.** *Contrib Nephrol* 2010, **165:**9-17.
9. Ronco C, Ricci Z: **Renal replacement therapies: physiological review.** *Intensive Care Med* 2008, **34:**2139-2146.
10. Vincent JL, Nelson DR, Williams MD: **Is worsening multiple organ failure the cause of death in patients with severe sepsis?** *Crit Care Med* 2011 [Epub ahead of print].

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