Conventional markers of kidney function

Sean M. Bagshaw, MD MSc, FRCPC; R. T. Noel Gibney, MB, FRCP(C)

Acute kidney injury remains a serious clinical problem for intensive care unit patients, and its incidence is rising. The detection and diagnosis of acute kidney injury in the intensive care unit currently require use of conventional markers of kidney function, specifically, serum creatinine and urea levels and, less frequently, other urinary tests. These conventional markers are familiar to clinicians and have long been used at the bedside. However, these markers are clearly not ideal, each has limitations, and none reflect real-time changes in glomerular filtration rate or a genuine acute injurious process to the kidney. More importantly, these conventional markers can contribute to delays in recognition of acute kidney injury and, hence, delays to appropriate supportive and therapeutic interventions. The early detection and diagnosis of acute kidney injury should be a clinical priority. A diagnostic test or panel of tests that are capable of evaluating aspects both of kidney function and acute injury are desperately needed in critical care nephrology. Cystatin C has been shown superior to conventional markers and may assume a greater role in intensive care unit patients for detecting both early changes in glomerular filtration rate and evidence of acute injury. Other newly characterized markers of kidney function or acute injury have the potential to revolutionized the field of critical care nephrology and greatly improve the supportive and therapeutic management of intensive care unit patients with acute kidney injury. (Crit Care Med 2008; 36[Suppl.]:S152–S158)

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Acute kidney injury (AKI) is a syndrome with serious clinical implications for critically ill patients. A diagnosis of AKI remains associated with unacceptably high morbidity and mortality (1–9). More recently, large epidemiologic investigations have indicated that the incidence of AKI is increasing, whereas mortality has only marginally improved (10–12).

This poor outcome is evident despite considerable progress in our understanding of the pathophysiology of AKI and in the dynamics of critical illness. Likewise, survival remains poor even after key developments in the supportive care afforded to critically ill patients (13–16). This relates, in part, to important changes that have occurred in the typical intensive care unit (ICU) patient, who is often older and has more comorbid illness (including chronic kidney disease), leading to diminished physiologic reserve (5). Likewise, the modern ICU patient is sicker and more likely to develop AKI in the context of multiorgan failure or in association with complex diagnostic or therapeutic interventions (e.g., organ transplant, cardiopulmonary bypass) (17).

However, another plausible explanation for this apparent lack of improvement in clinical outcomes associated with AKI is the limited capacity of conventional markers of kidney function for detection of early injury to the kidney. This may explain why novel therapeutic interventions with promise in animal models of AKI have proven disappointing in human clinical trials (18, 19). The diagnosis of AKI in these trials was likely characterized by an important interval from actual time of insult to the clinical recognition of AKI. As such, this may have translated into delay in detection and could be considered in retrospect as a missed opportunity for early intervention at a time before injury had become more established.

This now forms a key dilemma in critical care nephrology. Clearly, the early recognition of AKI is desirable and has both physiologic and clinical sensibility. The hypothesis, yet to be proven, is that the earlier an injurious process to the kidney can be identified, the more likely appropriate preventive (removal of stimulus for injury) or therapeutic measures (fluid resuscitation, renal replacement therapy) can be implemented.

In this article, we discuss the role of conventional markers of kidney function in the detection and diagnosis of AKI.

Ideal Marker of Kidney Function in AKI

An ideal marker of glomerular function (glomerular filtration rate [GFR]) and for detecting AKI for routine use in clinical practice would ideally incorporate several operative qualities (20) (Table 1). An ideal marker would be endogenous, nontoxic, freely filtered at the glomerulus, and excreted unchanged in the urine (i.e., not secreted, metabolized, or reabsorbed by renal tubular cells). Importantly, it would not be influenced by exogenous compounds (i.e., drugs), would be water soluble, and would have minimal protein binding. In addition, such a marker would be easy, rapid, and inexpensive to measure, would use readily available specimens (i.e., urine, serum), and would use standardized assay methods that could easily be applied in clinical practice (i.e., point-of-care testing). It would be a precise and reliable surrogate of GFR and possibly of injury across an array of populations and pathogeneses of AKI and be sensitive for both small changes in function and early injury. Moreover, it would have value for monitoring the course of injury over time

From the Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada.

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For information regarding this article, E-mail: bagshaw@ualberta.ca

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Table 1. Qualities and characteristics of an ideal endogenous marker of glomerular function

Constant rate of production
Water soluble
No protein binding
Freely filtered at glomerulus
No tubular secretion
No tubular reabsorption
No extrarenal metabolism or elimination
Assay precise and reliable
Assay rapid, inexpensive, and widely available

and have some capacity for predicting the trajectory or severity of AKI (i.e., probable need for renal replacement therapy, duration of AKI, renal recovery). Finally, it would be specific to aid in the discrimination and classification of subtypes of AKI. There would be tremendous value to a marker capable of discriminating the precipitant or pathogenesis of AKI. For example, variable expression in AKI associated with cardiopulmonary bypass, sepsis, ischemia, or various nephrotoxins.

Regrettably, no such marker will likely ever fulfill these qualities. More importantly, it is probable that no single marker will be proven to both accurately estimate GFR and indicate injury. The simple analogy to this is cardiac enzymes (i.e., cardiac-specific troponin) as a surrogate marker of cardiac muscle injury in acute myocardial infarction. For example, in the acute phase of myocardial injury, cardiac-specific troponin levels become elevated and are detected in the circulation by assay methods. These cardiac-specific troponin assays are simple to perform, inexpensive, widely available, and perform with high sensitivity and specificity for the detection of acute myocardial injury in patients presenting with symptoms (21). Cardiac-specific troponin levels can be observed to rise and fall in an appropriate time frame with the onset of cardiac injury that further increases their specificity for acute myocardial infarction. Finally, their absolute increase and duration of elevation can also be used as a ballpark surrogate for the severity of injury (22). Measurement of cardiac-specific troponins is now routine and considered standard of care for the diagnosis of acute myocardial injury in the appropriate setting. However, this surrogate marker of injury does not provide any information about changes to overall cardiac function and performance. Additional diagnostic investigations are necessary to evaluate cardiac performance (i.e., clinical examination, echocardiogram, cardiac catheterization). When this analogy is extended to critical care nephrology, the opposite is true. There are crude surrogate markers for GFR, such as creatinine and urea; however, these are not specific for detection of acute injury to the kidney. Overall, an approach that incorporates aspects of both function and injury is desperately needed in critical care nephrology. Newer biomarkers for AKI, such as neutrophil gelatinase–associated lipocalin, kidney injury molecule-1, and interleukin-18, have tremendous potential for the early detection of AKI and will likely have value in future research as triggers for intervention (see "New Biomarkers of Acute Kidney Injury" by Parikh and Devarajan is this issue of *Critical Care Medicine*). However, these new biomarkers will likely not replace conventional measures of kidney function but rather act as complementary for the overall assessment of the kidney in critical illness. For now, this approach certainly merits further investigation.

Therefore, in the end, we will likely be better served by a combination of markers for AKI. These would include many aspects of the aforementioned qualities but also would be capable of appropriately discriminating changes in GFR as a surrogate of function and of detecting an acute, potentially limited injurious process.

Limitations to Conventional Measures of Kidney Function

The diagnosis and etiological classification of AKI, at present, largely depend on the detection of changes in conventional endogenous surrogate markers of kidney function, specifically, serum levels of creatinine (SCr) and urea and, less frequently, other urinary tests. These tests are familiar to clinicians and have long been used at the bedside. Regrettably, however, these markers are not ideal, each has limitations, none reflect real-time dynamic changes in GFR, and none reflect genuine kidney injury. Moreover, these endogenous markers require time to accumulate before being detected in serum as abnormal, thus contributing to a potential delay in the diagnosis of AKI. Although there are other established exogenous serum markers to estimate GFR (e.g., inulin, iothalamate, EDTA, iohexol), their use is complex, expensive, and impractical for routine use in ICU patients. Here, we review in more detail the conventional markers commonly used to measure kidney function.

Serum Creatinine. Creatinine is an amino acid compound derived from the nonenzymatic conversion of creatine to phosphor-creatinine in skeletal muscle and subsequent liver metabolism of creatine through methylation of guanidine aminoacetic acid to form creatinine. Creatinine has a molecular weight of 113 Da, is released into the plasma at a relatively constant rate, is freely filtered by the glomerulus, and is not reabsorbed or metabolized by the kidney. The clearance of creatinine is the most widely used means for estimating GFR, and SCr levels generally have an inverse relationship to GFR (23). Thus, a rise in SCr is associated with a parallel decrease in GFR and generally implies a reduction in kidney function, and vice versa. In contrast to urea, there is no evidence of toxicity caused by accumulation of creatinine in the blood.

There are limitations, however, to the use of SCr as a marker of kidney function (Table 2). First, the production and release of creatinine into the serum can be highly variable. Differences in age, sex, dietary intake (i.e., vegetarian or creatine supplements), and muscle mass (i.e., neuromuscular disease, malnutrition, amputation) can result in significant variation in baseline SCr. Similarly, certain disease states may predispose to variable release of muscle creatinine. For example, in rhabdomyolysis, SCr levels may rise more rapidly due to release of preformed creatinine from damaged muscle or peripheral metabolism of creatine phosphate to creatinine in extracellular tissue.

Second, an estimated 10–40% of creatinine is cleared by tubular secretion into the urine (24). This effect has the potential to hide a considerable initial decline in GFR.

Third, several drugs (e.g., trimethoprim, cimetidine) are known to impair creatinine secretion and thus may cause transient and reversible increases in SCr levels.

Fourth, though less common, there can be factors that reduce the accuracy of SCr assays and lead to artifactual increases in SCr levels. For example, in diabetic ketoacidosis, increased serum concentration of acetoacetate can cause interference with selected assays (i.e., alkaline picrate method) and present a falsely elevated SCr referred to as the *Jaffe reaction* (25). Similarly, some drugs are known to cause similar effects (e.g., cefoxitin, flucytosine).

Finally, as mentioned previously, SCr levels do not depict real-time changes in GFR that occur with acute reductions in

Table 2. Factors affecting conventional markers of kidney function

Serum Marker	Factor	
	Increase	Decrease
Creatinine	Younger age	Older age
	Male sex	Female sex
	Large muscle mass	Protein restriction (renal disease, liver disease)
	Ingestion of cooked meat	Vegetarian diet
	Jaffe reaction (ketotic states, hyperglycemia)	Muscle wasting (neuromuscular diseases, malnutrition)
	Drugs (cimetidine, trimethoprim)	Amputation
	Vigorous exercise	Jaffe reaction (hyperbilirubinemia)
Urea	Decreased effective circulating volume	Aggressive volume expansion
	Increased dietary protein	Pregnancy
	Critical illness (fever, trauma, burns, sepsis)	SIADH
	Gastrointestinal bleeding	Dietary protein restriction
	Drugs (corticosteroids, tetracyclines)	Liver disease
Cystatin C	Older age	Female sex
	Male sex	Lower body mass
	Greater body mass	Immunosuppressive therapy (corticosteroids)
	Smoker	Hypothyroidism
	States of inflammation	
	Hyperthyroidism	

SIADH, syndrome of inappropriate antidiuretic hormone.

kidney function or "acute" injury. Rather, SCr requires time to accumulate before being detected as abnormal, thus leading to a potential delay in the diagnosis of acute changes to GFR or AKI, which are vital to recognize.

Serum Urea. Urea is a water-soluble, low molecular weight (60 Da) by-product of protein metabolism that is used as a serum marker of uremic solute retention and elimination. For chronic hemodialysis patients, the degree of urea clearance has clearly shown correlation with clinical outcome and is used to model hemodialysis adequacy over time. Acute and large rises in serum urea concentration are characteristic of the development of the uremic syndrome and retention of a large variety of uremic toxins (26). The accumulation of urea itself is believed to predispose to adverse metabolic, biochemical, and physiologic effects, such as increased oxidative stress, altered function of $Na^+/K^+/Cl^-$ co-transport pathways important in regulation of intracellular potassium and water, and alterations in immune function (27, 28). In addition, retention of uremic toxins may contribute to secondary organ dysfunction, such as acute lung injury (29).

Similar to SCr, urea levels exhibit a nonlinear and inverse relationship with GFR. However, the use of urea levels to estimate GFR is problematic due to the numerous extrarenal factors that influence its endogenous production and renal clearance independent of GFR (Table 2).

The rate of urea production is not constant. Urea values can be modified by a high protein intake, critical illness (i.e., sepsis, burns, trauma), gastrointestinal hemorrhage, or drug therapy, such as use of corticosteroids or tetracycline.

Relative adrenal insufficiency in septic shock is common, and clinical trials and meta-analyses have suggested that physiologic replacement with low-dose corticosteroid therapy leads to improved surrogate outcomes (e.g., vasopressor therapy withdrawal, shock reversal) and survival (30–34). Accordingly, in ICU patients with septic shock, corticosteroid replacement has become more widely practiced (35). However, such use of corticosteroids in ICU patients will most certainly contribute to an increase in protein catabolism and the overall hypercatabolism of critical illness. In a secondary analysis from a randomized, placebo-controlled trial of high-dose methylprednisolone (30 mg/kg intravenously every 6 hrs × 4 doses) in ICU patients with septic shock, Slotman et al. (36) described marked increases in serum urea in the 7 days after methylprednisolone treatment, despite no changes in SCr.

Thus, those ICU patients with AKI receiving corticosteroids may show large increases in serum urea consistent with uremic solute retention in the absence of a similar rise in SCr. Moreover, this hypercatabolism may be further compounded in AKI by metabolic acidosis–induced stimulation of muscle proteolysis (37). In all, this may contribute to the earlier development of uremic complications and lead to problems in providing adequate nutritional support (38).

Alternatively, ICU patients with chronic liver disease may have near-normal values for urea (i.e., due to decreased production, protein restriction) and SCr (i.e., decreased production due to decreased hepatic creatine synthesis, increased tubular creatinine secretion, or loss of skeletal muscle mass), despite severely reduced GFR and impaired kidney function.

The rate of renal clearance of urea is also not constant. An estimated 40–50% of filtered urea is passively reabsorbed by proximal and distal renal tubular cells. Moreover, in states of decreased effective circulating volume (i.e., volume depletion, low cardiac output), there is enhanced resorption of sodium and water in the proximal renal tubular cells along with a corresponding increase in urea resorption. Consequently, the serum urea concentration may increase out of proportion to changes in SCr and be underrepresentative of GFR. The ratio of serum urea to SCr concentration has, by tradition, been used as an index to discriminate so-called *prerenal azotemia* (PRA) from more established AKI (i.e., acute tubular necrosis [ATN]).

Overall, urea concentration is a poor measure of GFR. It does not represent real-time changes in GFR and requires time to accumulate. Likewise, urea does not reflect true "acute" kidney injury. As such, reliance on urea can lead to potential delays in diagnosis of acute changes to GFR or detection of AKI.

Cystatin C. Cystatin C is an endogenous cysteine proteinase inhibitor of low molecular weight (13,000 Da) that holds many ideal features for use as a surrogate marker of kidney function and estimate of GFR. Cystatin C is synthesized at a relatively constant rate and released into plasma by all nucleated cells in the body (39–41).

The principal catabolic site of cystatin C is the kidney, with >99% freely filtered by the glomerulus. Cystatin C is not secreted or reabsorbed. However, it is nearly completely metabolized by proximal renal tubular cells. As a consequence,

there is little to no detectable cystatin C present in the urine. Thus, a reduction in GFR correlates well with a rise in serum cystatin C level, and vice versa. Serum cystatin C concentrations have demonstrated good inverse correlations with radionuclide-derived measurements of GFR (40, 42).

The diagnostic value of cystatin C as an estimate of GFR has now been investigated in multiple clinical studies and has performed comparably with or superior to that of SCr for discrimination of normal from impaired kidney function (40, 42). In addition, cystatin C may be more sensitive to early and mild changes to kidney function compared with creatinine (43–45).

Recently, estimation equations for GFR based on serum cystatin C levels have been formulated (46, 47). These cystatin C–based estimates of GFR may perform superiorly in selected patient populations, in particular, those with lower SCr concentrations, such as elderly patients, children, renal transplant recipients, those with cirrhosis, and those who are malnourished (48, 49).

Cystatin C is supposedly not influenced by patient age, sex, muscle mass, or changes in diet, but this has recently been challenged. In a cross-sectional study of 8,058 patients, several factors were found to be associated with elevated cystatin C levels, including older age, male sex, greater height, greater weight, current smoking status, and elevated C-reactive protein levels (50). In addition, cystatin C levels may also be influenced by abnormal thyroid function, use of immunosuppressive therapy (i.e., corticosteroids), and the presence of systemic inflammation (50–53).

Unlike SCr and urea levels, cystatin C may have value both for detection of early changes in GFR and as a marker of acute injury to the kidney. First, in a small cohort study of critically ill patients, elevation in serum cystatin C consistent with AKI, defined by a ≥50% increase from baseline, was evident 1–2 days before changes in SCr (54). Second, as previously mentioned, cystatin C is normally not detected in the urine; however, it has been found in the urine in patients with AKI. This suggests urinary cystatin C may be an additional tool for detecting acute injury and potentially quantifying the severity of tubular injury (40, 41). In a small prospective study of critically ill patients with AKI, elevated urinary cystatin C was highly predictive of subsequent need for acute renal replacement therapy and outperformed several other urinary biomarkers (54).

Serum cystatin C levels are now increasingly becoming available due to the development of standardized particle-enhanced nephelometric immunoassays that can provide rapid, precise, and accurate results. The main drawbacks for use of cystatin C at present are a lack of recognition of its potential value for use in ICU patients with AKI and its not being broadly available or inexpensive. Thus, whether cystatin C can be incorporated into routine clinical practice and allow for improvements in the early detection of changes to GFR and AKI and positively affect outcome requires additional investigation.

Urine Output. Urine output via an indwelling catheter is standard practice and routinely measured in ICU patients. Trends in urine volume can be helpful in that continuous output can be used as a crude dynamic gauge of kidney function. Urine output may also be a more sensitive barometer for changes in renal hemodynamics than biochemical markers of solute clearance. The importance of dynamic changes to urine output has been recognized by having been integrated into the RIFLE diagnosis/classification system for AKI (55).

However, urine output in general lacks sensitivity and specificity as a marker of kidney function or acute injury in ICU patients with AKI, in whom free water and solute excretion is impaired. Even ICU patients with severe AKI, characterized by markedly elevated SCr or retention of uremic solutes, can still maintain a normal or elevated urine output.

Measures of Urinary Biochemistry and Derived Indices. Numerous tests of urinary biochemistry (e.g., fractional excretion of sodium [FeNa], fractional excretion of urea [FeU]) have been described as surrogates of renal tubular cell function and traditionally used to aid clinicians in the detection and classification of early AKI, in particular, into PRA and ATN (56–59). Regrettably, although relatively simple to perform, these tests completely lack sensitivity and specificity for the early characterization of AKI, particularly in ICU patients. Moreover, it should be recognized that these studies are highly prone to selection bias, observation bias, and confounding.

The FeNa, for example, is based on the principle that filtered sodium is avidly reabsorbed in the renal tubules from glomerular filtrate in the setting of PRA, in which tubular function remains intact, resulting in a FeNa of <1%, whereas in the setting of tubular injury, such as with ATN, the resulting FeNa is >1%. Although this is physiologically sensible, in clinical practice, the diagnostic accuracy of the FeNa is poor, and its value has been questioned (60–62). The FeNa is frequently >1% in patients receiving diuretics and has been found at <1% in numerous conditions, including sepsis, rhabdomyolysis, and exposure to radiocontrast media (63–66). Carvounis et al. (56) suggested the FeU is more sensitive and specific for discriminating PRA and ATN, in particular when diuretics have been administered; however, this study is also arguably biased and confounded.

There are several other traditional, time-honored urinary tests of biochemistry, including urinary sodium, urine/plasma creatinine ratio, serum urea/creatinine ratio, and urine/serum urea ratio (57, 67, 68); urine uric acid/creatinine ratio (69); fractional excretion of uric acid (67, 69); fractional excretion of chloride (67); and the renal failure index (57, 67, 70).

Overall, however, all these tests remain unproven and of questionable value in diagnosis and classification of AKI in ICU patients (62). These traditional measures of urinary biochemistry have no value for providing a quantitative measure of kidney injury or any useful prognostic information. Finally, it is fundamental that clinicians recognize that the classification of AKI into PRA and ATN is totally arbitrary, that these likely exist on a continuum of injury, and that their separation in diagnostic terms also has limited clinical implications and prognostic value (see "Acute Kidney Injury" by Kellum in this issue of *Critical Care Medicine*).

Proteinuria. Urinary excretion of protein has been described in numerous studies of AKI (54, 70–73) and is frequently detected in the urine of ICU patients (74). In a cohort of 104 critically ill patients, most with AKI or acute on chronic kidney disease, admitted to a medical ICU, 69% had evidence of microalbuminuria (<300 mg/g creatinine) or proteinuria (≥300 mg/g creatinine) on spot urine testing at the time of admission (74).

Urinary protein detection was more common in elderly patients, patients with diabetes, patients with chronic kidney disease, and those with shock. A high

albumin-to-creatinine ratio (≥100 mg/g) was also associated with a significantly increased adjusted odds of death (odds ratio, 2.7; $p = .04$). This has been similarly shown in larger cohorts of mixed medical/surgical ICU patients (75, 76). The detection of microalbuminuria, suggestive as a marker of increased capillary permeability to proteins (77), may yield predictive and prognostic value for illness severity and mortality. Regrettably, no studies have yet evaluated the value of microalbuminuria for predicting the development of AKI or the course of AKI once established in ICU patients (78). Detection of low molecular weight proteinuria of tubular origin has also been described in ICU patients with septic AKI (73). The detection of urinary α_1-microglobulin was found to predict need for renal replacement therapy in a small cohort of patients with AKI; however, few of these patients were critically ill (54). Overall, no studies have *a priori* assessed for urinary protein excretion as a diagnostic marker for AKI or for projection of downstream kidney function or recovery in ICU patients.

Urinary Sediment and Microscopy. Urinary sediment on microscopy has also been traditionally used to discriminate the diagnosis and severity of AKI (i.e., differentiate PRA from established AKI or ATN). The classic urinary profile in ATN contains renal tubular epithelial cells with coarse granular, muddy brown, or mixed cellular casts, whereas the sediment in PRA is bland and may reveal occasional hyaline or fine granular casts.

Few studies have described the urinary sediment in ICU patients with AKI. Moreover, the value of the urinary sediment for classifying the pathogenesis and severity of AKI is imperfect and often fails to correlate with traditional urinary biochemistry or derived indices (69). Regrettably, description of the urinary sediment, similar to urinary biochemistry, in ICU patients with AKI has been highly variable and confounded by inconsistencies in the timing of measurement, the duration of AKI, and the underlying pathophysiology predisposing to AKI. There have been no clinical studies to date that have *a priori* evaluated the value of the urinary sediment and microscopy as a marker of kidney function or AKI.

On the other hand, there are selected circumstances when examination of the urinary sediment may have definite value for ICU patients. In particular, urinary microscopy should be performed when a systemic vasculitis, an acute or rapidly progressive glomerulonephritis, or any pulmonary–renal syndrome is suspected. The detection of dysmorphic red blood cells or red blood cell casts will yield, in these circumstances, important diagnostic, prognostic, and therapeutic information.

CONCLUSION

AKI remains a serious clinical problem for ICU patients, and its incidence is increasing. The detection and diagnosis of AKI in the ICU currently require use of conventional markers of kidney function, specifically, serum levels of creatinine and urea and, less frequently, other urinary tests. These conventional markers are familiar to clinicians and have long been used at the bedside; however, these markers are clearly not ideal, each has limitations, and none reflect real-time changes in GFR or a genuine injurious process to the kidney. More importantly, these conventional markers can contribute to delays in recognition of AKI and, hence, delays to appropriate supportive and therapeutic interventions. The early detection and diagnosis of AKI should be a clinical priority. Likewise, a diagnostic test (or panel of tests) that is capable of evaluating aspects both of kidney function and acute injury are desperately needed. Cystatin C is superior to conventional markers and may assume a greater role in ICU patients for detecting both early changes in GFR and evidence of acute injury. Other newly characterized markers of kidney function or acute injury have the potential to revolutionize the field of critical care nephrology and greatly improve the supportive and therapeutic management of ICU patients with AKI.

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