KDIGO Controversies Conference on
Acute Kidney Injury

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Rome, Italy

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline updating efforts and other times they highlight areas for which additional research is needed.

BACKGROUND

One of the primary objectives of KDIGO is the improvement of care for patients with acute kidney injury (AKI). In 2012, KDIGO published a guideline on the classification and management of AKI. (1) The guideline was derived from evidence available gathered thru February 2011. As part of the process, important gaps in knowledge were also identified and recommendations for future research were proposed.

Since then, new evidence has emerged which has important implications for clinical practice and should be considered for integration into the guideline. New insight related to the epidemiology and risk profile of AKI is available from large observational international studies in adults and children, such as the AKI-EPI study (2), the 'zero by 25 campaign' (3) and the AWARE study (4). The effectiveness of KDIGO recommendations to prevent AKI has been confirmed in new randomized controlled trials, e.g., the PrevAKI (5) and BigpAKI (6) studies. In addition, results of randomized controlled trials have

provided new data relevant to the prevention and management of AKI, including early resuscitation, fluid therapy, prevention of contrast-associated AKI and timing of acute renal replacement therapy (RRT) (7-13). Finally, there has been important progress in the development of new tools to diagnose and manage AKI, including biomarkers, decision support programs, and electronic alerts which warrant consideration for inclusion in the guideline (2, 3, 14-18).

Therefore, KDIGO will convene a Controversies Conference to examine this new evidence as it relates to the diagnosis and management of patients with AKI. The goal is to inform not only the scope of the future AKI guideline update but also to explore new and ongoing areas of controversy.

CONFERENCE OVERVIEW

The objective of this KDIGO conference is to gather a global panel of multidisciplinary clinical and scientific expertise (i.e., nephrology, critical care, cardiology, radiology, pediatrics, infectious diseases, pharmacology, etc.) to identify key issues relevant to the optimal management of AKI. The goal of this KDIGO conference is to determine best practice and areas of uncertainties in the treatment of AKI, review key relevant literature published since the 2012 KDIGO AKI Guideline, address ongoing controversial issues, identify new topics or issues to be revisited for the next iteration of the KDIGO AKI guideline, and outline research needed to improve AKI management.

Drs. John A. Kellum (University of Pittsburgh, USA) and Marlies Ostermann (Guy's & St Thomas NHS Foundation Hospital, UK) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research in AKI.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012; 2: 1–138.

2. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015; 41: 1411-1423.

3. Mehta RL, Cerda J, Burdmann EA et al. International Society of Nephrology's 0-by-25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015; 385:.2616-2643.

4. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 2017; 376: 11-20.

5. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 2017; 43: 1551-1561.

6. Göcze I, Jauch D, Götz M, et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. Ann Surg 2018; 267: 1013-1020.

7. Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, Yealy DM, Huang DT, Angus DC; ProCESS and ProGReSS-AKI Investigators. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. Am J Respir Crit Care Med 2016; 193: 281-7.

8. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017; 389: 1312-1322.

9. Self WH, Semler MW, Wanderer JP, et al; SALT-ED Investigators. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med 2018; 378: 819-828.

10. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 2018; 378: 829-839.

11. Zarbock A, Kellum JA, Schmidt C et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN Randomized Clinical Trial. JAMA 2016; 315: 2190-2199.

12. Gaudry S, Hajage D, Schortgen F et al. Initiation strategies for renal replacement therapy in the Intensive Care Unit. N Engl J Med 2016; 375: 122-133.

13. Barbar SD, Clere-Jehl R, Bourredjem A et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med 2018; 379: 1431-1442.

14. Tollitt J, Flanagan E, McCorkindale S, et al. Improved management of acute kidney injury in primary care using e-alerts and an educational outreach programme. Fam Pract. 2018; 35: 684-689.

15. Breighner CM, Kashani KB. Impact of e-alert systems on the care of patients with acute kidney injury. Best Pract Res Clin Anaesthesiol 2017; 31: 353-359.

16. Wilson FP, Shashaty M, Testani J, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group randomised controlled trial. Lancet 2015; 385: 1966-74.

17. Kolhe NV, Staples D, Reilly T, et al. Impact of compliance with a care bundle on acute kidney injury outcomes: a prospective observational study. PLoS One 2015; 10: e0132279.

18. Goldstein SL, Mottes T, Simpson K, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney Int 2016; 90: 212-21.

APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: Nomenclature and Diagnostic Criteria

1. Is sufficient evidence now available to warrant a change in the definitions/classification/staging system for AKI?
    a. AKI/AKD/CKD continuum
    b. Definition of subclinical AKI / kidney stress
    c. Persistence (vs transient, vs relapsing?)
    d. How to define patients with falling creatinine
    e. Role of etiology/setting
    f. Urine output vs Creatinine criteria
    g. Role of biomarkers, biopsy, and imaging
    h. Fluid imbalance as indicated of decreased function
    i. Community vs. hospital-acquired (manifest?)
    j. Children vs adults

2. How should existing (or new) definitions of AKI be implemented at the bedside, in research?
    a. How should baseline kidney function be determined? (baseline creatinine, eGFR, renal reserve, imaging or combinations)
    b. How should urine output be evaluated (body composition? fluid balance? setting/context?)
    c. What is the role for real time or kinetic GFR?
    d. How and how often should kidney function / injury / stress be monitored?
    e. Role of expert interpretation/judgment

3. What is the best way to define renal recovery?
    a. AKI vs AKD?
    b. Complete vs partial
    c. How to define recovery of subclinical AKI: Renal reserve? Biomarkers? Fluid balance?

Breakout Group 2: AKI Risk Stratification and Assessment

1. What are the roles for risk-stratification of patients for AKI?
    a. Which patients? When?
    b. Clinical models
    c. Biomarkers
    d. Renal angina index (RAI)
    e. Renal functional reserve
    f. Applications to mitigate risk

2. Once AKI is diagnosed, what is the approach to determining the cause and prognosis?
    a. Evaluation and monitoring
    b. Endpoints/expected clinical course
    c. Clinical models
    d. Role of biomarkers, biopsy, and imaging
    e. Urine creatinine excretion, urine chemistries, sediment
    f. Furosemide stress test
    g. Renal functional reserve
    h. Framework for AKI classification (to replace pre-renal/intra-renal)?

3. How should patients be followed after AKI?
    a. Which patients should be followed up?
    b. Which parameters should be monitored?
    c. Short-term vs long-term
    d. Role for biomarkers, renal functional reserve

Breakout Group 3: Fluid Management and Hemodynamic Support

1. What are the indications for fluid administration in patients with or at risk for AKI?
    a. How should patients be selected for fluid therapy?
    b. What are the targets/endpoints/contraindications to fluid administration?
    c. Do differing clinical contexts & etiologies of AKI affect fluid management?
    d. Does the timing (early vs established) of AKI alter management?
    e. How to balance fluid management and vasopressor treatment?

2. How should fluids be given in patients at risk for/with AKI?
    a. How much fluid constitutes a fluid challenge/ initial fluid bolus in the setting of various stages of kidney dysfunction?
    b. Bolus therapy vs continuous infusions
    c. How should response to fluid be evaluated and monitored?

3. How does the composition of various intravenous fluid preparations affect kidney function or influence outcomes in patients with AKI?
    a. Electrolytes
    b. Tonicity, colloids/crystalloids
    c. Non-hemodynamic (drug-like) effects of fluids (on the kidney)

4. What are the indications/contraindications for fluid removal in patients with or at risk for AKI and how should fluid removal be affected in such patients?
    a. To what extent is fluid overload causative of organ injury including persistent kidney dysfunction compared to being merely a marker of illness severity?
    b. What are the risks of fluid removal?
    c. In what circumstances are extracorporeal therapies preferred over diuretics?
    d. How do we determine rate of fluid removal (tolerability) and eventual goal for fluid removal (quantification of fluid overload)?

Breakout Group 4: Nephrotoxic Agents and Drugs that Affect Kidney Function

1. In light of current evidence what can be recommended for the prevention and management of contrast-associated AKI?
    a. Does contrast-associated AKI exist? Relative impact?
    b. Prevention strategies (i.e., PRESERVE trial)
    c. Management

2. Is there sufficient evidence to classify drugs that affect kidney function and/or are nephrotoxic in a clinically useful way?
    a. Criteria for classification? (just association? change in function vs injury? Role of imaging? Role of biomarkers?)
    b. Variation of toxicity depending on susceptibility (age, clinical context, other medications?)
    c. Drug combinations: Impact of nephrotoxic burden; which combinations contribute to greater risk of AKI?
    d. Differentiation between essential and non-essential nephrotoxic drugs
    e. Role of ACE-I / ARBs in AKI
    f. Consequences of drug-associated AKI vs other causes? (degree of harm, reversibility)
    g. Contribution of nephrotoxins to other causes?

3. What prevention strategies should be applied for drug-associated AKI?
    a. Hypervigilance, early detection
    b. Clinical management (including fluids)
    c. Role of biomarkers
    d. Drug stewardship
    e. Computer decision tools

4. How should potentially nephrotoxic drugs be managed during AKI (including during RRT) and following an episode of AKI?
    a. Recommended patient-care plan for patients with drug-induced AKI (including prevention of progression of AKI)
    b. (Re-)initiation of medication that is potentially nephrotoxic following an episode of AKI? (chronic medications vs new medications)

Breakout Group 5: Renal Replacement Therapy

1. What criteria should be used to initiate RRT in patients with AKI?
   a. Severity/duration
   b. Biomarkers
   c. Demand/capacity balance
   d. Risk for complications
   e. Potential for recovery (note some overlap with Group 1)
   f. ICU vs outside the ICU
   g. Resource-limited environments
   h. Non-renal factors (e.g., sepsis, heart disease)

2. What is the optimal strategy (including modality) for providing acute RRT?
   a. Patient factors (hemodynamics, fluid balance, brain injury/edema)
   b. Etiology of AKI
   c. Clinical setting (ICU vs outside the ICU; resource-limited environment)
   d. Dose (including over time)
   e. Anticoagulation
   f. Nutrition management
   g. Monitoring
   h. Discontinuation and modality transition

3. How should RRT be combined with extracorporeal respiratory and cardiac support (e.g., ECMO, $ECCO_2R$)?
   a. Indications
   b. Technique and monitoring

4. How do RRT decisions affect long-term outcomes and how should patients be followed?
   a. Effects on renal recovery
   b. Approach to follow-up and timing

5. Is the terminology 'RRT' sufficiently accurate, descriptive, and patient-centered?