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Reading between the (guide)lines—the KDIGO practice guideline on acute kidney injury in the individual patient

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Abstract

The KDIGO guidelines for acute kidney injury (AKI) are designed to assist health-care providers around the world in managing patients with AKI. Clinical guidelines are intended to help the clinician make an informed decision based on review of the currently available evidence. Due to the generic nature of guidelines, it is sometimes difficult to translate a guideline for a particular individual patient who may have specific clinical circumstances. To illustrate this point, we have discussed the interpretation of the KDIGO guideline in patients who have subtleties in their clinical presentation, which may make treatment decisions less than straightforward.

Keywords

acute kidney injury; creatinine; KDIGO; RIFLE

There have been a plethora of clinical practice guidelines (CPG) produced by individual national and international specialist medical societies. By critically evaluating relevant scientific evidence (Table 1), CPG can provide recommendations for clinical practice[1] and help improve the quality of clinical decision making. However, there is often insufficient good quality scientific data to positively advocate one intervention over another, and as such recommendations made by CPG committees often become subjective and 'opinion-based'. Even when a generic recommendation is available, it may not always be suitable for an individual patient due to their particular circumstances.[2] In addition, CPG may be manipulated by health-care purchasers, and other organizations.[3] Although CPG have generally been reported to improve overall quality of patient care,[4] whether this is always achieved on a daily basis remains debatable.[2]

DEVELOPMENT OF THE KDIGO (KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES) GUIDELINE FOR ACUTE KIDNEY INJURY (AKI)

Reviewing evidence to develop guidelines is a prolonged process. An initial working group of recognized clinical experts in the field of acute kidney injury determined key topics to be addressed. This expert panel was expanded to include other clinicians not only from nephrology and intensive care but other relevant specialities to form individual workgroups, supported by an 'evidence review team' specialized in the field of guideline development,

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which formulated recommendations and provided reasoning for their guidance depending upon the quality of available evidence. Provisional guidelines were then posted on the KDIGO website for general comment and additionally sent to individual clinicians for review. Following external comments, the revised guidelines were finally published.

WHY DO WE NEED GUIDELINES FOR AKI?

One of the fundamental problems in interpreting studies in AKI has been the lack of a unified definition. There were discrepancies between the two more commonly used definitions,[5–7] leading to differences in incidence and outcomes of AKI. It was therefore essential to have an agreed definition for epidemiological studies, assessment of risk factors for AKI, evaluation of biomarkers predicting severity and recovery from AKI, and interventional trials. In addition, it was also important to review the basic resuscitation and management of patients with AKI, to standardize practices and establish not only whether interventional treatments could reduce the risk of developing or severity of AKI but also whether different supportive therapies could potentially hasten renal recovery, or reduce the risk of developing progressive chronic kidney disease (CKD) in AKI survivors.

The KDIGO AKI guidelines are intended to aid the diagnosis and provide informed decision-based management. As with any CPG, the KDIGO clinical guidelines cannot account for all the possible combinations of individual patients, health-care providers, and health-care systems. As such, clinicians need to assess the appropriateness of a particular recommendation or suggestion in the specific context of an individual patient. The KDIGO-AKI guidelines are an extensive document, and as such we cannot comment on all the aspects. We have therefore chosen to comment on those guidelines that will have the greatest impact on day-today clinical practice and those of a more contentious nature. Using examples of patients with AKI, we will attempt to underline the relevance of the complex interaction of factors, which often impact on the diagnosis and management of patients with AKI.

CLINICAL EXAMPLES OF THE APPLICATION OF THE KDIGO GUIDELINES FOR AKI

2: AKI DEFINITION

Guideline 2.1	Definition and classification of AKI
2.1.1	AKI is defined as any of the following (Not Graded): Increase in SCr by ≥0.3 mg/dl (≥26 mmol/l) within 48 h; 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 of 0.5 ml/kg/h for 6 h.
2.1.2	AKI is staged for severity according to the following criteria (Table 2). (Not Graded)
2.1.3	The cause of AKI should be determined whenever possible. (Not Graded)

A 74-year-old male with a history of diabetes mellitus, fever, hypotension abdominal distension, and leukocytosis. An ultrasound of his abdomen revealed fluid collections. He underwent exploratory laparotomy in which purulent fluid was removed and drains were placed. He remained oliguric and SCr trended upward from a preoperative value of 0.8–1.0 mg/dl over 48 h and continued to rise to 1.4 mg/dl over the next several days. He remained intubated on 40% FiO2 and received intravenous norepinephrine for BP support. His fluid balance was ∼26 l positive for the admission.

KDIGO has addressed an important need for a single definition of AKI that would impact patient care, research, and public health by combining the definitions derived from Acute Kidney Injury Network (AKIN)[6,7] and Risk, Injury, Failure, Loss and End stage kidney failure criteria,[5] which have been well validated. However, the diagnosis of AKI may be missed when using one or the other classification schemes.[5–7] Thus combining the two criteria ensures that the diagnosis is captured. Although a single definition has its merits, several issues remain with a creatinine-based definition of AKI, which are outlined in Section 2.4. Firstly, serum creatinine is reported as a concentration and hence is affected by hydration status. For example, there may be a dilutional effect on serum creatinine in patients who have received significant volume expansion with intravenous fluids. In this case, despite a significant reduction of glomerular filtration rate (GFR), there may only be a small rise in serum creatinine, which may not meet the definition of AKI according to AKIN criteria but would meet the criteria for Risk, Injury, Failure, Loss and End stage kidney failure. KDIGO combines the definitions, hence an absolute rise in serum creatinine of 40.5 mg/dl within 7 days would meet the criteria for AKI. The dilutional effect may alter the potential impact of early diagnosis and magnitude of injury. Adjustment of serum creatinine can be made by factoring for volume accumulation.[8] Creatinine production falls during AKI, due to reduced hepatic creatine synthesis. It remains to be determined whether the fall in creatine synthesis reflects systemic inflammation or is disease specific in AKI. On the other hand, muscle injury will increase creatinine release. Second, the KDIGO definition of AKI depends on the increase in serum creatinine from baseline, which in many instances is not available. KDIGO recommends that in the absence of a premorbid baseline serum creatinine an estimated creatinine should be determined based upon an MDRD (Modification of Diet in Renal Disease) GFR of 75 ml/min per 1.73 m^2, which has been shown to reliably predict Risk, Injury, Failure, Loss and End stage kidney failure—I and F.[9] Third, patients with very low baseline creatinine may have a 50% increased serum creatinine, but the difference may, in part, reflect variability in the measurement of serum creatinine or dietary changes that affect creatinine. Interlaboratory variation in measuring creatinine and the effect of bilirubin and other compounds which interfere with the colorimetric modified Jaffe assay will also affect the reporting and incidence of AKI stage 1.[10–12] Fourth, the prognosis of transient AKI is likely to represent a spectrum of AKI from prerenal with functional alterations to ‘established’ AKI with structural damage.[13] Although both may have similar degrees of increase in creatinine, the prognosis may be different.

Chapter 2.2 Risk assessment

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). (Not Graded)

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)

A 65-year-old male was postoperative from an aortic valve replacement, had cardiac tamponade with systolic blood pressures of 90–100 mm Hg, and was sent urgently for a contrast study. His baseline Cr was 0.9 mg/dl and had increased to 1.1 mg/dl postop and 1.7 mg/dl (reported estimated GFR (eGFR) 36 ml/min) on the day of the study. The patient received low-osmolar iodinated contrast (Omnipaque 350), and renal function continued to decline eventually requiring hemodialysis.

An important consideration in this case is the assessment of risk for additional injury from the contrast study, which must be balanced with a delay in performing the diagnostic study or a less definitive study. The increase in creatinine postoperative indicates that the true GFR was substantially lower than the reported eGFR. In the absence of steady state, reported eGFRs cannot be used. The increase in creatinine was due to hypotension, and presumed factors associated with aortic valve replacement are important considerations placing the patient at high risk for further injury. However, the acuity of the situation with assessment of the integrity of the aortic value likely warrants a definitive study as opposed to transthoracic echocardiogram. Understanding and modifying risk factors are important goals to the prevention of AKI. The use of iso-osmolar iodinated contrast agent in this case is probably not warranted, as current data do not substantiate improved efficacy in the prevention of AKI over low-osmolar iodinated contrast agents (see 4.3).

Chapter 2.3 Evaluation and general management of patients with and at risk for AKI

Chapter 2.4 Clinical applications

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 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)

- 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)

The Risk, Injury, Failure, Loss and End stage kidney failure and AKIN definitions have shown that increasing severity of AKI is not only independently associated with an increased risk for death[14] but is also associated with progressive kidney disease and end-stage renal disease (ESRD).[15] These definitions were developed by clnicians based in economically developed countries, and the etiology of AKI differs between economically developed, developing, and third world countries. In addition, AKI is more likely to occur on a background of CKD in economically developed countries compared with third world countries. As such, the question arises as to whether the same association between AKI severity defined by the KDIGO definition will have the same association with mortality in third world countries? In addition, it remains unclear as to whether the increased risk of mortality is primarily due to the severity of the renal injury *per se* or the severity of renal injury reflects underlying comorbidity. As, for example, if a patient doubles their baseline serum creatinine from 0.6 to 1.2mg/dl and another from 1.2 to 2.4mg/dl, then both patients will be classified as KDIGO stage 2, but is the severity of renal injury the same? The first patient will have lost renal reserve before the serum creatinine starts to rise, whereas the second has already lost renal reserve. On the other hand, the first patient has greater potential for renal recovery, whereas the second patient is more likely to develop progressive CKD.

After 1 week of hemodialysis the patient's urine output increased and endogenous renal function improved. Hemodialysis was discontinued and the patient was discharged with a creatinine of 2.1 mg/dl.

The impact of AKI in our patient is that he likely has residual renal damage and CKD. Because of the high likelihood for progressive renal disease and other comorbidities,[16] including ESRD,[17,18] it is important to transition to a coordinated care management plan involving at least a nephrologist and primary care physician.[19] These patients are at risk of hypertension, volume overload, coronary events, and ESRD, therefore the patient should have blood pressure, fluid status, proteinuria, and other metabolic parameters assessed at regular intervals. KDOQI CKD guidelines should be followed.

PREVENTION AND TREATMENT OF AKI

Guideline 3.1 Hemodynamic monitoring and support for prevention and management of AKI

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)

The kidney is a vital organ in the maintenance of fluid balance, and in critically ill patients it is essential to maintain optimal kidney function. Nearly all critically ill patients received intravenous fluids, and intravenous fluid resuscitation remains the mainstay treatment for patients with severe sepsis. However, despite the wide spread use of different types of intravenous fluids, the choice of intravenous fluid to use remains controversial. The Surviving Sepsis Campaign guidelines recommend the use of crystalloids as first line, albumin in severe sepsis, and advise avoiding hydroxyethyl starch in severe sepsis, whereas KDIGO recommends crystalloid rather than colloid. In a Cochrane report, there was no evidence from randomized control trials to support the use of colloids over crystalloid for resuscitation.[20] The Saline versus Albumin Fluid Evaluation study, a large multicenter randomized controlled trial, compared 4% albumin in 0.9% saline with 0.9% saline alone for fluid resuscitation in critically ill patients. There were no significant differences in mortality, days in intensive care unit/hospital, mechanical ventilation, or days on renal replacement therapy.[21] Recent studies have examined the use of hydroxyethyl starch. Older preparations of hydroxyethylstarch (hetastarch, hexastarch, and pentastarch) were shown to impair renal function and hemostasis. The efficacy of newer lower molecular weight formulations, with fewer substitutions, such as HES 130/0.4, in sepsis was recently studied.[22] The 6S Trial Group randomized intensive care unit patients with severe sepsis to fluid resuscitation with 6% HES 130/0.42 in Ringer's acetate or Ringer's acetate. The results showed more patients in the HES 130/4.2 compared with the Ringer's acetate group died, were treated with renal replacement therapy, or had severe bleeding episodes. Despite the theoretical advantage of colloids over crystalloid as plasma volume expanders, there was no difference in fluid volume administration between the groups. For these reasons, KDIGO recommends crystalloids over colloids. Given the absence of data supporting the superiority of colloid and the additional cost, their recommendations appear reasonable. However, in some specialized situations, such as malaria-induced AKI, overzealous fluid resuscitation may not only fail to prevent AKI but also increase the risk of malaria-induced acute lung injury and the need for ventilation.

Interestingly, a new debate has emerged regarding the choice of crystalloids. The use of normal saline that contains 153 meq of chloride induces a hyperchloraemic metabolic acidosis, thus large volumes will certainly induce abnormal fluid, electrolyte, and acid–base disturbances that might complicate the course of critically ill patients. Despite the lack of

definitive studies, accumulating data support the use of physiologically balanced crystalloid solutions,[23–25] with some reports showing reduced renal cortical perfusion with chloride-rich crystalloids.[26] Further prospectively designed studies will be necessary to address this issue.

3.1.2 We recommend the use of vasopressors in conjunction with fluids in patients with vaso-motor shock with, or at risk for, AKI. (1C)

Sepsis is invariably associated with hemodynamic instability, with hypotension manifested most commonly. Following volume resuscitation, the use of vasopressor is critically important in maintaining hemodynamic stability; however, its use is often associated with AKI. KDIGO recommends its use along with fluids but does not make a distinction between the commonly used vasopressors—norepinephrine, vasopressin, or dopamine. However, the use of dopamine is not recommended for the prevention of AKI (see 3.5.1). Vasopressin may offer additional value, as patients with septic shock are relatively deficient in vasopressin, and administration of vasopressin improves vascular tone and blood pressure.[26] However, in a multicenter study in which septic patients were given norepinephrine or norepinephrine and vasopressin, there was no significant beneficial effect of vasopressin. However, in those who are less ill, vasopressin reduced mortality, whereas it did not in those with more severe sepsis.[27] Thus current recommendations do not favor one vasopressor over the other; however, their use is vital along with fluid resuscitation in critically ill patients with sepsis.

3.1.3 We suggest using protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (2C) or in patients with septic shock (2C).

The goal of protocol-based therapy for the treatment of patients with septic shock is to manage hemodynamics in order maximize tissue oxygenation. The best-known study is the Early Goal Directed Therapy, which was a single-center randomized study of a strategy that used physiological parameters to drive the administration of fluid, blood products, and vasopressors.[28] Over the 6-h time period, this protocol-driven strategy led to a dramatic improvement in mortality. Whereas the Rivers study[28] was performed in the emergency department, similar findings have been observed in the intensive care[29] and post-surgical settings.[30] What is not evident from these studies and remains as areas of potential investigation is whether it is the timing of intervention or the specific components that comprise the intervention that improved outcomes.

Guideline 3.2 General supportive management of patients with AKI, including management of complications

Guideline 3.3 Glycemic control and nutritional support: Glycemic Control In Critical Illness: Renal Effects and Outcomes

3.3.1 In critically ill patients, we suggest insulin therapy targeting plasma glucose of 110–149 mg/d(6.1–8.3 mmol/l). (2C)

3.3.2 We suggest achieving a total energy intake of 20–30 kcal/kg per d in patients with any stage AKI. (2C)

3.3.3 We suggest avoiding restriction of protein intake with the aim of preventing or delaying initiation of RRT. (2D)

3.3.4 We suggest administering 0.8–1.0 g/kg per d of protein in noncatabolic AKI patients without need for dialysis (2D), 1.0–1.5 g/kg per d in patients with AKI on RRT (2D), and up to a maximum of 1.7

g/kg/d inpatients on continuous renal replacement therapy (CRRT) and in hypercatabolic patients. (2D)

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

The problem of treating critically ill patients confronted with nutritional challenges remains an active area of investigation. The evidence for any of the existing guidelines is modest, at best achieving only grade 2C. The target glucose of 110–149 mg/dl (6.1–8.3 mmol/l) was a result of extrapolation of data from randomized control trials and meta-analyses. Hyperglycemia is a stress response to critical illness, and it was hypothesized that tight control of blood glucose may lead to improved outcomes. Evidence to support this hypothesis came from a landmark trial of Van Den Berghe *et al*.,[31] conducted in critically ill surgical patients; targeting blood glucose of 80–110 (4.44–6.11) mmol/l was associated with reduced morbidity and mortality; however, in medical intensive care patients mortality was not reduced although there was a reduction in AKI.[32] Subsequently, numerous studies and meta-analyses could not confirm these findings. Perhaps the most definitive study, the NICE-SUGAR trial targeting blood glucose of 80–110 (4.44–6.11) mmol/l,[33] could not confirm the studies by Van den Berghe. In general, the composite of these studies suggests that lower blood glucose is not associated with improved outcomes, and there was a greater risk of hypoglycemia. Thus although there is no evidence, the KDIGO has settled on extrapolating the available data that moderate control is better than no control and tight control.

Guideline 3.4 The use of diuretics in AKI

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

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

The medullary region is metabolically active and relatively hypoxic, conditions ideally suited for a role of furosemide in the prevention of AKI. Despite preclinical studies demonstrating a beneficial effect,[34,35] randomized control trials and meta-analyses clearly demonstrate that furosemide does not prevent AKI and may lead to increased mortality.[36] However, in the cases where volume overload complicates AKI, diuretics may actually improve outcomes.[37] Using data from the Fluid and Catheter Treatment Trial, which was a multicenter randomized controlled trial evaluating a conservative versus liberal fluid treatment in patients with acute lung injury. A cumulative positive daily fluid balance in those patients who developed AKI was associated with higher mortality, whereas higher furosemide doses had a protective effect on mortality in those patients with AKI. Thus KIDGO suggested not using furosemide to prevent AKI but for the treatment of volume overload in patients with AKI. Most clinicians would use frusemide in hemodynamically stable and volume overloaded patients, but otherwise the potential benefit is outweighed by risk of precipitating volume depletion, hypotension, and further renal hypoperfusion.

Guideline 3.5 Vasodilator therapy: dopamine, fenoldopam, and natriuretic peptides

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

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

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

The concept of vasodilator therapy for the prevention and treatment of AKI has been around for many years; however, human studies have not verified the benefit seen in animals. The

basis for the proposed beneficial effect, i.e. vasodilation, is confounded by hypotension, especially in septic patients.

Guideline 3.6 Growth factor intervention

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

The role of erythropoietin and other growth promoters in AKI is uncertain. Thus additional research effort should be focused on these agents.

Guideline 3.7 Adenosine receptor antagonists

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

Adenosine causes vasoconstriction of the afferent arteriole, leading to decreased renal blood flow, and GFR, with sodium and water retention. Theophylline is a nonselective adenosine receptor antagonist and has been variously trialled to prevent AKI in perinatal asphyxia, iodinated radiocontrast exposure, and cardiorenal syndrome. Although theophylline clearly improves renal function in the first week of life in post-asphyctic neonates, there is no improvement on neonate survival or difference in recovery of renal function in survivors compared with placebo.

Guideline 3.8 Prevention of aminoglycoside- and amphotericin-related AKI

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

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

3.8.3 We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24 h. (IA)

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

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

Aminoglycosides continue to remain an important antibiotic for the treatment of severe infections. They are potent and effective against many Gram-negative bacteria, and when combined with beta lactams and cell wall inhibitors, are effective against some Gram-positive organisms. However, given their potential for nephrotoxicity, KDIGO recommends that alternative agents should be used. Single daily dosing is suggested for patients with stable normal kidney function rather than the traditional multiple dosing regimen. This suggestion is based upon modest benefit from controlled trials and meta-analyses.[38,39] For patients with cystic fibrosis, aerosolized tobramycin delivers high local levels of the aminoglycoside, and this delivery system has been shown to be effective,[40] although there are reports of nephrotoxicity.[41,42] Aminoglycosides are not the only antibiotics recognized to cause acute renal tubular damage, others include the glycopeptide vancomycin.

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

3.8.7 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)

Despite its nephrotoxic potential, amphotericin continues to be used because of its efficacy as an antifungal agent in serious infections. Liposomal preparations have been shown to be as effective as amphotericin B but with less nephrotoxic potential. However, there is an added cost and different dosing strategies that must be considered. Other antifungal agents are less nephrotoxic and should be considered if equally effective.

Chapter 3.9 Other methods of prevention of AKI in the critically ill

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

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

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

On pump coronary artery bypass grafting (CABG) in, which the heart and aorta are cannulated, ascending aorta is cross-clamped and the patient is subjected to cardioplegic arrest, has been primarily used in patients with symptomatic coronary artery disease. On the other hand, off-pump CABG in which surgery is performed on a beating heart was developed to avoid complications, including AKI. The results of randomized controlled trials, meta-analyses, and systematic reviews have yielded inclusive results..[43,44] Thus definitive conclusions remain elusive, and KDIGO does not recommend off-pump CABG for the prevention of AKI. With the growing concern of the progression of AKI to CKD/ESRD, a prospective randomized controlled trial on 4752 patients from 79 sites in 19 countries will be reported in 2013 comparing short-term and 1-year effect of on-pump versus off-pump procedure on AKI and AKI progression.[45]

Although the use of N-acetyl cysteine (NAC) is controversial in the setting of intravascular (i.v.) contrast exposure, the evidence against the use of NAC in critically ill patients and post surgery is even stronger.

Chapter 4.1 Contrast-Induced Acute Kidney Injury (CI-AKI)

4.1 Define and stage AKI after administration of intra-vascular contrast media as per Recommendations 2.1.1–2.1.2. (Not Graded)

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)

The definition of iodinated contrast-induced renal injury varies from series to series, typically ranging from an increase in serum creatinine of 25–50% or an absolute increase of ≥0.5 mg/dl (44 umol/l) occurring within 48 or 72 h. To aid comparison of studies designed to determine the incidence, risk factors, and preventative measures for CI-AKI, a standardization of definitions is required for all stake holders.

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)

A 76-year-old man with type 2 diabetes with acute chest pain and dynamic electrocardiograph (ECG) changes was brought by emergency paramedics to a primary angioplasty suite. He had been given aspirin, diamorphine, and supplemental oxygen by the paramedics. On examination he was distressed, sweating, blood pressure 145/85 mm Hg, tachycardic, rate 96/min, with detectable bilateral ankle oedema. ECGs showed S-T elevation across the anterior chest leads. Medications included ramipril 5 mg bd, fruse-mide 80 mg od, metformin 850 mg bd, gliclizide 80 mg bd, pioglitazone 30 mg od.

Millions of iodinated contrast examinations are undertaken worldwide, with the majority in ambulatory patients who do not require special preventative measures. This patient requires urgent coronary angiography, and although pre-existent CKD is the greatest risk factor for CI-AKI, the angiogram and proposed angioplasty and coronary artery stenting take precedent. He has other risk factors, including age, diabetes, the amount of iodinated contrast to be used, and possible pre-existent cardiac failure (Table 3). Most centers use a risk scoring system, developed locally or based on previously published scores,[46] or specialist societies[47] (Table 4).

The results from admission showed a hemoglobin of 115 g/l, serum creatinine 1.8 mg/dl (159 umol/l), blood sugar 288 mg/dl (16 mmol/l), and urate 8.07 mg/dl (0.48 mmol/l), with an eGFR of 39 ml/min per 1.73 m^2.

This man is at increased risk for CI-AKI, and concomitant administration of nephrotoxic drugs could increase the risk of AKI, and the question arises as to whether his ACEI (angiotensin converting enzyme inhibitor) and diuretics should be continued or withdrawn. Recent small trials have not reported any increased risk of CI-AKI by continuing these medications.[48,49] However, his diabetic control is sub-optimum, and he will require an insulin and dextrose infusion,[50] and the metformin and other oral hypoglycemics should be withdrawn.[51]

4.2.2 Consider alternative imaging methods in patients at increased risk for CI-AKI. (Not Graded)

4.3.1 Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. (Not Graded)

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. (1B)

Coronary angiography, angioplasty, and insertion of a drug eluting stent were performed using 125 ml of iodixanol.

In keeping with specialist society advice, the minimal dose of iodinated radiocontrast possible was used.[48,49] The cardiologists chose a non-ionic iso-osmolar contrast agent. The risk of CI-AKI for patients with pre-existing CKD, as in this case, is less with iso-osmolar iodixanol compared with the hypotonic agent iohexol.[50] The KDIGO guidelines recommended avoiding hypertonic contrast agent and using either an iso-osmolar or low osmolar iodinated contrast as the evidence that low-osmolar contrast agents reduce the risk of CI-AKI compared with iso-osmolar iodinated contrast agents remains unclear. Although iodixanol has been shown to reduce oxygenation in the renal medulla in animal models, compared with hypo-osmolar contrast agents,[52] in clinical practice the risk of CI-AKI with iodixanol has not been proven to be greater than that for the newer hypo-osmolar agents.[53,54] Similarly, as iodinated hypo-osmolar contrast agents differ in terms of charge and osmolality, there may well be differences between individual agents, and as such comparative studies are required.

4.4.1 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)

4.4.2 We recommend not using oral fluids alone in patients at increased risk of CI-AKI. (1C)

While preparing for the coronary angiogram, 3 ml/kg of isotonic sodium bicarbonate (1.26%) was started and infused over 60 min, and then continued at 1 ml/kg for 6 h post procedure.

Historically, patients were fluid restricted before radiological imaging, risking dehydration and both reducing urinary flow rate and increasing neurohumoral activation to maintain effective plasma volume. Animal models of CI-AKI have shown that sodium delivery to the kidney and increasing urinary flow rate reduce renal tubular toxicity, as does alkalinization of the urine. Thus, normal saline (0.9%) was reported to reduce CI-AKI compared with 0.45% saline.[55] More recently, the debate has centered on whether isotonic sodium bicarbonate offers additional benefit over 0.9% saline.[56] However, studies differ not only in terms of contrast agent, dose, and site of injection but also rehydration protocol, and as such isotonic bicarbonate does not appear to offer any significant advantage.[57] However, equally there is no optimal hydration protocol. Earlier studies suggested a protective effect on CI-AKI with urinary flow rates of >150 ml/h for the 6 h post procedure,[58] although simply forcing a diuresis with loop and osmotic diuretics does not reduce the risk of CI-AKI.[59] To achieve such a urinary flow rate, then patients probably require around 1.5 ml/kg per h of isotonic fluid.[60] The key question is whether more rapid volume fluid administration (3 ml/kg over 1 h) is as effective as 1 ml/kg/h for 6 h pre-procedure and for how long intravenous hydration should continue post procedure, 3 or 6 h, or even longer. In our emergency case, fluids were administered more rapidly, potentially precipitating or exacerbating pulmonary edema. Although extended rehydration times pre-procedure and post procedure are suitable for hospital inpatients, most patients attend on the day of the investigation and are discharged within 6 h. As such, in addition to providing patients with advice regarding withdrawal of nephrotoxic drugs, such as non-steroidal anti-inflammatories, it is also important that outpatients should not be fluid restricted.

Although the KDIGO guidelines do not recommend using oral fluids alone in patients at increased risk of CI-AKI, there have been a number of recent studies reporting a similar risk of CI-AKI with pre-procedure and post procedure oral rehydration compared with intravenous fluids in patients with eGFR >60 ml/min and diabetes attending for coronary artery CT and percutaneous coronary artery interventions.[61,62] If confirmed by larger multicenter trials, then active oral hydration regimes would simplify management for those with lower risk scores for CI-AKI (Table 4).

4.4.3 We suggest using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (2D)

Our patient was not given oral NAC. During hospital stay, serum creatinine peaked at 1.9 mg/dl (168 umol/l) and had fallen to 1.6 mg/dl (141 umol/l) on discharge, ACEIs and diuretics were continued.

The data supporting a role for NAC in reducing the risk of CI-AKI remains debatable. Trials differ, not only in terms of route of administration but also dosage and duration of therapy. NAC is readily absorbed but has a relative short half-life,[63] and dosages of >800 mg have been shown to alter plasma redox potential.[47] Although the majority of reports have not demonstrated any benefit for NAC, four of the seven studies reporting a positive effect used intravenous administration.[7,11,64] There is a small risk of anaphylaxis with intravenous

NAC. As such, after review of the evidence the KDIGO group could not recommend the use of NAC.

SUMMARY

The KDIGO Clinical Practice Guideline for AKI provides broad-based guidance for the practicing clinician designed to unify the definition of AKI and provide a series of general principles in terms of patient management, which have been designed to be applicable in different health-care settings. The authors are to be congratulated on their efforts. As with all guidelines, they should be interpreted in the context of both the individual patient and also the health-care setting. A unified definition for the diagnosis for AKI is to be welcomed to allow collaborative epidemiological studies, to estimate the incidence of AKI, and development of prospective interventional studies. However, studies are required to determine whether this definition is equally predictive of outcomes in Sdeveloping countries and in economically advanced countries and the differences in AKI between patients with pre-existing normal renal function and those with CKD. The introduction of simple protocols to optimize patients with sepsis, before surgery or radiocontrast administration designed to reduce the incidence of AKI, are similarly to be welcomed. However, these will need to be adapted and validated to specific patient groups and according to health-care setting.

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Table 1

Grading of evidence

Level 1 'We recommend'	**Most patients should receive the recommended course of action**
Level 2 'We suggest'	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences
Grade A high quality	Evidence obtained from at least one properly designed randomized controlled trial
Grade B good quality	Evidence obtained from well-designed controlled trials without randomization
Grade C moderate quality	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
Grade D poor quality	Evidence obtained from multiple time series with or without the intervention and uncontrolled trials

Table 2

Staging of AKI for adults

	Serum Creatinine		Criteria	Urine volume criteria
AKI stage	**KDIGO**	**AKIN**	**RIFLE**	**KDIGO/AKIN/ RIFLE**
1 (R)	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26 μmol/l) increase within 48h	Increase≥0.3 mg/dl (26.5 μmol/l) or≥1.5- to 2-fold from baseline	Increase×1.5 baseline or GFR decrease >25%	<0.5ml/kg/h for 6–12 h
2 (I)	2.0–2.9 times baseline	Increase >2- to 3-fold from baseline	Increase×2 from baseline or GFR decreased >50%	<0.5ml/kg/h for 12 h
3 (F)	3.0 times baseline or increase in serum creatinine to≥4.0 mg/dl (354 μmol/l) or initiation of renal replacement therapy or, in patients <18 years, decrease in eGFR to <35ml/min per 1.73 m^2	Increased >300% (>3-fold) from baseline, or ≥4.0 mg/dl (354mmol/l) with an acute increase of ≥0.5 mg/dl (44 μmol/l) or on renal replacement therapy	Increase × 3 from baseline, or serum creatinine >4mg/dl (>354 μmol/l) with an acute rise >0.5mg/dl (>44 μmol/l) or GFR decreased >75%	<0.3ml/kg/h for 24 h or anuria for 12 h

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

RIFLE, Risk, Injury, Failure, Loss and End stage kidney failure.

For AKIN, the increase in serum creatinine must occur in <48h. For RIFLE, AKI should be both abrupt (within 1–7 days) and sustained (>24 h).

Table 3

Risk factors for iodinated radiocontrast nephropathy

Iodinated contrast risk factors	Dose
	Intra-arterial administration
	Osmolality
	Charge
	Repeated administration <72 h
Procedure risk factors	Interventional versus diagnostic
	Blood loss
	Hypotension
Patient factors	Hypovolemia
	Age
	Pre-existing chronic kidney disease
	Comorbidity (diabetes, heart failure, myeloma, peripheral vascular disease, cerebrovascular disease)
	Concomitant drugs (NSAIDs, calcineurin inhibitors, aminoglycosides, cisplatin, amphotericin B)

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.

Table 4

Risk score for developing acute kidney injury due to iodinated radiocontrast nephropathy (CI-AKI)

Risk factors	Points awarded
Hypotension	5
Intra-aortic balloon pump	5
Chronic heart failure	5
Age >75 years	4
Anemia	3
Diabetes	3
Iodinated contrast volume	1 per 100 ml
Serum creatinine >1.5 mg/dl	4
Or eGFR <60ml/min	2 if eGFR 40–60 ml/min
	4 if eGFR 20–40 ml/min
	6 if eGFR <20ml/min
Score <5	7.5% risk CI-AKI 0.04% risk dialysis
Score 6–10	14% risk CI-AKI 0.12% risk dialysis
Score 11–16	26.1% risk CI-AKI 1.09% risk dialysis
Score >16	57.3% risk CI-AKI 21.6% risk dialysis

Abbreviations: CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate.

Adapted from www.esur.org/.../Guidelines/ESUR_2007_Guideline_6_Kern_Ubersite Accessed 1 July 2012.