Derivation of Urine Output Thresholds That Identify a Very High Risk of AKI in Patients with Septic Shock

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Abstract

Background and objectives To promote early detection of AKI, recently proposed pretest probability models combine sub–Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria with baseline AKI risk. The primary objective of this study was to determine sub-KDIGO thresholds that identify patients with septic shock at highest risk for AKI.

Design, setting, participants, & measurements This was a retrospective analysis of 390 adult patients admitted to the medical intensive care unit (ICU) of a tertiary, academic medical center with septic shock between January 2008 and December 2010. Hourly urine output was collected from the time of septic shock recognition (hour 0) to hour 96, urine catheter removal, or ICU discharge (whichever occurred first). All available serum creatinine (SCr) measurements were collected until hour 96. The AKI pretest probability model was assessed during the first 12 hours of resuscitation and included the initial episode of oliguria, increase from baseline to peak SCr level, and Acute Physiology and Chronic Health Evaluation (APACHE) III score in a multivariable receiver-operator characteristic (ROC) analysis. The primary outcome was the incidence of stage II or III (stage II+) AKI defined by KDIGO criteria. Secondary outcomes included the need for RRT and 28-day mortality.

Results Ninety-eight (25%) patients developed stage II+ AKI after septic shock recognition. APACHE III score and increase in SCr level in the first 12 hours were not statistically associated with stage II+ AKI in multivariable ROC analysis. Consecutive oliguria for 3 hours had fair predictive ability for achieving stage II+ AKI criteria (area under ROC curve, 0.73; 95% confidence interval [95% CI], 0.68 to 0.78), and oliguria for 5 hours demonstrated optimal accuracy (82%; 95% CI, 79% to 86%).

Conclusions Three to 5 hours of consecutive oliguria in patients with septic shock may provide a valuable measure of AKI risk. Further validation to support this finding is needed.


Introduction

Despite advances in the detection and treatment of AKI in critically ill patients, mortality from this condition remains alarmingly high (1–4). Among the array of renal failure causes, septic shock elicits particular concern: the incidence of AKI in this setting may exceed 60% (5,6). The combination of septic shock and AKI yields a nearly 2-fold risk of death compared with either alone (2,5). Therefore, tools for early detection of AKI in the septic patient are necessary to minimize delays in diagnosis and treatment.

Although definitions of AKI have varied historically, the Kidney Disease Improving Global Outcomes (KDIGO) working group has recently developed standard diagnostic criteria based on serum creatinine (SCr) and consecutive duration of oliguria (7,8). However, these criteria are difficult to interpret in a critically ill patient with varying SCr production and volume of distribution (9,10). Although the KDIGO urine output criterion requires >6 hours of oliguria for “risk of AKI” (stage I) and ≥12 hours of oliguria for stage II AKI, shorter durations are gaining clinical significance and may serve as an early clinical alarm for AKI (11–13).

The discovery of novel renal biomarkers and integration of real-time electronic alerts into clinical practice have reinvigorated interest in early detection of AKI (14,15). Unfortunately, routine use of these biomarker assays and electronic notification systems require significant clinical and financial resources. To enhance early, accessible, and cost-effective bedside identification of AKI risk in critical illness, experts have proposed the concept of renal angina (16–19). Renal angina is a conceptual clinical definition to operationalize and structure the pretest probability assessment for diagnosing AKI prospectively. The use of renal angina parallels the changing paradigm for many critical illnesses, wherein diagnoses pair radiographic imaging and laboratory evaluation with a patient’s pretest probability for a given disease state (20–22). The original renal angina concept...
categorized patients in one of three hazard levels based on a patient’s predisposition for AKI development (Supplemental Figure 1). Goldstein and Chawla proposed that adult patients with septic shock make up the highest risk hazard level for AKI. In other words, because of the high baseline risk associated with septic shock, minimal clinical evidence of kidney injury (sub-KDIGO evidence, known as adult renal angina [aRA]) should be used to identify patients at particular risk for the development of AKI (16). The proposed aRA model may facilitate earlier identification of AKI; however, this tool has yet to be derived or validated. Thus, we sought to derive the aRA model and characterize its ability to predict subsequent achievement of stage II or III (stage II+) AKI criteria among patients with septic shock.

Materials and Methods

Participant Identification

This retrospective analysis of a prospectively collected database examined adults with septic shock admitted to a 24-bed medical intensive care unit (ICU) at Mayo Clinic in Rochester, Minnesota, from January 2008 through December 2010 (23). The study ICU was staffed by a multidisciplinary team lead by intensivists 24/7 in house (24). The investigation was approved by the institutional review board with a waiver of informed consent and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. We included patients older than 18 years of age with a systolic BP < 90 mm Hg despite a fluid challenge of 20 ml/kg body weight of crystalloid or equivalent colloid, based on recommendations from the 2008 Surviving Sepsis Campaign (25). Treatment of septic shock was uniformly guided by our sepsis resuscitation bundle, which has been described previously (23). Exclusion criteria were applied in two stages to derive the study cohort (Figure 1). The first stage involved collection of data readily available by electronic query, and the second stage involved collection of data requiring manual abstraction or evaluation from the patient’s medical record. Patients having severe sepsis without shock, those with a history of ESRD, and those lacking research authorization were excluded from study eligibility. A random-number generator was used to select a subset of eligible patients who were then screened according to our study protocol (Figure 1).

Study Protocol

Figure 2 illustrates our a priori–defined study protocol. To briefly summarize, patients were followed from septic shock recognition (hour 0) to hour 96. Hour 0 urine output was disregarded because of presumed retention of urine volume in the bladder at the time of catheterization. Urine output was recorded until ICU discharge, urinary catheter removal, or hour 96, whichever came first. The “aRA window” encompassed hours 1–12 wherein patients were assessed for the first episode of consecutive oliguria and baseline to peak SCr level increase. This cutoff point at hour 12 ensured that, by definition, patients would be unable to meet KDIGO stage II urine output criterion (>12 hours of oliguria) during the aRA window. To avoid including patients with early septic AKI, we excluded any individual who met KDIGO stage II SCr criterion (doubled SCr from baseline) from an initial SCr level within 12 hours from septic shock recognition. The primary outcome of stage II+ AKI and secondary outcome of RRT were analyzed at hour 96. All-cause mortality was assessed at 28 days.

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Figure 1. A 390-patient cohort was included in the final analysis. ICD-9, International Classification of Diseases, Ninth Revision; KDIGO, Kidney Disease Improving Global Outcomes.
Data Collection and Definitions

Abstracted data pertained to demographic characteristics (age, sex, race, admission weight, comorbid conditions), severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] III score, vasopressor administration), and renal measures (urine output, SCr, RRT). Baseline SCr was calculated as the average of available SCr values within 6 months of hospitalization. When previous SCr values were not available, the lowest hospital SCr was used to estimate baseline renal function (26,27). Urine output was documented hourly in the electronic medical record after urinary catheter placement. Urine output charted as "0" was considered a true value. In the rare event that urine output charting was missing between hourly values, the subsequent recorded urine output value was divided evenly with the previous missing hours. To determine baseline to peak SCr level, the baseline SCr level was subtracted from the highest SCr level available in the first 12 hours after septic shock recognition. No formal criteria existed for RRT initiation during the study period. Use of RRT was per intensivist and attending nephrologist discretion and was individualized for each patient.

The time of septic shock recognition was defined according to the 2008 Surviving Sepsis Campaign consensus criteria at the time of documented hypotension despite 20 ml/kg crystalloid or equivalent colloid (28). No patients in the study received hydroxyethyl starch. If a colloid was used, it was 5% or 25% albumin. For patients transferred from outside hospitals with septic shock, the admission time was considered the time of septic shock recognition.

To account for severity of illness, APACHE III scores were calculated upon ICU admission. Only the first episode of consecutive oliguria was evaluated, with oliguria defined as urine output <0.5 ml/kg per hour based on actual admission body weight (8,13). The primary outcome of stage II+ AKI was defined as achieving stage II or III KDIGO criteria (8).

Physician order priority (stat or routine) dictated the specimen type collected (plasma or serum) for creatinine measurement. Creatinine was measured using the standardized (isotope dilution mass spectrometry traceable) Roche enzymatic creatinine assay. For patients receiving intravenous catecholamine therapy, our institution used an isotope dilution mass spectrophotometry–traceable Roche rate–Jaffe creatinine assay (Roche Cobas Integra 400 Plus chemistry analyzer) to avoid interference with enzymatic assays.

Statistical Analyses

Categorical variables were summarized as frequencies (percentages). Continuous variables were expressed as medians with interquartile ranges. Assuming an approximate 30% overall incidence of stage II+ AKI and 25% exclusion rate with equal sample sizes, it was determined that an initial sample of 530 patients (400 included patients) would provide 99% power to detect a difference of 20% in the incidence of AKI between patients with and without aRA (depending on definition derived) (29). Univariate logistic regression was performed to analyze the association of the initial duration of consecutive oliguria, baseline to peak SCr level, and APACHE III score with the end points of stage II+ AKI, RRT, and 28-day mortality. A multivariable logistic regression model including all three variables was used to estimate the predictive contribution of all variables simultaneously. Two-way interactions were assessed and were not found to be statistically significant, so were not considered further. Receiver-operating characteristic (ROC) curves and the areas under the curves (AUCs) were used to assess discriminative power and are reported with 95% confidence intervals (95% CI). We defined an AUC of 0.5–0.6 as demonstrating no predictive ability, 0.6–0.7 as demonstrating poor predictive ability, 0.7–0.8 as demonstrating fair predictive ability, 0.8–0.9 as demonstrating good predictive ability, and >0.9 as
demonstrating outstanding predictive ability (13). Binary prediction rules were applied to calculate sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. Data were analyzed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Three hundred ninety patients were included in the final analysis (Figure 1). Prehospitalization SCR was available for 86.7% of patients and was estimated in 13.3% (Table 1). At hour 96, 98 (25.1%) patients had achieved criteria for stage II+ AKI (58 patients stage II and 40 patients, stage III) and 33 (8.5%) had received RRT. Two patients received RRT after hour 96 (hours 167 and 174, respectively) and were not considered for the outcome of RRT by hour 96. Ninety-seven patients (24.9%) died by day 28.

Univariate logistic regression analysis revealed a statistically significant positive association between hours of consecutive oliguria and development of stage II+ AKI, need for RRT, and 28-day mortality. In contrast, baseline to peak SCR level increase was not associated with any outcome (Table 2). The multivariable model had good predictive ability for subsequently achieving stage II+ AKI criteria (AUC, 0.81; 95% CI, 0.76 to 0.87) and is included in Supplemental Figure 2. A sensitivity analysis that excluded patients in whom the baseline SCR was estimated by lowest hospital creatinine (n=52) yielded similar results (AUC, 0.80; 95% CI, 0.74 to 0.86) (Supplemental Figure 3). Excluding patients in septic shock transferred to the ICU from the emergency department or general ward (n=191) also demonstrated similar results (data not shown). No significant interaction was found between the requirement of vasopressors and consecutive oliguria for the outcome of stage II+ AKI by multiple logistic regression analysis (P=0.97). In the multivariable models for stage II+ AKI and need for RRT, consecutive oliguria was the sole variable with discriminatory power (Table 2).

Because the models suggested that consecutive oliguric hours was the only variable associated with stage II+ AKI, it was selected to define aRA (AUC, 0.82; 95% CI, 0.77 to 0.87). The ROC curve for a sensitivity analysis excluding patients without documented baseline SCR is displayed in Supplemental Figure 4. The discriminatory power of this tool, assessed by cutoff values for consecutive oliguria, is shown in Table 3. The cutoff of 5 hours maximized the sum of sensitivity and specificity, a suitable criterion to establish a good cutoff. Five hours of consecutive oliguria had good accuracy (82%; 95% CI, 79% to 86%) for prediction of subsequently achieving stage II+ AKI criteria with fair overall performance (AUC, 0.75; 95% CI, 0.69 to 0.80) (Table 4). However, 3 hours of oliguria achieved a similar overall performance (AUC, 0.73; 95% CI, 0.68 to 0.78) with an accuracy of 74% (95% CI, 70% to 78%). Patients who met criteria for the 3-hour oliguria cutoff received more fluid resuscitation than those who did not (1761 ml; 95% CI, 903 to 2618 ml; P<0.01). A scatterplot describing the association between fluid balance and oliguria duration, as well as our analysis of fluid balance for the 3- and 5-hour cutoff, may be found in Supplemental Figure 5 and Supplemental Table 1, respectively.

Secondary ROC analyses, wherein the 3- and 5-hour cutoffs were analyzed for predictive ability to subsequently achieve any KDIGO AKI criteria (e.g., including stage I) are included in Supplemental Figures 6 and 7. To account for differences in relevant clinical variables between patients with and without aRA and between included and excluded patients, additional secondary analyses were performed and are summarized in Supplemental Figure 8 and Supplemental Tables 2-4.

Discussion

To our knowledge, the present study is the first known attempt to derive the oliguria component of aRA in septic shock. Before the findings of our investigation, alterations in urine output had been proposed as a sensitive marker for AKI in ICU patients (30). In addition, the novel concept of aRA had been proposed as a sub-KDIGO duration of consecutive oliguria and increase in SCR level over baseline in combination with a measure of illness severity (16). The original renal angina concept placed patients with septic shock in the “very high risk” hazard level, requiring only 1 hour of oliguria or a 0.1-mg/dl baseline to peak SCR level increase to achieve the proposed aRA definition (Supplemental Figure 1). We found that 3–5 hours of consecutive oliguria demonstrated the greatest predictive power for subsequent achievement of stage II+ AKI and was the most clinically useful definition of aRA in patients with septic shock. The results also suggested that baseline to peak SCR increase and APACHE III score negligibly influenced the model. As expected, APACHE III score remained significantly associated with 28-day mortality (Table 2). Therefore, our findings endorse the notion that pretest probability as assessed by aRA is not a severity-of-illness metric but rather an oliguria-based clinical alarm with potential to identify evolving AKI earlier in a patient’s clinical course.

A well designed, prospective multicenter trial by Prowle and colleagues has assessed the ability of consecutive oliguria

<table>
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<tr>
<th>Table 1. Baseline characteristics</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Age (yr)(^a)</td>
</tr>
<tr>
<td>White patients, n (%)</td>
</tr>
<tr>
<td>Men, n (%)</td>
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<tr>
<td>Receiving vasopressors, n (%)</td>
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<tr>
<td>Mechanical ventilation, n (%)</td>
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<tr>
<td>APACHE III score(^a)</td>
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<tr>
<td>Actual body weight (kg)(^a)</td>
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<tr>
<td>Baseline measured SCR unavailable, n (%)</td>
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<tr>
<td>Baseline SCR (mg/dl)(^a)</td>
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<tr>
<td>No. of SCR measurements available in first 12 h(^a)</td>
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<tr>
<td>Comorbid conditions, n (%)</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes</td>
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<td>Congestive heart failure</td>
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<td>CKD</td>
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\(^a\)Values are given as median (interquartile range).
to predict SCr-based AKI in critically ill patients (13). Our finding that 3–5 hours of consecutive oliguria is a reasonable definition for aRA is in agreement with Prowle and colleagues, who concluded that 4 hours of oliguria provided the best cumulative sensitivity and specificity for SCr-based AKI (52% and 86%, respectively). Our study expands on the work of Prowle and colleagues in several ways. Whereas their study looked at an oliguria-only variable for an SCr-based AKI outcome, we analyzed the association between both consecutive oliguria and SCr variables with the incidence of oliguria or SCr-based AKI. Prowle and colleagues evaluated a rather diverse 239-patient ICU population, whereas our study specifically evaluated a 390-patient cohort with septic shock treated uniformly with a bundled approach. The longest duration of consecutive oliguria on each day, used for analysis in Prowle and colleagues’ study, may be suboptimal for a clinical alarm. Because we desired to evaluate a tool to promote early identification of patients at high risk for AKI, we evaluated only the first episode of consecutive oliguria in the first 12 hours, simulating bedside assessment in real time.

Our findings agree with those of a recent study by Ralib and colleagues, who demonstrated that the current KDIGO definition of AKI may be too liberal in a general ICU population. In their analysis, a 6-hour urine output threshold of 0.3 ml/kg per hour yielded the optimal sensitivity and specificity for death or need for dialysis (61% and 77%, respectively). Our 3-hour urine output threshold of <0.5 ml/kg per hour in a septic shock population had similar predictive power for stage II+ AKI, need for dialysis, and 28-day mortality (31).

To our knowledge, this is the first published study that attempts to translate the aRA paradigm from theory to practice in adult patients with sepsis. The internal validity is strengthened by the homogeneity of our patient population and resuscitative efforts. All included patients were required to have documented systolic hypotension after a 20-ml/kg bolus (25). The 12-hour “aRA window” (Figure 2) and analysis of the first episode of consecutive oliguria was chosen to mimic assessment in the early phase of septic shock up to the KDIGO II urine output criterion (oliguria for >12 hours). Since timing of interventions is vital in septic shock and AKI, a 12-hour aRA cutoff simulates a time point where an intensivist may choose to provide additional interventions or observe. Finally, given the debate about the optimal end point for AKI, we chose the outcome of KDIGO stage II+ to analyze a severity of AKI that we deemed clearly clinically relevant.

Our study has several limitations. Urine output data were collected retrospectively and relied on accurate nurse charting, introducing the potential for inherent biases and unmeasured confounding variables. Although reflective of most clinical practices, SCr data were ordered at the discretion of the attending physician and relied on the measurements available for each patient. We cannot
exclude the possibility that multiple measures of SCr or measuring SCr at the same time for each patient over the initial 12-hour window may have increased the predictive power of this variable for AKI. Fluid administration may have distorted SCr level measurements, but given the degree of fluid positivity in our patients, we anticipate at most a 0.1- to 0.2-mg/dl alteration in SCr would be present, which would not have meaningfully altered the findings (10). Diuretic use was not assessed because of the rare administration of such therapy to patients in the acute phase of shock. All patients receiving RRT had a primary renal indication (e.g., oliguria or anuria, hyperkalemia, fluid overload unresponsive to diuresis), but we cannot exclude the possibility that undetected or undocumented differences in the criteria to start RRT in our study may have influenced the results. We must also emphasize that we evaluated a patient cohort from the “very high risk” hazard level for aRA, and our definition does not apply to patient populations from lower hazard levels. This retrospective analysis of a prospectively collected septic shock cohort was conducted at a single ICU with predominantly white patients, and our definition of aRA from this study may not be generalizable to patients with different clinical scenarios, practice environments, or baseline risk factors for AKI. We feel it is important to address the position of aRA among other tools for AKI prediction, such as the renal angina index, which has been recently validated in a pediatric cohort (19). It is important to recognize that the concept of renal angina is subdivided into aRA and pediatric renal angina (pRA). The rationale for this distinction is based on the fact that the pediatric criteria use fluid overload and do not define AKI or pediatric renal angina using urine output. Although our findings demonstrated a statistical relationship between increased fluid overload and duration of oliguria, we cannot exclude the possibility that additional AKI risk factors (e.g., fluid balance) may have significantly contributed to AKI, RRT, or mortality in the aRA model (Supplemental Figure 5). However, the aRA criteria used in this study were congruent with the original aRA concept and KDIGO classification schema.

Our model of aRA provides an array of potential strengths. While most components of risk stratification are static (e.g., comorbid conditions, demographic characteristics, resuscitation measures), our proposed aRA definition of 3–5 hours of consecutive oliguria during the initial 12 hours after septic shock recognition provides a dynamic and responsive tool for the intensivist. Urine output is readily assessed at the bedside and already routinely collected, posing no additional laboratory costs. Our study promotes a culture of recording and reporting changes in hourly urine output for critically ill patients. If hourly urine output is documented, electronic alert mechanisms could be developed to actively survey for oliguria and facilitate patient assessment, fluid or vasopressor administration, nephrology specialist consultation, or early RRT before additional biochemical evidence of AKI is observed (32,33). Evaluating pretest probability using a 3-hour oliguria cutoff may aid in the decision to deploy other diagnostic tests (e.g., AKI biomarkers), potentially increasing their accuracy and cost-effectiveness (34). Finally, our definition of aRA may add value to an existing or investigational risk score for AKI in the ICU (35,36).

In conclusion, 3–5 hours of consecutive oliguria within 12 hours after septic shock recognition may provide a valuable measure of AKI risk. In practice, this would mean that once a patient with septic shock develops 3 hours of consecutive oliguria, the patient has adult renal angina. Further validation to support the proposed definition is needed.

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Disclosures
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References


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