AKI Biomarkers www (Who, Where, When): You Cannot Treat What You Do Not Know

Claudio Ronco

Department of Nephrology, Dialysis and Transplantation, International Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital, Vicenza, Italy

One of the main questions in critical care nephrology is whether or why biomarkers of structural kidney damage are important in today’s clinical practice [1, 2]. The next question is whether biomarkers are potentially useful to guide early assessment of kidney damage and/or management of patients at risk for acute kidney injury (AKI) [3–6]. There are several issues in the modern approach to AKI therapy and they can be summarized as follows. Which patient should be treated? What target should we consider important for therapy? How should we manage such complex patients? When should we begin the therapeutic strategy that has been proposed? What are the conditions for an appropriate intervention? What is the plan: prevent injury, avoid further injury, or mitigate present injury? What is the process of recovery? There are so many questions and so few answers. We must recognize that we cannot treat what we do not know.

As we learn more about AKI, our therapeutic strategy will likely become an integrated process of primary prevention (this applies to populations and ethnic or geographical groups based on epidemiology and risk analyses), early diagnosis of the injury together with assessment of organ susceptibility, secondary prevention or mitigation of injury, and finally removal of current stressors or exposures leading to injury. The last factors are specific to the individual and suggest the need for a personalized approach.

In this century, whenever a question is posed, scientists, students and the public at large rapidly ‘surf the Web’ to find an answer, possibly stumbling upon a page like www.biomarkers.something. Everything that is new in this area is online and reported on the Web in real time. However, I suggest the physician should look at the individual patient biomarker profile and develop a consequent diagnostic and therapeutic strategy that is personalized to that specific patient. In this area we must remove the barriers to early identification of patients at risk of developing AKI and possibly identify biomarkers useful for AKI risk assessment. The answers will come because the paradigm may shift and new biomarkers are probably capable of telling us the www: who should be monitored, where the damage is, and when treatment should start.

Who. Recent studies have been published including discoveries of new molecules characteristic of specific structural damage and validation of their capacity to predict the development of AKI later on in the history of a critically ill patient [7–9]. In particular, urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) are new biomarkers for AKI that were discovered in a cohort and validated in a large multicenter prospective study. They seem to perform better than existing markers with an AUC (area under the curve with 95% CI) higher than 0.8, especially when combined. [TIMP2] · [IGFBP7] also significantly improved risk stratification when added to a 9-variable clinical model. MAKE30 (major adverse kidney event within 30 days such as death, need for renal replacement therapy, or doubling of serum creatinine) increased sharply for [TIMP2] · [IGFBP7] >0.3 and doubled when values were >2.0 (ng/ml)²/1,000.
Where. It is well understood that damage- and pathogen-associated molecular patterns are typically found in the circulation of patients subject to stressor or toxin exposure. These molecules together with toxins may be filtered by the glomerular membrane and reach the region of the proximal tubular cells in high concentrations. Concentrations at the cellular level and in the peritubular capillary may be increased even further due to urine concentration, tubular reabsorption or simply extravasation into the interstitial space. Locally this process may result in the initial injury, with further amplification of pathophysiological mechanisms such as inflammation, oxidant stress and cell damage [10]. TIMP-2 and IGFBP7 have been identified to be excellent biomarkers of AKI. They block the effect of CyclD-CDK4 and CyclE-CDK2 on cell cycle promotion, becoming perfect markers of G1 cell cycle arrest. In practice, they tend to limit the extension of the damage by the blockage of cell division and multiplication. Also, they might be able to produce a beneficial effect by avoiding a potentially dangerous process of maladaptive repair attempted by the organism. Although this is not proven, there is a rationale for this statement. Thus, biomarkers in this case localize the site of injury or ‘cell stress’ with remarkable precision and accuracy, i.e. where the injury/stress is happening.

When. Following acute injury, the kidney normally initiates a burst of cellular proliferation to repopulate the tubule epithelium. Early G0/G1 cell cycle arrest may protect from further damage in AKI by blocking DNA damage and caspase 3/7 activation. These phenomena occur 24–48 h before creatinine rises due to a significant fall in glomerular filtration rate. Thanks to early detection of the insult and impending structural damage, new protective and therapeutic strategies could be implemented as suggested by the most recent KDIGO guidelines. The clinical phenotype of AKI may be a mild patchy tubular injury or a large structural damage with profound loss of the glomerular filtration rate, or even a condition of acute on chronic with a high fibrotic component in the renal parenchyma. Intrarenal inflammation can also lead to fibrosis and ineffective repair. This process will ultimately lead to nonrecovery of renal function and chronic kidney disease.

All these forms, however, start with an early injury, and its detection may be quintessential for improving the subsequent mid- to long-term outcome. Future treatments to prevent AKI and to facilitate renal recovery will likely focus on the pathophysiology of the syndrome, and a more detailed knowledge of the pathogenetic process will have an impact on success. Blood purification strategies to remove inflammatory mediators, DAMPs and other molecules may prevent AKI, and they should be considered at early stages as a mitigation remedy after an early insult. Pharmacologic blockade of the inflammatory response and treatment to redirect the healing process may be effective in facilitating renal recovery. While this was almost impossible until today, starting tomorrow we might be able to accomplish this difficult task because biomarkers now tell us the www: who is at risk, when to start, and where the damage is.

References


