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# Detection of Acute Kidney Injury Utilizing New Biomarkers

**Susan Dirkes***

*Fresenius Medical NA, USA*

***Corresponding Author:** Susan Dirkes, Fresenius Medical NA, USA.

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## Abstract

Acute kidney injury (AKI) is a common complication of hospitalized patient, particularly the critically ill. It is a syndrome of multiple clinical conditions. AKI carries a high morbidity and mortality worldwide. Among other causes of this healthcare problem, sepsis is the most common. Currently, kidney biomarkers which have been used to detect kidney failure such as serum creatinine and fractional excretion of sodium (FeNA) have been found to have limitations. New biomarkers such as NGAL, KIM-1, IL-18, TIMP-2 and IGFBP-7 have been researched as being more accurate to detect kidney injury before functional injury occurs. The importance of urine as a biomarker for detecting AKI and new tools for accurate urine output collection will be reviewed.

***Keywords:*** *Acute Kidney Injury (AKI); Chronic Kidney Disease (CKD); Biomarkers*

Acute kidney injury (AKI) is a serious complication of illness and has a mortality of 20 - 50% in hospitalized patients, and a mortality of up to 70% in the critically ill [1]. Acute kidney injury (AKI) in these patients is associated with higher length of stay and long term adverse outcomes. Mounting evidence from past and recent research shows AKI to be an independent risk factor for mortality and morbidity [2-7].

Acute kidney injury can cause a broad spectrum of kidney dysfunction from minor injury to severe kidney dysfunction requiring renal replacement therapy [8]. This dysfunction results in decreased solute clearance and decreased glomerular filtration rate (GFR) defined by the Kidney Disease Improving Outcomes (KDIGO) group as urine < 0.5 ml/kg/hr for >6 hrs [9] (See table 1). AKI causes a progressive loss of kidney function, and the process of development is often due to multiple factors, including complications post-operatively, treatment with nephrotoxic drugs, sepsis, and the use of contrast agents [10,11].

| Creatinine | Urine |
|---|---|
| Stage 1: SCr1.5-1.9 times baseline or higher or greater than 0.3 mg/dL increase | Urine output less than 0.5mL/kg/h for 6 - 12h. |
| Stage 2: sCr 2.0 - 2.9 times baseline | Urine output less than 0.5 mL/kg/h for greater than 12h. |
| Stage 3: sCr 3.0 times greater than baseline or increase in sCr to greater than or equal to 4.0 mg/dL. | Initiation of renal replacement Therapy (RRT). |

***Table 1:*** *KDIGO scoring criteria.*

*Khwaja A. 2012 [9].*

Over the past two decades, the incidence of AKI has increased significantly in North American and Europe, particularly within the United States, because of the rising prevalence of acute and chronic conditions, such as sepsis, heart failure, and diabetes [12-14]. Given the trends of increasing AKI as mentioned above, it appears we need to give more attention to this devastating complication of critical illness.

These findings have prompted the creation of much more specific criteria for AKI and the use of more accurate biomarkers to identify kidney injury. Research has resulted in creating methods to stage the severity of AKI. Two methods for used staging are the Risk, Injury, Failure, Loss, End stage disease criteria (RIFLE), and the Acute Kidney Injury Network (AKIN) criteria. These scoring systems were consolidated into one system, the Kidney Disease Improving Global Outcomes (KDIGO) criteria [9]. The KDIGO scoring incorporates changes in the creatinine and urine output over time to grade severity of AKI. Patients scored with these KDIGO criteria had better accuracy for the diagnosis of AKI than other classification systems such as RIFLE and AKIN criteria [15,16] (See table 2). These biomarkers are useful but may not be indicative of kidney injury when it is occurring, which is the focus more recently. Urine output especially is being examined for an earlier indicator of AKI, and will be examined along with other biomarkers later in this paper.

A comparison of the RIFLE, AKIN, and KDIGO definitions and classifications for AKI using SCr

| Criteria | RIFLE | AKIN | KDIGO |
|---|---|---|---|
| Diagnosis | — | Increase in SCr by ≥0.3 mg/dl within 48 h or a percentage increase in SCr of ≥50% within 48 h | Increase in SCr by ≥0.3 mg/dl within 48 h or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 d |
| Staging | Risk: increase in SCr≥1.5 times baseline; injury: increase in SCr≥2.0 times baseline; failure: increase in SCr≥3.0 times baseline or absolute SCr≥4.0 mg/dl with an acute rise of at least 0.5 mg/dl | (*1*) Increase in SCr of ≥0.3 mg/dl or increase to ≥1.5–2 times from baseline; (*2*) increase in SCr to >2–3 times from baseline; (*3*) increase in SCr to >3 times from baseline, SCr≥4.0 mg/dl with an acute increase of at least 0.5 mg/dl, or initiation of RRT | (*1*) Increase in SCr to 1.5–1.9 times baseline or ≥0.3 mg/dl increase; (*2*) increase in SCr to 2.0–2.9 times baseline; (*3*) increase in SCr to 3.0 times baseline, increase in SCr to ≥4.0 mg/dl, or initiation of RRT |

Staging occurs over 7 days in all criteria. RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine.

***Table 2:*** *Comparison of scoring criteria.*
*Uchino S, Takiniami M, Bellomo R. 2014 [16].*

## Mortality of AKI

Patients with comorbidities, those undergoing major surgeries or procedures have approximately a 12% risk for developing AKI [17]. In critically ill patients the incidence is much higher [18,19]. Evidence from studies suggests that even mild forms and short durations of AKI are associated with an increased risk of hospital mortality [20].

Long-term risks in patients who survive an episode of AKI include a greater risk of dying, the risk of developing end-stage renal disease (ESRD) [21,22] having a reduced quality of life [23] and cardiovascular events [8,22-26]. In light of this information, much research has been done in the last decade to improve the diagnosis and detect the occurrence of kidney injury of AKI.

## Costs of AKI

Costs for AKI are also substantial. Patients who develop AKI have costs ranging from $26,700 without AKI up to $42,600 with any AKI. These costs were similar at the University of Pittsburg for cardiac surgical patients [27]. AKI was associated with increases in length of stay in the index hospitalization in a recent study compared with length of stay for patients without AKI [28]. These costs are significant increases in a disease we may be able to prevent or modify.

## Epidemiology of AKI

AKI occurs abruptly and is a relationship between vascular factor, inflammation, tissue perfusion and drug toxicity [29,30]. These factors result in poor perfusion of the kidneys and consequently, renal ischemia. Septic shock is found to be the cause in 50% of all cases [31-34]. In fact, AKI has been shown to be twice as deadly as a myocardial infarction [35]. Uchino., *et al*. studied mortality of AKI. This study showed that in AKI patients, fifty-two percent of all patients died in the ICU. An additional 8% died in the hospital after discharge from the ICU, increasing the overall hospital mortality of AKI to 60.3% [31]. Fuchs found that only 42.5% of patients with moderate AKI survived 2 years from the intensive care unit admission [36]. One study showed that there was a significant deterioration of kidney function in patients who survived an episode of AKI with an apparent initial resolution [37].

The development of AKI is silent, and often is not recognized until the creatinine is elevated and the urine output is significantly decreased. Functional kidney impairment correlates poorly with structural injury to the kidneys. Functional change is not sufficient to define AKI as it is occurring8. Therefore, the need for biomarkers that detect injury of the kidneys in AKI is similar to the use of troponin levels to detect cardiac injury. Biomarkers needed ideally should be able to detect actual damage or warn of impending damage in the kidneys.

## Current biomarkers for AKI diagnosis: Creatinine

Serum creatinine (sCr) has been a benchmark for decades to determine loss of renal function. It has significant limitations, however. Daily creatinine production from the muscles fluctuates, even in normal subjects. Normal creatinine may vary by as much as 2-fold depending on age, race and body weight, and influence of drugs [38-41]. Second, as mentioned earlier, creatinine indicates an alteration in kidney function, not the occurrence of injury [4,41,42]. Serum creatinine (sCr) underestimates the degree of loss of renal function, and may not rise up to 72 hours after the injury [38-44]. One study showed that about 20% of AKI patients would have been missed by measurement of sCr criteria alone and can result in the misclassification of AKI severity [45].

Glomerular filtration rate (GFR) is a good indicator of kidney function in a normal condition. In the above study [45] done by Kaddorauh., *et al*. patients were studied on both the plasma creatinine level and urine output. Increase in the plasma creatinine level was the criteria to define AKI in 738 patients (22.2%). Urine output definition of AKI occurred in 528 patients (15.9%). This study found that the diagnosis of acute kidney injury would have been missed in 67.2% of the patients who met the urine-output criteria for acute kidney injury, if only the plasma creatinine criteria had been use. In another study, in adults who underwent major non-cardiac surgery, sCr-based AKI measurement increased the incidence of AKI to 8.1% with SCr alone versus an increase up to 64.0% when SCr and urine output were both monitored [46]. With this in mind, urine output as a biomarker will be examined in more detail.

## Urine output

Urine output is a key indicator of GFR as mentioned earlier. When urine output is a regarded as a biomarker, along with serum creatinine, according to the KDIGO criteria, patients are classified as having a higher severity of AKI [9]. Urine output is important, and a more timely and sensitive indicator of kidney stress than creatinine, but it deserves mention that it is not an infallible biomarker for AKI. RIFLE, AKIN and KDIGO criteria scores patients who exhibit changes in urine output may never manifest a change in creatinine [47]. The difference between reversible fluid volume reductions in glomerular filtration rate and accompanying kidney tubular injury is known to be not accurately indicated by urine output [48]. In addition, urine output may not be able to predict AKI in some cases such as congestive heart failure [49], during the use of vasopressor drugs or diuretics, the administration of large amounts of intravenous fluids, or acute tubular necrosis with volume overload [50,51].

Given this information, oliguria is common in ICU patients and therefore may still be better in identifying patients with AKI compared to serum creatinine criteria. An increased risk of death has been shown to occur in patients who have even short term oliguria [52]. In one study, Macedo., *et al*. found in critically ill patients that low urine output was associated with adverse outcomes and was shown to be an early biomarker for AKI. They also found that urine output is an early warning sign of tubular stress when it is monitored more often. This study found that when the diagnosis of AKI was based solely on serum creatinine, the incidence of AKI increased from 24%. When

the diagnostic criteria of urine output was added, the incidence of AKI increased from 24% to 52% [53]. In another single-center study involving adults, mortality and morbidity were higher when both the plasma creatinine level and urine output were used to diagnose acute kidney injury than when either was used alone [54].

Mizota., *et al*. studied living donors for liver transplantation. They demonstrated that in those with AKI, oliguria without serum creatinine increase had significantly longer hospital and ICU stays compared with only sCr-based AKI [55]. Jin., *et al*. also found that intensive monitoring of urine output improved detection of AKI and reduced 30-day mortality in patients experiencing AKI in ICU patients [56]. These studies indicate that urine output monitoring is critical in identifying AKI when used along with other diagnostic tools.

### Timely identification of AKI and the role of urine output

Recently, research has shown that we are now able to detect the potential for the development of AKI using electronic health record data. The statistical patterns in electronic health record and data corresponding to AKI-related outcomes can be used. Some data such as combining, respiratory rate, temperature and KDIGO criteria, patient creatinine values and other patient characteristics, are helpful to identify patient who may be at risk. The result is then a more accurate advance warning of AKI and can be used as a software-based prediction tool [57].

If we are to be able to effectively collect data that can indicate impending AKI, we need to have the tools to provide this data for electronic alerts. Creatinine measurement is easily done in our hospital labs today and is populated into the electronic record. Urine output measurement is entered into the EMR only if the bedside nurse manually enters the data every hour in order to monitor trends. Given the sizable workload of nurses today, this data is not guaranteed to be obtained and documented in a timely manner.

In addition, measurement of urine output is not standardized. Traditionally, monitoring urine output is done by the nurse visually reading the amount of urine accumulated in the foley bag or in a urimeter. This volume of urine output is accurate only if the nurse drains the foley tubing if there is urine in it, so that it is collected in the urimeter. This process is often inaccurate [58].

For example, the bedside nurse may measure the output themselves, or rely on adjunctive staff such as nurse aides or nurse technicians to obtain this measurement. This may not be as precise as it should be. Adjunctive staff such as nurse technicians or nurse aides may not understand the importance of accurate measurement urine or they may not drain the foley tubing in order to measure all the urine. In many cases, unless the tubing is manipulated, urine will not flow into the foley bag. This could be misconstrued as no urine output for that hour. In addition to the nurses many other tasks, measurement of urine output every hour is time-consuming for the nursing staff, since the nurse must go into the patient room, log into the electronic record, often drain the tubing, inspect the amount collected, and then manually record the data. Even though this process takes a small amount of time, it can add up over many hours. Therefore, automatic and continuous monitoring of urine output may provide an early alert to impending kidney/organ failure and also reduce human error, and in a busy environment as well as possibly to save nursing time [59].

Recently, automatic urine output collection devices which can measure urine hourly and transmit the hourly data into the electronic record have been developed. Although there is sparse data published yet on the use of automated urine output measurement [58] studies have shown, as mentioned previously in this paper, that applying the urine output criterion in addition to the sCr criterion have shown an increase in number of patients diagnosed with AKI, increasing the sensitivity of the diagnostic criteria.

Currently, there are three (3) providers of electronic measurement of urine output. Each measures the urine output differently. One measures the volume of urine as the urine passes by a flow sensor as it comes out of the foley catheter, Clarity, Renalsense LLC, Israel (Figure 1). Another weighs the additional volume collected in the foley bag each hour, Sensica UO, Adaptec Medical, Raleigh NC (Figure 2). The last device measures the urine with active drain line clearance and high fidelity ultrasound, Accuryn, Potrero Medical, San Francisco, CA (Figure 3). All three companies have the capability of wirelessly transmitting the hourly data to the electronic charting system. This capability provides a time-saving and accurate method to monitor urine output, therefore providing timely information to the medical

team and potentially improving the detection of AKI. However, the use of these devices questions nationwide efforts to prevent urinary tract infections by not placing indwelling bladder catheters or removing them early.


***Figure 1:*** *BD Sensica. Urine is measure when it comes into the foley bag, on the scale.*


***Figure 2:*** *Medline accuryn. Urine is measured when it collects into the container prior to going into the foley bag.*


***Figure 3:*** *Renalsense clarity. Urine is measured as it comes out of the foley catheter via a flow sensor.*

### Nursing implications

Nursing care and science continue to progress as research focuses on more accurate methods of preventing or potentially ameliorating the severity of AKI. Given the high morbidity and mortality of AKI, utilization of biomarkers that are currently FDA- approved can be helpful in the detection and prevention of AKI. New biomarkers that are monitored along with creatinine can provide early notification and alerts to the medical staff. Additional tools, such as electronic alerts via the electronic medical record and those for automatic hourly monitoring of urine output increases the ability to be alerted that urine output is below the KDIGO threshold (0.5 mL/kg/hr) along with either a visual or audible alert on the measuring device that AKI may be developing. Tools for continuous urine output measurement as well provide nursing staff with accurate, real-time data, similar to hourly blood pressure, pulse oximetry, respiratory rate and other vital signs. The time saved from just one small task such as urine measurement may impact overall nursing workload as well as potentially improve patient outcomes from AKI.

## Conclusion

AKI is a serious and deadly consequence of critical illness. Methods of detection used in the past may no longer be are not timely or adequate to determine of renal injury is occurring. We now have a biomarker which indicates the stage of AKI and that AKI is likely to, or is occurring, although currently this is the only one has been approved by the FDA for use in the US. There are many other biomarkers that have been studied which have been shown to be specific and accurate, but are not yet approved for use in the US. Many additional biomarkers are not mentioned here.

In order to prevent the serious consequences and high mortality of AKI, we need to reassess the use of newer biomarkers which can indicate tubular injury is occurring. Additional tools such as electronic measurement of urine output to provide accurate and timely urine output data to team members could alert staff that interventions may be required sooner. If we are able to utilize biomarkers and real-time urine output, we can potentially improve outcomes and prevent the consequences of failed kidneys.

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