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Review

Earlier diagnosis of acute kidney injury in critically ill patients by novel biomarkers: Moving from supportive care to targeted renoprotection?

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Abstract

Introduction

Current assessments of renal function by serum creatinine or blood urea nitrogen display poor sensitivity and specificity for indicating early changes in kidney function and do not differentiate between causes of acute kidney injury (AKI). The discovery, characterization and validation of novel biomarkers specific for structural kidney damage, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, interleukin-18 and liver fatty acid binding protein enable a timely diagnosis of AKI through better reflection of real-time damage of AKI, promise discrimination of the underlying aetiology and may enable incremental risk identification for worsening AKI, need of renal replacement and death. However, case-mix, comorbidities, aetiology of the renal insult, timing of measurements and selected thresholds for diagnosis influence the performance of these novel biomarkers. Additional studies are necessary before novel biomarkers can be used in routine clinical practice. To answer the question of how to optimally utilize novel biomarkers (the right test, at the right time, on the right patient, for the right clinical setting of AKI) all promising AKI biomarkers should undergo systematic evaluation in various clinical setting of AKI in order to validate the temporal expression patterns of these biomarkers for early detection of AKI, to determine how to combine multiple biomarkers for earlier diagnosis and to discover how the temporal course relates to onset, severity and outcome of AKI. There is a vital need that large future investigations demonstrate the association between biomarkers and hard clinical outcomes independent of serum creatinine concentrations. It needs to be shown that early renoprotective treatment for AKI based on high biomarker levels actually results in an improved outcome. The aim of this review is to discuss early diagnosis of acute kidney injury in critically ill patients by novel biomarkers.

Conclusion

Until effective renoprotective therapies are available, there is little benefit from early diagnosis of AKI during critical illness.

Introduction

Acute kidney injury in the intensive care setting (ICU AKI) is a complex disorder with multiple aetiologies and risk factors, various clinical presentations and unpredictable outcomes. Various combinations of ischemic, septic and nephrotoxic effects are the main causes of hospital-acquired AKI in critically ill patients. Today, ICU AKI is often found in the setting of multiple organ failure and occurs rarely as single organ dysfunction. In general, the incidence of hospital-acquired AKI is increasing as physicians subject an increasingly aged patient population to major surgery, aggressive medical therapeutics and extended radiologic interventions. AKI is widespread and occurs in up to 18% of all hospital admissions with reports of up to 67% in critically ill patients in the ICU. ICU AKI represents a continuum of morbidity that can vary from subclinical injury, in which serum creatinine changes minimally, to severe oligo-anuric kidney failure requiring renal replacement therapy (up to 4–6%)[1].

The diagnosis of AKI has a significant negative impact on the prognosis of critically ill patients and is associated with a poor short- and long-term outcome. Recently, it has been recognized that kidney function does not completely recover in many patients and that AKI represents an antecedent to the development to chronic kidney failure, particularly in patients with pre-existing chronic kidney disease[2]. Even the mildest forms of AKI are independently associated with increased, early as well as late, mortality, and the risk increases in the wake of increasingly severe renal injury[1].

Current management of ICU AKI is restricted to supportive care. Reports on specific pharmacologic interventions to treat established AKI showed minimal effects, if any. The attributable mortality of hospital-acquired AKI, however, remains distressingly high (up to 70%), despite numerous advances in intensive care medicine and renal replacement therapy[1]. This review discusses targeted renoprotection used in earlier diagnosis of acute kidney injury in critically ill patients.

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Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Traditional biomarkers for the detection of AKI

In the most generic sense, AKI is an abrupt and sustained decline in glomerular filtration rate (GFR) leading to a significant fall of solute excretion. AKI results in the retention of metabolic end-products and in disturbances in acid-base, electrolyte and fluid balance. Current consensus recommendations (i.e. RIFLE, AKIN or KDIGO classification schemes) rely on absolute or relative changes in serum creatinine concentrations and/or urine output as well as on the duration of these changes[3]. Thus, the diagnosis of AKI has essentially not changed over a century. By comparison, progress in the early diagnosis of the acute coronary syndrome by sensitive and specific novel biomarkers, such as troponin, has resulted in the parallel improvements of treatment and survival of patients with acute myocardial infarction.

Measurements of serum creatinine concentrations and urine output have a number of severe limitations as a screening test in ICU AKI. First, the non-linear relationship between GFR and serum creatinine, as a marker of renal function rather than kidney injury, means that GFR may decrease by more than 50% from normal baseline before a significant rise in serum creatinine occurs, rendering serum creatinine insensitive to small but significant declines in GFR. Second, numerous non-renal factors such as patient characteristics (age, gender, muscle mass), co-morbid diseases (liver disorders) or over-hydration (fluid resuscitation)may be associated with decreased creatinine production or dilution of serum creatinine concentrations blunting or masking a rise in the traditional biomarker level although the GFR is in fact reduced. Third, a further limitation of the use of serum creatinine to diagnose AKI is the inevitable delay between more extensive kidney injury and the subsequent rise of serum creatinine. In fact, the majority of patients who develop AKI after a well-known precipitating kidney insult (e.g. cardiac surgery) do not meet the diagnostic criteria of AKI until the second post-operative day or later. Finally, increased serum creatinine levels do not distinguish between pre-, intra- and post-renal causes nor do they aid in the differential diagnosis of acute kidney injury and chronic kidney disease. The current paradigm for diagnosing AKI largely by the detection of changes in creatinine remains susceptible both to delays in diagnosis but also to missing relevant declines of GFR[4]. However, the change in terminology of acute kidney dysfunction reflects that rises in serum creatinine as small as 0.3 mg/dl may be associated with adverse outcomes. Thus, clinicians must be vigilant for small changes in renal function and not just focus on overt acute kidney failure. The forest fire theory of acute kidney injury proposes that serum creatinine levels are a marker for functional nephron number, but not a real-time indicator of the extent of active injury[5].

The accurate measurement of urine output is generally confined to patients with urinary catheters and is modified by the use of diuretics. It must be remembered that AKI in critically ill patients can be oliguric, normuric or even polyuric so that rises in serum creatinine may occur despite an adequate urine output.

Urine microscopy helps diagnose acute renal parenchymal diseases. Urine sediment analysis can detect erythrocyte casts (glomerulonephritis), leukocyte casts (tubulo-interstitial nephritis) or eosinophiluria (interstitial nephritis) in critically ill patients. Microscopy is most commonly used to differentiate the featureless sediment of pre-renal azotaemia from acute tubular necrosis, showing pathognomonic muddy brown casts and renal tubule epithelial cells. However, investigations of the interobserver reliability of urine microscopy demonstrate that nephrologists achieve only slight to moderate agreement, and as such urine microscopy remains a good but imperfect diagnostic tool for AKI[6].

Urinary indices such as fractional excretion of sodium (FENa) or urea (FEurea) are used as an aid for the differential diagnosis of acute kidney injury, particularly to differentiate pre-renal azotaemia (intact tubular function) from renal causes (acute tubular necrosis, impaired tubular function). Several caveats need to be considered when these urinary indices are used in clinical routine. First, the recent administration of diuretics may give rise to misleading urine sodium values. Second, these indices are obtained at a single time point, whereas AKI is dynamic in nature. For example, early phases of the pre-renal forms of AKI are associated with intact tubular function. If the cause of the pre-renal insult cannot be rapidly reversed, ischemic ATN develops with impaired tubular function. Such a sequence of events may explain the low FENa rates in sepsis, contrast medium induced AKI or after exposure to non-steroidal anti-inflammatory drugs. Third, the specificity of urine indices is limited and differentiation between pre-renal and intrinsic renal causes or pre-renal and urinary obstruc-

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tion may be impossible—at least in the early course[7].

Traditional blood or urinary markers of kidney injury do not allow for an early diagnosis of acute kidney injury and may hamper progress in the treatment of patients with AKI.

Characteristics of an ideal biomarker

The ideal biomarker must be generated by the damaged cells and exhibit organ specificity. Its concentration in body fluids must be proportional to the extent of the damage. It should be expressed early after the organ damage when such injury is still potentially reversible. The concentrations in body fluids should decrease quickly after the acute injury episode to enable its use as a therapeutic monitoring tool. The best biomarkers are obtained non-invasively. The serum or urinary concentrations of ideal biomarkers must be stable across a wide range of temperatures, easy to measure, and should be detectable at the bedside by rapid, reliable and inexpensive measurements using standardized assay platforms. The levels of an ideal biomarker should be unaffected by drugs or endogenous substances. Urinary biomarkers should be undetectable in healthy subjects and extra-renal biomarker synthesis should not augment significantly urinary biomarker levels. Of great clinical relevance, ideal biomarkers add significantly to clinical judgement. An ideal biomarker would identify patients at highest risk in a timely manner, thus allowing early and potentially effective intervention[4,8]. The potential for novel biomarkers is great. The integration of novel biomarkers should enable incremental diagnostic and/or prognostic information beyond that found by clinical evaluation or traditional markers of kidney function alone.

Novel biomarkers should enable a timely diagnosis of AKI through better reflection of a real-time injury to kidneys, stratification according to injury severity and discrimination of the underlying aetiology (differential diagnosis pre-renal from established AKI or AKI from chronic kidney disease). These markers of renal injury should allow incremental risk identification for worsening of AKI, dialysis-dependant acute kidney failure, death and recovery from AKI, and they should aid in assigning priorities for triage disposition, timing of initial injury and for the discontinuation of renoprotective interventions[9].

Update on novel biomarkers for AKI

Novel biomarkers are proteins that are expressed in response to kidney injury, predominantly by tubular injury. These markers may be classified as (1) tubular epithelial cell enzymes released into the urine after cellular stress or injury, (2) inflammatory mediators or cytokines released by kidney specific cells or by infiltrating inflammatory cells during AKI, and (3) low molecular weight proteins, which are filtered freely in the glomerulus and then not adequately digested and re-absorbed by damaged tubular cells.

More than 300 candidates' biomarkers emerged through the application of functional genomics and proteomics[10]. More than 25 novel biomarkers have been evaluated in human AKI, and the list is by no means exhaustive[11]. A wealth of clinical data has been generated by four novel biomarkers in human AKI. Neutrophil gelatinase-associated lipocalin (NGAL, in plasma and urine), kidney injury molecule-1(KIM-1, urine), interleukin-18 (IL-18, urine) or liver fatty acid binding protein (L-FABP), measured either alone or in combination in five clinical settings (paediatric AKI, emergency department, ICU, cardiac surgery and contrast-induced nephropathy). Clearly all novel biomarkers specific for kidney damage have added unique information on the pathobiology of human AKI. There is no doubt that the four most promising novel biomarkers, predominantly NGAL enable an earlier diagnosis of AKI than serum creatinine and provide an early warning signal[9,12–20]. Nevertheless, recent multicentre investigations found that two cell cycle arrest biomarkers—urinary insulin-like growth factor binding protein 7(IGFB7) and tissue inhibitor of metalloproteinases 2 (TIMP-2)—may be superior to existing markers[10]. Finally, existing AKI biomarkers have also enabled the characterization of a subgroup of patients at risk for AKI who have detectable elevations in biomarkers but not in serum creatinine. This novel cohort of patients with subclinical kidney damage consists of up to 19% and has a worse clinical outcome compared to patients with no rise in serum creatinine and biomarker concentrations[9].

Unfortunately, the performance of the existing novel biomarkers is influenced by case-mix, comorbid illness, aetiology of AKI, drugs, timing of specific biomarker measurements and the selected threshold for cut-off values[9,11].

Limitations of novel biomarkers in ICU AKI patients

There is no doubt that promising novel biomarkers enable an earlier diagnosis of AKI in critically ill patients. However, evaluation of novel biomarkers for an early diagnosis is difficult in the ICU as the performance of the most promising biomarkers is influenced by patient characteristics, severity of the underlying illness and aetiology and severity of AKI. Undoubtedly, there are many circumstances where traditional markers are sufficient and the incremental value of a novel AKI biomarker is questionable. First, the majority of patients admitted to the ICU have established AKI already. The use of biomarkers in these ICU patients is uninformative. Second,

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baseline creatinine values are lacking in many patients admitted to the ICU, but 30% of the patients have pre-existing chronic kidney disease. This clearly increases the risk of misclassification of the AKI diagnosis and hampers an early differentiation of AKI from chronic kidney disease by novel biomarkers. Chronic kidney disease is more easily diagnosed using traditional tests of renal function with little additional benefit from novel biomarkers. Third, the timing of the kidney insult is unknown. Therefore, the optimal timing for serial measurements is uncertain. Finally, critically ill patients display a heterogeneous mixture of comorbidities and the aetiology of AKI in the ICU setting is often multifactorial including ischemic insults, nephrotoxic drugs and sepsis. Sepsis is the cause of AKI in the majority of critically ill patients (up to 50%). The effects of sepsis or multiple organ failure on urinary NGAL, L-FABP or IL-18 are not clear. It is known that septic patients have not only higher plasma NGAL but also increased IL-18 levels. Furthermore, cardiopulmonary bypass per se appears to increase urinary NGAL levels independent of AKI. Urinary IL-18 may represent a non-specific marker of cardio-pulmonary bypass-associated inflammation rather than reflect true tubular damage, limiting its use in cardiac surgery. The incremental diagnostic or prognostic information obtained by novel biomarkers beyond that found by perioperative clinical evaluation (time on cardio-pulmonary bypass, duration of aorta clamp, pre-existing renal function) is questionable in patients with post-cardiac surgery AKI.

Future challenges for urinary biomarkers of AKI

Despite the widespread optimism regarding novel AKI biomarkers, there are important limitations using the existing novel biomarkers. The most promising AKI biomarkers have both strengths and weaknesses. The question of how to optimally use them in clinical routine remains unanswered. It may be essential that the clinical context should be incorporated into the use of novel AKI biomarkers to better enable their ideal utilization (i.e. right patient, right clinical setting).

The heterogeneity of AKI suggests that more than one novel biomarker may be necessary to obtain sufficient sensitivity and specificity to predict AKI (prior to changes in serum creatinine) as well as severity of AKI or patient outcomes in all clinical settings. The pathophysiology of ischemia-reperfusion AKI is different from that of sepsis AKI, which is different from radio-contrast nephropathy. As such each of the clinical entities may be best detected by a different set of biomarkers at different clinical time points. Currently, there is no standard procedure to combine the multiple novel biomarkers for clinical use. Larger prospective studies are necessary to validate the temporal expression patterns of various biomarkers for the early detection of AKI and to determine the optimal timing for measurements of urinary biomarkers and to discover how the temporal course of urinary biomarker excretion relates to onset of AKI. Many of the published studies used serial measurements through the early ICU phase to define the typical pattern of biomarker increase and decrease. However, such repeated measurements are expensive in comparison with a daily determination of serum creatinine, and may ultimately limit their clinical applicability. Further studies are needed to establish accurate population reference values according to age, gender and ethnicity as well as reliable and specific cut-off values concerning the more common clinical settings of AKI.

Only few clinical investigations have prospectively identified patients at a higher risk for progression of AKI and worse outcomes. Most studies had very low event rates (progression of AKI by worsening AKIN stage or death).

Many studies assessing the early diagnostic and prognostic performance have excluded patients with baseline renal insufficiency. This is problematic, not only because it excludes a large proportion of subjects (up to 30% of critically ill patients) who frequently develop AKI in the hospital, but also because chronic kidney disease in itself can result in increased concentrations of AKI biomarkers, thereby representing a confounding variable. The performance of novel biomarkers must therefore be characterized across a broad spectrum of baseline renal function before their widespread clinical use can be recommended in hospitalized patients.

Biomarkers are being increasingly investigated for their ability to complement, rather than replace creatinine. The ability to detect adverse patient's outcomes in the absence of significant changes in serum creatinine by high urine biomarker concentrations[21] represents a paradigm shift. It will be crucial in future studies to evaluate the clinical course of those patients who may be prone to AKI and are 'biomarker positive' but 'creatinine negative', since this will determine whether the novel biomarker is overtly sensitive.

Novel biomarkers should not distract attention from clinical evaluation. Each promising biomarker should improve risk classification compared to clinical model alone. Paediatric studies have begun to identify which clinical risk factors may predict development of post-operative AKI, and early results show that some promising biomarkers add little information to clinical evaluation.

There is a need to normalize the concentration of some (except NGAL) biomarkers in the urine for the degree of urine dilution. This is often performed by calculating the ratio of urine biomarkers to urine

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creatinine concentrations. However, urinary excretion of creatinine is affected by the changes in GFR that occur during AKI.

The performance characteristics of all promising biomarkers are generally compared against creatinine-based measurements as an existing gold standard. However, a creatinine-based diagnosis of AKI is in itself imperfect, potentially influencing the acumen of novel biomarkers and necessitating other means of evaluating the accuracy and clinical implications of a new test. In fact, a new biomarker with perfect sensitivity and specificity, when compared with serum creatinine, would simply replicate the inaccuracies of creatinine, perhaps a little earlier in the clinical course of AKI.

There is a vital need to perform large future investigations to determine the association between biomarkers and hard clinical outcomes independent of serum creatinine concentrations, and to prove that randomization to renoprotective treatment for AKI based on high biomarker levels actually results in an improved clinical outcome.

Earlier diagnosis and renoprotective treatment of AKI

Novel biomarkers of AKI are moving closer towards clinical relevance, but there is still much that we do not know about their usefulness. Importantly, we must recognize that biomarkers are not an end in themselves but rather a means to an end. The track record so far for specific renoprotective regimes in AKI is poor. Therapies designed to address issues such as conversion of oliguria to normuria by diuretics, improvement of suboptimal renal perfusion by low dose dopamine or fenoldopam, reduction of inflammation by statins, or prevention of renal toxicity from free radicals (N-acetylcysteine), while seemingly rational, have not proven to be an effective method to prevent or treat evolving AKI. Moreover, growth factors such as erythropoietin, hepatocyte growth factor and insulin-like growth factors, appear to reduce or limit a poptosis in experimental models of renal injury, but have not shown benefit to patients. Finally, it remains uncertain in the absence of a large prospective randomized trial whether the earlier institution of renal replacement therapy of AKI results in better outcomes of these patients[22]. Although retrospective data analysis and observational studies have suggested improved survival with very early initiation of renal replacement therapy, interpretation of these studies are confounded by the inclusion of patients with AKI who recover renal function or die without need for initiation of renal replacement therapy according to generally accepted indications.

Conclusion

Urinary biomarkers have the potential to revolutionize the diagnosis of AKI and the prognosis of patients with acute kidney dysfunction. However, until effective renoprotective therapies are available, there is little benefit from early diagnosis using novel biomarkers. Thus, it is not surprising that current guidelines on diagnosing, preventing and treating AKI in critically ill patients continue to recommend serum creatinine, in association with urine output, as the primary test for assessing patients with evolving AKI.

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