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Acute Kidney Injury scoring systems: from over 30 to 4 (or 1)?

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Research into acute kidney injury (AKI) took a significant step forward with the introduction of the Risk, Injury, Failure, Loss, End stage (RIFLE) AKI criteria in 2004 by the Acute Dialysis Quality Initiative Group [1]. These consensus criteria for AKI replaced the more than 30 different definitions that had existed prior to this point. The RIFLE criteria include many advances. They provide for a standard threshold (Risk) at which AKI is recognized based on either increased serum creatinine (50% increase above baseline) or decreased urine output (<0.5 mL/kg/h for 6 h). They also allow for three different degrees of AKI to be categorized (Risk, Injury, Failure) (Table 1). Although it can be argued that the thresholds set by RIFLE are somewhat arbitrary, the utility of the RIFLE criteria have been validated in that studies that have correlated the Risk, Injury, and Failure criteria with patient morbidity and mortality (reviewed in [2]).

Building upon the RIFLE criteria, Akcan-Arikan *et al.* introduced a pediatric modification to RIFLE (pRIFLE) in 2007 [3]. The pediatric criteria are both similar and different from the adult RIFLE criteria. Both pRIFLE and RIFLE use changes in serum creatinine and decreases in urine output to indicate AKI, however, pRIFLE requires the conversion of a serum creatinine into an estimated glomerular filtration rate (eGFR) so that a percentage decline in eGFR is used to define the Risk, Injury, and Failure criteria. This modification is necessary to provide a consistent change in kidney function as normal serum creatinine values dramatically increase as children grow and gain muscle mass. Similar to the standard RIFLE criteria, the severity of AKI as determined by the pediatric RIFLE criteria correlate with patient morbidity and mortality (reviewed in [4]).

The AKI field did not stop with the RIFLE and pRIFLE criteria, and in 2007 (the same year that the pRIFLE criteria were introduced), the Acute Kidney Injury Network introduced the

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AKIN criteria [5]. In many ways, the AKIN criteria are similar to the RIFLE criteria. They recognize 3 stages of AKI (stage 1-3) just like the RIFLE criteria (Risk, Injury, Failure), and they use similar degrees of serum creatinine increase and decreases in urine output (Table 1). There are, however, important differences between AKIN and RIFLE: (i) since adult studies showed that small increases in serum creatinine correlated with increase in morbidity and mortality, the AKIN criteria introduced a separate threshold for stage 1 AKI based on a serum creatinine increase of 0.3 mg/dL as well as continuing a 50% increase from baseline from RIFLE; (ii) The AKIN criteria introduced a time component: the changes in serum creatinine need to occur within 48 hours; and (iii) The AKIN criteria formalized that all patients on renal replacement therapy (RRT) fall into stage 3 AKI.

Building upon the RIFLE, pRIFLE, and AKIN criteria, the Kidney Disease Improving Global Outcomes (KDIGO) group established a fourth set of AKI criteria in 2012 that combined elements of all 3 previous AKI definitions [6]. The KDIGO criteria retain the concept of 3 stages of AKI (Table 1). They retain the AKIN serum creatinine criteria for the diagnosis of AKI but with some modifications. For example, within stage 1 AKI, the KDIGO criteria continue to require that a 48 hour time window is needed for a 0.3 mg/dL increase in serum creatinine, but KDIGO allows for a 7 day time period for a 50% increase in serum creatinine. With stage 3 AKI, the KDIGO criteria retain the eGFR threshold from pRIFLE and retain from AKIN the requirement that all patients on RRT fall into stage 3.

Given the slight differences between the four AKI definitions, several studies have compared these AKI criteria to one another. Using a pediatric population, Sutherland *et al.* found differences in the ability of pRIFLE, AKIN, and KDIGO criteria to identify AKI [7]. In particular, pRIFLE identified the most children with stage 1 (or Risk) AKI, while the KDIGO criteria identified the most children with stage 3 AKI. Overall, they found AKI in 37-51% of the hospitalizations. Independent of the AKI definition used, children with AKI had higher in-hospital mortality and longer hospital length of stay, especially in those patients who were in the ICU. Similar findings have been observed in several adult studies, with AKI being associated with increased morbidity and mortality independent of the AKI criteria used [8-12].

If all of the existing AKI definitions are useful at recognizing clinically meaningful AKI, does it matter which definition is used? Sutherland *et al.* were concerned that the differences between the various AKI definitions may make it difficult to compare the results of studies that use different definitions, and stated that there is a “need for a single, unified AKI definition” [7]. Fortenberry *et al.* in a review on pediatric AKI also advocated for consistently using a single set of criteria by stating “KDIGO AKI definition and staging criteria should be used at the current time unless further modifications are warranted by prospective study” [13]. Despite this, a search of Pubmed.gov for “acute kidney injury” and each criteria shows that all 4 criteria continue to be widely used (Table 2).

In this issue of *Pediatric Critical Care Medicine*, a manuscript by Slater *et al.* is published in which they look at the risk factors for the development of pediatric AKI in a tertiary care children's hospital ICU using the original RIFLE criteria [14]. The authors state in the discussion that there were unable to use pRIFLE because patient heights were documented

in less than 10% of the patients in the study, and as such were unable to use pediatric eGFR equations. While Slater *et al.* did not discuss why they chose RIFLE over KDIGO, they did conduct a post-hoc analysis which shows that the KDIGO definition would have only resulted in a 0.3% increase (14 patients out of over 3800) in the overall incidence of AKI. We agree that it is a worthwhile goal for the AKI research community to agree on a single AKI definition and we agree with Fortenberry *et al.* about the use of the KDIGO AKI criteria, but does the use of RIFLE over KDIGO alter the conclusions of the Slater *et al.* manuscript that the use of nephrotoxic medications is a significant risk factor for the development of AKI? We think not. Instead, we think that the results of this article should heighten the awareness of using nephrotoxic medications in critically ill children. As Slater *et al.* demonstrate, there are risk factors that clinicians can modify to reduce the risk of AKI and we should focus on prospectively identifying the impact of such factors on the development of AKI.

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Table 1
Acute Kidney Injury Classification Systems

System	Injury Stage	Criteria (serum creatinine)	Criteria (urine output)
RIFLE	R (risk)	1.5-fold Cr increase or GFR decrease > 25%	<0.5 mL/kg/h for 6 h
	I (injury)	2-fold Cr increase or GFR decrease > 50%	<0.5 mL/kg/h for 12 h
	F (failure)	3-fold Cr increase or Cr ≥ 4.0 mg/dL	<0.3 mL/kg/h for 24 h or anuria for 12 h
	L (loss)	Persistent failure >4 wk	
	E (end stage)	Persistent failure >3 mo	
pRIFLE	R (risk)	eGFR decrease ≥ 25%	<0.5 mL/kg/h for 8 h
	I (injury)	eGFR decrease ≥ 50%	<0.5 mL/kg/h for 16 h
	F (failure)	eGFR decrease ≥ 75% or eGFR < 35 mL/min/1.73 m ²	<0.3 mL/kg/h for 24 h or anuria for 12 h
	L (loss)	Persistent failure >4 wk	
	E (end stage)	Persistent failure >3 mo	
AKIN	Stage 1	0.3 mg/dL Cr increase or 150-200% increase above baseline	<0.5 mL/kg/h for 6 h
	Stage 2	Cr increase of 200-300% of baseline	<0.5 mL/kg/h for 12 h
	Stage 3	Cr increase ≥ 300% of baseline or 4.0 mg/dL with an acute increase of 0.5 mg/dL	<0.3 mL/kg/h for 24 h or anuria for 12 h
KDIGO	Stage 1	0.3 mg/dL Cr increase or 1.5-1.9 times baseline	<0.5 mL/kg/h for 6-12 h
	Stage 2	Cr increase of 2.0-2.9 times baseline	<0.5 mL/kg/h for 12 h
	Stage 3	Cr increase of 3.0 times baseline or Cr ≥ 4.0 mg/dL or initiation of renal replacement therapy or eGFR <35 mL/min per 1.73 m ² in patients <18 years	<0.3 mL/kg/h for 24 h or anuria for 12 h

Table 2
Yearly Pubmed.gov Citations for AKI Classifications

	2014	2015	2016
RIFLE	121	101	51
pRIFLE	13	10	3
AKIN	71	82	30
KDIGO	48	76	48