

# Creatinine Kinetics and the Definition of Acute Kidney Injury

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## ABSTRACT

Acute kidney injury (AKI) is a common and devastating medical condition, but no widely accepted definition exists. A recent classification system by the Acute Dialysis Quality Initiative (RIFLE) defines AKI largely by percentage increases in serum creatinine (SCr) over baseline. The Acute Kidney Injury Network defines the first stage by either an absolute or a percentage increase in SCr. To examine the implications of various definitions, we solved differential equations on the basis of mass balance principles. We simulated creatinine kinetics after AKI in the setting of normal baseline kidney function and stages 2, 3, and 4 chronic kidney disease (CKD). The percentage changes in SCr after severe AKI are highly dependent on baseline kidney function. Twenty-four hours after a 90% reduction in creatinine clearance, the rise in SCr was 246% with normal baseline kidney function, 174% in stage 2 CKD, 92% in stage 3 CKD, and only 47% in stage 4 CKD. By contrast, the absolute increase was nearly identical (1.8 to 2.0 mg/dl) across the spectrum of baseline kidney function. Time to reach a 50% increase in SCr was directly related to baseline kidney function: From 4 h (normal baseline) up to 27 h for stage 4 CKD. By contrast, the time to reach a 0.5-mg/dl increase in SCr was virtually identical after moderate to severe AKI (>50% reduction in creatinine clearance). We propose an alternative definition of AKI that incorporates absolute changes in SCr over a 24- to 48-h time period.

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The diagnosis of acute kidney injury (AKI), previously termed acute renal failure, is based typically on an elevation in the serum creatinine (SCr) concentration. There is still no broadly accepted consensus on the degree of SCr elevation required to qualify for the diagnosis of AKI. Two recent and highly publicized consensus definitions/classification systems have been proposed. The Acute Dialysis Quality Initiative's "RIFLE" criteria<sup>1</sup> include five categories (Risk, Injury, Failure, Loss, ESRD), the first three of which define AKI and its severity largely by percentage increases in SCr over baseline. The Acute Kidney Injury Network (AKIN) criteria<sup>2</sup> include three stages, the last two of which are identical to the RIFLE criteria. Stage 1 of the AKIN criteria, however, defines AKI by an absolute increase of 0.3 mg/dl or a 50% increase (*viz.*, 0.3-mg/dl increase if baseline  $\geq 0.6$  mg/dl and 50% increase if baseline is  $\leq 0.6$  mg/dl). Both definitions also incorporate severity and duration of oliguria as alternative criteria.

Previous definitions have used absolute increases in SCr over baseline to define AKI (Table 1). The implications of the decision to use absolute or percentage increases in SCr to define AKI have not to our knowledge been explicitly explored, particularly in the context of the time over which SCr rises.

Presumably, defining AKI by higher SCr thresholds in patients with higher baseline SCr levels (*i.e.*, chronic kidney disease [CKD]) is based on the well-described inverse correlation between creatinine clearance (CrCl) and SCr. If all determinants of SCr concentration are kept constant except for CrCl,

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**Table 1. SCr-based definitions of AKI**

Parameter	Definition
Acute Kidney Injury Network <sup>2</sup>	Stage 1: $\geq 0.3$ -mg/dl increase or 50% increase over baseline within 48 h Stage 2: $\geq 100\%$ increase over baseline (doubling) Stage 3: $\geq 200\%$ increase over baseline or 0.5-mg/dl increase to at least 4.0 mg/dl
Acute Dialysis Quality Initiative <sup>1</sup>	RIFLE "R": $\geq 50\%$ increase over baseline RIFLE "I": $\geq 100\%$ increase over baseline (doubling) RIFLE "F": $\geq 200\%$ increase over baseline or $\geq 0.5$ -mg/dl increase to at least 4.0 mg/dl
Contrast nephropathy <sup>9</sup>	$\geq 0.5$ -mg/dl increase or 25% increase over baseline
Hou et al. <sup>26</sup>	$\geq 0.5$ -mg/dl increase if admission SCr $\leq 1.9$ mg/dl $\geq 1.0$ -mg/dl increase if admission SCr of 2.0 to 4.9 $\geq 1.5$ -mg/dl increase if SCr $> 5.0$ mg/dl

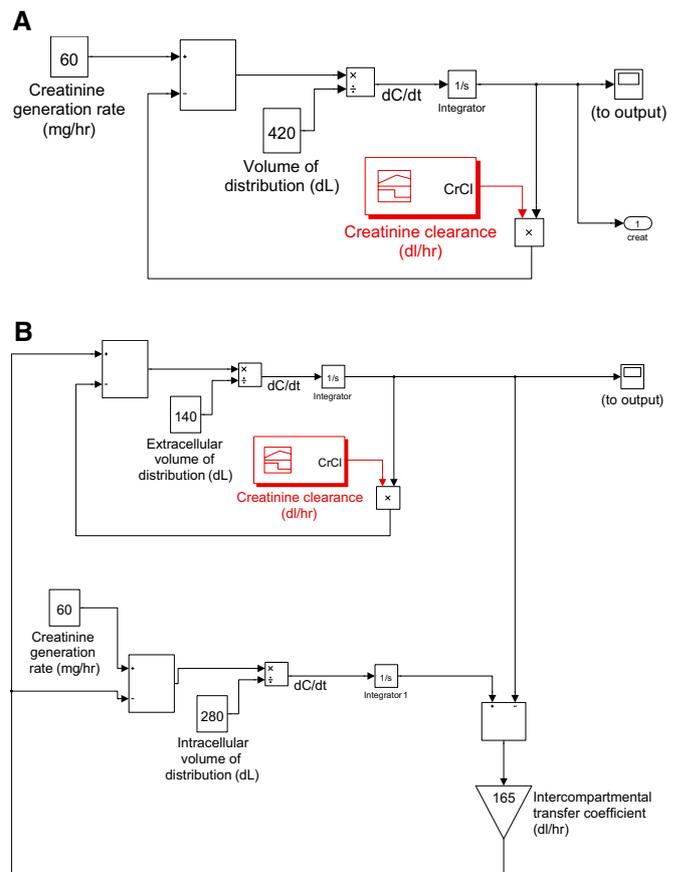
then a 50% reduction in CrCl from baseline will lead eventually (*i.e.*, at steady state) to a 100% increase in SCr, irrespective of the presence or absence of CKD. The steady state, however, may not be reached for several days after an episode of AKI.<sup>3,4</sup>

We hypothesized that the arbitrary percentage change thresholds incorporated in the RIFLE criteria<sup>1</sup> "R" and "I" and the second stage of the AKIN criteria<sup>2</sup> will significantly delay the diagnosis of AKI in patients with CKD, because the level of baseline kidney function may influence the kinetics of creatinine rise after an acute injurious event to the kidney. CKD, which may affect  $>10\%$  of the US population,<sup>5</sup> is a major risk factor for AKI and is present in  $>30\%$  of patients who develop severe AKI.<sup>6</sup> We therefore explored the implications of defining AKI by percentage *versus* absolute increases in patients with and without CKD in the time frames encountered in common clinical practice (*i.e.*, before steady state is achieved). To do this, we solved differential equations that describe SCr kinetics after a change in CrCl at various levels of baseline kidney function. We propose that the definition of AKI should take into account the time course of the increase in SCr, and that early after injury absolute increases in SCr are superior to percentage increases because of the effects of CKD on creatinine kinetics.

**RESULTS**

**Serum Creatinine after Changes in CrCl: One- versus Two-Compartment Models**

The one-compartment and two-compartment Simulink models used for analyses are shown in Figure 1. The change in SCr over time after an abrupt reduction in CrCl from 90 to 10

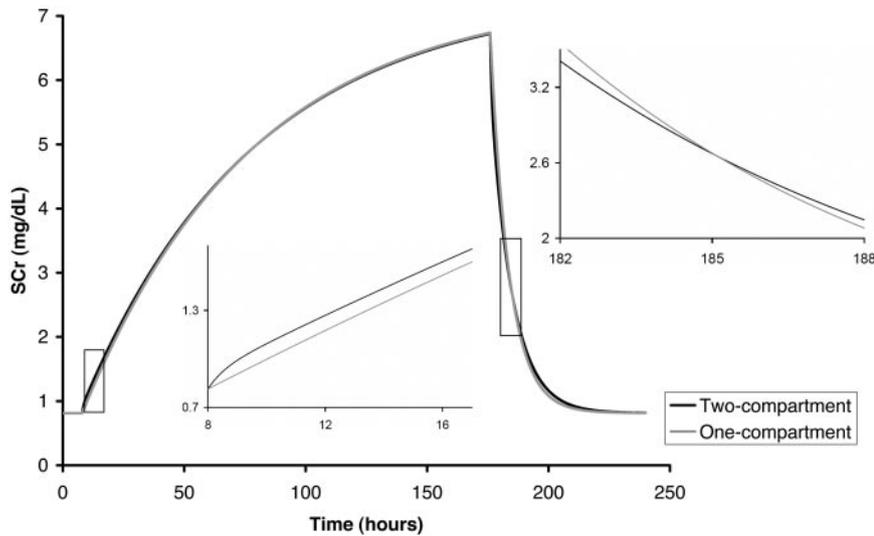


**Figure 1.** (A) One-compartment model of creatinine kinetics. (B) Two-compartment model of creatinine kinetics.

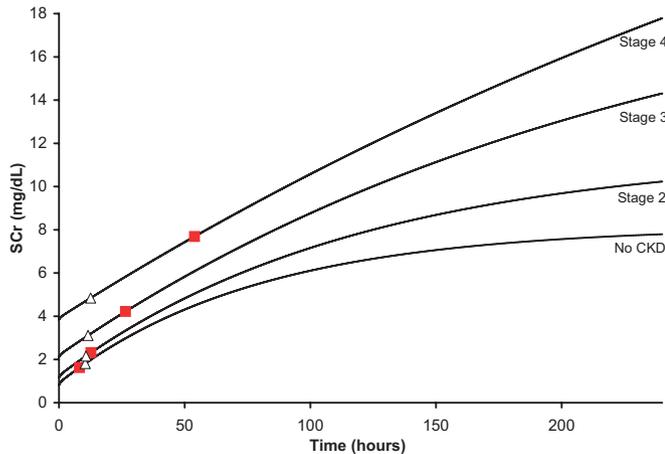
ml/min for 7 d followed by abrupt recovery back to 90 ml/min is shown in Figure 2. After changes in CrCl, the two-compartment model exhibited a higher initial rate of change followed later by a slower rate of change compared with the one-compartment model. Overall, the differences between the one- and two-compartment models were minor.

**Rise in SCr after AKI with and without Underlying CKD**

The rise in SCr after severe AKI, defined as a 90% reduction in CrCl from baseline, is shown in Figure 3 (two-compartment model), according to baseline kidney function (no CKD and stages 2, 3, and 4 CKD). At 24 h after severe AKI, the *absolute* increase in SCr is nearly identical (1.8 to 2.0 mg/dl) irrespective of whether CKD is present. By contrast, the *percentage* increases over baseline are 246% (no CKD), 173% (stage 2), 92% (stage 3), and 47% (stage 4). The results are similar for less severe AKI, defined as a 50% reduction in CrCl from baseline (Figure 4). After 24 h, the *absolute* increase in SCr ranges from 0.6 mg/dl (no CKD) to 0.9 mg/dl (stage 4), whereas the *percentage* increase in SCr ranges from 23% (stage 4) to 78% (no CKD). For both severe and less severe AKI, the time necessary to reach a 50% percent increase in SCr increases markedly with increasing stages of CKD, whereas the time necessary to reach an absolute 0.5-mg/dl increase remains relatively constant



**Figure 2.** The rise and fall of SCr after severe AKI and recovery. In this simulation, creatinine clearance dropped acutely by 90% at 8 h and then recovered acutely to baseline levels 7 d later. Results from one- and two-compartment models of creatinine kinetics are shown.



**Figure 3.** SCr concentrations after an abrupt 90% reduction in CrCl, superimposed on four different levels of baseline kidney function (no CKD and stages 2 through 4 CKD). Solid squares show the point at which a 100% increase in SCr has occurred; open triangles show the point at which a 1.0-mg/dl increase in SCr has occurred.

(Figures 3 and 4). Table 2 illustrates the application of the RIFLE criteria to AKI in patients with and without CKD and how different AKI stages are reached despite an identical reduction in CrCl.

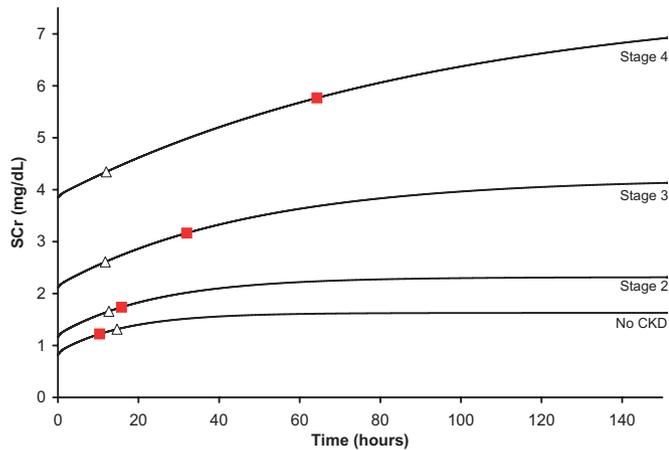
The trajectory of the SCr increase differs according to the severity of AKI and baseline kidney function, as seen in Figures 3 and 4. The time to reach within 0.1 mg/dl of predicted steady-state SCr concentrations is shown in Table 3, according to baseline kidney function and percentage reduction in CrCl. At any given level of baseline kidney function, the more severe the AKI, the longer it takes to approach steady-state SCr concentrations. Sim-

ilarly, at any given percentage reduction in CrCl, the higher the baseline SCr (*i.e.*, higher CKD stage), the longer it takes to approach steady-state SCr concentrations. Simple calculations from a single-compartment model also illustrate this point. A 100% increase in SCr from 2.0 to 4.0 mg/dl requires retention of 2.0 mg/dl creatinine throughout the volume of distribution (420 dl), or 840 mg of creatinine. By contrast, the same percentage increase from 1.0 to 2.0 mg/dl requires retention of 420 mg of creatinine. At a constant creatinine generation rate of 60 mg/h and complete cessation of CrCl, the time required to reach a 100% increase is 14 h, when baseline SCr is 2.0, and 7 h, when baseline SCr is 1.0 mg/dl.

**Time to Reach Absolute versus Percentage End Points after AKI**

The differential equation used to describe a one-compartment model of creatinine kinetics can be solved for time (see equation 5, Appendix). The equation was used to examine the time required to reach a given end point in SCr after a given reduction in CrCl. Figure 5 shows the time to reach a 50% increase in SCr as a function of percentage reduction in CrCl for varying levels of baseline kidney function, whereas Figure 6 shows the same analysis for an absolute 0.5-mg/dl increase in SCr. As seen in Figure 5, at any given reduction in CrCl from baseline, the time to reach a 50% increase in SCr is greater for increasing stages of CKD. For example, after complete cessation of CrCl (*e.g.*, anuric AKI), SCr increases by 50% after 4 h in the case of no preexisting CKD, whereas it takes 23 h to achieve a 50% increase in SCr for a patient with stage 4 CKD. By contrast, when the criterion is an absolute increase in SCr, the results are very different. As seen in Figure 6, the time to reach a 0.5-mg/dl increase in SCr is virtually identical after  $\geq 50\%$  reductions in CrCl irrespective of baseline kidney function. The curves begin to diverge at CrCl reductions  $< 50\%$ ; after less severe AKI, such as a 30% reduction in CrCl, a 0.5-mg/dl increase never occurs in the setting of no preexisting CKD and stage 2 CKD, whereas it occurs after 24 h in the setting of stage 4 CKD. By contrast, as shown in Figure 5, a 50% increase in SCr never occurs at any level of baseline kidney function after a 30% decline in CrCl. Results using the one- or two-compartment model of creatinine kinetics were similar (data not shown).

The CrCl reduction required to account for a given rise in SCr over time *t* can be calculated (equation 4, Appendix). The equation was used to compare the implications of absolute versus percentage increases in SCr as the definition of AKI. For these analyses, we compared absolute cutoffs of 0.3-, 0.5-, 1.0-, and 1.5-mg/dl increases against the RIFLE criteria (Table 1) at 12, 24, and 48 h. Ideally, a given stage of AKI should denote a similar reduction in CrCl across a range of baseline kidney function. As shown in Table



**Figure 4.** SCr concentrations after an abrupt 50% reduction in CrCl, superimposed on four different levels of baseline kidney function (no CKD and stages 2 through 4 CKD). Solid squares show the point at which a 100% increase in SCr has occurred; open triangles show the point at which a 1.0-mg/dl increase in SCr has occurred.

4, this is the case when using absolute increases in SCr to define AKI at early stages after injury. Table 4 also highlights the importance of considering the time over which SCr rises when inferring the degree of AKI: A patient who has stage 4 CKD and whose SCr increases by 0.3 mg/dl over 12 h has suffered a 33% reduction in CrCl; the same absolute increase over 48 h corresponds to a modest 11% reduction in CrCl (assuming constant generation rate and volume of distribution).

## DISCUSSION

The lack of a standardized definition of AKI has been lamented for years. The recent introduction of consensus definitions (RIFLE<sup>1</sup> and AKIN<sup>2</sup>) was widely hailed by the nephrology and critical care communities as an important step forward in the effort to launch high-quality observational, prevention, and interventional studies in AKI.

The choice of a definition for AKI has critical consequences. The definition directly determines our estimates of the incidence, costs, and outcomes of AKI. It influences the timing of consultation to nephrologists across the world. It shapes the way interventional and prevention studies are performed. It influences our analysis of novel biomarker studies that aim to replace serum creatinine as the diagnostic gold standard.

Our studies of creatinine kinetics have uncovered a significant and previously unrecognized flaw in definitions of AKI that use percentage increases in SCr over baseline. In patients with CKD (high baseline SCr), any given percentage reduction in CrCl will lead to a slower rate of rise in SCr compared with a patient without CKD. This results in a different classification of AKI severity depending on baseline kidney function despite an identical percentage reduction in CrCl (see Table 2). Although the percentage increase in SCr after AKI at steady state

does not depend on baseline kidney function (*i.e.*, a 50% reduction in CrCl will lead to a 100% increase in SCr no matter the baseline), it is important to note that steady state may not be achieved in clinically relevant time frames. As shown in Figures 2 and 3, steady state may not be achieved for days after a sustained reduction in CrCl and in fact takes longer to achieve at higher baseline SCr (Table 3).

Accounting for CKD in a definition of AKI is essential. CKD is a clearly established risk factor for AKI<sup>7–12</sup> and was present in >30% of patients in large cohort studies of established AKI.<sup>6,13</sup> The importance of accounting for CKD in definitions of AKI has been noted by others,<sup>14,15</sup> but the implications of elevated baseline SCr on AKI definitions have not been investigated to date.

The implications of time required for changes in SCr after a reduction in renal function are not simply theoretical. Consider the design of an interventional study in AKI that initiates a therapeutic agent at the earliest stage of AKI by the RIFLE criteria (*i.e.*, 50% increase in SCr over baseline). The time of entry into the study would depend not only on the degree of kidney injury but also on the baseline SCr level. Using percentage increases as criteria for AKI diagnosis would lead to delayed enrollment of patients with CKD. Indeed, the bias against diagnosing patients with CKD as having AKI by percentage increases in SCr has been borne out in a clinical study. Shaw *et al.*<sup>16</sup> studied the effect of aprotinin on outcomes after cardiac surgery ( $n = 10,275$ ), including renal outcomes analyzed as percentage increases in SCr over baseline values. In a multivariable linear regression model, the investigators found an inverse relationship between baseline SCr and percentage change in SCr: Patients with higher baseline SCr had on average *lower* percentage increases in SCr after cardiac surgery, despite that CKD is a clear risk factor for AKI after cardiac surgery.<sup>7,10</sup> The probable reason for this seemingly paradoxical finding is that the percentage rate of rise in SCr after AKI is slower at higher baseline SCr, as shown here.

Ideally, a creatinine-based definition of AKI would take into account a patient's creatinine generation rate, volume of distribution of creatinine, and dynamic changes over time as well as "renal reserve." These variables, of course, are not predictable and even if they could be modeled or estimated would lead to an unwieldy tool for diagnostic purposes. On the basis of our simulation studies, an absolute increase in SCr seems to be better suited for the early diagnosis of AKI than a percentage increase.

What are the problems, then, with using an absolute increase in SCr to define AKI? Objections may be raised at both ends of the spectrum of baseline SCr. Individuals with low SCr (pregnant women, children, and those with cirrhosis or muscle wasting) may not be adequately identified as having AKI using absolute cutoffs of SCr equal in magnitude to the ones used for patients with higher baseline SCr. For such individuals, smaller increases may be preferable (*e.g.*, AKIN stage 1, which defines AKI as a 50% increase when SCr is  $\leq 0.6$  mg/dl). It is worth noting from Figures 5 and 6 that a 30% reduction in CrCl never leads to a 50% increase in SCr (the earliest stage of the RIFLE criteria) and leads only to a 0.5-mg/dl increase in SCr in advanced CKD. In advanced CKD (high baseline SCr), relatively

**Table 2.** Classification of AKI as proposed by the RIFLE criteria after severe (90% reduction in CrCl) and moderate (50% reduction in CrCl) AKI, according to baseline level of kidney function<sup>a</sup>

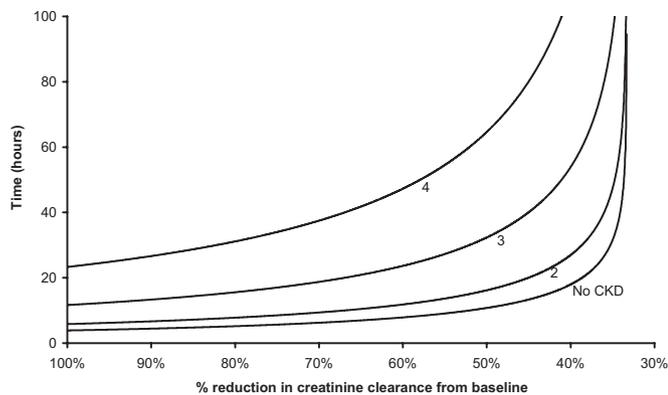
Parameter	Hours after AKI				
	12	24	36	48	72
90% reduction in CrCl					
no CKD	Injury	Failure	Failure	Failure	Failure
stage 2 CKD	Risk	Injury	Failure	Failure	Failure
stage 3 CKD	None	Failure	Failure	Failure	Failure
stage 4 CKD	Failure	Failure	Failure	Failure	Failure
50% reduction in CrCl					
no CKD	Risk	Risk	Risk	Risk	Injury
stage 2 CKD	None	Risk	Risk	Risk	Risk
stage 3 CKD	None	None	Risk	Risk	Risk
stage 4 CKD	Failure	Failure	Failure	Failure	Failure

<sup>a</sup>Results were obtained using a two-compartment model of creatinine kinetics. Risk:  $\geq 50\%$  increase in SCr over baseline; Injury:  $\geq 100\%$  increase; Failure:  $\geq 200\%$  increase or  $\geq 0.5$ -mg/dl increase to at least 4.0 mg/dl.

**Table 3.** Time (hours) to reach within 0.1 mg/dl of predicted steady-state SCr concentration after a given reduction in CrCl<sup>a</sup>

Parameter	Reduction in CrCl		
	75%	50%	25%
No CKD	102	34	10
Stage 2 CKD	159	59	21
Stage 3 CKD	223	139	62

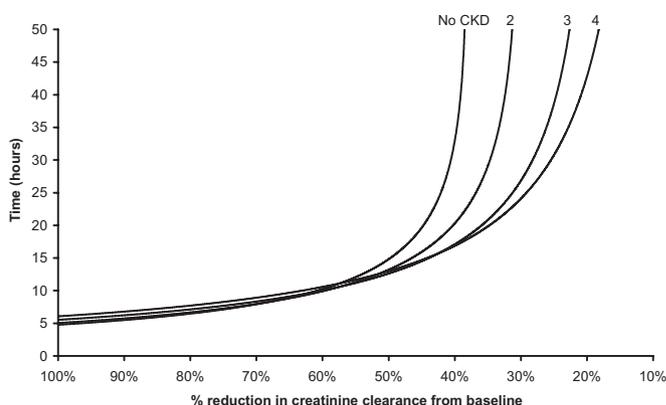
<sup>a</sup>Results were obtained using a two-compartment model of creatinine kinetics.



**Figure 5.** Time to reach a 50% increase in SCr after a given percentage reduction in CrCl, according to the absence or presence of stages 2 through 4 CKD 4.

minor and perhaps physiologically irrelevant reductions in CrCl will lead to small increases in SCr: In stage 4 CKD, a 0.3-mg/dl increase in SCr over 48 h requires only an 11% reduction in CrCl (Table 4). Importantly, when the same increase in SCr occurs over 12 h, the reduction in CrCl is 33%.

Our results suggest that recently proposed definitions of AKI using percentage increases in SCr (e.g., RIFLE<sup>1</sup> stages “R” and “I” and AKIN<sup>2</sup> stage 2) may not perform adequately in patients with CKD and that absolute increases in SCr are more appropriate to define AKI at early time points after injury (e.g., AKIN stage 1). Percentage increases in SCr reasonably reflect changes in CrCl at steady state, assuming that AKI is sustained (i.e., CrCl is reduced



**Figure 6.** Time to reach a 0.5-mg/dl increase in SCr after a given percentage reduction in CrCl, according to the absence or presence of stages 2 through 4 CKD.

and stays at a constant level over  $\geq 48$  h); however, steady state may not be achieved for days in the case of severe and sustained reductions in GFR. Importantly, steady state may not be achieved in the case of transient reductions in CrCl, which may be common clinically. In such cases, absolute increases in SCr are superior to percentage increases in identifying AKI. Our results highlight the importance of considering the time over which SCr increases take place, particularly when considering small changes in SCr, such as the 0.3-mg/dl cut point suggested by AKIN.

Our calculations are based on theoretical considerations of mass balance principles assuming constant values of several important variables, including creatinine generation rate and volume of distribution. On the basis of the calculations presented in Table 4, we propose the following SCr-based definition for AKI, which applies more equally across the spectrum of baseline kidney function:

**Stage 1:** A 0.3-mg/dl increase over 24 h or a 0.5-mg/dl increase over 48 h.

Rationale: An increase of 0.3 in 24 h corresponds to a 19 to 29% reduction in CrCl; an increase of 0.5 mg/dl over 48 h corresponds to a 19 to 39% reduction in CrCl.

**Table 4.** Percentage reduction in CrCl required to achieve a given SCr-based definition of AKI over a given period (12, 24, or 48 h), according to the presence or absence of CKD<sup>a</sup>

Time	SCr					RIFLE <sup>1</sup>				
	Rise (mg/dl)	No CKD (%)	Stage 2 CKD (%)	Stage 3 CKD (%)	Stage 4 CKD (%)	Class	No CKD (%)	Stage 2 CKD (%)	Stage 3 CKD (%)	Stage 4 CKD (%)
12 h	0.3	37	35	33	33	R	47	59	98	54
	0.5	55	53	52	54	I	77	98	–	54
	1.0	87	89	94	100	F	–	–	–	54
24 h	0.3	29	25	20	19	R	37	42	59	30
	0.5	43	37	32	30	I	58	67	91	30
	1.0	65	61	57	57	F	83	99	91	30
48 h	0.3	27	21	14	11	R	34	35	42	19
	0.5	39	31	23	19	I	51	54	63	19
	1.0	57	50	40	34	F	70	76	63	19
	1.5	68	62	54	49					

<sup>a</sup>The absolute rise in SCr required for RIFLE “R” was 0.4, 0.6, 1.1, and 0.5 mg/dl for no CKD (baseline SCr 0.8), stage 2 CKD (baseline SCr 1.2), stage 3 CKD (baseline SCr 2.1), and stage 4 CKD (baseline SCr 3.8), respectively; for RIFLE “I” 0.8, 1.2, 1.9, and 0.5 mg/dl; and for RIFLE “F” 1.6, 2.3, 1.9, and 0.5 mg/dl, respectively. Missing values denote that AKI cannot be reached within the time frame specified even with 100% reduction in CrCl.

**Stage 2:** A 0.5-mg/dl increase over 24 h or a 1.0-mg/dl increase over 48 h.

**Rationale:** An increase of 0.5 mg/dl over 24 h corresponds to a 30 to 43% reduction in CrCl; an increase of 1.0 mg/dl over 48 h corresponds to a 34 to 57% reduction in CrCl.

**Stage 3:** A 1.0-mg/dl increase over 24 h or a 1.5-mg/dl increase over 48 h.

**Rationale:** An increase of 1.0 mg/dl over 24 h corresponds to a 57 to 65% reduction in CrCl; an increase of 1.5 mg/dl over 48 h corresponds to a 49 to 68% reduction in CrCl.

Our proposal incorporates absolute rather than percentage increases in SCr as the basis to define AKI. Most important, we incorporate time as well as magnitude of SCr increases into the assessment of AKI severity. Our definition differs slightly from stage I AKI of AKIN, which includes a 48-h period for a 0.3-mg/dl increase or 50% increase in SCr. According to our calculations, 0.3 mg/dl increases in SCr are likely significant only when they occur within 24 h, and 0.5 mg/dl is a more appropriate cutoff for a 48-h period. The inclusion of a 50% increase in the AKIN definition was designed to capture AKI in children and those with low SCr as a result of other causes (e.g., liver disease, pregnancy, malnutrition) and is a reasonable addition to our proposed stage 1 AKI in these populations, if the rise occurs over 24 hr. It should be noted that we limit the period of observation changes in SCr to 48 h. The potential disadvantage is that patients with subacute rises in SCr may not be captured as having AKI if the daily increase in SCr is <0.3 mg/dl. The extent to which such subacute rises in SCr occur and their significance and prognosis compared with more acute rises is unknown and should be studied.

Epidemiologic studies should examine the pattern of SCr rise—in both magnitude and rate—and their associations with clinically relevant outcomes including mortality (in-hospital and longer term) as well as long-term changes in kidney function to validate and/or refine our suggestions. Previous studies have examined different SCr thresholds (absolute and percent-

age) as the basis for defining AKI,<sup>17,18</sup> but the time over which SCr increased was not investigated.

The ideal diagnosis of AKI may rest on the validation of emerging urinary and/or serum tissue injury biomarkers<sup>19–21</sup> that do not suffer the drawbacks of glomerular filtration markers such as creatinine or cystatin C. If SCr is used as the diagnostic criterion for AKI, then we suggest that the definition proposed here may be well suited to the task.

## CONCISE METHODS

According to basic mass balance principles, the change in the amount of creatinine in the body over a given time  $\Delta t$  is equal to the amount of creatinine generated over time  $\Delta t$  minus the amount of creatinine excreted over time  $\Delta t$ . We solved differential equations that describe both one- and two-compartment models of creatinine kinetics (see Appendix for equations). We used the software packages Matlab and Simulink (The Mathworks, Natick, MA), a graphic environment that enables simulation of time-varying systems. The simulations permitted independent adjustment of baseline SCr and all of the determinants of SCr listed in equations 1 through 7 in the Appendix. Time-varying determinants were entered using a graphic signal generator, which permitted ramp or step changes over time. Diagrams of the one- and two-compartment models used in Simulink are shown in Figure 1. We used a variable-step continuous solver using the fourth-order integration technique of Runge-Kutta with a maximum step size of 6 min. We confirmed that the single-compartment model simulated in Simulink produced identical results (to the fourth decimal place) compared with directly calculated values from the differential equation 2.

## Values Used in Simulation Studies

We examined SCr kinetics in simulation studies across a spectrum of baseline kidney function, as defined by baseline estimated GFR (eGFR)<sup>22</sup>: 90 (no CKD), 60 (stage 2 CKD), 30 (stage 3 CKD), and 15 ml/min per 1.73 m<sup>2</sup> (stage 4 CKD). According to an estimating equa-

tion for eGFR,<sup>23</sup> the corresponding baseline SCr levels were 0.8, 1.2, 2.1, and 3.8 mg/dl, respectively; the corresponding creatinine generation rates (eGFR \* SCr) were 1056, 1000, 912, and 831 mg/d. We assumed no extrarenal degradation of creatinine and equivalence of CrCl and eGFR. For all simulations, the volume of distribution was set at 42 L for the one-compartment model and 28 L intracellular and 14 L extracellular for the two-compartment model;  $K_{ie}$  for the two-compartment model was set at 275 ml/min.<sup>24</sup>

## APPENDIX

According to basic mass balance principles, the change in the amount of creatinine in the body over time  $\Delta t$  is equal to the amount of creatinine generated over time  $t$  minus the amount of creatinine excreted over time  $\Delta t$ . Let  $G$  be the generation rate of creatinine;  $C$ , the serum creatinine concentration;  $V$ , the volume of distribution of creatinine; and  $K$ , creatinine clearance. In a single-compartment model, as  $\Delta t$  approaches 0, the following differential equation can be written:

$$d(CV)/dt = G - KC$$

Applying the product rule:

$$(VdC/dt) + (CdV/dt) = G - KC$$

Rearranging this equation:

$$dC/dt = [G - KC - (CdV/dt)]/V \quad (1)$$

When  $dV/dt$  is 0 (*i.e.*, no change in volume of distribution), equation 1 becomes

$$dC/dt = [G - KC]/V \quad (2)$$

Rearranging this equation:

$$dC/dt + KC/V - G/V = 0 \quad (3)$$

The general solution of the above differential equation is

$$C(t) = G/K + [C_0 - G/K] * e^{-Kt/V} \quad (4)$$

The time required for serum creatinine to increase from  $C_0$  to  $C_t$  can be described by

$$t = -V/K * \ln [(C_t - G/K)/(C_0 - G/K)] \quad (5)$$

The creatinine clearance ( $K$ ) required to account for a given increase in SCr from  $C_0$  to  $C(t)$  over time  $t$  can be calculated using equation 4, which cannot be solved exactly but can be approximated by graphic means.

Equations 1 through 5 assume a single-compartment model for creatinine: The generation and clearance of creatinine both occur in a single theoretical compartment where creatinine is uniformly distributed (*i.e.*, the extracellular volume). In fact, creatinine is generated primarily intracellularly in skeletal muscle as a result of the nonenzymatic dehydration of muscle creatine and phosphocreatine<sup>25</sup>; therefore, creatinine must dif-

fuse out of skeletal muscle cells and into the circulating extracellular volume before being cleared by the kidney.

A two-compartment model better represents the metabolism of creatinine, where creatinine is generated intracellularly and then diffuses by first-order kinetics into the extracellular space, where clearance by the kidney occurs. To evaluate the importance of considering this in the simulation, let  $K_{ie}$  represent the intercompartmental mass transferrate (a clearance term) between the intra- and extracellular compartments, denoted by the subscripts  $i$  and  $e$ , respectively. The kinetics of intracellular creatinine metabolism can then be described by the following equation (assuming no change in volume of distribution of the intra- or extracellular compartments):

$$dC_i/dt = [G - K_{ie} * (C_i - C_e)]/V_i \quad (6)$$

The extracellular creatinine concentration can then be described by

$$dC_e/dt = [K_{ie} * (C_i - C_e)] - KC_e/V_e \quad (7)$$

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## DISCLOSURES

None.

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