Clinical Question
In the primary care setting, what is the accuracy and utility of neutrophil gelatinase-associated lipocalin (NGAL) tests to predict, diagnose, and manage acute kidney injury?

BACKGROUND
In current clinical practice, the consensus diagnosis of acute kidney injury (AKI) depends on the detection of an acute rise in serum creatinine and/or oliguria. Recognition of AKI in the community is important, as it is relatively common and associated with excess mortality and morbidity. In a primary-care-based cohort of around 61,000 patients, 7% had an episode of AKI over a 6-month period. However, detection is difficult on clinical grounds alone. In a population-based study among patients retrospectively diagnosed with AKI from laboratory samples using the NHS England AKI algorithm, those who were managed at home by GPs had a higher risk of death than those admitted to hospital. Improving the recognition of AKI in the community is a national priority, but the optimal strategy to achieve this is unclear. This horizon scanning article explores the potential for neutrophil gelatinase-associated lipocalin (NGAL) to detect AKI and how this could translate to community settings.

ADVANTAGES OVER EXISTING TECHNOLOGY
The traditional biomarker of creatinine has several important limitations. Creatinine is a product of muscle breakdown and therefore several non-renal factors also influence its concentrations, compromising its performance as a surrogate marker, including age, sex, muscle mass, muscle disease, metabolism, and diet. Further, creatinine is a suboptimal indicator of acute changes in kidney function as studies have shown that >50% of renal function may be lost before creatinine rises are detectable above the upper reference limit. And it is of particular concern that it may not be useful until steady-state equilibrium has been reached, which may not occur until days after injury. Rapid detection and early intervention in AKI can significantly improve outcomes. A number of renal tubular damage-specific biomarkers have emerged in recent years, which could diagnose AKI earlier, as well as facilitate differential diagnosis of structural and functional kidney injury. NGAL, a small polypeptide, is one of the most promising and best-studied AKI biomarkers. The majority of NGAL, secreted by injured renal tubule epithelial cells, is in a 25kDa monomeric form. In contrast, neutrophils have been claimed to release NGAL primarily as a 45kDa homodimer, that is, two NGAL monomers linked by a disulfide bridge. In good health, there are only low levels of NGAL detectable in urine. Immediately following acute kidney injury, NGAL is substantially upregulated in the distal part of the nephron leading to increased urinary and plasma NGAL levels. Reduced reabsorption from the proximal tubule in the setting of tubular injury may also potentiate the increased NGAL levels in urine. NGAL is easily detected in blood and urine due to its small size and resistance to degradation. Furthermore, NGAL concentration in both urine and plasma rises rapidly in a dose-dependent manner that is proportional to the degree of acute kidney damage and is detectable at a point where injury is still potentially limitable and reversible. Therefore, NGAL may enable prospective diagnostic and prognostic stratification in the primary care setting.

DETAILS OF TECHNOLOGY
A variety of assays are currently available for the measurement of NGAL in both urine and blood. Three CE-marked clinical analytical platforms that deliver a result in <1 hour, using either urine or plasma, were identified. All are yet to obtain US Food and Drug Administration approval for diagnostic use.

PREVIOUS RESEARCH
The clinical NGAL assays have been tested in various clinical settings, including following cardiac surgery, in critical care, and in the emergency department (ED). However, no studies performed in primary care were identified. Cardiac surgery as a setting presents the advantage that the...
time point of injury is known. Most of these studies showed NGAL both in the blood and urine to be a good early predictor of AKI, although areas under the receiver operating characteristic curves (AUC) have varied between 0.65–0.998 for urine and 0.64–0.98 in plasma. NGAL measurement significantly improved risk prediction over the clinical models alone. Several studies also revealed that both elevated plasma and urine NGAL levels are associated with longer length of hospital stay, severity and duration of AKI, and higher risk of adverse outcomes, including renal replacement therapy or death.10–12

In contrast with cardiac surgery patients, critically ill patients with AKI and those admitted from the ED have a timing of renal insult that is less clear. This makes it difficult to interpret an elevated NGAL result, in particular in the presence of sepsis and, as a result, AUC varied more widely in these studies (between 0.48–0.98 in urine and 0.53–0.92 in plasma). A single-centre prospective study involving 635 patients admitted to an ED assessed the use of NGAL for emergency admissions. A single measurement of urinary NGAL, obtained at presentation, distinguished normal kidney function from intrinsic AKI, prerenal azotaemia, and non-progressive chronic kidney disease (CKD), with an AUC of 0.95, sensitivity of 99%, and specificity approaching 100%.13 These results were validated in another study involving 616 ED patients. In this study plasma NGAL values taken at 12 hours after hospitalisation reliably distinguished intrinsic AKI from normal function (AUC 0.85), transient azotaemia (AUC 0.73), and CKD (AUC 0.82).14 The concept of NGAL cut-off values was examined in this study. A distinct plasma NGAL cut-off values for differentiating between AKI and non-AKI could not be identified. Instead, a grey zone of plasma NGAL concentrations (97–133 ng/mL) that was associated with a moderate risk for AKI was identified. Patients who had plasma NGAL concentrations >133 ng/mL were found to have a 10-fold greater risk of AKI,14 which in combination with a clinical presentation suggestive of AKI is sufficient to triage and manage these patients as having true intrinsic AKI. Patients whose plasma NGAL levels fall within the ‘grey zone’ and who have clinical AKI risk factors should also be considered at high risk for intrinsic AKI.

It should be noted that the diagnostic ability of NGAL in these clinical studies is dependent on the reference standard used to detect the diagnostic outcome. Using a diagnosis of AKI based on creatinine may not be an accurate measure of kidney injury.

WHAT THIS TECHNOLOGY ADDS

Based on the current evidence both urine and plasma NGAL measurement improve the prediction of AKI risk over the clinical model alone. NGAL correlates with severity of AKI and can predict poor outcomes. With regards to urine versus plasma NGAL, the availability of biofluid and the assay used are likely to be the key determinants. However, once biomarkers of tubule damage are fully established, markers of renal function, such as creatinine, are likely to remain relevant for diagnosing and quantifying loss of excretory function and prognosis.

SUGGESTED NEXT STEPS

Studies on the predictive value, suitability, and utility of NGAL testing for AKI and CKD management are required in primary care settings. NGAL has multiple molecular forms, and a clinical test method that can clearly distinguish between these two NGAL forms will undoubtedly be key to enhancing sensitivity for the purpose of monitoring renal and/or vascular integrity.

It is also worth noting that there is no specific cut-off value for NGAL above which AKI can be diagnosed, and these cut-offs may be different in primary care. The lack of a reference standard AKI definition and differences in clinical assay characteristics are additional limitations to the widespread use of NGAL in clinical practice at the present time.

Methodology

Standardised methodology was applied in writing this report, using prioritisation criteria and a comprehensive, standardised search strategy and, critical appraisal. The search for this article was conducted in July 2015.

Funding

This article presents independent research funded by the National Institute for Health Research (NIHR) Diagnostic Evidence Co-operative Oxford. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. The study sponsors had no role in the design, analyses, or reporting of the study. The researchers retained complete independence in the conduct of this study.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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