Renal Angina

Stuart L. Goldstein* and Lakhmir S. Chawla†‡

**Department of Pediatrics, Renal Section, Baylor College of Medicine, Houston, Texas; and †Division of Renal Diseases and Hypertension, Department of Medicine, and ‡Department of Anesthesiology and Critical Care Medicine, George Washington University Medical Center, Washington, DC*

Small elevations in serum creatinine may reflect significant kidney damage and be associated with poor patient outcomes, thus rendering creatinine to be a late marker of acute kidney injury (AKI). AKI researchers refer to the AKI biomarker quest as the "search for the renal troponin I," implying that such putative earlier AKI biomarker use could allow for earlier intervention. We consider the analogy to troponin I and its acceptance to prompt evaluation and therapeutic intervention to treat myocardial ischemia and prevent myocardial infarction an informative and potentially applicable model to the AKI field. Because AKI does not hurt, there is no validated equivalent of chest pain or anginal equivalent to increase suspicion for AKI presence on the part of the clinician. So, although biomarkers may ultimately be validated to detect AKI early, unless nephrologists and intensivists can define "renal angina" to initiate "renal troponin I" assessments, AKI biomarkers may never realize their full potential to improve patient care and outcomes. The purpose of this article is to review both adult and pediatric AKI literature to devise a definition for a renal anginal syndrome equivalent.

Clin J Am Soc Nephrol 5: 943–949, 2010. doi: 10.2215/CJN.07201009

Intensive basic and translational research has been expended in the past decade to discover and validate urinary biomarkers to diagnose acute kidney injury (AKI) before rises in serum creatinine. The impetus for this research resulted from the understanding that even a small elevation in serum creatinine may reflect significant kidney damage and be associated with poor patient outcomes, thus rendering creatinine a late marker of AKI. AKI researchers refer to the AKI biomarker quest as the "search for the renal troponin I," implying that such putative earlier AKI biomarker use could allow for earlier intervention, resulting in mitigation or even prevention of AKI progression to severe acute renal failure and resultant morbidity and mortality.

We consider the analogy to troponin I and its acceptance to prompt evaluation and therapeutic intervention to treat myocardial ischemia and prevent myocardial infarction an informative and potentially applicable model to the AKI field; however one obvious but nevertheless important difference exists. Simply put, AKI does not hurt. Thus, there is no validated equivalent of chest pain or anginal equivalent to increase suspicion for AKI presence on the part of the clinician. So, although biomarkers may ultimately be validated to detect AKI early, unless nephrologists and intensivists can define "renal angina syndrome" to initiate "renal troponin I" assessments, AKI biomarkers may never realize their full potential to improve patient care and outcomes.

The troponin analogy is particularly instructive. When troponin is measured in patients without a clinical syndrome of coronary angina, the performance of this heralded biomarker drops dramatically (1). In addition, when cardiac troponin is measured in cohorts of critically ill patients without a coronary angina syndrome, elevations of troponin that are not indicative of myocardial infarction or atherosclerotic coronary disease are found (2). We believe that if AKI biomarkers are used in conjunction with a renal angina syndrome, then the performance of these biomarkers will be significantly improved.

The purpose of this article is to review both adult and pediatric AKI literature to devise a definition for a renal anginal syndrome equivalent. Although all hospitalized adults and children can experience AKI, we limit our discussion to patients who receive care in an intensive care unit (ICU), where mortality risk is greatest.

First Steps: Determination of Patients Who Are at Risk for AKI

Adult Patients

In critically ill patients, multiple risk factors for the development of AKI have been identified. Demographic and clinical risk factors that have been identified for the development of AKI include advanced age, diabetes, cirrhosis/hepatic failure, congestive heart failure, chronic kidney disease, volume depletion, sepsis, cardiopulmonary bypass time, and exposure to nephrotoxins (3–8). The biochemical risk factors that have been identified include increased levels of IL-6, plasminogen activator inhibitor 1, and soluble TNF-α receptors (Table 1) (9–11). Patients who are on mechanical ventilation and require vasoactive agents also represent a cohort at risk for the development of AKI; however, in all of the studies referenced thus far, certain subsets (*e.g.*, sepsis) of patients have been assessed as opposed to all comers.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Lakhmir S. Chawla, Department of Anesthesiology and Critical Care Medicine, 900 23rd Street, NW, Washington, DC 20037. Phone: 202-715-4573; Fax: 202-715-4759; E-mail: lchawla@mfa.gwu.edu

ISSN: 1555-9041/505–0943

Table 1. Risk factors for developing AKI

Demographic and Clinical	Biochemical Markers
Adults	
age >65 years	Elevated IL-6
diabetes	Elevated soluble TNF-α receptor
cirrhosis/hepatic failure	PAI-1
CHF	
CKD	
volume depletion	
sepsis	
cardiopulmonary bypass	
exposure to nephrotoxins	
Children	
invasive mechanical ventilation	IL-6 (10)
vasoactive medications	IL-8
nephrotoxic medications	
sepsis	
multiorgan failure	
volume depletion	
thrombocytopenia	
hypoxemia	
neurologic dysfunction	
stem cell transplantation	

CHF, congestive heart failure; CKD, chronic kidney disease; PAI-1, plasminogen activator 1.

As a continuum of the coronary artery disease analogy, the identified risk factors can be used in same way that the Framingham data risk factors (hypercholesterolemia, hypertension, diabetes, tobacco use, and family history) are used to identify patients who are high risk for coronary disease.

In addition to risk factors, clinical context must be assessed. For example, a single hour of oliguria in an appropriately resuscitated patient with sepsis is considered an organ failure (12). In addition, small changes in serum creatinine in patients with sepsis likely provide evidence of a profound drop in GFR as compared with a patient with normal creatinine production. Thus, the pretest assessment for ruling in/out AKI must take into account identifiable AKI risk factors and the patient's clinical context. For this assessment to occur for AKI, trainees must be taught to apply this type of screening in the same way they are taught to assess coronary artery disease. Similarly, clinicians who care for critically ill patients should adopt these concepts to screen patients who are at risk for AKI development.

Children

Children typically do not have the comorbid conditions noted for adult patients; however, the epidemiology of AKI in children *has* changed in the past decade from primary kidney disease, such as hemolytic uremic syndrome, to diseases in which the kidneys are affected as a result of another systemic disease or its treatment (13–15). However, no prospective study has evaluated the rate of AKI development in matched control subjects who are exposed to the same multiple potential AKI causes to identify truly who is at risk. In response, we have had to reverse-engineer to be cognizant of those who are at greatest risk for death with AKI, to guide vigilance and low threshold for evaluation for AKI (not of AKI). Critically ill children who have multiorgan dysfunction or are exposed to nephrotoxic medications represent the most prevalent pediatric cohorts who develop AKI (13). The rates of AKI development in pediatric ICUs depend on the populations studied and the AKI definition used, ranging from 4.5% (16) (all admitted patients with AKI defined as a doubling of serum creatinine, whereby worse organ dysfunction, thrombocytopenia, neurologic dysfunction, nephrotoxic mediations, and hypoxemia were risk factors for AKI) to 82% (17,18) (only children who receive invasive mechanical ventilation and one or more vasoactive medications with AKI defined by a 25% decrease in estimated creatinine clearance). Thus, we suggest that all children with any of these risks factors be monitored closely for the development of AKI.

Next Step: Renal Angina Syndrome Equivalents of AKI

As noted already, patients with AKI do not display a characteristic syndrome that prompts concern and investigation. This lack of an AKI angina equivalent is problematic because we often determine that a patient has AKI well after the window for potentially successful intervention has passed. As a consequence, we offer some AKI angina syndrome equivalents to "chest tightness, shoulder pain, and shortness of breath" that can be symptoms of acute chest pain syndrome.

Adult Patients

On the basis of the available evidence, three objective criteria should prompt the concern of evolving AKI: (*1*) oliguria, (*2*) any increase in serum creatinine, and (*3*) fluid overload (19–21). More specifically, we recommend using oliguria and/or serum creatinine with clinical context and risk factors as a definition of renal angina (Figures 1 and 2). Once an AKI anginal syndrome equivalent is recognized, the process of ruling in/out AKI should begin in earnest. The essential nature of this process is to look for signs and symptoms of kidney injury and to consider whether renal blood flow is adequate. In clinical practice, the process of ruling out AKI is as important as ruling in AKI. Widely available investigations include assessment of urinalysis, urine electrolytes, urine sediment, and presence of urine eosinophils and calculating the fractional excretion of sodium or the fractional excretion of urea in patients who receive diuretics. More frequent sampling of serum creatinine should be initiated when the current routine is only every 24 hours. Cystatin C should be assessed as well in centers with access to its measurement. If any of these inves-

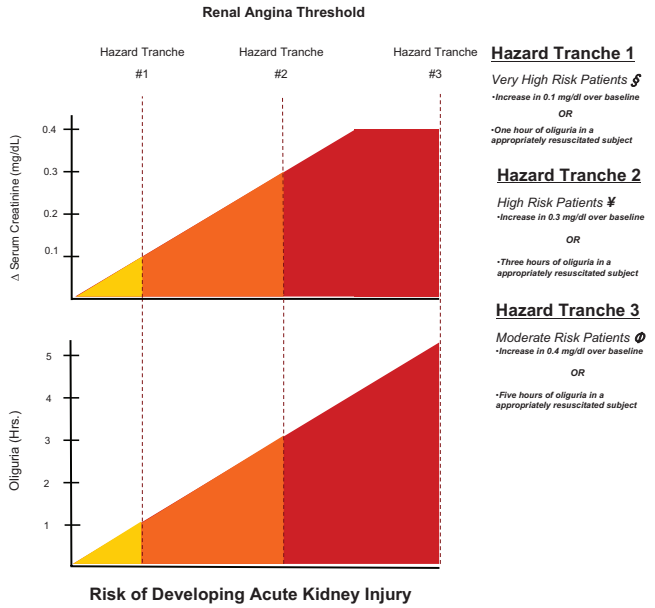

Figure 1. Renal angina threshold as a function of predisposition to develop AKI in adults. §Patients with septic shock or patients receiving vasopressors and mechanical ventilation (12,36). Because a change of 0.1 mg/dl is within interassay range for serum creatinine in many laboratories, a repeat of a serum creatinine or more frequent measurement may be required to make sure that the trend is not a consequence of laboratory error. ¥After cardiac surgery: Thakar score ≥5 (7); after general surgery: Michigan classes III through V (6); general ICU: High-risk patients (37,38). ΦAfter cardiac surgery: Thakar score >3 (7); after general surgery: Michigan class II (6); general ICU: Low-risk patients (37,38).

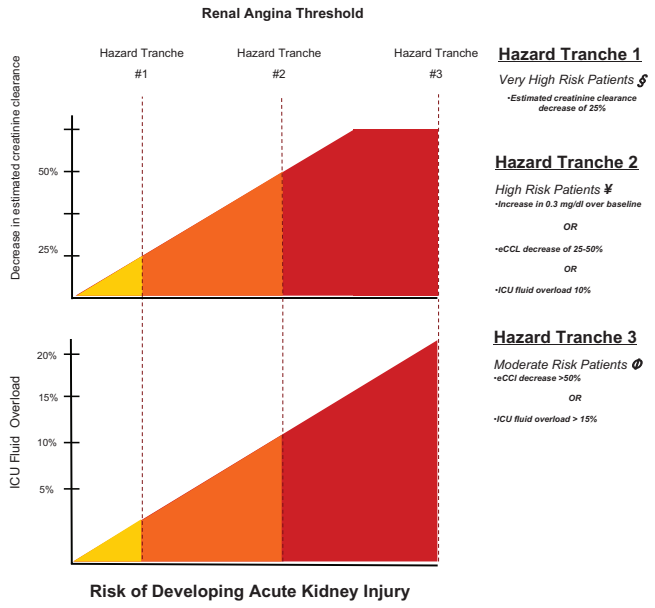

Figure 2. Renal angina threshold as a function of predisposition to develop AKI in children. §Patients receiving mechanical ventilation and one or more vasoactive medications (17,18). ¥Patients with acute decompensated heart failure (24) or patients after stem cell transplantation (30,31). ΦPatients admitted to pediatric ICU (16).

tigations are consistent with injury (*e.g.*, urinary casts consistent with tubular necrosis), then AKI management should be instituted. In addition, if the patient progresses to RIFLE (Risk, Injury, Failure, Loss, ESRD) R (1.5× increase in serum creatinine or >6 hours of oliguria in an appropriately resuscitated patient [Table 2]) (20), then AKI is ruled in and AKI management should begin. Centers with available access and experience can use current AKI biomarkers (*e.g.*, NGAL, KIM-1) to help identify patients with AKI. In the future and with larger clinical trials, biomarkers can serve the role of ruling in/out AKI as well as be tools for assessing severity, phenotyping, and prognosis (22,23).

Children

As noted previously, few data exist to identify children who may be truly at risk for developing AKI. Recent data do exist, however, to show that children with small changes in serum creatinine/estimated creatinine clearance or with increasing degrees of fluid overload are at risk for poor outcome. It is these characteristics that have provided a transformative conceptual framework for focusing on detecting AKI development and its effects earlier in its course. Two pediatric studies demonstrated that the pediatric modified RIFLE AKI classification system (pRIFLE) can be useful to determine AKI severity and potential associations with poor outcome, because critically ill intubated children who develop pRIFLE I or pRIFLE F (>50% decrease in estimated creatinine clearance) are at increased risk for persistent AKI of >48 hours and exhibit higher mortality rates (17,18). A previous study showed that a pRIFLE equivalent of serum creatinine doubling (pRIFLE I) was associated with a 27.4% mortality compared with 2.4% mortality in a cohort of all children were admitted to an ICU (16). Another study that assessed the association of AKI in children with acute decompensated heart failure revealed that in-hospital serum creatinine increase of >0.3 mg/dl was independently associated with patient mortality, need for mechanical ventricular assistance, or heart transplantation (24). Thus, we suggest that attention must be paid to critically children who have small increases in serum creatinine (>0.3 mg/dl) or decreases in estimated creatinine clearance (> 25%) and propose that children who meet either of these thresholds are demonstrating a renal angina equivalent. Furthermore, critically ill patients who develop pRIFLE I or F or doubling of serum creatinine are "ruled in" for AKI (Table 3). Although the urine output pRIFLE criteria did not add any precision in the association between pRIFLE strata and outcome, we still recommend assessing urine output pRIFLE criteria given the small cohorts of patients reported to date.

Critically ill children often require aggressive fluid and inotropic support to maintain adequate perfusion. Substantial single-center (25–28) and multicenter (29) pediatric studies in the past decade demonstrated that increasing degrees of relative fluid accumulation or percentage of fluid overload at the time

Table 2. RIFLE classification system (35)

Class	GFR Criteria	Urine Output Criteria
Risk	Serum creatinine 1.5×	<0.5 ml/kg per h for 6 hours
Injury	Serum creatinine 2×	<0.5 ml/kg per h for 12 hours
Failure	Serum creatinine 3× or serum creatinine ≥4 mg/dl with an acute rise >0.5 mg/dl	<0.3 ml/kg per h for 24 hours or anuria for 12 hours
Loss	Persistent acute renal failure = complete loss of kidney function for >4 weeks	
ESRD	ESRD for >3 months	

Table 3. pRIFLE AKI classification system

Class	eCrCl	Urine Output
Risk	Decrease by 25%	<0.5 ml/kg per h for 8 hours
Injury	Decrease by 50%	<0.5 ml/kg per h for 16 hours
Failure	Decrease by 75% or <35 ml/min per 1.73 m^2	<0.3 ml/kg per h for 24 hours or anuria for 12 hours

eCrCl, estimated creatinine clearance.

Table 4. Fluid overload and outcome in children receiving continuous RRT

Study	Cohort (*n*)	Outcome	*P*
Goldstein (25)	Single center (22)	Survivors 16% FO Nonsurvivors 34% FO	0.03
Gillespie (27)	Single center (77)	%FO >10% with OR for death 3.02	0.002
Foland (28)	Single center (113)	3 patients with MODS Survivors 9% FO Nonsurvivors 16% FO 1.78 OR for death for each 10% FO increase	0.01
Goldstein (29)	Multicenter (116)	≥2 patients with MODS Survivors 14% FO Nonsurvivors 25% FO <20% FO: 58% survival >20% FO: 40% survival	0.002
Hayes (26)	Single center (76)	Survivors 7% FO Nonsurvivors 22% FO OR for death 6.1 >20% FO	0.001

FO, fluid overload; MODS, multiorgan dysfunction syndrome; OR, odds ratio.

of renal replacement therapy initiation in children with AKI is independently associated with mortality. Percentage of fluid overload is calculated by totaling fluid volumes from ICU admission to renal replacement therapy (RRT) initiation using the following equation:

[(fluid input in liters) − fluid output in liters)/patient ICU admission weight in kg]

Analysis of various percentage thresholds from these studies suggests that mortality increases from 40 to 60% in children with >10 to 20% fluid overload at RRT initiation, independent of patient severity of illness (Table 4). The pediatric stem cell transplant patient seems to be especially vulnerable to the ill effects of fluid accumulation; although these patients have multiple comorbidities, including the need for mechanical ventilation and sepsis, maintenance of <10% fluid overload is necessary, albeit insufficient alone, to ensure survival of children with pRIFLE I AKI (30,31). Thus, we suggest that critically ill children or children who receive stem cell transplants and develop AKI and >10% ICU fluid overload may be exhibiting a renal angina equivalent and should be monitored closely to determine the cause of AKI and assess the likelihood of prompt kidney function recovery. If such patients develop >15% fluid overload and optimal care requires administration of essential fluids (*e.g.*, total

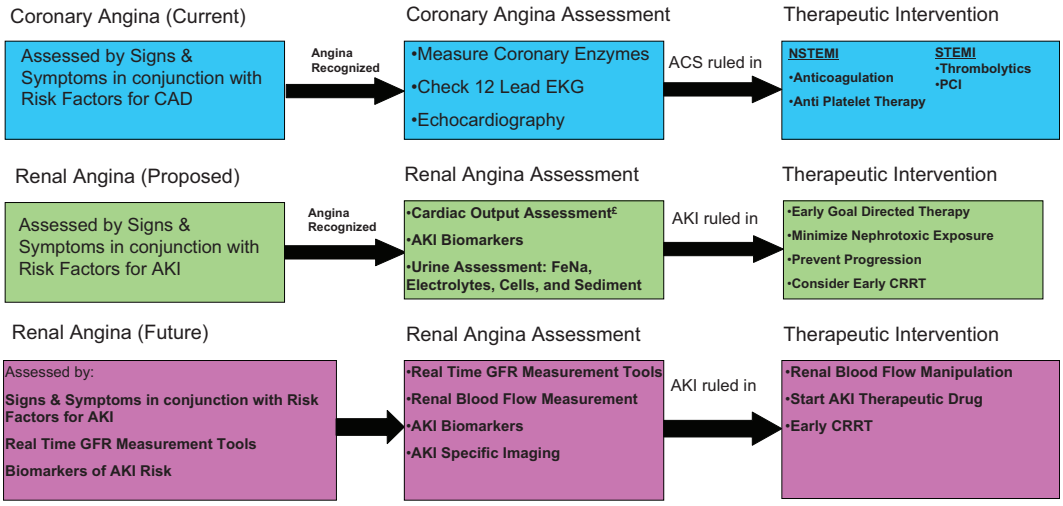

Figure 3. Framework of coronary and renal angina. £Cardiac output monitoring is currently the most precise form of intravascular volume status assessment; therefore, volume status is not listed separately.

parenteral nutrition, antibiotics, blood products), we suggest that the patient has been ruled in for severe AKI and RRT should be initiated to allow for essential fluid provision and to prevent further fluid overload.

AKI Ruled in

If renal injury is confirmed and the patient is ruled in for AKI, then multiple interventions can be initiated. A full review of interventions in beyond the scope of this article and has been reviewed in detail in recent reviews (32,33). We offer an abbreviated list here:

1. Evaluate treatable causes of AKI: (*a*) Rhabdomyolysis, (*b*) obstruction, (*c*) volume depletion, (*d*) glomerulonephritis, (*e*) sepsis, (*f*) acute interstitial nephritis, (*g*) vascular events (*e.g.*, arterial dissection, atheroembolic disease, thrombotic thrombocytopenic purpura).
2. Optimize hemodynamics and consider objectively assessing cardiac output (*e.g.*, pulmonary artery catheter, echocardiography, noninvasive cardiac output monitoring *via* arterial line).
3. Consider initiating goal-directed therapy with an emphasis on conservative late fluid management after the initial resuscitation (34).
4. Minimize exposure (discontinue when possible) all nephrotoxic drugs (*e.g.*, nonsteroidal anti-inflammatory drugs, aminoglycosides, amphotericin, radiocontrast material).
5. If the patient is fluid overloaded and resistant to diuretics, then consider ultrafiltration.

Limitations of Recommendations

The renal angina equivalent thresholds recommended in this article are based on available epidemiologic literature and clinical practice. We suggest that the proposed thresholds are testable hypotheses, and the validity of these recommendations should be assessed. In developing this article, some of our colleagues suggested that Acute Kidney Injury Network (AKIN) stage 1/RIFLE R should be the definition of renal angina. As our understanding of early AKI develops, renal angina thresholds will need to be recalibrated; however, it is our strong belief that the combination of clinical risk factors and the patient's clinical context in conjunction with kidney function parameters will be more effective than either alone (Figure 3).

It should also be noted that we did not address or recommend specific pharmacologic strategies to prevent or mitigate AKI, such as loop diuretics, adenosine antagonists, or fenoldopam. Although some of these agents have shown promise in animal studies or select human populations, large, well-designed studies have not demonstrated any benefit from a specific pharmacologic agent. The lack of positive study likely resulted from the late diagnosis of AKI in the study design, which relied on much greater changes in serum creatinine than suggested here, to herald a renal angina syndrome equivalent.

Although the associations between fluid overload at RRT initiation and mortality in the pediatric population have been consistent, no published have detailed the "fluid overload epidemiology" in pediatric patients who do not receive continuous RRT. Thus, these data have internal validity only in the continuous RRT subset cohort but may not generalize well to patients without AKI. Further study is needed to assess AKI incidence in children with fluid overload and without AKI (*e.g.*, heart failure, liver failure, sepsis with capillary leak) to determine the sensitivity and specificity of fluid overload to predict poor patient outcome.

In addition, we have not recommended a dosage of dialysis small solute clearance or one RRT modality over another, because this was not the purpose of this article. We hope that we have provided evidence for a change in the conceptual approach to an earlier focus on changes in kidney function or, more appropriate, earlier recognition of kidney dysfunction with tools that are available today to prompt therapeutic ma-

neuvers to prevent potentially unnecessary ill effects of AKI, once it is ruled in.

Appendix (reproduced from reference 37): Prediction of Acute Kidney Injury (AKI) by Risk Factors Classification

Rakesh Malhotra, Etienne Macedo, Josee Bouchard, Susan Wynn, Ravindra L. Mehta

Medicine, University of California, San Diego, San Diego, CA

Background

Identifying patients at risk for AKI is necessary to enable preventive and early therapeutic strategies. Chawla *et al.* (*Kidney International*; 2005) proposed combining individual risk factors to improve predictive value for AKI. We evaluated the performance of their criteria in critically ill patients.

Methods

Patients admitted to a surgical intensive care unit were screened for a prospective observational study on the incidence of AKI. Risk factors were classified as chronic major comorbidities (*e.g.*, advanced age, diabetes mellitus, chronic kidney disease, chronic cardiovascular disease), chronic minor (*e.g.*, hypertension, elevated bilirubin, morbid obesity, chronic lung disease), and acute (*e.g.*, hypotension, sepsis, high-risk surgery, mechanical ventilation or nephrotoxin exposure). Patients were stratified as high risk (HR), low risk (LR), and no risk (NR) based on their risk factor profile at the time of intensive care unit admission. Outcomes included the incidence of AKI, need for RRT, and mortality. AKI was defined by an absolute increase of 0.3 mg/dl from the first measured sCr within 48 hours.

Results

The overall incidence of AKI was 19.5% (63 cases). The LR and NR groups had similar outcomes, whereas HR patients had a higher incidence of AKI (40.2 *versus* 6.4%; $P < 0.001$). HR patients also had a significantly higher mortality (12.9 *versus* 0.7%; $P < 0.001$) and need for RRT (10.3 *versus* 0.7%; $P = 0.001$) compared with LR.

Characteristics and outcome of the patients based on risk factor group

Variable	All	HR	LR	NR	*P*
No. of patients	323	132	141	50	
Age (years)	51.03	53.45	53.49	37.72	<0.0001[a]
% Incidence of AKI	19.5	40.2	6.4	2.0	<0.001
% Need for RRT	3.1	7.6	0.0	0.0	0.001
% ICU mortality	5.6	12.9	0.7	0.0	<0.001

[a]HR *versus* NR.

Conclusion

A simple risk classification system based on chronic comorbidities and acute events can identify patients at high risk to develop AKI and adverse outcomes. Future studies on AKI should incorporate these factors to stratify patients for prevention and early therapeutic interventions.

Acknowledgments

We thank John Kellum for reviewing the manuscript and his insights about the RIFLE classification system.

Disclosures

L.S.C. has received consulting fees/honoraria from Astute Medical, Quark Biotech, Sanofi-Aventis, and Nxstage Medical and has received research support from Astute Medical, Quark Biotech, Nephrion, Eli Lilly & Company, and Biosite Medical; S.L.G. has received research support from Gambro Renal Products and serves on the Medical Advisory Board for Gambro Renal Products and Baxter.

References

1. Stein R, Gupta B, Agarwal S, Golub J, Bhutani D, Rosman A, Eng C: Prognostic implications of normal (<0.10 ng/ml) and borderline (0.10 to 1.49 ng/ml) troponin elevation levels in critically ill patients without acute coronary syndrome. *Am J Cardiol* 102: 509–512, 2008
2. Gunnewiek JM, Van Der Hoeven JG: Cardiac troponin elevations among critically ill patients. *Curr Opin Crit Care* 10: 342–346, 2004
3. Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DR, Platt R: Correlates of acute renal failure in patients receiving parenteral amphotericin B. *Kidney Int* 60: 1452–1459, 2001
4. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F: Acute renal failure in the ICU: Risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 26: 915–921, 2000
5. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA: Acute renal failure in patients with sepsis in a surgical ICU: Predictive factors, incidence, comorbidity, and outcome. *J Am Soc Nephrol* 14: 1022–1030, 2003
6. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, Campbell DA Jr: Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. *Anesthesiology* 110: 505–515, 2009
7. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP: A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 16: 162–168, 2005
8. Yegenaga I, Hoste E, Van Biesen W, Vanholder R, Benoit D, Kantarci G, Dhondt A, Colardyn F, Lameire N: Clinical characteristics of patients developing ARF due to sepsis/systemic inflammatory response syndrome: Results of a prospective study. *Am J Kidney Dis* 43: 817–824, 2004
9. Chawla LS, Seneff MG, Nelson DR, Williams M, Levy H, Kimmel PL, Macias WL: Elevated plasma concentrations of IL-6 and elevated APACHE II score predict acute kidney injury in patients with severe sepsis. *Clin J Am Soc Nephrol* 2: 22–30, 2007
10. Liu KD, Altmann C, Smits G, Krawczeski CD, Edelstein CL, Devarajan P, Faubel S: Serum interleukin-6 and interleukin-8 are early biomarkers of acute kidney injury and predict prolonged mechanical ventilation in children undergoing cardiac surgery: A case-control study. *Crit Care* 13: R104, 2009
11. Liu KD, Glidden DV, Eisner MD, Parsons PE, Ware LB,

Wheeler A, Korpak A, Thompson BT, Chertow GM, Matthay MA: Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. *Crit Care Med* 35: 2755–2761, 2007
12. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 101: 1644–1655, 1992
13. Hui-Stickle S, Brewer ED, Goldstein SL: Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. *Am J Kidney Dis* 45: 96–101, 2005
14. Vachvanichsanong P, Dissaneewate P, Lim A, McNeil E: Childhood acute renal failure: 22-Year experience in a university hospital in southern Thailand. *Pediatrics* 118: e786–e791, 2006
15. Williams DM, Sreedhar SS, Mickell JJ, Chan JC: Acute kidney failure: A pediatric experience over 20 years. *Arch Pediatr Adolesc Med* 156: 893–900, 2002
16. Bailey D, Phan V, Litalien C, Ducruet T, Merouani A, Lacroix J, Gauvin F: Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. *Pediatr Crit Care Med* 8: 29–35, 2007
17. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL: Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 71: 1028–1035, 2007
18. Plotz FB, Bouma AB, van Wijk JA, Kneyber MC, Bokenkamp A: Pediatric acute kidney injury in the ICU: An independent evaluation of pRIFLE criteria. *Intensive Care Med* 34: 1713–1717, 2008
19. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL: Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 76: 422–427, 2009
20. Kellum JA, Bellomo R, Ronco C: The concept of acute kidney injury and the RIFLE criteria. *Contrib Nephrol* 156: 10–16, 2007
21. Lopes JA, Jorge S, Silva S, de Almeida E, Abreu F, Martins C, Alves do Carmo J, Lacerda JF, Prata MM: Prognostic utility of the Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in myeloablative haematopoietic cell transplantation. *Bone Marrow Transplant* 40: 1005–1006, 2007
22. Parikh CR, Garg AX: Acute kidney injury: Better biomarkers and beyond. *Kidney Int* 73: 801–803, 2008
23. Waikar SS, Bonventre JV: Biomarkers for the diagnosis of acute kidney injury. *Nephron Clin Pract* 109: c192–c197, 2008
24. Price JF, Mott AR, Dickerson HA, Jefferies JL, Nelson DP, Chang AC, O'Brian Smith E, Towbin JA, Dreyer WJ, Denfield SW, Goldstein SL: Worsening renal function in children hospitalized with decompensated heart failure: Evidence for a pediatric cardiorenal syndrome? *Pediatr Crit Care Med* 9: 279–284, 2008
25. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R: Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* 107: 1309–1312, 2001
26. Hayes LW, Oster RA, Tofil NM, Tolwani AJ: Outcomes of critically ill children requiring continuous renal replacement therapy. *J Crit Care* 24: 394–400, 2009
27. Gillespie RS, Seidel K, Symons JM: Effect of fluid overload and dose of replacement fluid on survival in hemofiltration. *Pediatr Nephrol* 19: 1394–1399, 2004
28. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, Rogers K, Reid C, Tanner AJ, Easley KA: Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis. *Crit Care Med* 32: 1771–1776, 2004
29. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, Bunchman TE, Baker C, Mottes T, McAfee N, Barnett J, Morrison G, Rogers K, Fortenberry JD: Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. *Kidney Int* 67: 653–658, 2005
30. Flores FX, Brophy PD, Symons JM, Fortenberry JD, Chua AN, Alexander SR, Mahan JD, Bunchman TE, Blowey D, Somers MJ, Baum M, Hackbarth R, Chand D, McBryde K, Benfield M, Goldstein SL: Continuous renal replacement therapy (CRRT) after stem cell transplantation: A report from the prospective pediatric CRRT Registry Group. *Pediatr Nephrol* 23: 625–630, 2008
31. Michael M, Kuehnle I, Goldstein SL: Fluid overload and acute renal failure in pediatric stem cell transplant patients. *Pediatr Nephrol* 19: 91–95, 2004
32. Himmelfarb J, Joannidis M, Molitoris B, Schietz M, Okusa MD, Warnock D, Laghi F, Goldstein SL, Prielipp R, Parikh CR, Pannu N, Lobo SM, Shah S, D'Intini V, Kellum JA: Evaluation and initial management of acute kidney injury. *Clin J Am Soc Nephrol* 3: 962–967, 2008
33. Molitoris BA, Melnikov VY, Okusa MD, Himmelfarb J: Technology insight: biomarker development in acute kidney injury—What can we anticipate? *Nat Clin Pract Nephrol* 4: 154–165, 2008
34. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, Micek ST, Kollef MH: The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 136: 102–109, 2009
35. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P: Acute renal failure: Definition, outcome measures, animal models, fluid therapy and information technology needs—The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 8: R204–R212, 2004
36. Levy MM, Macias WL, Vincent JL, Russell JA, Silva E, Trzaskoma B, Williams MD: Early changes in organ function predict eventual survival in severe sepsis. *Crit Care Med* 33: 2194–2201, 2005
37. Malhotra R, Macedo E, Bouchard J, Wynn S, Mehta RL: Prediction of acute kidney injury (AKI) by risk factors classification [Abstract]. *J Am Soc Nephrol* 20: 979A, 2009
38. Chawla LS, Abell L, Mazhari R, Egan M, Kadambi N, Burke HB, Junker C, Seneff MG, Kimmel PL: Identifying critically ill patients at high risk for developing acute renal failure: A pilot study. *Kidney Int* 68: 2274–2280, 2005

See related editorial, "Acute Renal Syndrome/Renal Angina: A New Paradigm for Studies of Acute Kidney Injury?" on pages 753–755.