The impact of biomarkers of acute kidney injury on individual patient care

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ABSTRACT

Acute kidney injury (AKI) remains a common clinical syndrome associated with increased morbidity and mortality. In the last several years there have been several advances in the identification of patients at increased risk for AKI through the use of traditional and newer functional and damage biomarkers of AKI. This article will specifically focus on the impact of biomarkers of AKI on individual patient care, focusing predominantly on the markers with the most expansive breadth of study in patients and reported literature evidence. Several studies have demonstrated that close monitoring of widely available biomarkers such as serum creatinine and urine output is strongly associated with improved patient outcomes. An integrated approach to these biomarkers used in context with patient risk factors (identifiable using electronic health record monitoring) and with tests of renal reserve may guide implementation and targeting of care bundles to optimize patient care. Besides traditional functional markers, biochemical injury biomarkers have been increasingly utilized in clinical trials both as a measure of kidney injury as well as a trigger to initiate other treatment options (e.g. care bundles and novel therapies). As the novel measures are becoming globally available, the clinical implementation of hospital-based real-time biomarker measurements involves a multidisciplinary approach. This literature review discusses the data evidence supporting both the strengths and limitations in the clinical implementation of biomarkers based on the authors' collective clinical experiences and opinions.

Keywords: acute kidney injury, biomarker, patient outcome, renal replacement therapy

INTRODUCTION

The last 15 years have seen significant investigations into the performance of new biomarkers of acute kidney injury (AKI). This work has been aided by the development and

standardization of consensus definitions of AKI [1–4]. As the size and scope of investigations of novel biomarkers of kidney injury have increased, several novel biomarkers (biochemical and electronic) have been developed. While these new measures have not made their way into the definition of AKI, globally there are several clinically available biomarkers. This is a narrative review dedicated to discussing recent literature around traditional and novel biomarkers of AKI as well as the common issues and pitfalls that occur when implementing a new clinical assay. The discussion delineates the strengths and limitations related to the integration of markers (both old and new) into practice. Innovative incorporation of novel diagnostics may lead to more personalized care for AKI and inform the next generation of AKI surveillance.

THE TRADITIONAL MARKERS: SERUM CREATININE AND URINE OUTPUT AS BIOMARKERS OF AKI

Serum creatinine (SCr) and urine output (UOP) have been known to be biomarkers of kidney function for >120 years [5]. Their inclusion in internationally recognized consensus definitions has furthered our knowledge of AKI and enhanced our understanding of these functional biomarkers [1–3]. These standardized definitions have both informed the epidemiology of AKI as well as the renal and nonrenal outcomes of those with all stages of AKI. Despite the development of novel biomarkers of AKI to improve upon the earlier recognition of AKI risk, SCr and UOP remain informative tests and are required to diagnose and stage AKI [4].

SCr—upgrading the operational standard of care

Although the limitations of SCr evaluation are extensively documented, SCr remains the universally recognized (and accessible) standard of care for AKI evaluation. Checking SCr levels regularly in hospitalized patients [ward and intensive care

FIGURE 1: The Renal Angina Index (RAI) represents a risk stratification tool for the development of persistent severe AKI. The RAI consists of the product of risk and injury strata, where the risk strata include weighted clinical information about the patient and the injury strata include weighted scores based on changes in SCr and the degree of FO. Patients with an RAI ≥ 8 have been shown to be at the highest risk for the development of severe AKI. While most of the data around the RAI have been based on pediatric patients, it has shown promise in adults but requires further validation [13].

unit (ICU)] has been shown to identify more cases of AKI compared with sporadic SCr checks; daily checks also identify AKI events earlier and may mitigate AKI risk in high-risk patients [6]. Inclusion of all measurements and changes in SCr in the mathematical construct of kinetic estimated glomerular filtration rate (KeGFR) offers insights into the trajectory of filtration injury or recovery [7]. Adjustment of the KeGFR for total body volume, often significantly labile in critically ill patients, may further refine the prognostic value of this methodology [8]. While some have argued that this lability is due in part to the loss of muscle mass that occurs in hospitalized patients receiving daily SCr measures, an increase in KeGFR for >12 –48 h is much more likely to signify improvement of AKI over a loss of muscle mass [9]. Similarly, several reports demonstrate the importance of correcting SCr for total body water (adjudicated by net fluid balance) when ascertaining AKI status [10, 11]. While KeGFR along with other novel real-time measures of GFR [12] have been more extensively studied in recent years, these tools have yet to be widely validated or approved for clinical use in ward or ICU patients.

Risk prediction models can be created using changes in SCr. Several models have been derived in pediatric populations for the purposes of predicting AKI and for tracking the progression of kidney injury. The renal angina index, initially validated in nearly 600 patients, has been validated in several recent reports to provide a practical, easy-to-implement bedside predictive tool on the day of ICU admission for severe AKI on ICU Day 3 (Figure 1) [13–19]. While the majority of renal angina investigations have been performed in critically ill pediatric patients, it has shown promise in adults as well [13]. A continuous

AKI tracking score using SCr, more detailed than an organ-specific injury score, can identify patients as they change during their ICU course (versus prediction of initial AKI event only) [20, 21].

There have been several recent efforts to embed SCr-based risk scores within the electronic medical record (EMR). A recent systematic review found 11 different prediction models for hospital-acquired AKI specifically in general hospital patients (non-ICU). These risk models provided areas under the curve (AUCs) that ranged from 0.71 to 0.80 in their derivation cohorts and 0.66 to 0.80 in their validation cohorts. However, to date, none of the models discussed in this review have been widely adopted or externally validated in subsequent papers [22]. More recently, Malhotra *et al.* [23] performed a multicenter development ($n = 573$) and validation ($n = 1300$) study for an AKI risk prediction score for patients specifically in the ICU (Table 1). The score, which uses values from within 48 h of ICU admission, was devised to predict the development of Kidney Disease: Improving Global Outcomes (KDIGO)-based AKI. The model provided an AUC of 0.79 [95% confidence interval (CI) 0.70–0.89] for the derivation cohort and 0.81 (95% CI 0.78–0.83) in the validation cohort [23].

Separately the AKI-123 score was developed to account for the changing status of critically ill patients and is comprised of data from four different time points around the time of ICU admission and beyond [24]. This dynamic score was built to detect any stage AKI during the first 7 ICU days (AKI-123) as well as the development of Stages 2 and 3 AKI within the first week (AKI-23). The AKI-123 score provided an AUC of 0.75 (95% CI 0.75–0.75) while the AKI-23 score was slightly more

effective at 0.77 (95% CI 0.77–0.77) [24]. This AKI prediction model is publicly available at <http://akipredictor.com/en/>.

SCr can be integrated into automated models of AKI detection to facilitate identification of patients. Kashani *et al.* [25] developed and validated an SCr-based AKI sniffer in two independent retrospective cohorts of ICU patients [26]. Their automated electronic algorithm was able to reliably detect ICU-based AKI and provided a sensitivity and specificity of 88% and 96% in their 462-patient validation cohort. This was not the first study to use or develop AKI alerts. In a seminal trial,

Table 1. Malhotra *et al.* [23] AKI risk prediction score

Risk factors	Points
Chronic	
CKD	2
Chronic liver disease	2
Congestive heart failure	2
Hypertension	2
Atherosclerotic coronary disease	2
Acute	
pH ≤ 7.30	3
Nephrotoxin exposure	3
Severe infection/sepsis	2
Mechanical ventilation	2
Anemia	1

A cutoff value of >5 points provided a positive predictive value of 32% and a negative predictive value of 95% [23].

Wilson *et al.* [27] performed an investigator masked, parallel-group, randomized controlled single-center trial where patients with KDIGO Stage 1 AKI were randomized to receive a text-based AKI alert to their covering provider and unit pharmacist indicating a new case of AKI or no alert/usual care. The primary outcome of this study was a composite of relative maximum change in SCr, need for renal replacement therapy (RRT) and death at Day 7. They randomized 2393 patients (1201 to the alert group) and were unable to demonstrate that these alerts led to a difference in the primary (or any other) outcome. There was no difference in the change in SCr ($P = 0.81$), need for RRT ($P = 0.18$) or death (0.40) [27]. Importantly, the alerts in this trial were not linked to any action items or kidney-focused order sets, they solely alerted the health care providers to the presence of AKI and then allowed them to determine their desired care plan.

Since this original publication, there have been several investigations and clinical trials that have utilized electronic alerts that have been linked to kidney-focused care. Table 2 summarizes several of these trials, many of which have demonstrated significantly improved AKI and patient outcomes.

UOP—the noninvasive AKI vital sign

The independent significance of changes in UOP in relation to AKI on patient outcomes has now been reported in multiple populations. Kellum *et al.* [32] demonstrated that intensive monitoring of UOP in hospitalized patients (defined as no gaps

Table 2. Summary of studies investigating electronic AKI alerts linked to action plans

Study	Study design	Size	Results	Limitations
Kolhe <i>et al.</i> [28]	Prospective observational study of AKI care bundle coupled with an AKI alert	2297 patient with 2500 episodes of AKI	The care bundle was only completed in 12.2% of patients within the first 24 h. Completion of the bundle was associated with significantly less severe AKI, less AKI progression and lower inpatient and 60-day mortality	Observational, nonrandomized study
Park <i>et al.</i> [29]	Before and after quality improvement study of AKI alert system with option for automated nephrology consults	1884 patients in the before group and 1309 in the intervention (after) group	AKI alert led to less overlooked AKI, defined as the absence of a follow-up SCr within 2 weeks of the original AKI. Despite being sicker, those in the intervention phase less likely to develop severe AKI and more likely to recover their SCr to within 20% of baseline	Nonrandomized, single-center data. There were clear differences between the before and after groups. The AKI alert was not always real time sometimes delayed several hours
Hodgson <i>et al.</i> [30]	Controlled before and after study across two hospitals (one with intervention and one without)	30 295 acute medical admissions across two distinct 10-month periods	In the intervention period, a clinic prediction rule (CPR) flagged both patients at high risk for the future development of AKI as well as those with early AKI. Doctors for the flagged patients also received alerts with attached AKI care bundles. They demonstrated a difference in hospital-acquired AKI (HA-AKI) in the intervention hospital. There was also decreased inpatient mortality in the HA-AKI. There was no change in any outcomes for those with community-acquired AKI	Nonrandomized data. The CPR (risk assessment) was reliant on diagnosis codes
Selby <i>et al.</i> [31]	Multicenter, pragmatic stepped-wedge cluster randomized trial of a multifaceted intervention (AKI e-alert, AKI care bundle and education program)	24 059 AKI episodes across five hospitals	Over the intervention period, there was no change in 30-day mortality. Hospital length of stay was reduced over the course of the intervention period. There was improved AKI recognition and AKI care (e.g. medication reconciliation)	Strict reliance on SCr-based AKI. Some portions of the intervention may not be generalizable outside of the National Health Services in England

in UOP data for >3 h) leads to not only improved AKI detection, but also less cumulative fluid balance. This decrease in positive fluid balance reduced the incidence of fluid overload (FO; 2.49% compared with 5.68%; $P < 0.001$) and improved survival in those who do develop AKI [33]. While this single-center retrospective cohort study demonstrated a link between UOP monitoring and AKI outcomes, it defined AKI based on the KDIGO criteria. Recently a retrospective cohort study demonstrated that a cutoff of <0.3 mL/kg/h of intraoperative UOP was associated with increased odds of SCr-based AKI [34]. While this novel cutoff needs to be prospectively validated, there is increasing evidence of the importance of close UOP monitoring and its impact on patient care in those at risk for AKI. The largest pediatric AKI epidemiology study to date identified oliguria-defined AKI as not only associated with high morbidity and mortality, but also was alarmingly unrecognized. Failure to account for UOP would miss approximately one in three children with AKI and these children suffered poor outcomes both without SCr-based AKI (mortality 7.8% versus 2.9%; $P < 0.001$ for oliguria versus no AKI patients) and synergistically with an SCr-based AKI definition (mortality 38.1%; $P < 0.001$) [35, 36]. Similar results were shown for adult ICU patients [32].

Outside of traditional monitoring of UOP, the advent of the furosemide stress test (FST) has led to increased recognition of the importance of UOP in those with early AKI. The standardized FST was first published by Chawla *et al.* [37], who demonstrated that monitoring UOP in the first several hours following a protocolized dose of furosemide (1.0 mg/kg loop diuretic naïve and 1.5 mg/kg in those with prior exposure) in patients with euvolemic or hypervolemic Stage 1 or 2 AKI can help to determine the risk of progression to Stage 3 AKI. They demonstrated that those with <200 mL of UOP total in the first 2 h following furosemide administration were at increased risk of AKI progression. The 2-h urine volume provided an AUC of 0.87 [standard error (SE) 0.05] and this 200 mL cutoff provided a sensitivity of 87.1% and a specificity of 84.1%. Since this original publication, the same investigative group has published a separate prospective validation mirroring these original findings [38]. Others have also validated the utility of monitoring UOP following a dose of loop diuretics in the setting of early AKI in pediatric cardiac surgery [39, 40], adults undergoing deceased donor kidney transplantation [41] and mixed medical and surgical ICU cohorts [42].

Additionally, the FST has been paired with more novel biomarkers of kidney injury [neutrophil gelatinase-associated lipocalin (NGAL) and tissue inhibitor of metalloproteinase-2–insulin-like growth factor binding protein 7 (TIMP2*IGFBP7)]. Pairing a functional marker of nephron capacity with injury biomarkers led to a more accurate assessment of severe AKI risk in patients with early AKI [42, 43]. This pairing of two classes of biomarker highlights the synergistic capabilities of these new tests, especially when one considers that patients in these FST cohorts already had Stage 1 or 2 AKI, potentially diminishing the power of these biochemical damage biomarkers that have the ability to detect AKI earlier than SCr and UOP.

Recently the FST has been investigated as a potential trigger to initiate RRT as part of a prospective randomized trial [44]. In this prospective randomized feasibility trial, only 6 of 44 patients who passed their FST (14%) went on to require RRT during their hospital admission, compared with 75% (45/60) in the control arm. Thus in this trial the FST served as a biomarker for severe AKI risk and provided insight into how readily available biomarkers such as SCr and UOP can be harnessed to improve AKI risk stratification [44]. Finally, the appreciation of quantifiable ‘fluid overload’ as an independent risk factor for patient outcome (particularly in children) has elevated net fluid balance as an important AKI biomarker and potential modifiable risk factor [11, 45–48].

While the FST examines tubular integrity in the setting of early AKI, other investigators have similarly sought to examine the ability of the kidneys to handle stress as a marker/risk assessment tool for the future development of AKI. In a prospective cohort study of 110 patients with normal GFRs undergoing elective cardiac surgery, Husain-Syed *et al.* [49] measured renal functional reserve (RFR) utilizing a preoperative high (1.2 g/kg of body weight) oral protein load to determine the kidney’s ability to hyperfilter in response to the protein load. RFR was defined as the difference between a baseline and protein loading GFR, with a normal RFR being defined as ≥ 30 mL/min/1.73 m². Fifteen patients (13.6%) developed KDIGO AKI. Preoperative RFR predicted the development of AKI, with AKI being more likely in those with lower RFR (mean $\pm$ SE, 27.0 ± 8.6 versus 15.5 ± 5.9 ; $P < 0.001$). The RFR provided an AUC of 0.83 (95% CI 0.70–0.96) for the development of postoperative AKI with patients with an RFR < 15 mL/min/1.73 m² having an 11.8-fold (95% CI 4.6–29.9) increased risk of developing AKI [49]. Thus, as in the FST, the ability of the kidney to respond to a physiologic stress, even in the pre-operative setting, can predict the future development of AKI.

Although nascent, the increasing incorporation of UOP into prognosis and diagnosis offers the potential to noninvasively track renal injury. EMRs can and should be leveraged for this purpose [50]. More importantly, urine quantification (with or without the context of diuretic therapy) is universally available and performable as practical bedside monitoring for AKI (particularly in resource-limited settings).

INTEGRATION OF AKI: MONITORING TO TARGETING

As discussed above, UOP and SCr are functional biomarkers of AKI. They have multiple limitations, particularly for the purpose of AKI prediction. SCr has a low sensitivity, as SCr levels only increase if $>50\%$ of the GFR is lost. Conversely, UOP has a low specificity, as this marker of functionality can decrease secondary to several factors. SCr interpretation is also particularly difficult in children—patients for whom normative data are frequently imputed vary greatly by age and gender and often demonstrate marked variation based on the method of measurement. Based on these limitations, research efforts have focused on identifying new biomarkers with changes in concentration detectable before UOP declines and/or SCr increases [51–54]. Additionally, biomarkers specific for location or

FIGURE 2: The Acute Dialysis Quality Initiative consensus delineated criteria for defining AKI in terms of changes in biomarkers of renal function (SCr, UOP) and biomarkers of kidney damage/injury. This paradigm allows for the combination of injury biomarkers with SCr and has proven useful in the discrimination of patients with AKI. Additionally, it has led to the generation of novel cohorts of those with ‘subclinical AKI’. Subclinical AKI has been repeatedly defined as the significant increase in kidney damage biomarkers that occurs in the absence of a significant change in functional biomarkers (SCr, UOP), thus not meeting the current criteria for consensus definitions of AKI. Adapted from Endre *et al.* [56].

pathophysiology of injury may improve the actual definition of injury, that is, they may refine the ‘AKI phenotype’ [55]. Finally, recent studies have demonstrated that AKI biomarkers can detect ongoing injury within the kidney without a significant change in functional biomarkers (e.g. increasing creatinine or a decrease in UOP) (‘subclinical AKI’) [51, 52] (Figure 2). Different AKI biomarkers may identify different mechanisms of injury and can potentially differentiate specific aspects of kidney function (e.g. tubular damage, drop in filtration).

Given the increased dimensionality of diagnosis potentially afforded by the incorporation of biomarkers, it is reasonable to anticipate the ability of biomarkers to identify specific therapeutic targets for intervention. Taken together, the incorporation of biomarkers may move the needle from simply assessing ongoing AKI to prediction, monitoring, targeting and personalized AKI medicine (e.g. initiating vasoactive medications in cirrhotic patients with relative hypotension, de-escalation of fluid resuscitation in patients with adequate hemodynamics and more aggressive drug dose monitoring strategies in patients receiving aminoglycosides or vancomycin).

Despite promising results for prediction of AKI and early detection, biomarker integration into practice has remained slow. A primary barrier to integration remains the need to identify the clinical need to be filled by an additional test or series of tests. Given the paucity of options to treat AKI itself, the justification for a new series of diagnostic evaluations must be balanced by the relative clinical value added. Identification of goals

of care in the nonacute and acute care setting in the setting of data identifying AKI rates and associated outcomes at a given institution or medical center can provide the indication for a change in practice. Identification of champions (advocates) from critical care, nephrology, emergency medicine, laboratory medicine and pharmacology who are able to work together to develop guidelines for integration, use and monitoring of novel biomarkers is necessary. These basic steps obviate and supersede the ‘lack of a cure’; for reference, mortality secondary to acute coronary syndrome declined in the mid-1960s not secondary to the advent of coronary bypass surgery or clot-dissolving medications or stents, but rather the identification of risk factors for heart disease, the development of coronary care units and the introduction of a test specific for myocardial ischemia (creatinine kinase). Pathophysiology and several limitations of measurement and interpretation must also be addressed. The most important problem is the lack of sensitivity and specificity related to the etiological heterogeneity of AKI. Performance of AKI biomarkers was best when well-defined kidney injury, such as after particular operations, was investigated [57]. In contrast, the performance of biomarkers was less effective in more heterogeneous populations with variable onset of AKI. The use of biomarkers in the context of a risk stratification system such as the renal angina index (Figure 1) may increase the specificity and positive prediction for AKI [14]. Additionally, Martensson and Bellomo [58] recommended the use of biomarker panels instead of single molecules to increase

the robustness of predicting postoperative AKI. This is similar to the approach discussed in the section about the FST [42, 43], but it is important to remember that using multiple new biomarkers does not exclude the importance of continued SCr and UOP monitoring, as modern tests may have false positives and false negatives and older functional biomarkers remain clinically relevant. However, modern biomarker panels may elucidate more aspects of AKI—including severity and timing of AKI—enriching the specificity for AKI phenotype discovery and decodifying to some extent the marked heterogeneity of the AKI syndrome.

The two markers with the most extensive study to date are TIMP2*IGFBP7 and NGAL. Initial promising studies of excellent discrimination and prediction by NGAL have been tempered by more recent reports identifying marginal performance adjudicated by the presence of existent chronic kidney disease, timing of assessment and level of patient heterogeneity [59–61]. Additionally, existing reported data on NGAL performance relies on the measurement of a single isoform of the molecule, whereas multiple isomeric forms exist in both serum and urine. The upregulation of NGAL genetic and protein expression in response to critical illness also limits the specificity of NGAL for AKI itself, as several systemic injury syndromes such as sepsis, acute respiratory distress syndrome and malignancy demonstrate increased circulating NGAL levels.

Several large, multicenter adult studies have validated the utility of TIMP2*IGFBP7 for identifying renal stress [26, 62, 63]. Renal stress is a novel term that has been used to describe the preinjury state of a kidney that is highly susceptible to impending damage, and biomarkers may be clinically apparent in these times of vulnerability to injury [64]. TIMP2*IGFBP7 appears to be one such stress biomarker and resultantly demonstrates solid positive predictive value for risk of AKI and major adverse kidney events (death, the need of RRT or persistent renal dysfunction) [25] and also high negative predictive value for the absence of AKI [62, 65]. Table 3 covers several of the limitations of TIMP2*IGFBP7 testing.

Combining functional and damage biomarkers identifies patients with creatinine elevation with functional or reversible injury with high predictive specificity compared with creatinine alone [66]. Additionally, the phenotype of ‘subclinical’ AKI can be identified—patients who never develop a significant change in functional biomarkers (e.g. creatinine elevation or oliguria) but who have elevation of stress or damage biomarkers are at increased risk for poor ICU and renal outcomes (length of stay

prolongation, increased requirement of RRT, higher rate of death). While this concept of ‘subclinical AKI’ remains somewhat controversial, when investigated it has repeatedly been shown to exist. Several studies have demonstrated that biomarker-positive SCr/UOP-negative patients are at increased risk for adverse outcomes (Figure 2). This has held true regardless of the biomarker investigated (e.g. NGAL, TIMP2*IGFBP7, kidney injury molecule-1) or the patient cohorts (single-center versus multicenter studies, emergency department cohorts versus mixed medical and surgical ICUs) [51, 52, 67, 68]. Elevated biomarkers of kidney injury appear to be highly associated with adverse patient outcomes even in the absence of changes in SCr or UOP (e.g. Stage 1 AKI). As such, further investigation of this phenomenon seem warranted and the implications of these elevations should not be clinically ignored as merely ‘false positives’.

A biomarker panel may facilitate simultaneous patient monitoring and targeting. This approach is utilized for management of respiratory failure. Progressive respiratory distress is assessed, managed and treated in a sequential, iterative way using multiple diagnostic inputs ranging from physical exam, radiography, blood gas assessment and capnography to pulse oximetry. These markers are used over time (and in the context of global stability) and in concert with one another to personalize the approach to a patient. Interventions have concurrently evolved over time, spanning the breadth of specific support for impairments in oxygenation, ventilation, secretion load, bronchospasm, etc. A dynamic diagnostic approach to AKI, mirroring the approach to critical illness in general (not just respiratory disease), integrating multiple inputs along the trajectories of critically ill patients, could ultimately lead to more precise and effective therapeutic options. With SCr and UOP serving as the overall markers of renal health (essentially the pH and partial pressure of oxygen on an arterial blood gas), TIMP2*IGFBP7 may identify varying levels of renal stress, serving akin to a kidney equivalent of lactate for homeostasis. The aforementioned FST and RFR can be utilized as a functional capacitance marker, identifying the amount of reserve left in the renal system. Sequential urinary NGAL measurements may identify renal tubular epithelial cell dysfunction, similar to the imputation of alveolar epithelial functionality determined by an arterial partial pressure of carbon dioxide (pCO₂) [69]. Finally, incorporation of the percent FO (FO%) into the calculus may serve as a real-time assessment of compensation in relation to AKI, similar to the base excess or deficit equivalent. In total, a combined and multifaceted AKI biomarker composite may be created allowing a pragmatic and trackable set of markers, theoretically refining the understanding of ongoing renal insult compared with any of the markers in isolation (Figure 3). Although not yet operationalized, this approach on a marker-to-marker level merits sufficient theoretic background for investigation and if true would, at the very least, delineate individual severity and FO AKI phenotypes.

Many unknowns related to biomarker interpretation remain and questions exist requiring further investigation. Normal biomarker value for the age of the patient (problematic at the ends of the age spectrum), adjudication of concentration for context

Table 3. Limitations and unapproved uses of TIMP2*IGFBP7

- The test is validated for use in critically ill and ICU patients at high risk for severe AKI. This does not include ambulatory patients or low-risk patients (medical or surgical).
- There are limited published data on its use in those <18 years old.
- Not for use in patients with established severe KDIGO AKI (Stage 2 or 3).
- Should not be used to replace SCr or UOP measurement.
- Nephrotic range proteinuria will invalidate the assay results, with lower degrees of proteinuria leading to assay interference.
- Bilirubinuria >7.2 g/dL will interfere with the assay results.

FIGURE 3: A theoretical parallel can be constructed to integrate available markers of renal function in the adjudication of AKI status and progression. Similar to an arterial blood gas used to assess cardiopulmonary stability, an AKI biomarker composite integrates a marker of homeostasis (UOP), filtration (SCr), tubular damage (NGAL), renal reserve (FST, RFR), renal compensation (FO%) and stress (TIMP2*IGFBP7). BD/BE, base deficit/base excess

and concurrent illness, correction for urinary creatinine or protein concentration, serum versus urine value, timing of measurements and reliance on single versus sequential markers are but a few of the issues requiring attention. However, there are emerging data that for TIMP2*IGFBP7 there may be a utility in serial biomarker measurements in response to nephrotoxin exposures [70]. The clinical relevance of identifying AKI in the absence of directed, functional and effective therapy also limits enthusiasm from those who believe AKI is a ‘fait accompli’. In the absence of randomized controlled trial data comparing the biomarkers to SCr or UOP or each other, critical care providers and nephrologists must adjudicate observational data to determine if the integration of single or multiple biomarkers into practice is ‘best practice’. Although this review is narrative and not systematic and the discussion has been limited to a selection of positive reported biomarker data, the balance of available observational data (evaluation of positive versus negative results) suggests that biomarkers add value for early recognition and risk stratification in the AKI syndrome. The continued study of biomarkers and how they can best be integrated into practice is certainly pursued.

PERSONALIZED AKI MANAGEMENT—THE NEXT STEP

Prevention of AKI

In recent years, several trials have been performed investigating different measures to prevent AKI. However, all the preventative trials were negative, as in these trials the therapy was often implemented after a significant decline of kidney function had already occurred. In contrast, biomarkers help to identify a kidney injury without a loss of function, making it possible to

start therapy earlier. This opens the door for individualized and tailored AKI therapy.

The KDIGO guidelines suggest implementing of bundle of supportive measures in patients at high risk for the development of AKI. This bundle includes maintenance of volume status and perfusion pressure (mean arterial pressure >65 mmHg), maintenance of normoglycemia (avoidance of prolonged hyperglycemia: ≥ 150 mg/dL for >3 h), monitoring of SCr and UOP, functional hemodynamic monitoring, discontinuation and avoidance of nephrotoxic agents (including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers within 48 h after cardiac surgery) and the use alternatives to radio contrast agents [2]. Until recently it has not been shown that implementing the KDIGO bundle improves renal outcomes. However, a recently published single-center, Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial showed that TIMP2*IGFBP7-guided implementation of the KDIGO guidelines as compared with standard care significantly reduced the AKI rate in cardiac surgery patients [absolute risk reduction 16.6% (95% CI 5.5–27.9); $P = 0.004$] [71]. In contrast to previous studies, this study used an individualized approach, because the authors started the intervention when a kidney injury was present without waiting until a change in a functional marker of AKI was present. A study with a similar design in patients undergoing major abdominal surgery confirmed the benefits of biomarker-guided KDIGO care bundles [72]. Table 4 provides examples of potential components of a postoperative AKI KDIGO-based care bundle based on the published literature. Importantly, despite the promise of these studies, they remain limited in that they require multicenter validation and data

Table 4. Potential components of a KDIGO-based postoperative AKI care bundle

<ul style="list-style-type: none">• Avoidance of nephrotoxic agent• Discontinuation of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for the first 48 h after surgery• Close monitoring of SCr and urinary output• Avoidance of persistent hyperglycemia (≥ 150 mg/dL for >3 h) for the first 72 h after surgery• Consideration of alternatives to radio contrast• Utilization of balanced crystalloid solutions over hyperchloremic 0.9% saline• Close hemodynamic monitoring by using a prespecified algorithm during the first 12–24 postoperative hours with specific hemodynamic parameters that trigger the use of intravenous fluids and/or vasoactive medications• Early nephrology consultation

Combined from KDIGO [2], Meersch *et al.* [71] and Gocze *et al.* [72].

from postoperative patients cannot be readily extrapolated to other patient populations; however, emerging alternative treatment strategies are being investigated [68, 73]. Additionally, implementation of a KDIGO care bundle is not an insignificant process, as the costs involved, in terms of increased monitoring or nephrology-based care, may be prohibitive in several situations, and as such a protocol that identifies high-risk patients through biochemical or electronic biomarker that then triggers a nephrology-focused care bundle may turn out to be the ideal strategy.

The next generation—automated detection and AKI clinical decision support

Finally, several groups have begun harnessing the full power of the EMR to help identify patients at risk for AKI regardless of hospital location (ICU or ward). Koyner *et al.* [74] used 121 158 individual admissions to develop and validate a machine learning prediction model of SCr-based AKI. The model was able to predict the development of Stage 2 AKI [within the next 48 h with an AUC of 0.84 and 0.85 (95% CI 0.85–0.85) for patients on the wards and ICU, respectively. Additionally, it predicted the need for RRT in the next 48 h with an AUC of 0.96 (95% CI 0.96–0.96) across all hospitalized patients [74]. Similarly, Wilson *et al.* [27] used data from their aforementioned AKI alert trial in combination with uplift algorithms/modeling to improve and personalize AKI alert targeting [75]. They demonstrated that older adults, women and those who were admitted/randomized at lower SCr levels with slowly developing AKI are most likely to receive high uplift scores [75]. While these techniques are beyond the capabilities of most institutions, they offer a glimpse into the future where AKI risk scores are dynamic, tailored to an individual hospital's patient population and calculated in real time based on data from the EMR.

In addition to the development of these risk models, others have investigated patient outcomes utilizing decision support care algorithms in the setting of AKI [76, 77]. In a 13-month prospective cohort study of patients in an academic medical ICU, the impact of a decision-making algorithm in patients with AKI was assessed. The algorithm provided recommendations about the optimal indications for starting and stopping RRT. Compliance with the algorithm was associated with improved patient outcomes; those whose clinicians adhered to the

protocol had lower in-hospital mortality (42% versus 63%; $P < 0.01$) as well as lower 60-day mortality ($P < 0.01$) [77]. The most common reasons from deviating from the protocol were expected renal recovery, which occurred in nearly half of the 105 patients in whom RRT was recommended but not performed [77].

Separately, a multicenter, sequential period analysis of 528 108 patients from 2012 to 2015 was conducted to determine whether the use of a different clinical decision support system (CDSS) improved AKI patient outcomes (length of stay, inpatient mortality) [76]. In this before and after study, they found that the CDSS resulted in a small sustained decrease in mortality [odds ratio 0.91 (95% CI 0.86–0.96); $P = 0.001$] [76]. Additionally, there was a 0.3 day decrease in length of stay for patients with AKI, but there was no difference in length of stay in those without AKI. Thus implementation of a CDSS resulted in a small but sustained improvement in AKI morbidity and mortality [76]. A pharmacist-driven nephrotoxin surveillance system embedded within the EMR can significantly reduce the exposure of children to nephrotoxins and overall AKI rate [78].

Together, the EMR is a nexus for clinical decision support, targeting AKI management on multiple levels. Proper integration with human factors engineering and the response of the medical team will be paramount to optimal utilization of the EMR. The lack of data discussing how risk prediction, biomarker modeling and human factors integrate has likely handcuffed the integration of biomarkers into care and limited the ability to move the needle. Prospective analyses of the cost:benefit ratio of biomarkers are lacking, although modeled and exploratory analyses do exist [65, 79]. In addition to simple implementation, a feasible and context-specific usability tool must be in place. The applied model of health technology assessment (HTA) is an example of such a tool in action. The HTA is a multidisciplinary process that has the ability to make the case and justify adoption of new health technologies such as biomarkers, provided a short- and long-term benefit for the patients, the payers, the decision makers and the other stakeholders is highlighted. The cost of development and utilization of this model can be easily justified based on the costs of AKI and its consequences in the long term [80]. HTA analysis facilitates rigorous evaluation of results and rapid response strategies to potentially justify the implementation of new information provided by biomarkers toward use in actual patients.

Implementation of a nephrology rapid response team (NRRT) to respond to biomarker elevation demonstrates increased accuracy of risk prediction and ultimately improved outcomes for patients (Figure 4). In a study of TIMP2*IGFBP7 as the study biomarker, integration with an NRRT resulted in increased specificity for AKI prediction and identification and a 10.5% reduction in the overall number of SCr- and UOP-based AKI cases. Furthermore, the number of AKI cases requiring continuous RRT (CRRT) decreased significantly (–18.2%). The value added in this select example is clear, as theoretically a high-reliability system with near real-time usability at the bedside could guide a critical care team [65] (nephrologist in collaboration with the critical care physician) to quickly evaluate a patient for further hydration, diuresis or RRT [81] (Figure 5).

FIGURE 4: This figure demonstrates the reduction in patients with both AKI and more specifically CRRT requiring AKI following the implementation of routine checking of TIMP2*IGFBP7 in concert with a Nephrology Rapid Response Team (NRRT) (Data from Vicenza Hospital only).

FIGURE 5: Flowchart of the NRRT process (reprinted with permission). The first step is to screen adult patients in the critical care setting to triage appropriate high-risk patients for the test. In the NRRT protocol, patients are divided into low, high and very high AKI risk categories. The TIMP2*IGFBP7 test is not necessary for the low- or very high-risk patients. Adapted from Rizo-Topete *et al.* [81].

The metrics of efficacy in this situation would be fewer episodes of AKI, a decrease in the severity of AKI episodes and fewer patients requiring dialysis.

CONCLUSION

In total, the last decade has seen several advances in the detection of and care for patients with AKI. Improved risk scores

and near real-time biomarkers of kidney injury have helped to move the field forward, but they are not yet part of a global standard of care. The data for the utility of biomarkers are a balance of positive and negative results, but more data exist supporting continued and expanded study of these markers—specifically in the manner of integration into practice (versus isolated observational study). Increased incorporation into practice will uncover more questions needing to be addressed, including the ones mentioned and acknowledged in this narrative review. Over the next several years, we anticipate increased use of these new tools as well as the development of the next generation of scores and biomarkers. Additionally, interventions like care bundles and NRRTs will be further validated while other more novel therapeutics continue to be developed and examined. We are entering a golden age of AKI investigation. As we gain more familiarity with these new tools and more physicians gain access to them, we anticipate improved short- and long-term outcomes for patients with AKI.

CONFLICT OF INTEREST STATEMENT

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(See related article by Vanmassenhove and Lameire. Should the novel biomarkers be incorporated in future definitions of acute kidney injury? *Nephrol Dial Transplant* 2020; 35: 1285–1288)

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