Canadian Society of Nephrology Commentary on the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury

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INTRODUCTION

Acute kidney injury (AKI) is associated with prolonged hospitalization, substantial health care resource consumption, high mortality, and can lead to progressive chronic kidney disease (CKD), including chronic kidney failure, in survivors. The Canadian Society of Nephrology (CSN) believes there is a need to develop clinical practice guidelines for patients with AKI; however, efforts to synthesize knowledge from clinical studies evaluating the prevention and treatment of AKI and to generate guidelines have been limited. One barrier has been the absence of consensus on the definition of AKI, with more than 35 definitions of AKI published to date. Further, there is a perceived lack of effective prophylactic and treatment strategies for AKI, and it is challenging to develop guidelines that involve multiple stakeholders from diverse disciplines including nephrology, critical care, and radiology, all of which are important end users of guidelines for AKI. In this context, the KDIGO (Kidney Disease: Improving Global Outcomes) AKI working group has recently published new criteria for the definition and classification of AKI, as well as a clinical practice guideline addressing both AKI prevention and treatment.1 The working group is part of KDIGO, which was established in 2003 with its stated mission to “improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.”2 The CSN applauds the efforts of KDIGO in evidence synthesis and development of global clinical practice guidelines, but also believes that local factors require consideration when making recommendations to guide care. Therefore, the CSN guidelines committee formed a work group to evaluate the KDIGO AKI guideline and its relevance to the Canadian context.

REVIEW AND APPROVAL PROCESS FOR CSN GUIDELINES AND COMMENTARIES

The development and review of this commentary have been described previously3 and was consistent with CSN policies set out for the conduct of clinical practice guidelines. The CSN guidelines committee determined that this commentary was of priority, and a Chair was selected to guide the commentary process. Individual members were selected based on their interest and expertise, taking into consideration relevant conflicts of interest. Commentary development took place during spring 2012 using the 2012 KDIGO AKI guideline; additional literature searching was left to the discretion of individual members. The AGREE (Appraisal of Guidelines for Research and Evaluation) II instrument was used to evaluate overall guideline quality.4 After repeated teleconferences, all authors approved the final text of the commentary. Because this was a commentary rather than a guideline, consensus was sought, and when it could not be achieved, different perspectives were included. The CSN guidelines committee sent out the final document for peer review. The reviews were considered and responded to, with incorporation of further revisions before ratification by the CSN guidelines committee and CSN executive.

STRUCTURE OF THIS COMMENTARY

This commentary does not seek to discuss all KDIGO recommendations; rather, it was our intent to focus commentary on recommendations that are based

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on better quality evidence or are more controversial. The KDIGO recommendations that were chosen for further discussion are provided in boxes; implications and commentary relevant to Canadian health care are offered in the text when appropriate.

**ASSESSMENT OF GUIDELINE QUALITY**

Four pairs of CSN work group members independently completed the AGREE II instrument for the KDIGO AKI guideline. Overall, the guideline was thought to be of good quality (average score, 5.75/7) and all members agreed that they would recommend the guideline for use. Several areas for improvement in guideline development were identified, including the incorporation of the views and preferences of patients and development of tools to put recommendations into practice. A summary of the AGREE scores is provided in Table S1 (provided as online supplementary material).

**REVIEW OF KDIGO RECOMMENDATIONS**

**Definition and Classification of AKI (KDIGO Section 2.1)**

**Commentary**

The KDIGO recommendations for the definition and staging of AKI are mainly derived from AKIN (Acute Kidney Injury Network) and RIFLE (risk, injury, failure, loss, end-stage renal disease) definitions. Those definitions have been independently validated in multiple studies and are now widely accepted.

The definition proposed by KDIGO (Box 1) is a combination of AKIN and RIFLE definitions, but some elements that were common to both were modified. Because some modifications were not part of the initial definitions, they have not been validated and may need further evaluation. While different time frames were previously used for AKI diagnosis (48 hours) and staging (7 days), the new KDIGO AKI definition introduces differential timing only for AKI diagnosis (48 hours for ≥0.3-mg/dL increase in serum creatinine [SCr] level and 7 days for ≥1.5-fold increase in SCr level from baseline). It should be noted that the new KDIGO recommendation suggests that patients are staged over the entire course of AKI, regardless of timing. This distinction is somewhat arbitrary (as detailed in section 2.4 of the guideline) and may need to be investigated further. Beyond the proposed time frame, a 0.3-mg/dL increase may be a significantly smaller increase in SCr level than a 50% increase depending on the baseline SCr level. Because only one of these criteria is needed, AKI stage 1 may include a heterogeneous group of patients with AKI. Of note, this limitation was already present in the AKIN definition. Similarly, the contribution of urine output to this definition is not well described in the literature because most large population-based studies lack these data. The CSN work group agreed with the KDIGO recommendations for further research on the AKI definition and classification system, including the use of relative versus absolute changes in SCr level or estimated glomerular filtration rate (GFR), the importance of the duration of these changes, the influence of urine output on the staging criteria, and their prognostic associations with nonfatal complications of AKI.

Another area of uncertainty with the new AKI classification is the criterion for reaching stage 3 AKI. In order for patients to reach stage 3 AKI with an SCr level >4.0 mg/dL, the new KDIGO definition requires an acute increase in SCr level by 0.3 mg/dL within 48 hours. This is in contrast to the prior AKIN and RIFLE definitions, which require an SCr level >4.0 mg/dL and increase of 0.5 mg/dL over an

**Box 1. Selected Recommendations From Section 2 of the KDIGO AKI Guidelines**

2.1.1: AKI is defined as any of the following (Not Graded):
- Increase in SCr by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 mL/kg/h for 6 hours

2.1.2: AKI is staged for severity according to the following criteria. (Not Graded)
- Stage 1: Increase in SCr 1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 mmol/L) OR urine output <0.5 mL/kg/h for 6-12 hours
- Stage 2: Increase in SCr 2.0-2.9 times baseline OR urine output <0.5 mL/kg/h for ≥12 hours
- Stage 3: Increase in SCr 3.0 times baseline OR increase in SCr to ≥4.0 mg/dL (≥353.6 mmol/L) OR initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 mL/min/1.73 m², OR urine output <0.3 mL/kg/h for ≥24 hours OR anuria for ≥12 hours

2.3.4: Evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. (Not Graded)
- If patients have CKD, manage these patients as detailed in the KDOQI CKD Guideline (Guidelines 7-15). (Not Graded)
- 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)

Note: Conversion factor for SCr in mg/dL to μmol/L, ×88.4. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDOQI, Kidney Disease Outcomes Quality Initiative; SCr, serum creatinine.

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*The staging information is adapted from a table presented in the guideline.*
unspecified period. Small fluctuations in SCr level such as an increase from 4.0 to 4.3 mg/dL (<10% variation) over less than 48 hours may be considered within the “normal” daily variation in patients with CKD. The change in the KDIGO AKI classification system is justified by a goal to simplify the criteria, but is not an evidence-based recommendation. While such a small change in SCr level among patients with normal kidney function is clearly associated with worse outcomes, some evidence shows this may not be true to the same extent in people with pre-existing CKD. This definition has not been validated among patients with CKD, and members of the CSN work group thought that caution was warranted applying this definition for AKI to the CKD population in clinical practice.

Finally, there has been an undefined gap in the timeline for definitions of AKI and CKD because AKI is defined as a ≥1.5 fold increase in SCr level within 7 days (or ≥0.3 mg/dL increase within 48 hours) and CKD is defined as GFR <60 mL/min/1.73 m² for at least 3 months. Therefore, the KDIGO AKI guideline proposes a new definition of acute kidney disease (AKD) to classify patients with a GFR <60 mL/min/1.73 m² for less than 3 months; GFR decrease ≥35%, or increase in SCr level >50% in less than 3 months. The proposed AKD definition also includes AKI as a criterion, and so AKD may include people with or without AKI. This period between 7 days and 3 months is an arbitrary function of the timeline of definitions for AKI and CKD. While this period of “AKD” may help identify a period of overlap between AKI and CKD, it may just represent an artifact of the definitions for AKI and CKD. Indeed, it has been suggested that AKI and CKD may represent processes along a common pathophysiologic pathway. The CSN work group recognizes the importance of developing accurate classification schemes for research purposes and the need to identify all patients with renal injury. However, this recommendation is not graded and it is currently unknown if AKD represents a pathophysiologically, diagnostically, therapeutically, or prognostically unique entity. Several clinical syndromes, including rapidly progressive glomerulonephritis, acute interstitial nephritis, atheroembolic disease, and urinary tract obstruction, typically share many of the proposed features of AKD. Specific interventions are often required for management of these conditions, and the work group thought it was important to caution that recognition of AKD should not preclude appropriate clinical investigations to identify these underlying causes and timely initiation of therapy.

**Implications Within Canadian Health Care**

1. While using a single definition of AKI has clear implications for research purposes and early recognition, it remains unclear how useful the current AKI staging system is in clinical practice. When diagnosing and managing AKI, clinicians should consider other factors in addition to SCr level and urine output, such as trends in renal function, cause of AKI, concurrent diseases and comorbid conditions, as well as fluid balance and acid-base and/or electrolyte complications.

2. The CSN work group believes that the definition proposed for AKD should be limited to research purposes at this time, including further studies to distinguish the prevalence, prognosis, and potential clinical impact of case identification based on the AKD definition.

**Risk Assessment (KDIGO Section 2.2)**

**Commentary**

The Canadian population has a unique, multicultural composition that may not be represented in large American, Australian, or European studies. Specifically, Canadian Aboriginals are underrepresented in the current literature. There is some evidence to suggest that aboriginal children in New Zealand have a higher risk of developing AKI, but it is unknown if this applies to the Canadian aboriginal population.

**Implications Within Canadian Health Care**

The CSN work group supports further research to identify potential at-risk populations, including aboriginals, in future Canadian studies of AKI in order to improve risk assessment and identification of people with susceptibilities to AKI.

**Management of Patients With and at Risk for AKI (KDIGO Section 2.3)**

**Commentary**

The KDIGO AKI guideline suggests management of patients according to the stage and cause of AKI, and provides a stage-based management scheme with specific considerations for each stage. In stage 2, the guideline lists consideration of renal replacement therapy (RRT) initiation and intensive care unit admission (Box 1), which carry substantial health utilization and economic implications. The work group thought that the clinical context of each individual patient must be an additional consideration in the decision making process. For example, in patients with a potentially reversible cause of AKI without features of severe sepsis or shock, consideration of intensive care unit admission is usually not necessary, regardless of AKI stage. In those with rapidly progressive AKI due to acute tubular necrosis with oliguria or anuria, anticipation of RRT in stage 2 may well be appropriate.
The risks of developing CKD or chronic kidney failure following an episode of AKI are well documented in both pediatric \(^1\text{12,13}^\) and adult \(^6\text{1,4-19}^\) cohort studies. The KDIGO guideline suggests that patients with AKI should be evaluated for resolution, new onset, or worsening of pre-existing CKD at 3 months. This latter recommendation is not graded, but may have major implications within the Canadian health care system because the overall clinical utility and cost-effectiveness of this strategy is unknown. There are many questions that remain unanswered regarding the appropriate management of patients after AKI, including who should be followed up (all patients or only those at high risk), how to identify high-risk patients, when renal function should be re-evaluated, and what ongoing management should encompass. Indeed, CKD following AKI is typically a late event. In a recent meta-analysis evaluating the risk of CKD following an episode of AKI, the range of study follow-up was 12-74 months, indicating that assessment at 3 months alone is likely to be insufficient as a first step in identifying patients at high risk for CKD progression. \(^6,20\)

In addition to the uncertainties outlined, the cost-effectiveness of evaluating all patients with AKI at 3 months is unknown. Evaluation of all patients who experience AKI at 3 months represents a potentially significant financial burden on Canada’s single-payer public health care system and this may not be an effective use of finite resources. Furthermore, Canada’s large geographical area combined with its relatively sparse population present a unique challenge with respect to provision of access to care. While much of the population is concentrated around urban centers, there are also remote sites for which Tele-health or nursing stations are the primary care access points. In addition, many patients located in urban centers do not have a primary care physician, making uniform implementation of this recommendation difficult. This may place an undue burden on nephrology subspecialty clinics.

**Implications Within Canadian Health Care**

The CSN work group agrees that clinical follow-up for resolution, new onset, or worsening of pre-existing CKD following an episode of AKI is an important clinical concept. However, we believe it is premature to broadly apply this recommendation to all people with AKI. We recommend further work to develop clinical tools to identify patients at high risk for progressive CKD, and additional research on the clinical impact and cost-effectiveness of this approach, before introduction into the Canadian health care system. In the meantime, the CSN work group recommends that clinical follow-up after AKI should be determined on an individual basis. Such clinical follow-up appears most necessary for patients with identified risk factors for progression to CKD or end-stage renal disease, such as those who suffered from severe AKI (ie, requiring temporary RRT). Furthermore, patients with persisting renal dysfunction at hospital discharge could be targeted for clinical follow-up. In many cases, primary care physicians could perform initial follow-up for CKD after AKI, with subsequent referral to nephrology for ongoing management of CKD as necessary.

### Prevention and Treatment of AKI

Chapter 3 of the KDIGO guideline provides recommendations regarding the prevention and treatment of AKI. Of the 27 recommendations, 7 are derived from level 1A or B evidence and as such were identified as opportunities for knowledge translation by the work group. Of note, fully 5 of these higher grade recommendations are based on negative results from efficacy trials, and consist in suggestions not to use specific agents for treatment of AKI (dopamine, diuretics, N-acetylcysteine [NAC], and recombinant human insulin-like growth factor 1 [IGF-1]) or for treatment of other conditions (aminoglycosides and amphotericin). This telling observation highlights the urgent need for significant advancement in understanding of the pathophysiology and treatment of AKI. The CSN work group generally agreed with these recommendations, but thought that one level 1 and 3 level 2 recommendations required further discussion (Box 2).

#### Hemodynamic Monitoring and Support (KDIGO Section 3.1)

**Commentary**

The KDIGO AKI guideline emphasizes adequate goal-directed fluid and vasopressor management, close hemodynamic monitoring and appropriate insulin man-

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**Box 2. Selected Recommendations From Section 3 of the KDIGO AKI Guidelines**

- **3.1.1:** In the absence of hemorrhagic shock, we suggest using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI. \((2B)\)
- **3.1.2:** We suggest using goal-directed therapy as initial management for volume resuscitation of patients at risk for AKI or with AKI. \((2B)\)
- **3.1.3:** We suggest not using diuretics to prevent AKI. \((1B)\)
- **3.1.4:** We suggest not using diuretics to treat AKI, except in the management of volume overload. \((2C)\)
- **3.1.5:** We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. \((2A)\)

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**Abbreviation:** AKI, acute kidney injury.

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management, and also recommends using isotonic crystalloids rather than colloids as initial management for volume expansion in patients with or at risk for AKI. This recommendation is based on the lack of evidence favoring use of colloids (ie, human albumin solution or hydroxyethyl starches) over crystalloids (eg, normal saline solution) in resuscitation observed in randomized controlled trials, as well as cost considerations. Furthermore, some forms of hydroxyethyl starch have been associated with harm (increased AKI incidence). While the CSN work group supported these recommendations, it was recognized that there are some specific subgroups of patients who often receive albumin solutions and in whom their use may be rational (eg, those in whom high fluid volume needs are expected and for whom tissue edema would complicate management; patients with severe hyperalbuminemia, and patients with cirrhosis and spontaneous bacterial peritonitis).21-31

Imlications Within Canadian Health Care

There is little controversy about the importance of appropriate intravascular volume expansion in managing AKI risk. However, the work group notes that there is significant physician and center variation in selection of fluid type in Canada. In the Canadian health care context, the recommendation focusing on use of isotonic crystalloids may be a potential area for knowledge translation and research.

Medication Use and AKI (KDIGO Sections 3.4-3.8)

Commentary

These sections of the guideline make specific recommendations about avoidance of medications either known to be associated with AKI or proved to be ineffective in the treatment of AKI. Despite the high-quality evidence supporting many of these recommendations, many of these medications are used in clinical practice across the country. Diuretics in particular are still commonly used in Canada for the treatment of oliguria, particularly in surgical patients with significant AKI. Although the work group thought that judicious diuretic use may be appropriate for the management of fluid overload in certain patients, the appropriate use of diuretics in AKI represents an opportunity for knowledge translation in the Canadian setting. It must be acknowledged that the question of diuretic versus dialysis management of AKI and severe fluid overload still remains unanswered.

The guideline also recommends avoidance of intravenous aminoglycosides unless deemed absolutely necessary, as well as appropriate dosing and monitoring, with measurement of aminoglycoside levels. While aminoglycosides are clearly nephrotoxic, they are still commonly used because they are effective, exhibit synergy with other antibiotics for several invasive organisms, and are inexpensive.22-36 Restricting the use of aminoglycosides in all patients has significant implications with regard to antimicrobial stewardship, as well as health care costs. Implementing such a guideline in Canada (and elsewhere) would require developing and implementing treatment algorithms in collaboration with infectious diseases colleagues, which effectively restrict aminoglycoside use to patients in whom these agents are the only available option or are required for synergy with other agents.

Implications Within Canadian Health Care

1. The CSN work group agrees with the recommendations addressing the ineffectiveness of specific therapies for the treatment of AKI, and identifies them as an opportunity for knowledge translation.

2. While there is general agreement that aminoglycosides should be used with caution and appropriate monitoring, the work group thought it is premature to recommend that aminoglycosides should never be used in patients at risk for AKI. Such a large and resource-intensive interdisciplinary effort must be carried out within a rigorous evaluative framework capable of testing whether restriction of aminoglycosides effectively changes practice patterns, reduces adverse outcomes, and is cost-effective.

3. Further research is required to identify patients at greatest risk for aminoglycoside-associated AKI.

Contrast-Induced AKI

This section of the KDIGO guideline primarily addresses risk assessment and prophylaxis strategies for contrast-induced AKI. In this section, there were 4 level 1 recommendations. One ungraded, 2 level 1, and one level 2 recommendations were identified for further discussion (Box 3).

Assessment of Population at Risk for AKI (KDIGO Section 4.2)

Commentary

The KDIGO guideline suggests considering alternative imaging methods in patients at increased risk for contrast-induced AKI. The CSN work group agreed that it is generally desirable to avoid iodinated contrast media in the setting of AKI if adequate diagnostic tests or therapeutic interventions can be obtained without contrast administration. However, the work group also thought it was important to recognize that procedures involving the administration of contrast remain important in Canada for the management of many clinical syndromes.

For example, randomized trials in the setting of ST-elevation myocardial infarction have established
that primary percutaneous coronary intervention, when done promptly, is the preferred reperfusion therapy for most patients and leads to significant reductions in mortality, reinfarction, or stroke.37 Furthermore, randomized trials in non–ST-elevation myocardial infarction have shown that a strategy of early coronary angiography reduces recurrent angina, rehospitalization, and myocardial infarction and improves long-term survival in appropriately selected high-risk patients compared to a conservative approach (employing medical therapies and reserving invasive procedures only for patients with signs of ongoing ischemia despite medical management).38 Based on clinical experiences alone, the work group agreed that similar consideration would also apply to imaging methods for the diagnosis of other life-threatening vascular emergencies, such as aortic dissection, aneurysm rupture, and ischemic bowel.

There are concerns that fear of precipitating contrast-induced AKI may contribute to underuse of these procedures in people at high risk of AKI (including those with pre-existing CKD).39,40 Furthermore, such patients with acute illnesses may also be at risk of AKI regardless of iodinated contrast media exposure.41 Given these caveats, the CSN work group thought that it was also important when considering imaging methods to consider the risks of restricting or delaying access to diagnostic and therapeutic contrast imaging procedures, particularly when such actions may deny patient important diagnostic or therapeutic benefits.

Implications Within Canadian Health Care

Primary percutaneous coronary intervention is widely employed in Canadian tertiary care centers for management of myocardial infarction. Given the improvement in cardiovascular outcomes and long-term survival observed with coronary angiography and revascularization for ST-elevation myocardial infarction as well as for high-risk patients with non–ST-elevation myocardial infarction, the risks and benefits of these and other iodinated contrast imaging tests and procedures for life-threatening cardiovascular emergencies should be carefully evaluated in each patient.

Selection of Contrast Agent (KDIGO Section 4.3)

Commentary

This section of the guideline recommends using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media, in patients at increased risk of contrast-induced AKI. High-osmolar contrast media are no longer used in the majority of Canadian radiology departments because of their association with adverse events, including contrast-induced AKI in patients with CKD. Although one high-profile trial has suggested a lower risk of contrast-induced AKI with an iso-osmolar agent (iodixanol) compared to a low-osmolar agent (iohexol),42 subsequent trials have not demonstrated strong consistent differences in the risk of contrast-induced AKI attributable to iso-osmolar versus low-osmolar contrast agents.43 The cost of iso-osmolar contrast media (eg, Can $328 per 100 mL) is significantly greater than low-osmolar contrast media (eg, Can $128 per 100 mL), and given budget limitations within Canada’s publicly funded health care system, the widespread use of iso-osmolar agents could direct resources away from treatments with better established benefits. Many radiology departments in Canada currently reserve the use of iso-osmolar agents for people at high risk of complications of contrast-induced AKI.

Implications Within Canadian Health Care

The CSN work group agrees that either iso-osmolar or low-osmolar iodinated contrast media are appropriate for patients at risk of contrast-induced AKI. However, there is variable but selective use of iso-osmolar contrast media in Canada because of the high costs of these agents and lack of consistent data linking these agents to a lower risk of contrast-induced AKI. Until more definitive benefits of iso-osmolar contrast media have been established, it would seem unwarranted to broadly use iso-osmolar contrast media in people at low risk of contrast-induced AKI.

Pharmacological Prevention of AKI (KDIGO Section 4.4)

Commentary

The efficacy of intravenous sodium bicarbonate versus isotonic saline solution for prevention of
contrast-induced AKI has been controversial. The results of randomized controlled trials comparing these fluids have been heterogeneous, and there is a concern that small, poor-quality studies may have biased estimates of the efficacy of sodium bicarbonate. Normal bicarbonate solutions require additional preparation by pharmacy or nursing staff and cost more (Can $11.80 to prepare a 1-L solution) than equivalent volumes of normal saline solution (Can $1.20 per liter). Although the work group agreed that administration of isotonic intravenous fluid should be a fundamental prophylactic strategy for contrast-induced AKI prevention, the coordination of hydration protocols with diagnostic imaging and angiography procedures can be challenging. The selection of normal saline solution for such protocols may enhance their utilization in Canada because this solution is broadly available and poses a lower financial barrier to implementation.

The KDIGO guideline also recommends the use of NAC in conjunction with intravenous hydration for the prevention of contrast-induced AKI. Since the evidence base for the KDIGO recommendations was compiled, a large, high-quality, randomized trial evaluating the efficacy of NAC for the prevention of contrast-induced AKI has been published.42 The Acetylcysteine for Contrast Nephropathy Trial (ACT) was a double-blinded placebo-controlled trial that randomly assigned 2,308 patients undergoing an intravascular angiographic procedure with at least one risk factor for AKI (age, CKD, diabetes, heart failure, or hypotension) to receive 1,200 mg of oral acetylcysteine twice daily for 2 doses before and 2 doses after the procedure. Most participants (98%) also received a cointervention of 0.9% normal saline solution, 1 mL/kg/h, from 6-12 hours preprocedure to 6-12 hours postprocedure. Approximately 50% of enrolled study participants had an estimated creatinine clearance (Cockcroft-Gault) <60 mL/min. The incidence of contrast-induced AKI was 12.7% in the NAC group and 12.7% in the control group. The investigators did not detect a significant difference between groups in the combined secondary endpoint of mortality or need for dialysis (hazard ratio, 0.97; 95% confidence interval [CI], 0.56-1.69). There was no evidence of a subgroup effect in any of the prespecified subgroups, including those participants with diabetes or an estimated creatinine clearance <60 mL/min. The event rate in this study was slightly lower than that used for sample size calculations; however, the study still had 84% power to detect a 30% difference in the primary end point.

This is the largest trial testing the effects of NAC for the prevention of contrast-induced AKI to date. Furthermore, in an accompanying meta-analysis, stratification of trials according to adequacy of methodological characteristics (allocation concealment, double blinding, and intention-to-treat analysis) revealed a reduction in the pooled relative risk (RR) of contrast-induced AKI with NAC treatment observed among low-quality studies (RR, 0.63; 95% CI, 0.47-0.85; \( I^2 = 56\% \)), yet no effect for NAC among studies meeting all 3 methodological criteria (RR, 1.05; 95% CI, 0.73-1.53; \( I^2 = 0\% \)). The CSN work group believes that the results of ACT, in conjunction with the accompanying meta-analysis, suggest that the benefits reported in prior studies of NAC were confined to trials with a high risk of bias and do not support continuing recommendations for the use of NAC to prevent contrast-induced AKI.

**Implications Within Canadian Health Care**

1. Intravenous volume expansion with either isotonic sodium chloride or sodium bicarbonate solution is appropriate for prevention of contrast-induced AKI. However, intravenous hydration regimens using normal saline solution could enhance the feasibility of institutional protocols given the broad availability and lower cost of normal saline across Canada.

2. Since the publication of the KDIGO guideline, new evidence from a large randomized trial (ACT) has reported that NAC did not reduce the risk of contrast-induced AKI or death or dialysis in patients undergoing angiography.42 The results of ACT are consistent with the findings of other smaller high-quality NAC trials showing a lack of effect for prevention of contrast-induced AKI. The updated evidence base does not support a recommendation to use NAC for prophylaxis of contrast-induced AKI in Canada.

**Dialysis Interventions for Treatment of AKI**

This section of the KDIGO AKI guideline presents 31 recommendations for the management of AKI requiring RRT. Of these recommendations, 9 were graded as level 1 and 8 were opinion based, reflecting the paucity of high-quality data informing decisions with regards to RRT for AKI. The work group thought that several of the recommendations (Box 4) require further discussion in a Canadian context.

**Dialysis Initiation for AKI (KDIGO Section 5.1)**

**Commentary**

The CSN work group agrees that in the absence of a life-threatening complication of AKI such as medically refractory hyperkalemia and severe volume expansion, the optimal timing of RRT initiation is controversial. In this setting, the guideline recommends using the “broader clinical context” and trends in laboratory tests to guide treatment decisions. While reasonable on the surface, these recommendations...
Box 4. Selected Recommendations From Section 5 of the KDIGO AKI Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>5.1.1</td>
<td>Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. <em>(Not Graded)</em></td>
</tr>
<tr>
<td>5.1.2</td>
<td>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. <em>(Not Graded)</em></td>
</tr>
<tr>
<td>5.3.2.2</td>
<td>For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. <em>(2B)</em></td>
</tr>
<tr>
<td>5.3.2.3</td>
<td>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. <em>(2C)</em></td>
</tr>
<tr>
<td>5.6.1</td>
<td>Use continuous and intermittent RRT as complementary therapies in AKI patients. <em>(Not Graded)</em></td>
</tr>
<tr>
<td>5.6.2</td>
<td>We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. <em>(2B)</em></td>
</tr>
<tr>
<td>5.8.3</td>
<td>We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. <em>(1A)</em></td>
</tr>
<tr>
<td>5.8.4</td>
<td>We recommend delivering an effluent volume of 20–25 mL/kg/h for CRRT in AKI. <em>(1A)</em> This will usually require a higher prescription of effluent volume. <em>(Not Graded)</em></td>
</tr>
</tbody>
</table>

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

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provide little practical guidance to clinicians and highlight the subjectivity that guides current decision making around the optimal timing of RRT initiation. Not surprisingly, there is substantial variability in the timing of initiation of RRT across the world, including Canada. In a recent survey of Canadian nephrologists and critical care physicians, hyperkalemia and volume expansion factored strongly in deciding when to initiate RRT for AKI, while the absolute values of SCR and urea influenced decision making for 57% and 59% of respondents, respectively. The survey highlighted other factors that influence the decision to start RRT, namely the time of day when laboratory results become available, patient age and comorbid conditions, urine output following diuretic administration, and the specialty of the attending physician. In clinical practice, hyperkalemia was infrequently present at the time of RRT initiation and RRT initiation tended to occur early (a median of 1 day following intensive care unit admission). In addition, in a large and sparsely populated country such as Canada, the actual timing of RRT initiation in relation to the development of AKI may be influenced by potential delays in arranging patient transfer to centers that offer RRT.

More than 90% of respondents to the survey cited agreed that performing a randomized controlled trial on the timing of RRT initiation is ethical. The Standard Versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial has recently started in Canada (ClinicalTrials.gov identifier NCT01557361). This multicenter pilot randomized trial is studying critically ill individuals with AKI who have a high likelihood of needing RRT but with no life-threatening complications of AKI. The trial aims to determine if randomly assigning patients to accelerated/preemptive (RRT started within 12 hours of eligibility) compared to standard RRT (initiation guided by the emergence of significant AKI complications) initiation is feasible and safe. The CSN work group acknowledges that randomized controlled trials addressing this question are highly needed, and given the absence of evidence around the optimal timing of RRT initiation in the absence of life-threatening complications of AKI, specific criteria for RRT initiation cannot be delineated.

**Implications Within Canadian Health Care**

In the absence of life-threatening complications of AKI, the optimal timing of RRT initiation is uncertain. Recent Canadian studies suggest that there is great variability in the indications for initiation of RRT in AKI. A more aggressive approach to RRT initiation will likely lead to the consumption of more resources and widespread adoption of this strategy should await the results of randomized trials.

**Anticoagulation for RRT (KDIGO Section 5.3)**

**Commentary**

The CSN work group acknowledges that the lower risk of bleeding with regional citrate anticoagulation represents a clinically relevant advantage in favor of this anticoagulation strategy. However, not all centers in Canada have extensive experience with the performance of continuous RRT (CRRT) with regional citrate anticoagulation and this technique may not be available in every center, especially when initiating a CRRT program. Furthermore, regional citrate anticoagulation is more costly than heparin-based anticoagulation due to the cost of citrate and the need for more intensive monitoring of metabolic parameters. However, if the use of regional citrate anticoagulation leads to prolonged filter life, then the additional costs may be offset. There are insufficient data on the most cost-effective form of anticoagulation at the present time.

The CSN work group believes that prior to introducing a regional citrate anticoagulation program, a strict protocol and adequate staff education must be in place to avoid prescription pitfalls leading to metabolic...
complications. A recent systematic review on the efficacy and safety of regional citrate anticoagulation supported its use and concluded that hypernatremia, metabolic alkalosis, and hypocalcemia could easily be controlled without clinical consequences using a strict protocol. A protocol should detail the infusion rates of citrate and calcium, the composition of the dialysate and replacement fluid, and the intensity of metabolic monitoring, including acid-base status and serum sodium and total and ionized calcium levels.

The KDIGO guideline cites “severely impaired liver function or shock with muscle hypoperfusion” as “major” contraindications for the use of regional citrate anticoagulation. The work group agrees that regional citrate anticoagulation should be used cautiously in these settings, but we do not believe that these represent absolute contraindications. In the setting of liver failure, in which patients are often coagulopathic, heparin-based anticoagulation would likely be contraindicated, and clinicians may wish to consider the performance of CRRT with no anticoagulation or the use of intermittent modalities in which anticoagulation-free regional citrate anticoagulation may be more feasible (eg, sustained low-efficiency dialysis [SLED]). However, the severity of liver disease is often difficult to objectively quantify and even in the setting of severe liver failure, citrate accumulation can be tracked by carefully following the systemic ionized calcium level and the total calcium to ionized calcium ratio. Adapted regional citrate anticoagulation has been safely performed in CRRT and extracorporeal liver assist devices in patients with severe liver failure.

We view the recommendation to avoid regional citrate anticoagulation in the setting of shock as somewhat impractical. In the North American setting, CRRT is primarily employed during periods of hemodynamic instability, as illustrated in a recent large trial of RRT intensity. Moreover, the dangers of regional citrate anticoagulation in the setting of shock have not been defined. A recent study reported the safety of regional citrate anticoagulation in patients with severe septic shock, and in a Canadian randomized controlled trial, shock was not a contraindication to regional citrate anticoagulation. Several other randomized controlled trials using regional citrate anticoagulation in CRRT also did not consider shock to be a contraindication. Therefore, the CSN work group believes that the use of regional citrate anticoagulation may still be considered in the setting of shock.

**Implications Within Canadian Health Care**

Prior to introducing regional citrate anticoagulation, a strict protocol and adequate staff education should be in place to avoid prescription errors leading to complications. Regional citrate anticoagulation should be used cautiously in the settings of liver failure and muscle hypoperfusion; however, the work group did not believe that these represent absolute contraindications.

**Dialysis Modality (KDIGO Section 5.6)**

**Commentary**

The CSN work group agreed that in the absence of evidence showing a survival benefit of any one modality, continuous and intermittent RRTs should be used as complementary therapies with utilization dictated by the dynamic clinical circumstances and local availability and expertise. For patients with hemodynamic instability, CRRT has many theoretical advantages, but is also more expensive with no survival benefit over intermittent hemodialysis (IHD). In some Canadian centers, SLED has replaced CRRT as the modality utilized for hemodynamically unstable patients and has been shown to offer comparable results to CRRT in terms of hemodynamic stability. The guideline suggests that SLED may be viewed as an alternative to CRRT “in settings where other forms of CRRT are not available.” Some work group members agreed with this assertion while others thought that SLED could be used interchangeably with CRRT. Those with the latter view objected to the implication that CRRT should be the standard of care for individuals with AKI and hemodynamic instability because the totality of evidence does not support an advantage of CRRT over IHD with respect to patient-relevant outcomes, including survival. In light of this, it would seem inappropriate to characterize SLED as an inferior alternative to CRRT. Finally, in the table comparing the relative advantages of the different RRT modalities, both IHD and SLED were characterized as “technically more complex and demanding,” whereas “user-friendly machines” was a characteristic attributed to CRRT. These perceptions may be center specific because some have cited the relative ease of delivering therapy as an advantage of SLED.

In the Canadian context, where patients are often referred from rural or community hospitals to tertiary-care centers for the provision of RRT, the advent of SLED may enable the administration of RRT in centers that have dialysis capability but not necessarily CRRT. This may obviate the need for transfers that are otherwise driven by the receiving center’s capacity to perform CRRT. However, even in centers that offer conventional dialysis, the feasibility of administering the longer treatment hours associated with SLED may be limited by the availability of hemodialysis personnel.
Implications Within Canadian Health Care

There is remaining controversy surrounding the optimal RRT modality for AKI. Although CRRT has not been shown to confer superior short-term outcomes as compared to IHD, the work group acknowledged that clinical strategies are needed for the administration of RRT to hemodynamically unstable patients. SLED may present a practical and cost-effective alternative to CRRT for such patients. The adoption of SLED in Canadian centers will require consideration of multiple factors, including clinical outcomes and personnel availability.

Dose of RRT (KDIGO Section 5.8)

Commentary

The CSN work group generally agreed with the recommendations on dose thresholds for RRT in AKI. Although there is little evidence for a dose “floor” below which patient outcomes are adversely affected, we believe that striving to meet basic clearance parameters is in the patient’s best interest. For intermittent therapies (IHD or SLED), the proposed urea-based clearance targets are extrapolated from the maintenance hemodialysis setting with the caveat that urea clearance per se may be of limited relevance in AKI.69 However, in the absence of AKI-specific metrics for RRT adequacy, borrowing such targets from end-stage renal disease is appropriate in order to ensure that a basic minimum RRT dose is delivered. Because recent trials have not demonstrated the clinical superiority of CRRT doses of 35–40 mL/kg/h,58,70 adoption of the “less intensive” effluent flow rates used in these trials (ie, 20–25 mL/kg/h) as the target dose for clinical practice will reduce costs associated with CRRT and is sensible unless future trials suggest that lower rates are equally acceptable. However, compared to practices within randomized controlled trials, the provision of CRRT in routine clinical practice may be more often temporarily interrupted for a variety of reasons (eg, circuit clotting, medical imaging, and surgery) and the prescribed dose is usually not adjusted for these interruptions. In addition, the efficiency of filters in CRRT declines over time due to decreased porosity of the membrane. In one large clinical trial of dialysis dose (RENAI [Randomized Evaluation of Normal Versus Augmented Level]), participants received ~85% of the prescribed dose,70 whereas in an observational study by Venkataraman et al,71 patients received on average only 68% of the prescribed dose due to “down time,” and another observational study suggested that prescribed clearance could overestimate the actual delivered clearance by almost 25%.72 Although some members of the work group thought it was reasonable to increase prescribed flow rates by 20%-25% above the “less intensive” target for these reasons, some members believed this was not warranted based on the existing evidence from trials, and others instead suggested a role for quality improvement programs in acute dialysis to ensure that delivered doses approximate targets. The work group agreed that individualization of the intensity of CRRT or IHD may be required to meet a patient’s requirements for maintenance of electrolyte and fluid balance.

CONCLUSION

The KDIGO AKI guideline represents an important advance in synthesizing evidence about the identification and management of AKI; however, it also highlights many areas of clinical practice that remain driven by opinion and/or low-quality data. The CSN work group believes that any limitations of the guideline relate not to the effort of the KDIGO work group, but to the lack of information currently available regarding the validity and clinical application of the newly proposed AKI definition and the paucity of evidence that supports a number of management recommendations.

AKI is a common event, associated with poor outcomes. As health care providers, we often feel compelled to try whatever is feasible in our efforts to avoid these outcomes. However, as Canadians, it is also our responsibility to ensure that our limited health care resources are directed toward providing effective therapies. The many therapeutic interventions identified as ineffective or having low-quality evidence for efficacy for AKI prevention and treatment are an important contribution of the guideline. While somewhat discouraging, these findings also represent a key opportunity to disseminate knowledge within the medical community about what therapies do not work or are not evidence based for preventing or treating AKI.

However, there are reasons to be optimistic about the progress of research in the field of AKI. While the clinical applications remain unclear, the KDIGO AKI definitions are an important step in promoting a common dialogue about AKI. The emerging use of biomarkers to further delineate and categorize AKI is an exciting development and may assist in risk stratification, early diagnosis, and better tailoring of therapies to specific forms of AKI in the future. Nationally, the multicenter STARRT-AKI trial reflects a growing recognition in Canadian nephrology that multicenter trials on AKI are needed to answer many of the basic questions we all face in providing care to our patients with AKI. Several recent, large randomized trials of RRT in AKI have
proved that with collaboration and perseverance, these trials can be done.

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SUPPLEMENTARY MATERIAL

Table S1: Summary of AGREE II scores.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.02.350) is available at www.ajkd.org

REFERENCES


**APPENDIX**

**Conflict of Interest Information for Work Group Members**

<table>
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<tr>
<th>Member</th>
<th>Type of Conflict of Interest</th>
<th>Role</th>
<th>Period</th>
<th>Sponsor</th>
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<td>Josée Bouchard</td>
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<td>Co-PI for a study on new biomarkers for AKI</td>
<td>2010-2012</td>
<td>Astute Medical Inc</td>
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<td>Julie Ho</td>
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<td>Matthew James</td>
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<td>Jean-Philippe LaFrance</td>
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<td>Neesh Pannu</td>
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<td>Claudio Rigatto</td>
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<td>Ron Wald</td>
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<tr>
<td>Michael Zappitelli</td>
<td>Research funding</td>
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<td>2012</td>
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*Note:* Information provided concerns the past 3 years and is restricted to companies that make products related to the diagnosis or management of AKI, including dialysis companies.
Abbreviations: AKI, acute kidney injury; PI, principal investigator.