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Orbital shaker for use in high humidity CO_2 incubators

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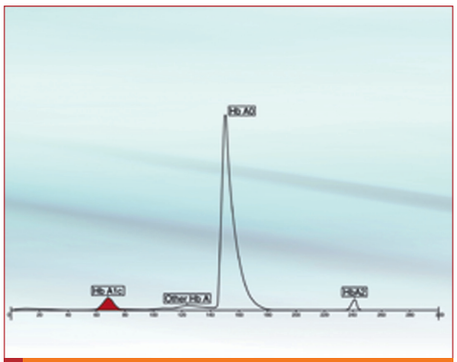

Assay for direct HbA_{1C} measurement

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Semi-automated nephelometer

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Is NGAL the "troponin of the kidney"?

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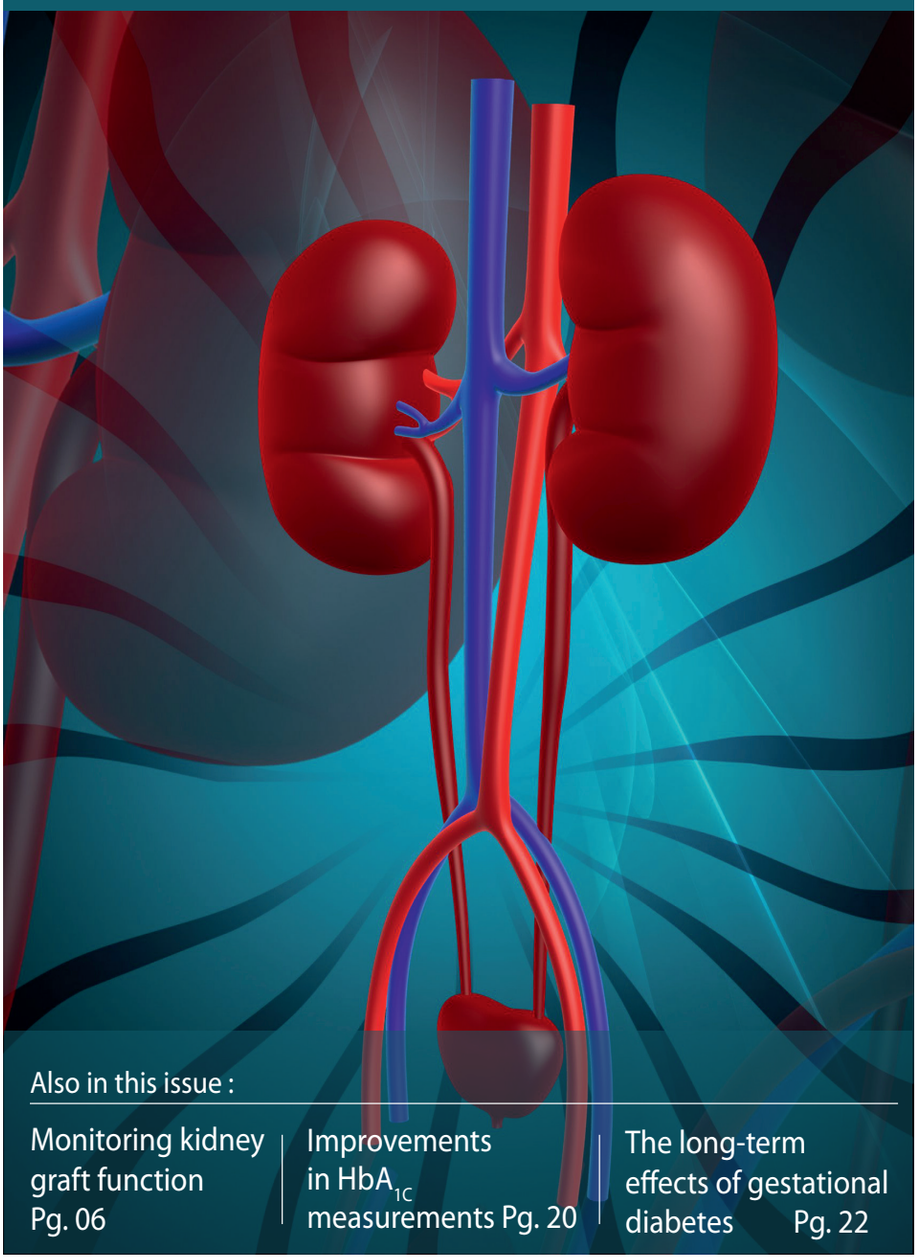


Also in this issue :

Is NGAL the "troponin of the kidney"?

Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a promising biomarker for acute kidney injury (AKI). The ultimate goal is for NGAL to enable clinicians to intervene as early as possible and to change the prognosis of AKI. This article discusses the current position of NGAL in the race to become the "troponin of the kidney".

by Dr M. Ostermann and Prof. D. Bennett

After decades of being deemed a byproduct of severe illness, acute kidney injury (AKI) has gained recognition as a serious contributor to morbidity and mortality in hospitalised patients, in particular in critically ill patients in the Intensive Care Unit (ICU). Numerous studies have confirmed a clear association between severity of AKI and short and long-term mortality, length of stay in hospital and healthcare costs [Figure 1]. There is also increasing evidence that AKI *per se* may cause problems in non-renal organs, such as lungs, brain and myocardium, and lead to multi-organ dysfunction.

Patients who survive AKI have an increased risk of developing chronic kidney disease (CKD) and of needing long-term dialysis for end-stage renal disease (ESRD). A study of 556,090 patients showed that an episode of dialysis-requiring AKI was independently associated with a 28-fold increased risk of CKD stage 4 or 5 and a greater than 2-fold increased risk of death [1]. Using data from the National Center for Health Statistics in the United States from 2001, the annual healthcare expenditures attributable to hospital-acquired AKI are estimated to exceed $10 billion [2].

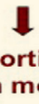
The diagnosis of AKI is traditionally based on a rise in serum creatinine and/or a fall in urine output. It has been acknowledged that even small rises in serum creatinine of >26.4 µmol/L in 48 hours represent a significant reduction in renal function and are independently associated with an increased risk of dying. Although the literature contains more than 500 publications since 1965 on the renoprotective efficacy of various diverse interventions in experimental AKI, therapeutic options are limited in clinical practice. Management of AKI consists of correction of hypovolaemia and hypotension, avoidance of further renal insults, and treatment of the underlying disease. There are several possible explanations for this lack of therapies: i) a large number of interventions were tested in animals without the typical comorbities that are seen in humans with AKI, ie. diabetes, CKD, proteinuria; and ii) it is possible that the interventions in clinical trials were given too late, ie. when the renal insult had become treatment resistant. The main reason for this delay is the fact that decisions to treat were based on serum creatinine, a late marker of renal damage which can lag behind renal injury by up to two days. The absence of any cure for AKI coupled with a high risk of mortality underscore the urgent need for new diagnostic and therapeutic approaches in the management of AKI.

Figure 1. Impact of AKI.

Several new AKI biomarkers have been identified with better diagnostic and prognostic capabilities than serum creatinine. Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a very promising marker [3]. Studies in different patient populations have confirmed that urine and plasma NGAL levels can indicate the onset of AKI within a few hours after a renal insult and 24-48 hours before serum creatinine rises. However, unlike developments in cardiology, there has been little progress with the incorporation of AKI biomarkers into clinical practice. The goal is for NGAL to allow clinicians to intervene as early as possible, and thus change the prognosis of AKI, similar to the way that troponin has altered the management of acute myocardial infarction.

Period	Acute MI	Acute kidney injury
1960s	LDH	Serum creatinine / urine output
1970s	CPK, myoglobin	Serum creatinine / urine output
1980s	CK-MB	Serum creatinine / urine output
1990s	Troponin T	Serum creatinine / urine output
2000s	Troponin I	Serum creatinine / urine output
2010s	Highly sensitive Troponin	Serum creatinine / urine output

Multiple therapies
Reduction in mortality



Supportive care
High mortality

Figure 2. Development of biomarkers in acute myocardial infarction and acute kidney injury.

For a biomarker to be integrated into routine clinical practice, several criteria need to be met. First, the assay needs to be precise, accurate and rapidly available to the clinician at an affordable price. Second, the biomarker must provide additional information beyond that obtained through clinical evaluation and standard laboratory tests. Finally, the information provided should influence clinical decision-making and ideally improve outcome.

In the field of AKI, NGAL tests are now available for routine diagnostic purposes on several assay platforms, including turbidimetric clinical chemistry tests which ensure rapid results in a timely manner. Studies have confirmed that measurement of urine and plasma NGAL provides new information and indicates the onset of AKI significantly earlier than conventional markers of renal function. Data on the role of NGAL in the routine clinical decisionmaking process are still sparse but slowly emerging.

Recent studies confirming a potential role for NGAL in clinical practice

a) NGAL as a marker to differentiate between "pre-renal failure" and intrinsic AKI

The term "pre-renal failure" is widely used to describe a reversible form of renal dysfunction which is usually caused by compensatory processes within the kidney without any structural damage. Determining whether an increase in serum creatinine represents this type of reversible "pre-renal" functional change or is due to established AKI with structural damage is very important, especially as therapeutic strategies and prognosis are different.

A recent study provides support for NGAL in discriminating between "pre-renal" and "intrinsic" AKI. In 145 hospitalised patients with an elevated serum creatinine who met the RIFLE criteria for AKI (increase in serum creatinine by >50% or a >25% decrease in glomerular filtration rate compared with baseline), urine NGAL was measured at enrolment and two days later [4]. The study in these patients confirmed that urine NGAL levels greater than 104 µg/L and less than 47 µg/L identified patients who had intrinsic and pre-renal AKI, respectively, with an overall area under the receiver operating characteristic curve of 0.87. In clinical practice, the knowledge that a raised serum creatinine is not simply due to "pre-renal failure" but represents a more severe form of AKI is very important. It should prompt the clinician to initiate further diagnostic tests, avoid any procedures or medications which may be nephrotoxic, and seek expert advice early.

b) NGAL as an outcome measure to demonstrate efficacy and safety

The evaluation of any new procedure or therapy includes sensitive efficacy testing as well as safety monitoring. NGAL has become a very attractive tool for this purpose. A recent example is a randomised controlled double-blind intervention trial in 80 infants undergoing cardiopulmonary bypass surgery, where plasma and urinary NGAL were measured as parameters of renal outcome [5]. Forty infants were randomised to receive a fenoldopam infusion during surgery. Comparison was made with 40 infants randomised to receive placebo. Although no difference was observed in urinary and plasma creatinine, patients in the fenoldopam group had significantly lower urinary NGAL levels. This study demonstrates that NGAL can confirm renoprotective effects not identified by serum creatinine.

Future studies which are necessary to integrate NGAL into routine clinical practice

a) Determination of "normal" ranges of NGAL

Published studies of NGAL show wide variation in levels, with non-parametric distributions and wide confidence intervals. In order for NGAL to be adopted into clinical practice, large scale population studies are necessary to describe normal ranges of urine and/or plasma NGAL in different patient populations. Furthermore, it is essential to determine the exact cut-off values for AKI in patients with normal baseline renal function as well as patients with pre-existing CKD.

b) Role of NGAL as a trigger for clinical therapies

Analogous to the success with early interventions in patients with a myocardial infarction

triggered by troponin levels [Figure 2], the obvious therapeutic goal of an early diagnosis and effective therapy for AKI is to reduce the progression to severe AKI, decrease associated morbidity and mortality and treatment costs, and prevent late complications. In patients undergoing high risk surgery, pre-emptive strategies of goal-directed haemodynamic optimisation (e.g. targeting a 'supranormal' oxygen delivery value) have been shown to reduce postoperative mortality and morbidity, including a reduction in the incidence of AKI from 8.0% to 5% [6]. The benefit is believed to relate to increased oxygen delivery to tissues with prevention of a significant tissue "oxygen debt" and subsequent organ dysfunction. Studies are required in critically ill patients to demonstrate that the earlier confirmation of AKI with urinary and/or plasma NGAL enables timely haemodynamic optimisation to prevent the development of severe AKI and death. It is possible that other therapies which previously proved to be disappointing in clinical trials are in fact renoprotective if administered at an early stage of AKI before serum creatinine rises.

Conclusion

NGAL is a strong contender in the race to become the "troponin of the kidney" but there are still a few hurdles to overcome before the finishing line is reached. More studies are needed to evaluate its performance in conjunction with clinical and basic biochemical parameters and coupled with an intervention. The ultimate goal is that NGAL may aid the physician in identifying more precisely the time when specific therapies are most effective and in altering the prognosis of AKI.

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