KDOQI Commentary

KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury

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In response to the recently released 2012 KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for acute kidney injury (AKI), the National Kidney Foundation organized a group of US experts in adult and pediatric AKI and critical care nephrology to review the recommendations and comment on their relevancy in the context of current US clinical practice and concerns. The first portion of the KDIGO guideline attempts to harmonize earlier consensus definitions and staging criteria for AKI. While the expert panel thought that the KDIGO definition and staging criteria are appropriate for defining the epidemiology of AKI and in the design of clinical trials, the panel concluded that there is insufficient evidence to support their widespread application to clinical care in the United States. The panel generally concurred with the remainder of the KDIGO guidelines that are focused on the prevention and pharmacologic and dialytic management of AKI, although noting the dearth of clinical trial evidence to provide strong evidence-based recommendations and the continued absence of effective therapies beyond hemodynamic optimization and avoidance of nephrotoxins for the prevention and treatment of AKI.

Am J Kidney Dis. 2013;61(5):649-672. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is a US Government Work. There are no restrictions on its use.

INTRODUCTION

KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative to develop and implement clinical practice guidelines for patients with kidney disease. In March 2012, KDIGO published its guideline for the evaluation and management of acute kidney injury (AKI). This guideline covers numerous topics, including the definition and classification of AKI, the prevention and treatment of AKI in general with specific recommendations for the prevention of contrast-induced AKI, and the management of renal replacement therapy (RRT) in patients with AKI. Because international guidelines need to be adapted for the United States, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) convened a multidisciplinary work group with expertise in adult and pediatric nephrology and critical care medicine to comment on the applicability and implementation of the KDIGO AKI guideline in the United States. This commentary provides a summary of the KDIGO recommendation statements along with the supporting rationales and comments on their applicability to clinical practice in the United States. The KDOQI Work Group congratulates KDIGO, the members of the AKI Guideline Work Group, and the evidence review team for producing such a comprehensive document and believes that this guideline will be of great value to health professionals and will advance both current clinical care of patients with AKI and future clinical research.

AKI represents the sudden loss of kidney function, generally occurring over the course of hours to days and resulting in the retention of metabolic waste products and dysregulation of fluid, electrolyte, and acid-base homeostasis. During the past decade, this acute loss of kidney function, previously referred to as acute renal failure, has been the subject of significant re-examination, with increased recognition of the impor-
Our understanding of the epidemiology of AKI and interpretation of results across clinical trials has been hindered by the prior absence of a broadly accepted clinical definition, with more than 30 operational definitions of AKI used in published studies. During the past decade, there has been a considerable effort to forge a consensus definition. The first attempt at developing a consensus definition, known as the RIFLE criteria, was developed by the Acute Dialysis Quality Initiative (ADQI) in 2002 (Table 1). This definition considered 3 strata of severity (risk, injury, and failure) based on the magnitude of increase in serum creatinine level and/or the duration of oliguria, as well as 2 outcome stages (loss of kidney function and end-stage kidney disease). The risk, injury, and failure categories were constructed to provide gradations in severity of kidney dysfunction, with greater sensitivity associated with risk and greater specificity with failure. The RIFLE criteria subsequently were modified by the AKI Network (AKIN) by the addition of an absolute increase in serum creatinine level >0.3 mg/dL or on RRT, renal replacement therapy; SCr, serum creatinine.

<table>
<thead>
<tr>
<th>Class</th>
<th>SCr*</th>
<th>Urine Output (common to both)</th>
<th>Stage</th>
<th>SCr‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Increased SCr to &gt;1.5× baseline</td>
<td>Urine output &lt;0.5 mg/kg/h for &gt;6 h</td>
<td>1</td>
<td>Increase in SCr ≥0.3 mg/dL or increase in SCr to ≥150%-200% of baseline</td>
</tr>
<tr>
<td>Injury</td>
<td>Increased SCr to &gt;2× baseline</td>
<td>Urine output &lt;0.5 mg/kg/h for &gt;12 h</td>
<td>2</td>
<td>Increase in SCr to &gt;200%-300% of baseline</td>
</tr>
<tr>
<td>Failure</td>
<td>Increased SCr to &gt;3× baseline; or an increase of ≥0.5 mg/dL to a value of ≥4 mg/dL</td>
<td>Urine output &lt;0.3 mg/kg/h for &gt;12 h or anuria for &gt;12 h</td>
<td>3</td>
<td>Increase in SCr to &gt;300% of baseline; or to ≥4 mg/dL with an acute increase of ≥0.5 mg/dL; or on RRT</td>
</tr>
</tbody>
</table>

Loss       | Need for RRT for >4 wk |
End Stage   | Need for RRT for >3 mo |

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; RIFLE, risk, injury, failure, loss, end-stage disease; RRT, renal replacement therapy; SCr, serum creatinine.

*For RIFLE, the increase in SCr should be both abrupt (within 1-7 days) and sustained (>24 hours).
‡For AKI, the increase in SCr must occur in less than 48 hours.

AKI may develop in a wide variety of settings, including in ambulatory outpatients, hospitalized patients, and, in particular, critically ill patients, for whom AKI represents a common complication of both underlying disease and treatment. AKI is associated with substantial morbidity and mortality. For example, severe AKI occurs in >5% of critically ill patients and is associated with mortality rates of 40%-70%. Although recovery of kidney function occurs in the majority of patients surviving an episode of AKI, many patients remain dialysis dependent or are left with severe renal impairment. More recently, it has been recognized that even patients who have complete or near-complete recovery of kidney function are at increased risk of progressive chronic kidney disease (CKD) and that superimposition of AKI on CKD is associated with acceleration in the rate of progression to end-stage disease.

Table 2. Pediatric Modified RIFLE (pRIFLE) Criteria for Diagnosis and Classification of AKI in Children

<table>
<thead>
<tr>
<th>Class</th>
<th>eCCr</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>eCCr decrease by &gt;25%</td>
<td>Urine output &lt;0.5 mL/kg/h for &gt;8 h</td>
</tr>
<tr>
<td>Injury</td>
<td>eCCr decrease by &gt;50%</td>
<td>Urine output &lt;0.5 mL/kg/h for &gt;16 h</td>
</tr>
<tr>
<td>Failure</td>
<td>eCCr decrease by &gt;75%; or eCCr &lt;35 mL/min/1.73 m²</td>
<td>Urine output &lt;0.3 mL/kg/h for &gt;12 h; or anuria for &gt;12 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent failure for &gt;4 wk</td>
<td></td>
</tr>
<tr>
<td>End Stage</td>
<td>Persistent failure for &gt;3 mo</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations and definitions: AKI, acute kidney injury; eCCr: estimated creatinine clearance using the Schwartz formula; RIFLE, risk, injury, failure, loss, end-stage disease.

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mg/dL to the definition of AKI, a shortening of the time for the increase in serum creatinine level from 7 days to no more than 48 hours, and elimination of the 2 outcome criteria (Table 1). A modification of the RIFLE criteria for use in pediatric patients (pRIFLE) has also been developed (Table 2). Validation studies using these definitions have demonstrated increased mortality risk associated with progressively more severe stages of AKI. The KDIGO AKI guideline builds upon these earlier efforts in defining AKI, with a full section of the guideline devoted to the definition of AKI.

The development of successful therapeutic strategies for the prevention and treatment of most forms of AKI has been disappointing. Although numerous agents have shown promise in experimental models, none has demonstrated utility in clinical care. A particular area of focus has been in the prevention of contrast-induced AKI. This common cause of AKI has been the focus of multiple preventative interventions because individuals at high risk of contrast-induced AKI can be readily identified and the timing of exposure can be predetermined, allowing an opportunity for intervention. In the absence of effective pharmacologic therapy, the management of established AKI is predominantly supportive care, with the use of RRT in severe AKI. There has been tremendous advancement in the technology and modalities available for providing RRT; however, the optimal approach to management of RRT in this setting remains controversial. The KDIGO AKI guideline provides specific recommendations, based on the current literature, for best practices in the prevention and management of AKI. In this KDQI commentary, we have attempted to place this international guideline in the context of care practices in the United States. However, our commentary should be viewed in conjunction with the full KDIGO document when making clinical decisions.

**REVIEW AND APPROVAL PROCESS FOR THIS COMMENTARY**

This commentary was developed by a Work Group convened by the NKF-KDOQI, beginning with selecting Co-Chairs by the KDOQI steering committee and individual members selected based on their clinical expertise and interest in the guideline process. Teleconferences took place during 2011 and 2012 to determine the specific areas for focus for this commentary. Individual sections focusing on each of the topical areas of the KDIGO AKI guideline were drafted by groups of coauthors based on detailed review of the particular KDIGO chapter supplemented by additional literature review, as needed. Because this was a commentary, no specific voting occurred; rather, consensus among coauthors was achieved through discussion. The document was reviewed and approved by all coauthors and by the KDOQI leadership.

**ASSESSMENT OF GUIDELINE QUALITY**

The KDIGO AKI guideline contains 87 individual recommendations, of which 26 (30%) are ungraded, 39 (45%) are level 2 recommendations, and only 22 (25%) are level 1 recommendations, reflecting the relative paucity of high-level data guiding the management of AKI. In addition, many of the level 1 recommendations advise against the use of specific agents or therapeutic interventions.

All members of the Work Group completed the AGREE (Appraisal of Guideline for Research and Evaluation) II instrument to assess the quality of the KDIGO AKI guideline. Mean Work Group scores for each of the 23 elements and scaled domain scores for the 6 domains are provided in Table 3, along with the scoring range for domain and overall scores. The domain scores ranged from 0.53 for applicability to 0.85 for editorial independence. The mean overall score provided was 5.3 ± 1.0 on a 7-point scale. All Work Group members recommended the KDIGO AKI guideline for use, although the majority suggested that modifications could improve the guideline.
Definition and Classification of AKI

Overview. The first group of recommendation statements in the KDIGO AKI Guideline addresses the definition of AKI (Box 1). Of these 13 recommendation statements, 12 are not graded. The KDIGO Work Group began by defining AKI by harmonizing the prior RIFLE and AKIN criteria. In the RIFLE criteria (Table 1), AKI was defined based on a ≥50% increase in serum creatinine level occurring over 1-7 days or the presence of oliguria for more than 6 hours. The AKIN criteria added an absolute increase in serum creatinine level of 0.3 mg/dL and reduced the timeframe for the increase in serum creatinine level to 48 hours (Table 1). The KDIGO Work Group harmonized these 2 definitions, keeping the absolute increase in serum creatinine level of ≥0.3 mg/dL within 48 hours from the AKIN definition, but returning to
the 7-day timeframe for the \( \geq 50\% \) increase in serum creatinine level. With regard to pediatric AKI, the KDIGO definition did not adopt the smaller changes in estimated creatinine clearance proposed in the pRIFLE criteria. Rather, the KDIGO Work Group suggested that the absolute change in creatinine level of \( \geq 0.3 \text{ mg/dL} \) that is part of the KDIGO AKI definition would capture most pediatric AKI. The KDIGO definition considers a decrease in estimated glomerular filtration rate (eGFR) to \(< 35 \text{ mL/min/1.73 m}^2\) to be stage 3 AKI in pediatric patients, as initially proposed in the pRIFLE criteria.20

Overall, while our KDOQI Work Group concurred with the efforts on the part of KDIGO to meld the RIFLE and AKIN criteria into a uniform definition of AKI, we have significant reservations regarding the applicability of this definition and staging system to clinical practice. The RIFLE and AKIN definitions and staging systems have substantially enhanced the ability to conduct epidemiologic studies, and we support the use of the KDIGO AKI guideline definition and staging strategy for future epidemiologic research until novel biomarkers facilitate the development of better criteria. We concur that the rigorous application of a standard definition will permit epidemiologic comparisons across populations and over time. In addition, the definitions as described have value in standardization of entry criteria and endpoints in clinical trials of AKI. However, we question whether these criteria are currently appropriate to guide clinical management of adult patients.

The successive stages of a serum creatinine–based AKI definition reflect a tradeoff between sensitivity and specificity. At low stages, sensitivity is high (ie, almost every patient with true AKI is identified), but specificity is low (ie, many patients without true AKI are misidentified as having AKI). As part of the decision to recommend a cutoff value based on a biomarker such as serum creatinine or physiologic variable such as urine output, the implications of the cutoff need to be carefully considered. We thought that particularly in the United States, where defensive medicine is common due to the highly litigious environment in which many physicians practice, the KDIGO definition may result in a dramatic increase in nephrology consultations and have the unin-

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**Box 1. Summary of KDIGO Recommendation Statements: Definition of AKI.**

2.1.1: AKI is defined as any of the following (Not Graded):
- Increase in SCr by \( \geq 0.3 \text{ mg/dL} \) (\( \geq 26.5 \mu\text{mol/L} \)) within 48 hours; or
- Increase in SCr to \( \geq 1.5 \times \) baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume \(< 0.5 \text{ mL/kg/h} \) for 8 hours.

2.1.2: AKI is staged for severity according to the following criteria.\(^a\) (Not Graded)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase in SCr by 1.5–1.9 times baseline; OR increase in sSCr by ( \geq 0.3 \text{ mg/dL} ) (( \geq 26.5 \mu\text{mol/L} )); OR urine output (&lt; 0.5 \text{ mL/kg/h} ) for 6–12 hours</td>
</tr>
<tr>
<td>2</td>
<td>Increase in SCr by 2.0–2.9 times baseline; OR urine output (&lt; 0.5 \text{ mL/kg/h} ) for ( \geq 12 ) hours</td>
</tr>
<tr>
<td>3</td>
<td>Increase in SCr by 3.0 times baseline; OR increase in SCr to 4.0 mg/dL (353.6 ( \mu\text{mol/L} )); OR initiation of renal replacement therapy; OR in patients ( &lt; 18 ) years, decrease in eGFR to 35 mL/min/1.73 m(^2); OR urine output (&lt; 0.3 \text{ mL/kg/h} ) for ( \geq 24 ) hours; OR anuria for ( \geq 12 ) hours</td>
</tr>
</tbody>
</table>

2.1.3: The cause of AKI should be determined whenever possible. (Not Graded)

2.2.1: We recommend that patients be stratified for risk of AKI according to their susceptibilities and exposures. (1B)

2.2.2: Manage patients according to their susceptibilities and exposures to reduce the risk of AKI (see relevant guideline sections).

2.2.3: Test patients at increased risk for AKI with measurements of SCr and urine output to detect AKI. (Not Graded) Individualize frequency and duration of monitoring based on patient risk and clinical course. (Not Graded)

2.3.1: Evaluate patients with AKI promptly to determine the cause, with special attention to reversible causes. (Not Graded)

2.3.2: Monitor patients with AKI with measurements of SCr and urine output to stage the severity, according to Recommendation 2.1.2. (Not Graded)

2.3.3: Manage patients with AKI according to the stage (Fig 2) and cause. (Not Graded)

2.3.4: Evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. (Not Graded)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.2.1</td>
<td>If patients do not have CKD, consider them to be at increased risk for CKD and care for them as detailed in the KDOQI CKD Guideline 3 for patients at increased risk for CKD. (Not Graded)</td>
</tr>
<tr>
<td>2.1.2.2</td>
<td>If patients have CKD, manage these patients as detailed in the KDOQI CKD Guideline (Guidelines 7-15). (Not Graded)</td>
</tr>
<tr>
<td>2.1.2.3</td>
<td>Increase in SCr to ( 26.5 \mu\text{mol/L} ) (( 0.3 \text{ mg/dL} )) within 48 hours; or</td>
</tr>
<tr>
<td>2.1.2.4</td>
<td>Increase in SCr by ( \geq 0.3 \text{ mg/dL} ) (( \geq 26.5 \mu\text{mol/L} )); OR</td>
</tr>
<tr>
<td>2.1.2.5</td>
<td>If patients do not have CKD, consider them to be at increased risk for CKD and care for them as detailed in the KDOQI CKD Guideline 3 for patients at increased risk for CKD. (Not Graded)</td>
</tr>
</tbody>
</table>

**Note:** Conversion factor for SCr mg/dL to \( \mu\text{mol/L} \), \( \times 88.4 \).

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Reproduced with permission of KDIGO from the KDIGO Clinical Practice Guideline for Acute Kidney Injury.\(^1\)

\(^a\)The staging information is adapted from a table presented in the guideline.
tended adverse consequence of diverting limited resources toward a large number of patients for whom specialty referral may have uncertain benefit.

However, we recognize that the clinical application of the KDIGO AKI definition could increase the early recognition of AKI. Given the current lack of effective pharmacologic interventions for AKI, early recognition based on small changes in serum creatinine level or urine output could allow implementation of simple interventions—such as avoiding potentially nephrotoxic medications or diagnostic or therapeutic procedures that are associated with increased risk of AKI unless clearly clinically indicated, or judicious protocol-driven volume resuscitation—that could reduce the risk of more severe kidney injury.

In addition to these more global concerns, our Work Group identified several specific issues regarding the definition and staging criteria that we believe require specific comment, as discussed next.

Inclusion of urine output into the definition of AKI. Both RIFLE and AKIN included duration of oliguria in their definitions and staging criteria (Table 1). Several criticisms have been offered of these urine output criteria, many of which are acknowledged by the KDIGO AKI Guideline Work Group but deserve further mention. Only a small number of studies have examined the urine output criteria for AKI and correlated them with adverse clinical outcomes, in contrast to the numerous studies that have focused on the serum creatinine criteria. The studies that have evaluated the urine output component of the criteria have found poor calibration between these criteria and the serum creatinine criteria. Specifically, when assessed, there was poor prognostic correlation between the briefer durations of oliguria and small changes in serum creatinine level. Second, oliguria may be an appropriate response to volume depletion and hence reflect under-resuscitation rather than injury to the kidney, which is implicit in the term “AKI.” Therefore, even demonstrating an association between oliguria and adverse clinical outcomes is insufficient to justify its incorporation into the definition of AKI. Third, the use of a weight-based definition for AKI limits its use in the obese due to the nonlinear relationship between body weight and urine output. Under the current definition, urine output of 40 mL/h in a 90-kg patient for 12 hours would lead to classification as stage 2 AKI. Fourth, diuretic administration has been shown to change RIFLE classification by urine output criteria, as would be expected when a definition is based on a physiologic variable that can be manipulated pharmacologically. Finally, the use of oliguria in a definition of AKI may promote its use in clinical practice as a surrogate end point. We know from several studies that pharmacologic agents that can increase urine output independent of augmentation of kidney function, such as loop diuretics or dopamine, may not be helpful and may even be harmful in some settings. While the inclusion of these criteria in the AKI guideline may have the beneficial effect of encouraging more rigorous documentation of urine output and overall fluid balance in settings outside the operating room and critical care units, there are also risks of unintended consequences with defining transient oliguria as AKI. In particular, we believe that current data are inadequate to support the reliance on oliguria as a surrogate end point in clinical trials or in performance metrics. We note that pediatric, and in particular neonatal, providers rely heavily on urine output and weight-based fluid balance and therefore inclusion of these parameters in the pediatric AKI criteria is reasonable; furthermore, neonates in particular are unlikely to have morbid obesity and therefore the methodological issues with weight-based urine output are somewhat less problematic. Nonetheless, further research is needed in the pediatric population to determine what metrics are best used to define AKI, and practitioners should recognize that many of the same limitations to the use of urine output criteria apply in the pediatric population.

Use of small changes in serum creatinine to define AKI. The inclusion of a small absolute change in serum creatinine level in the AKIN definition of AKI was based on the demonstration by Chertow et al that minor fluctuations in serum creatinine concentration were strongly associated with adverse outcomes in a retrospective analysis of data from individuals hospitalized at a single medical center. Although the association remained, albeit attenuated, after multivariable adjustment, only administrative data were available for construction of the multivariable models, and residual confounding may have been present. Small changes in serum creatinine level have also been identified to be of prognostic importance in subsequent studies. Even a 0.1-mg/dL increase in serum creatinine level appears to be associated with increased risk compared to no change in serum creatinine level. Whether these small changes in serum creatinine level reflect clinically meaningful fluctuations in kidney function that are causally linked to adverse outcomes or are merely a marker of underlying vascular disease or diminished renal reserve, which could be the actual mediators of the adverse outcomes, remains unresolved. Furthermore, an implicit assumption underlying the incorporation of small changes in serum creatinine concentration into the definition of AKI is that GFR in an individual is constant over time and not subject to physiologic fluctuation. In addition, biological fluctuation in serum creatinine level may also result from variations in
diet, creatinine generation, tubular secretion, medications, and variability in sodium and volume homeostasis that are within the physiologic range. Such fluctuations in serum creatinine concentration are more prominent in individuals with decreased renal reserve or overt CKD. For all these reasons, an absolute change in serum creatinine level of 0.3 mg/dL may represent a relatively inconsequential change in GFR in patients with underlying CKD and not reflect superimposed acute pathology. Despite these concerns in adult patients, in neonatal/pediatric patients, such small changes in serum creatinine level may represent relatively large changes in actual GFR that should not be disregarded. Whether novel biomarkers of tubular injury may enhance risk stratification of patients with small changes in serum creatinine level is a question that requires further investigation and may lead to further refinement of AKI staging.

The independent role of duration of AKI. Several recent studies have suggested that duration of AKI may be a more important predictor of outcomes than the magnitude of change in serum creatinine level. For example, in one study, even a transient elevation in creatinine level (<3 days) was associated with increased risk of death, and the risk of mortality was greater in patients with prolonged duration of AKI. After adjustment for duration of AKI, staging was no longer predictive of adverse outcomes. Unfortunately, this important dimension can only be assessed retrospectively and cannot be included in prospective staging criteria; however, consideration should be given to including an assessment of duration of AKI in future criteria designed for epidemiologic studies.

Pediatric-specific concerns. The KDOQI Work Group also had several concerns regarding the application the KDIGO definition and staging of AKI to the pediatric population. One of the major concerns with both the RIFLE and AKIN criteria is that they are problematic for smaller (pediatric) patients with low muscle mass. The pRIFLE criteria were developed to address the issues of applying the adult criteria to the pediatric population. For example, because abnormally elevated serum creatinine measurements are often overlooked in pediatric patients (due to adult normative data in laboratory readouts), utilization of the pRIFLE criteria might improve identification of those with true AKI. The pRIFLE criteria have been used widely in pediatric clinical research and efforts are now being made to apply these criteria in clinical practice. However, there are significant differences between the KDIGO and pRIFLE criteria. Consequently, further validation will be required prior to the adoption of the KDIGO criteria into research and practice. Specifically, pediatric nephrologists will want to better understand whether the differences in the 2 definitions result in the identification of different patient groups, and if so, what systematic biases may be introduced by these differences. Thus, it was unclear to the KDOQI Work Group whether pediatric nephrologists would widely embrace the new KDIGO AKI definition or continue to apply the pRIFLE criteria.

In addition, most pediatric patients will not necessarily have had previous serum creatinine measurements and therefore baseline renal function determination is often assumed to be normal, which may be problematic. In addition, the neonatal population remains an enigma in terms of renal function determination, making both the definition and identification of AKI in this population difficult. Many neonates have not attained full renal mass development at birth and are obligatorily born with low GFR, which improves with growth and development. AKI in neonates is often associated with high urine output, which may go unrecognized given the paucity of serum creatinine measurements in this patient cohort. Finally, immediately after birth, serum creatinine level in neonates often reflects maternal creatinine levels, which must be considered when evaluating renal function. However, the recommendation of a 0.3-mg/dL increase in serum creatinine level (even in the context of baseline maternal creatinine level) should be sufficient to trigger concern, and this component of the definition is applicable in the neonatal population.

In addition to defining and staging AKI, the KDIGO guideline introduces the new term acute kidney disease (AKD), defined as AKI, or GFR < 60 mL/min/1.73 m² for less than 3 months, or a decrease in GFR by ≥35% or an increase in serum creatinine level by >50% for less than 3 months, or structural kidney damage of less than 3 months’ duration. While we understand the nosological rationale for developing terminology to describe patients with kidney disease that does not meet the criteria for either AKI or CKD, we have concern that the introduction of this terminology may confuse clinicians and inappropriately divert attention away from diagnostic considerations. While CKD encompasses a number of pathophysiologically and histopathologically distinct diseases, arguably the majority of patients with CKD have diseases such as hypertensive nephrosclerosis and diabetic nephropathy, for which treatment approaches are similar. However, in the acute setting, distinctions between causes of disease have greater consequence. To lump the broad range of conditions that result in acute and subacute kidney disease, ranging from acute tubular necrosis to obstructive uropathy, atheroembolic disease, and rapidly progressive glomerulonephritis, into the single umbrella term of AKD runs the risk of promoting diagnostic laziness among clinicians who...
would have a convenient name to apply rather than an abnormal laboratory value to investigate. We would have welcomed a more in-depth discussion of what specific kidney diseases are likely to segregate to AKD as opposed to AKI or CKD and how the introduction of a new term was thought by the authors to help in clinical practice. While AKD may be a useful construct in epidemiologic studies, we believe the use of this term should be discouraged in clinical practice.

In contrast to our reservations regarding the introduction of the AKD terminology, we strongly concur with the KDIGO recommendations that the cause of AKI should be determined whenever possible and that patients with AKI should be evaluated promptly to determine the cause, with special attention to reversible causes. However, our Work Group had several concerns regarding several of the other recommendations related to the evaluation and general management of patients with and at risk of AKI. Specifically, our Work Group has concerns regarding the recommendation to manage patients with AKI according to the stage and cause. We believe that the stage-based management recommendations (Fig 2) are not adequately evidence based. These recommendations implicitly assume homogeneity within each AKI stage and successive increases in severity across stages. As a result of the lack of correlation between serum creatinine level and GFR in the acute setting, a patient’s serum creatinine level may increase, resulting in apparent progression in AKI stage, despite improvement in GFR. Clearly no guideline can accommodate all the subtleties of clinical practice or substitute for clinical judgment, but the recommendations for management overall were relatively nonspecific and unlikely to help in daily clinical practice. We are especially concerned that the development of clinical action plans based on AKI stage may result in inappropriate protocolization of care. While recommendations such as discontinuation of nephrotoxic agents when possible and ensuring volume status and perfusion pressure in high-risk patients or patients with AKI, waiting until stage 2 AKI to check for changes in drug dosing implies that this need not be done earlier, while the recommendations for considering initiation of RRT and intensive care unit admission in stage 2 AKI seem premature. Overall, we thought that the extreme heterogeneity of AKI and its lack of consistent mapping to stages 1, 2, and 3 make the proposed stage-based management of AKI clinically unhelpful and inapplicable to many patients.

We agree with the emphasis on close postdischarge clinical evaluation of patients with moderate to severe AKI given the recent identification of an association between AKI and long-term outcomes such as renal dysfunction.

Figure 2. Stage-based management of acute kidney injury (AKI). Shading of boxes indicates priority of action—solid shading (with white lettering) indicates actions that are equally appropriate at all stages whereas graded shading (with black lettering) indicates increasing priority as intensity increases. Abbreviation: ICU, intensive care unit. Reproduced with permission of KDIGO from the KDIGO Clinical Practice Guideline for Acute Kidney Injury.1
function decline and mortality. However, we are concerned that clinicians may be overwhelmed by 3-month follow-up of many patients with stage 1 AKI, who will constitute the majority of individuals identified by the AKI definition due to transient oliguria or small changes in serum creatinine level. The risk of progressive CKD after AKI is related to the severity of AKI\textsuperscript{16,29,30} suggesting that risk stratification on the basis of AKI severity may be useful in guiding the timing of outpatient follow-up. Those with stage 3 AKI, for example, will likely require far earlier post-discharge follow-up. Furthermore, patients with AKI in the setting of pre-existing CKD or those who develop worsening CKD as a consequence of an episode of AKI could represent a particularly high-risk group.

In the pediatric population, the 3-month time to follow-up may be reasonable. The CKiD (Chronic Kidney Disease in Children) national trial has identified that a large number of the patients available for that patient cohort were at-risk patients in the neonatal population.\textsuperscript{31} Although the evidence for transition from AKI to CKD in the pediatric population is also observational and further epidemiologic research is required, the number of pediatric patients with AKI is much smaller than in the adult population and the stakes of missing nascent CKD may be greater given the potential longer duration of follow-up than in the adult population. Thus, we would suggest that early follow-up among pediatric patients with AKI is advisable.

**Implications Within US Health Care**

1. The KDIGO definition and staging system for AKI provides an important tool for conducting epidemiologic studies and for the design of clinical trials and helps increase awareness of the importance of small changes in kidney function in the acute setting. However, there is insufficient validation of this definition and staging system for its use in the diagnosis and clinical management of patients. In particular, we do not believe that there are sufficient data to support use of the stage-based management approach proposed in the KDIGO guideline. Rather, management of patients with AKI should be based on assessment of overall clinical status, including specific cause of AKI, trends in kidney function over time, comorbid conditions, assessment of volume status, and concomitant acid-base and electrolyte disturbances.

2. While AKI is an important risk factor for the development and progression of CKD, the majority of patients with mild, readily reversible AKI (e.g., the patient with no baseline CKD who presents with reversible AKI in the setting of volume depletion) are at relatively low risk of progressive CKD. From a public health standpoint in the United States, follow-up of kidney function after an episode of AKI should be targeted to the highest risk populations, including neonatal/pediatric patients, individuals with baseline CKD, and patients with severe AKI or who have incomplete recovery of kidney function at hospital discharge.

3. The KDIGO recommendations for definition and staging of adult AKI should not be used for the development of clinical performance measures.

4. Administrative coding for AKI should not be based solely on this definition and staging system.

**Prevention and Treatment of AKI**

**Commentary**

The section of the KDIGO guideline on prevention and treatment of AKI includes 7 level 1 recommendations and 22 level 2 recommendations (Box 2). Our KDOQI Work Group agreed with the 7 level 1 recommendations and thought that they were generally applicable in the United States. These focused on the use of vasopressors and fluids to treat patients in shock; avoidance of diuretics, dopamine, and recombinant human IGF-1 (insulin-like growth factor 1) to prevent or treat AKI; therapeutic drug monitoring during the use of aminoglycosides; and avoidance of nephrotoxic medications when possible. Importantly, avoidance of nephrotoxins is not always possible. For example, some pathogens are not effectively treated by azoles or echinocandins: *Candida krusei* is intrinsically resistant to azoles, and *Candida parapsilosis* is frequently resistant to echinocandins.

The KDOQI Work Group largely agreed with the recommendation to use isotonic crystalloids rather than colloids for volume expansion in patients at risk of AKI or with AKI. In addition, we noted that there appears to be harm with starch-containing fluids.\textsuperscript{32-36} Therefore, these solutions should be avoided in patients at risk of AKI or with AKI. Along the same lines, albumin resuscitation has been associated with harm in patients with traumatic brain injury and should be avoided in that setting.\textsuperscript{37,38}

There are also specific settings in which albumin is appropriate for initial management of expansion of intravascular volume. Specifically, in patients with liver disease, intravenous albumin administration appears to be beneficial for the prevention of renal failure and death in patients with spontaneous bacterial peritonitis, as well as for the prevention of renal failure in those undergoing large-volume paracentesis.\textsuperscript{39,40} Along the same lines, the most recent diagnostic criteria for hepatorenal syndrome include a lack of improvement in renal function after volume expansion with albumin (1 g/kg/d up to 100 g/d) for at least 2 days and withdrawal of diuretic therapy.\textsuperscript{41} Data
published since the KDIGO AKI guideline first appeared suggest that there may be harm associated with the administration of hyperchloremic intravenous solutions, including crystalloids;42,43 however, these studies have all been observational and this premise needs to be tested in a randomized clinical trial given the enormous effect size observed and the inability to control for other temporal trends in care in the prior studies.

With regard to the use of vasopressors in addition to intravenous fluids in patients with vasomotor shock, we noted that fluid resuscitation is typically insufficient to fully restore blood pressure to normal levels, which is critical for the prevention and management of AKI. However, whether one vasopressor is more effective for patients with or at risk of AKI is unknown. In a large multicenter clinical trial of patients with shock comparing dopamine and norepinephrine for first-line vasopressor support, the use of dopamine was associated with more adverse events in those with sepsis and with an increased risk of death in those with cardiogenic shock.44 In a subsequent meta-analysis and systematic review of patients with septic shock, dopamine was associated with an increased risk of death and arrhythmias.45,46 Thus, we believe that dopamine should be used with caution as the first-line agent of choice in patients with shock at present.

Our Work Group did not fully agree with the recommendation to use protocol-based management of hemodynamic and oxygenation parameters to prevent the development or worsening of AKI in high-risk patients in the perioperative setting or in patients with septic shock. The group noted that the recommendation to use protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting or in patients with septic shock (2C) was associated with an increased risk of death and worsening of AKI (2C).

In critically ill patients, we suggest insulin therapy targeting plasma glucose 110-149 mg/dL (6.1-8.3 mmol/L) (2C). In patients with AKI on RRT (2D), and up to a maximum of 1.7 g/kg/d in patients on continuous renal replacement therapy (CRRT) and in hypercatabolic patients. (2D)

We suggest providing nutrition preferentially via the enteral route in patients with AKI. (2C)

We recommend not using diuretics to prevent AKI. (1B)

We suggest not using diuretics to treat AKI, except in the management of volume overload. (2C)

We recommend not using low-dose dopamine to prevent or treat AKI. (1A)

We suggest not using fenoldopam to prevent or treat AKI. (2C)

We suggest not using atrial natriuretic peptide (ANP) to prevent or treat (2C) or treat (2B) AKI.

We recommend not using recombinant human (rh)IGF-1 to prevent or treat AKI. (1B)

We suggest that a single dose of theophylline may be given in neonates with severe perinatal asphyxia, who are at high risk of AKI. (2B)

We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (2A)

We suggest that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single dose daily rather than multiple-dose daily treatment regimens. (2B)

We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24 hours. (1A)

We suggest monitoring aminoglycoside drug levels when treatment with single-daily dosing is used for more than 48 hours. (2C)

We suggest using topical or local applications of aminoglycosides (e.g., respiratory aerosols, instilled antibiotic beads), rather than i.v. application, when feasible and suitable. (2B)

We suggest using lipid formulations of amphotericin B rather than conventional formulations of amphotericin B. (2A)

In the treatment of systemic mycoses or parasitic infections, we recommend using azole antifungal agents and/or the echinocandins rather than conventional amphotericin B, if equal therapeutic efficacy can be assumed. (1A)

We suggest that off-pump coronary artery bypass graft surgery not be selected solely for the purpose of reducing perioperative AKI or need for RRT. (2C)

We suggest not using NAC to prevent AKI in critically ill patients with hypotension. (2D)

We recommend not using oral or i.v. NAC for prevention of postsurgical AKI. (1A)

Abbreviations: AKI, acute kidney injury; IGF-1, insulin-like growth factor 1; i.v., intravenous; NAC, N-acetylcysteine; RRT, renal replacement therapy.

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in the original randomized clinical trial, so it is unclear if the intervention had any impact on renal outcomes. Similarly, perioperative protocols have similarly shown aggregate improvement when assessed in a meta-analysis, but individual studies have been limited by small numbers and single-center design. Furthermore, our Work Group thought that the protocol must be specified. That is, any protocol that is instituted based on this recommendation should be one that has been previously studied and validated. For example, previous studies of increasing oxygen transport have demonstrated that the use of dobutamine to increase oxygen transport can worsen mortality, although the Rivers et al study of early goal-directed therapy suggests that dobutamine in an appropriate clinical context may not be harmful and may have benefit. Thus, medical centers adopting protocolized care should only adopt protocols that have been previously shown to be helpful and demonstrated no harm. If de novo protocols are developed for use, they should be used in the confines of a clinical trial to ensure no harm.

With regard to glycemic control, we agreed with the recommended target of 110-149 mg/dL, but noted that emerging evidence suggests that rapid and sustained correction of glycemia in diabetic patients with the recommended target of 110-149 mg/dL, but noted that emerging evidence suggests that rapid and sustained correction of glycemia in diabetic patients with previous poor glycemic control may have worse outcomes. Our Work Group agreed with the recommendations for nutritional support in AKI, but noted that the evidence base for these recommendations is limited. Specifically, the guideline recommends total energy intake of 20-30 kcal/kg/d in patients with any stage of AKI with administration of 0.8-1.0 g/kg/d of protein in noncatabolic patients with AKI without need for dialysis, 1.0-1.5 g/kg/d in patients with AKI on RRT, and up to a maximum of 1.7 g/kg/d in patients on continuous RRT (CRRT) and in hypercatabolic patients. The provision of protein to patients with AKI is intended to avoid marked net negative nitrogen balance. Patients with AKI on RRT will have additional protein loss as amino acids are removed. Therefore, these patients require additional protein compared with patients with AKI who are not on RRT. Similarly, patients who are hypercatabolic will require additional protein to avoid net negative nitrogen balance. Along the same lines, the KDOQI Work Group agreed with the recommendation to avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT. We also agreed with the recommendation to provide nutrition preferentially by the enteral route in AKI. The Work Group noted that although evidence is more limited in the setting of AKI, in a recent large randomized clinical trial of critically ill patients, early parenteral nutrition was associated with a higher rate of complications, primarily infectious complications. Along the same lines, recent trials suggest that enteral feeding is tolerated by either the nasogastric or nasojejunal routes.

Nutritional support in pediatric patients must include the recognition that these patients are generally in a developmental growth phase; thus, their requirements may be increased compared with adult patients. Recent estimates have been published in terms of estimated protein/amino acid supplementation in critically ill children and suggest that protein requirements are on the order of 2-3 g/kg/d for children aged 0-2 years, 1.5-2.0 g/kg/d for children aged 2-13 years, and 1.5 g/kg/d for adolescents aged 13-18 years. Children requiring RRT appear to need supplementation beyond this.

There are no pharmacotherapies available for the prevention or treatment of AKI in adults, so recommendations to avoid these are reasonable. Specifically, we agreed that although there is theoretical benefit to the use of loop diuretics to prevent AKI, there are no data to support the use of diuretics to prevent AKI. Recent studies in patients undergoing cardiac surgery or contrast studies suggest that the use of diuretics does not prevent AKI and, in the case of contrast administration, increases the risk of AKI. The KDOQI Work Group thought that it was important to comment on the use of diuretics in patients with AKI and rhabdomyolysis. With regard to osmotic diuretics, one retrospective study has suggested that the use of mannitol administration may be of benefit only in patients with marked elevations in creatinine kinase level (>30,000 U/L). However, even in these patients with severe rhabdomyolysis, the true benefit associated with mannitol administration remains undefined. Furthermore, mannitol should be administered carefully and is contraindicated in patients with oligoanuria. Diuretics may be used for the treatment of volume overload in AKI. We agree that low-dose dopamine, fenoldopam, IGF-1, and N-acetylcysteine (NAC) should not be used for the treatment or prevention of AKI.

We concur with the recommendation to administer a single dose of theophylline to neonates with severe perinatal asphyxia who are at high risk of AKI. Several clinical trials in the neonatal population suggest that although mortality outcomes are not affected, improved fluid control and higher GFR are associated with theophylline administration in this setting. A similar renal-selective response has been demonstrated in asphyxiated term newborns receiving a single theophylline dose in the first 60 minutes of life. Given the generally physiologic hyperactive state of the renal autoregulatory system apparent at transition from in utero to ex utero environments and the role that adenosine plays in these
processes, the use of theophylline in the aforementioned settings is reasonable.

A substantial number of recommendations were made with regard to the use of aminoglycosides and antifungal agents. Our Work Group agreed with these recommendations but noted that there are situations in which aminoglycosides or multidose regimens are preferable (eg, multiple dose regimens remain the standard of care for enterococcal endocarditis). We also noted that while local instillation of aminoglycosides is reasonable, it is unknown what the incidence of nephrotoxicity is with local administration of aminoglycosides; for example, there are case reports of nephrotoxicity associated with inhaled tobramycin therapy.71-73

With regard to the use of lipid formulations of amphotericin B rather than conventional formulations of amphotericin B, we note that it has been suggested that the decreased incidence of AKI and the associated decrease in hospitalization costs makes the lipid formulations cost-effective compared to conventional formulations of amphotericin B.74,75 Furthermore, other simple strategies that may reduce the risk of nephrotoxicity include discontinuation of diuretics, sodium loading and volume repletion, and potassium and magnesium supplementation, particularly when using non-liposomal preparations of amphotericin B.76

The 2 most significant risk factors for the development of AKI following cardiac surgery are cardiopulmonary bypass time and a history of CKD.77,78 As a result, there has been considerable interest in the potential for off-pump bypass to decrease the risk of AKI. The largest retrospective study focused on patients with CKD was published after the KDIGO AKI guideline.79 This study examined nonemergent isoflurane patients with CKD was published after the KDIGO AKI guideline.79 This study examined nonemergent isoflurane patients and patients with sepsis is a reasonable approach, but the protocols for such management need to be further developed and tested. We note that several large randomized clinical trials will test protocols for patients with sepsis (ClinicalTrials.gov identifiers NCT00975793 and NCT00510835 and International Standard Randomised Controlled Trial Number ISRCTN36307479). Until then, care should not be benchmarked based on the implementation of such protocols within a given time frame; it is reasonable to use time to antibiotics and time to fluid administration as benchmarks for care in sepsis.

4. A target blood glucose level of 110-149 mg/dL in critically ill patients may be associated with decreased risk of AKI and other morbidity and mortality. However, emerging evidence suggests that rapid and sustained correction of hyperglycemia in diabetic patients with previous poor glycemic control may have worse outcomes.

5. Nutritional support in patients with AKI should be provided by the enteral route when possible. Protein supplementation should not be withheld to delay the initiation of RRT. Patients with AKI are often highly catabolic and protein requirements typically increase with RRT due to amino acid loss, so nutritional prescriptions for patients with AKI need to reflect these considerations.

6. No agents are recommended for the treatment or prevention of AKI in adults; a single dose of theophylline can be provided to neonates at risk of AKI.

7. The cost-effectiveness of the widespread use of liposomal amphotericin B should be studied. Therapeutic drug monitoring for aminoglycosides should remain standard of care.

8. Off-pump CABG may be of benefit to reduce the risk of RRT in those with advanced CKD, but further
studies are warranted. Off-pump CABG should not be considered standard of care in those with CKD.

**Contrast-Induced AKI**

*Commentary*

The KDIGO guideline contains 12 recommendations on prevention of contrast-induced AKI; 5 are not graded, 4 are level 1 recommendations, and the remaining 3 are level 2 recommendations (Box 3). The first of these recommendations is that contrast-induced AKI be defined and staged using the KDIGO definition and staging criteria. This recommendation makes sense from the standpoint of consistency and is generally applicable in the United States, albeit with the limitations noted in the previous comments on definition and staging. However, we note that most clinical studies related to contrast-induced AKI have used alternative definitions based on increments in serum creatinine level, with serious adverse events, the causal nature of such associations remains unproved, leaving unanswered the question of how to best define “clinically significant” contrast-induced AKI. Thus, the recommendation to operationalize the definition of contrast-induced AKI within the KDIGO framework is justified. Furthermore, applicability of the urine output criteria to the diagnosis and staging for this form of AKI is uncertain. Most episodes of contrast-induced AKI are nonoliguric. In addition, most contrast-enhanced radio-

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**Box 3. Summary of KDIGO Recommendation Statements: Contrast-Induced AKI**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1: Define and stage AKI after administration of intravascular contrast media as per Recommendations 2.1.1-2.1.2. (Not Graded)</td>
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</tr>
<tr>
<td>4.1.1: In individuals who develop changes in kidney function after administration of intravascular contrast media, evaluate for CI-AKI as well as for other possible causes of AKI. (Not Graded)</td>
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<tr>
<td>4.2.1: Assess the risk for CI-AKI and, in particular, screen for pre-existing impairment of kidney function in all patients who are considered for a procedure that requires intravascular (i.v. or i.a.) administration of iodinated contrast medium. (Not Graded)</td>
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<tr>
<td>4.2.2: Consider alternative imaging methods in patients at increased risk for CI-AKI. (Not Graded)</td>
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<tr>
<td>4.3.1: Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. (Not Graded)</td>
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<tr>
<td>4.3.2: We recommend using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media in patients at increased risk of CI-AKI. (1A)</td>
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<tr>
<td>4.3.3: We suggest using N-acetylcysteine (NAC) to prevent CI-AKI. (1B)</td>
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<tr>
<td>4.3.4: We recommend using oral fluids alone in patients at increased risk of CI-AKI. (1C)</td>
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<tr>
<td>4.3.5: We recommend using fenoldopam to prevent CI-AKI. (1B)</td>
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<tr>
<td>4.3.6: We recommend not using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (2D)</td>
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<tr>
<td>4.3.7: We suggest not using theophylline to prevent CI-AKI. (2C)</td>
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<tr>
<td>4.3.8: We recommend not using fenoldopam to prevent CI-AKI. (2C)</td>
<td></td>
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<tr>
<td>4.3.9: We recommend i.v. volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no i.v. volume expansion, in patients at increased risk for CI-AKI. (1A)</td>
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<tr>
<td>4.3.10: We recommend not using prophylactic intermittent hemodialysis (IHD) or hemofiltration (HF) for contrast-media removal in patients at increased risk for CI-AKI. (2C)</td>
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<tr>
<td>4.3.11: We recommend using the lowest possible dose of contrast medium in patients at risk for CI-AKI. (1B)</td>
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<tr>
<td>4.3.12: We recommend using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (2D)</td>
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<tr>
<td>4.3.13: We suggest using theophylline to prevent CI-AKI. (2C)</td>
<td></td>
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<tr>
<td>4.3.14: We recommend using oral fluids alone in patients at increased risk of CI-AKI. (1C)</td>
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<tr>
<td>4.3.15: We recommend using fenoldopam to prevent CI-AKI. (1B)</td>
<td></td>
</tr>
<tr>
<td>4.3.16: We recommend not using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (2D)</td>
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<tr>
<td>4.3.17: We suggest using theophylline to prevent CI-AKI. (2C)</td>
<td></td>
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<tr>
<td>4.3.18: We recommend using oral fluids alone in patients at increased risk of CI-AKI. (1C)</td>
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<tr>
<td>4.3.19: We recommend using fenoldopam to prevent CI-AKI. (1B)</td>
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<tr>
<td>4.3.20: We recommend not using prophylactic intermittent hemodialysis (IHD) or hemofiltration (HF) for contrast-media removal in patients at increased risk for CI-AKI. (2C)</td>
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</table>

Abbreviations: AKI, acute kidney injury; CI-AKI, contrast-induced acute kidney injury; i.a., intra-arterial; i.v., intravenous; NAC, N-acetylcysteine.

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tor blocker therapy prior to contrast administration persists and the KDIGO AKI guideline acknowledges the inadequacy of the evidence to support the discontinuation of these agents prior to contrast-enhanced procedures. While the administration of loop diuretics for the purpose of preventing contrast-induced AKI is ineffective and potentially harmful, there are no data to support the recommendation to routinely discontinue these agents in all patients prior to contrast administration.

In patients at increased risk of contrast-induced AKI, it is appropriate to discuss the risk to benefit ratio of the planned procedure with the practitioner performing the study (ie, radiologist or interventionalist), as well as with the patient. In considering alternative procedures that do not involve the administration of iodinated contrast, the risk of nephrogenic systemic fibrosis associated with the administration of gadolinium-based contrast agents is important given the potential morbidity associated with this condition. Patients with eGFR <30 mL/min/1.73 m² and patients with AKI are at risk of nephrogenic systemic fibrosis and appropriate cautionary measures should be taken regarding gadolinium-based contrast agents in this group. While the KDOQI Work Group agrees with the importance of avoiding unnecessary radioccontrast administration in high-risk patients, a cautionary note is required because several studies have suggested that concern over contrast-induced AKI leads to underutilization of imaging techniques, particularly coronary angiography, in high-risk patients with CKD.83

Studies of the association of dose of contrast medium, considered as overall volume and grams of iodine per eGFR ratio, with risk of contrast-induced AKI suggest that higher doses are associated with greater risk.84-86 Recommendations to consider not only the total volume of contrast, but also the grams of iodine per eGFR ratio, are reasonable based on available evidence, yet are most likely to be applicable to radiologists and interventionalists performing contrast-enhanced procedures. Furthermore, routine calculation of the grams of iodine per eGFR ratio adds a layer of complexity to the conduct of contrast-enhanced procedures that may not be readily acceptable to all clinicians.

The specific contrast agent used also has an effect on the risk of contrast-induced AKI. High-osmolar contrast media are associated with higher rates of contrast-induced AKI compared with low-osmolar agents in at-risk patients and should not be used in this patient group.57 Clinical trials and meta-analyses comparing the nephrotoxicity of low-osmolar contrast agents with iso-osmolar contrast have yielded conflicting results.88,89 Guidelines issued by the American Heart Association/American College of Cardiology in 2009 recommended the use of iso-osmolar or low-osmolar contrast exclusive of iohexol and ioxaglate in patients with non–dialysis-dependent CKD undergoing angiography based on data demonstrating higher rates of contrast-induced AKI among patients who received these 2 agents compared with iso-osmolar contrast and other low-osmolar agents.90 The recommendation of our Work Group is to follow the guidelines outlined by the American Heart Association/American College of Cardiology in 2009. It is important to note that ioxithal (Visipaque) is the only iso-osmolar contrast agent clinically available in the United States; there is a substantially higher cost for brand-name Visipaque than the low-osmolar contrast agents, which may be important to consider in decisions related to choice of contrast.

The provision of intravenous fluids prior to and after the administration of iodinated contrast media is the primary intervention with demonstrated effectiveness for the prevention of contrast-induced AKI in high-risk patients. We concur with the recommendation to not use oral fluids alone in patients at increased risk of contrast-induced AKI. Controversy exists regarding the benefit of isotonic sodium bicarbonate administration compared to isotonic saline solution, with divergent results reported from the multiple small- to medium-sized clinical trials91-99 and meta-analyses.100-110 Given the divergent results of studies to date and the recognition that none of the randomized clinical trials to date have demonstrated that isotonic bicarbonate is less effective than isotonic saline solution, the KDIGO guideline recommendation to use either isotonic fluid in high-risk patients is appropriate. The guideline makes an important mention of the potential for compounding errors with sodium bicarbonate administration because no commercially available isotonic bicarbonate solutions are available, and the attendant risk for the administration of hypertonic solutions. This risk is not associated with the provision of premixed saline solution. It is also important to note that the additional time needed to prepare isotonic sodium bicarbonate solution is not required when administering standard saline solutions. Therefore, the administration of isotonic saline solution may be preferable in situations in which emergent contrast procedures are indicated.

Acute administration of both mannitol and furosemide has been associated with increased risk of contrast-induced AKI.63,64 However, a series of recent trials examined the benefit of generating high urine flow rates using furosemide and saline solution infusions combined with a device that matches intravenous fluid administration with urine output.111,112 These trials, which randomly assigned patients to this strategy or to conventional periprocedural intrave-
nous fluids, reported lower rates of contrast-induced AKI among patients randomly assigned to this device. However, these studies were relatively small and did not confirm whether sodium intake in the form of intravenous fluids was matched to urinary sodium excretion in patients randomly assigned to the device. Recognizing that urine composition following furosemide administration is likely to be hypotonic relative to saline, patients randomly assigned to the device-based protocol may have experienced net positive sodium balance, which could confound the interpretation of the benefits of this device.

A multitude of clinical trials have investigated NAC for the prevention of contrast-induced AKI and generated, much like the studies comparing isotonic bicarbonate with isotonic saline solution, highly conflicting findings.113–138 These studies have been limited by small study populations, clinically implausible effect sizes, and a paucity of data for the effect of NAC on “hard” patient outcomes. Meta-analyses based on these trials also documented conflicting findings on the efficacy of NAC and underscore the limitations in the primary clinical trials.139–142 In 2011, a large randomized controlled trial of 2,308 patients reported no reduction in the rate of contrast-induced AKI with 1,200 mg of oral NAC dosed daily for 2 days as compared to placebo.143 While this study is larger than all prior published trials of NAC, several limitations to its design have been raised, including the fact that only 15.7% of study participants had a serum creatinine level >1.5 mg/dL and the baseline serum creatinine level may have been obtained up to 90 days prior to the angiographic procedure. Intravenous NAC is associated with potentially serious adverse effects and, in the absence of sound data supporting its effectiveness, should not be routinely administered for the prevention of contrast-induced AKI. However, oral NAC is inexpensive and largely devoid of adverse side effects in the doses employed to prevent contrast-induced AKI. Therefore, the recommendation to administer oral NAC together with intravenous isotonic crystalloid is not inappropriate despite the questions of its efficacy. However, oral NAC should not be used in lieu of intravenous isotonic crystalloid in high-risk patients. While the KDIGO guideline does not recommend a specific dose or duration of therapy, data suggesting a possible dose-dependent effect justify the administration of 1,200 mg by mouth twice daily for 2 days.

Our Work Group concurred with the KDIGO recommendations against the use of fenoldopam and theophylline for prevention of contrast-induced AKI. Although preliminary uncontrolled trials of fenoldopam suggested a benefit with regard to prevention of contrast-induced AKI, this was not confirmed in a randomized controlled trial.144 While studies have suggested a potential benefit to the adenosine antagonist theophylline for the prevention of contrast-induced AKI, the data to date are not conclusive.145 Moreover, unlike NAC, theophylline is associated with potential cardiovascular side effects and has numerous drug interactions. Our KDOQI Work Group also concurred with the recommendations not to use prophylactic hemodialysis or hemofiltration for contrast media removal and prevention of contrast-induced AKI. Although extracorporeal therapies are able to remove contrast media from the circulation, the rate of removal is unlikely to prevent the kidney damage, which develops within minutes of contrast administration. Meta-analysis of clinical trials of hemodialysis and hemofiltration have demonstrated an absence of benefit and potential risk of harm with prophylactic hemodialysis.146

**Implications Within US Health Care**

1. All patients undergoing contrast-enhanced imaging procedures should be evaluated for risk of AKI. Screening can most appropriately be performed using standardized questionnaires. Routine measurement of serum creatinine in patients identified as low risk by questionnaire is not indicated; however, if there is any question regarding risk of kidney disease, serum creatinine level should be obtained prior to contrast administration.

2. The risks and benefits of contrast administration need to be carefully evaluated in patients at high risk of contrast-induced AKI. The risk of contrast-induced AKI should not preclude the performance of needed diagnostic imaging and therapeutic procedures in high-risk patients.

3. Iso-osmolar or selected low-osmolar contrast in the lowest possible dose should be used in high-risk patients.

4. The only intervention that has consistently been demonstrated to decrease the risk of contrast-induced AKI is periprocedural intravenous volume administration using isotonic crystalloid. Thus, all patients at increased risk of contrast-induced AKI should receive periprocedural intravenous isotonic crystalloid. The optimal rate of fluid administration remains uncertain, and whether bicarbonate administration is associated with greater benefit at risk reduction than saline remains unresolved.

5. The benefit associated with NAC administration remains uncertain. Given the minimal risk and cost associated with this agent, we do not recommend against its use, although it should not be used in lieu of more effective interventions, particularly periprocedural administration of isotonic crystalloid.
5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (Not Graded)
5.1.2: Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (Not Graded)
5.2.1: Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. (Not Graded)
5.2.2: We suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT. (2B)
5.3.1: In a patient with AKI requiring RRT, base the decision to use anticoagulation for RRT on assessment of the patient’s potential risks and benefits from anticoagulation (see Figure 17). (Not Graded)
  5.3.1.1: We recommend using anticoagulation during RRT in AKI if a patient does not have an increased bleeding risk or impaired coagulation and is not already receiving systemic anticoagulation. (1B)
  5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:
  5.3.2.1: For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (1C)
  5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (2B)
  5.3.2.3: For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (2C)
5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:
  5.3.3.1: We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. (2C)
  5.3.3.2: We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. (2C)
5.3.4: In a patient with heparin-induced thrombocytopenia (HIT), all heparin must be stopped and we recommend using direct thrombin inhibitors (such as argatroban) or Factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other or no anticoagulation during RRT. (1A)
  5.3.4.1: In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (2C)
5.4.1: We suggest initiating RRT in patients with AKI via an uncuffed nontunneled dialysis catheter, rather than a tunneled catheter. (2D)
5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences (Not Graded):
  - First choice: right jugular vein;
  - Second choice: femoral vein;
  - Third choice: left jugular vein;
  - Last choice: subclavian vein with preference for the dominant side.
5.4.3: We recommend using ultrasound guidance for dialysis catheter insertion. (1A)
5.4.4: We recommend obtaining a chest radiograph promptly after placement and before first use of an internal jugular or subclavian dialysis catheter. (1B)
5.4.5: We suggest not using topical antibiotics over the skin insertion site of a nontunneled dialysis catheter in ICU patients with AKI requiring RRT. (2C)
5.4.6: We suggest not using antibiotic locks for prevention of catheter-related infections of nontunneled dialysis catheters in AKI requiring RRT. (2C)
5.5.1: We suggest to use dialyzers with a biocompatible membrane for IHD and CRRT in patients with AKI. (2C)
5.5.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (2B)
5.5.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (2B)
5.5.4: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI. (2C)
5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients.
5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients.
5.6.3: We suggest using CRRT, rather than intermittent RRT, for hemodynamically unstable patients.
5.6.4: We recommend delivering an effluent volume of 20-25 mL/kg/h for CRRT in AKI (1A). This will usually require a higher prescription of effluent volume. (Not Graded)

Abbreviations: AKI, acute kidney injury; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; ICU, intensive care unit; RRT, renal replacement therapy.

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6. Fenoldopam, theophylline, and prophylactic hemodialysis and hemofiltration should not be used to decrease the risk of contrast-induced AKI.

**Dialysis Interventions for Treatment of AKI**

**Commentary**

In the KDIGO AKI guideline, there are 33 recommendations on dialysis interventions for treatment of AKI; 9 are not graded, 10 are level 1 recommendations, and 14 are level 2 recommendations (Box 4). The 9 recommendations that are not graded are largely practical suggestions with the exception of the recommendation for dialysis catheter-site selection. There are data to suggest that the risk of subclavian stenosis is greater with large, nontunneled catheters and data for the association of catheter site with catheter function and risk of infection from the Cathedria trial.147 Our Work Group recommends that in addition to site selection, dialysis catheters should be of an adequate length to minimize the risks of access recirculation and catheter malfunction. The remaining recommendations are largely practical statements about the initiation and termination of dialysis, as well as the use of anticoagulation. The Work Group thought that it was important to note the paucity of evidence to support a recommendation regarding the timing of initiation of RRT in AKI and believes that this is an area in need of well-designed clinical trials.

The KDOQI Work Group also agreed with the 10 level 1 recommendations. These included using anticoagulation for patients who are receiving RRT who are not at increased risk of bleeding, using heparin for anticoagulation during intermittent hemodialysis, avoiding heparin products in patients with heparin-induced thrombocytopenia, using ultrasound for dialysis catheter insertion and chest radiography to confirm line placement, and appropriate dosing of both intermittent and continuous RRTs. With regard to the level 1 recommendation to use bicarbonate-containing dialysate and replacement fluid in patients with shock, the KDOQI Work Group noted that bicarbonate has replaced lactate and acetate as the dialysate buffer of choice for intermittent RRT. The evidence of the benefit of bicarbonate-based over lactate-based solutions for CRRT is inconsistent.148-150 Nevertheless, the increased availability of commercially prepared bicarbonate-based CRRT fluids in the United States seems to support their use as the buffer of choice.

The recommendations regarding dose of RRT in AKI are based upon some of the most rigorous evidence for the entire guideline. The RENAL (Randomized Evaluation of Normal Versus Augmented Level) Replacement Therapy study, conducted in Australia and New Zealand, randomly assigned 1,508 patients to continuous venovenous hemodiafiltration (CVVHDF) at an effluent flow rate of either 40 or 25 mL/kg/h.12 The VA/NIH Acute Renal Failure Trial Network (ATN) study randomly assigned 1,124 patients in the United States to a strategy of more intensive (CVVHDF at 35 mL/kg/h or intermittent hemodialysis or SLED [sustained low-efficiency dialysis] on a 6-day-per-week schedule) or less intensive (CVVHDF at 20 mL/kg/h or intermittent hemodialysis or SLED on a 3-day-per-week schedule) RRT.11 In the ATN study, patients moved between modality of therapy as their hemodynamic status changed. In both studies, there was no added benefit with regard to survival or recovery of kidney function associated with more intensive therapy. Although the KDIGO Guideline bases their target doses of therapy for both intermittent and continuous therapy on the results of these studies, it should be recognized that neither study was designed to identify the minimum adequate dose of therapy. In addition, it should also be noted that the KDIGO recommended weekly delivered Kt/V of 3.9 is based upon the arithmetic sum of the dose per individual treatment. Kinetic modeling suggests that this is erroneous and that prescription of intermittent hemodialysis to provide a Kt/V of 1.3 three times per week or a Kt/V of 0.65 six times per week are not equivalent.151 Available evidence suggests that delivery of RRT often falls short of the prescribed dose,152-155 supporting the need for frequent assessment of the actual delivered dose.

With regard to the level 2 recommendations, our Work Group agreed that diuretics should not be used specifically for improving kidney function or reducing the need for RRT. However, with regard to the use of anticoagulation for CRRT, the Work Group believed that there is no consensus on which anticoagulant should be first choice for CRRT. Rather, the choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring, and pharmacy issues. Monitoring should include evaluation of anticoagulant effect, filter efficacy, and circuit life and complications. Although regional citrate anticoagulation is gaining wide acceptance with the development of simpler and safer protocols,156,157 citrate is not approved by the US Food and Drug Administration (FDA) as an anticoagulant for CRRT. As a result, the commercially available citrate solutions in the United States are used for blood banking and are hypertonic, increasing the risk of metabolic complications. Because citrate is not universally available in the United States, it cannot be recommended over heparin. Along the same lines, citrate cannot be recommended over no anticoagulation during CRRT at present. Addi-
tional work is needed to create standardized citrate administration and monitoring protocols. There is also a need for development and approval of commercially available citrate solutions before this approach can be routinely recommended.

With regard to alternative anticoagulation strategies, our Work Group noted that danaparoid, fondaparinux, and hirudin are all renally excreted with extended half-lives in AKI and have no specific antidote. Therefore, these agents must be used with caution in patients with AKI on CRRT. Danaparoid is not available in the United States. Argatroban has been used at doses ranging between 0.7 and 1.7 μg/kg/min as anticoagulation for CRRT.158,159

Our Work Group thought that there was insufficient evidence to support the recommendation for use of nontunneled dialysis catheters for initiation of RRT in patients with AKI. In a small, single-center, randomized, controlled trial, tunneled femoral catheters were found to give better flow characteristics, fewer postinsertion complications, greater longevity, and less likelihood of inadequate prescription as compared to nontunneled femoral catheters.160 Furthermore, patients with AKI in the setting of advanced CKD (and suspected long duration of dialysis-dependent AKI or development of end-stage renal disease) may benefit from a tunneled catheter to avoid increased risk of vessel stenosis with multiple catheter insertions.

Our Work Group noted that no high-quality data currently exist to support the routine use of topical antibiotics or antibiotic locks for short-term dialysis catheters. The KDOQI Work Group suggests reserving the catheter exclusively for extracorporeal treatment only to prevent unnecessary manipulation and risk of infection of the catheter.

Our Work Group concurred with the KDIGO recommendation that the continuous and intermittent modalities of RRT are complementary. While we also agreed with the general recommendation for the use of CRRT rather than standard intermittent hemodialysis for the management of hemodynamically unstable patients, we noted a paucity of discussion of the various modalities of prolonged intermittent RRT (PIRRT, also known as SLED; and extended duration dialysis [EDD]). We believe that these modalities can be safely used in hemodynamically unstable adult patients and that additional clinical research is required to compare outcomes with these therapies to the other modalities of RRT. Experience with these modalities in pediatric patients is extremely limited, precluding the ability of the Work Group to make recommendations. With regard to the recommendation to use CRRT, rather than intermittent RRT, for patients with AKI with acute brain injury or other causes of increased intracranial pressure or generalized brain edema, the KDOQI Work Group noted that although published data in support of this approach are limited, the available data support this approach.161-164 Furthermore, based on the lower amount of solute flux per unit time with CRRT versus intermittent RRT, the rate of solute shifts should be slower with CRRT and therefore better tolerated by the patient with increased intracranial pressure or brain edema.

Implications Within US Health Care

1. In the United States, given the lack of FDA-approved citrate solutions for regional anticoagulation during CRRT, this approach cannot be recommended at present.

2. Given the increased risk of AKI with underlying CKD and the high prevalence of CKD in the United States, the selection of a tunneled versus nontunneled dialysis catheter should take into account the likelihood of end-stage renal disease.

3. Given the widespread availability of ultrasound in the United States, ultrasound should be used for dialysis catheter insertion to minimize the risk of complications. Along the same lines, internal jugular catheter placement should be confirmed with a chest radiograph.

4. It is reasonable to use bicarbonate-based dialysate and replacement fluid for intermittent hemodialysis and CRRT given the widespread availability of these solutions in the United States.

5. Along the same lines, given the relative availability of CRRT compared with developing countries, CRRT is preferable in hemodynamically unstable patients and those with acute brain injury with increased intracranial pressure or generalized edema.

6. The modalities of PIRRT are reasonable alternatives to CRRT in hemodynamically unstable adult patients. Additional research is required to compare both the effectiveness and cost of these modalities of RRT. In addition, there is a need for assessment of the role of peritoneal dialysis in the acute setting, particularly in the neonatal/pediatric population in whom hemodialysis/hemofiltration-based techniques beyond CRRT are not readily available or utilized at most centers.

7. Optimal timing of initiation of RRT remains uncertain and is a topic that requires additional research.

8. There is a need to implement quality improvement strategies to ensure that the desired dose of RRT is actually delivered.

RESEARCH

Throughout the guideline, the KDIGO Work Group makes multiple recommendations of areas that require further research. Our KDOQI Work Group concurs
with the critical importance for further research in these areas. In particular, we note that the majority of the KDIGO recommendation statements are based on relatively low levels of evidence. Research in these areas is needed to develop the evidence upon which future practice guidelines can be based.

CONCLUSION

The KDIGO Clinical Practice Guideline for AKI represents a landmark effort in improving the care of patients with AKI. The guideline is broad in scope, spanning the spectrum from definition and staging through prevention and nondialytic management and the management of short-term RRT. While our KDOQI Work Group concurred with many of the KDIGO recommendations, we had reservations regarding several aspects of the guideline. Our Work Group recognizes the need for a consensus definition of AKI and commends KDIGO for harmonizing the prior definitions and staging criteria. While we recognized the utility of the consensus definition in the epidemiology and clinical research arenas, we do not believe that it is sufficiently validated for use in the diagnosis and clinical management of patients. In particular, we do not believe that there are sufficient data to support use of the stage-based management approach proposed in the KDIGO guidelines. Rather, management of patients with AKI should be based on assessment of overall clinical status, including specific cause of AKI, trends in kidney function over time, comorbid conditions, assessment of volume status, and concomitant acid-base and electrolyte disturbances. While we generally agreed with the recommendations for prevention and nondialytic management of AKI, including the prevention of contrast-induced AKI, we note the paucity of high-level evidence and the absence of highly effective therapies. While we can support the use of protocol-based management of perioperative patients and patients with sepsis to decrease the risk of AKI, we note that such protocols need to be further developed and validated and do not believe that there are sufficient data to benchmark care based on the implementation of such protocols. With regard to the management of RRT in AKI, while we are in general agreement with the KDIGO recommendations, we have some reservations regarding the application of several of these to care in the United States. Given the lack of FDA-approved citrate solutions for regional anticoagulation during CRRT, we do not believe that this approach can be currently recommended; however, we believe that this will need to be reconsidered if approved citrate solutions become available. We also note that the KDIGO recommendations provide little discussion of the modalities of PIRRT and believe that these modalities are a reasonable alternative to CRRT in hemodynamically unstable patients.

ACKNOWLEDGEMENTS

Guideline recommendations included in this article originally were published in Kidney International Supplements and were reproduced with permission from KDIGO.

We thank Drs Jeffrey Berns, Michael Choi, Holly Kramer, Michael Rocco, and Joseph Vassalotti for careful review of this manuscript; and Kerry Willis and Emily Howell from the National Kidney Foundation for their help in coordinating the work of the group and preparing the manuscript.

Financial Disclosure: Dr Chawla has consulted for Abbott Medical, Affymax Medical, Alere Medical, AM Pharma, Astute Medical, Covidien Medical, Gambro Medical, and Sanofi; has received grant support from Eli Lilly, Medical University of South Carolina and UPMC; has lectured for Nxtstage Medical and Gambro; and holds MAKO Corp stock. Dr Liu has received research support from Abbott and CMIC; has served on the Scientific Advisory board for Complexa, the Data and Safety Monitoring Board for Cytophers, and the Clinical Events Adjudication Committee for Astute; and holds Amgen stock. Dr Palevsky has research support from Spectral Diagnostics and is a consultant for Sanofi, Complexa and Cytophers. Dr Thakar is a member of the Clinical Events Committee of Cytophers; is Co-Editor of Springer Nephrology; and has offered clinical trial support to Reata. Dr Tolwani has consulted for Gambro Renal Products and served as an expert panelist for Gambro Renal Products. Dr Waikar is consultant for CVS Caremark, Bio Trends Research Group, and Salix; and has served as expert witness for GE Healthcare, North Star Rx, and Salix. Drs Brophy, Parikh, and Weisbord have no financial relationships with any commercial entity producing health care-related products and/or services.

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