

Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference



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In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published a guideline on the classification and management of acute kidney injury (AKI). The guideline was derived from evidence available through February 2011. Since then, new evidence has emerged that has important implications for clinical practice in diagnosing and managing AKI. In April of 2019, KDIGO held a controversies conference entitled *Acute Kidney Injury with the following goals: determine best practices and areas of uncertainty in treating 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.* Here, we present the findings of this

conference and describe key areas that future guidelines may address.

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KEYWORDS: acute kidney disease; acute kidney injury; fluid management; nephrotoxicity; renal replacement therapy; risk stratification

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In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published a guideline on the classification and management of acute kidney injury (AKI).¹ Since then, new evidence has emerged that has important implications for clinical practice. Large epidemiology studies and risk profiles for AKI have become available in adults and children, such as the AKI–Epidemiologic Prospective Investigation (AKI-EPI) study,² the Obby25 Initiative,³ the Southeast Asia–AKI (SEA-AKI) study,⁴ and the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE)⁵ and Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN)⁶ studies. The effectiveness of the KDIGO recommendations in preventing AKI has been confirmed in small single-center randomized controlled trials (RCTs), such as the Prevention of AKI (PrevAKI)⁷ and the Biomarker Guided Intervention for Prevention of AKI

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Table 1 | Definitions of AKI, CKD, and AKD¹

Acronym	Functional criteria	Structural criteria
AKI	Increase in SCr by $\geq 50\%$ within 7 d, OR Increase in SCr by ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/l}$) within 48 h, OR Oliguria	No criteria
CKD	GFR < 60 ml/min per 1.73 m ² for > 3 mo	Kidney damage > 3 mo
AKD	AKI, OR GFR < 60 ml/min per 1.73 m ² for < 3 mo, OR Decrease in GFR by $\geq 35\%$ or increase in SCr by $> 50\%$ for < 3 mo	Kidney damage < 3 mo
NKD	GFR ≥ 60 ml/min per 1.73 m ² Stable SCr without AKI/AKD/CKD	No damage

AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no kidney disease; SCr, serum creatinine.

(BigpAK)⁸ studies. In addition, results of RCTs have provided new data relevant to several facets of preventing and managing AKI, including early resuscitation, fluid therapy, prevention of contrast-associated AKI, and timing of acute renal replacement therapy (RRT).^{9–15} Finally, there is now evidence from large studies in different countries that the use of KDIGO criteria for AKI, as part of computer decision-support systems, can improve clinical outcomes.^{16,17} However, there has also been important progress in the development of new tools to diagnose and manage AKI, including biomarkers, decision support programs, and electronic alerts, that go beyond the current KDIGO definition/staging criteria, and these warrant consideration for inclusion in AKI guidelines.^{17–24}

These advances are not without controversy. Adoption of new biomarkers has been heterogenous,²⁵ and there are calls to revise KDIGO AKI staging based on creatinine and urine output,²⁶ and even calls to discard the KDIGO staging completely.²⁷ Thus, in April 2019, KDIGO held a controversies conference entitled *Acute Kidney Injury*, in Rome, Italy. Participants examined and summarized evidence published since 2012 as it relates to the risk assessment, diagnosis, and management of patients with AKI and provided commentary on areas of controversy and agreement. The ultimate goals were to provide the clinical and research communities with a snapshot of the current state of the art for diagnosis and management of AKI and to prepare for future revision of the 2012 guideline.

NOMENCLATURE AND DIAGNOSTIC CRITERIA

AKI-related definitions

AKI and chronic kidney disease (CKD) are increasingly recognized as related entities representing a continuum of disease. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2002 guideline and the 2012 KDIGO AKI guideline defined CKD as measured or estimated glomerular filtration rate (GFR) < 60 ml/min per 1.73 m², or the presence of markers of kidney damage (e.g., albuminuria) for > 90 days.¹ The 2012 KDIGO guideline defined AKI as an abrupt decrease in kidney function occurring over 7 days or fewer (Table 1).¹ To complete the continuum, the 2012 guideline proposed the term acute kidney diseases and disorders (AKD) to define conditions of impaired kidney function not meeting the criteria for either

AKI or CKD but having adverse outcomes and requiring clinical care. However, consensus on the exact criteria and indicators of severity is urgently needed.

Because the diagnosis of AKI should be tied to management decisions, and because changing disease definitions may have major implications for disease epidemiology, the case for revising the 2012 KDIGO definition of AKI should be strong before changes are proposed. Furthermore, in the context of an AKI guideline revision, several classification systems in addition to the stages of AKI should be rigorously defined. These relate to the distinctions among persistent, transient, relapsing, and recovered AKI; various etiologies of AKI; and community-onset versus hospital-onset AKI. In addition, there is emerging evidence that markers of structural kidney damage may be associated with clinically relevant outcomes and therefore identify potentially actionable entities. For an AKI guideline revision, the evidence base should be reviewed to determine whether markers of kidney damage constitute risk factors for AKI, define a new entity (such as subclinical or preclinical AKI), or should be incorporated into the AKI definition. Finally, the future guideline should use nomenclature that is precise and patient-centered.

The clinical importance of AKD needs to be further assessed. Retrospective cohort data based only on changes in serum creatinine values and with limited clinical context suggest a relevance for AKD: the population of patients who meet laboratory criteria for AKD but not CKD or AKI is relatively large, and these individuals have increased risks of incident and progressive CKD, kidney failure (formally referred to as “end-stage kidney disease”), and death,²⁸ confirming the need to better define and classify AKD. Furthermore, a revised definition and classification of AKD could be better harmonized with both the definitions and classifications of AKI and CKD and tie to clinical management. As in adults, the AKI/AKD/CKD spectrum should be unified in children, and definitions should be the same for children and adults. A special consideration in children, as well as in adults with low muscle mass, is a reduced serum creatinine concentration, which may impact AKI diagnosis.

The assessment of renal recovery is still controversial, and its definition is essential given the implications for patients and clinicians. Issues related to assessment of recovery include

Table 2 | Research priorities and questions for investigation in AKI**Diagnostics**

1. Evaluate the clinical applicability of real-time or kinetic GFR.
2. Determine the magnitude of change in serum creatinine concentration that indicates AKI.
3. Explore how differences in body composition (e.g., overweight, fluid overload) affect urine output, and whether these differences need to be considered regarding the thresholds for AKI.

Risk stratification

1. Conduct multicenter studies for external validation of AKI risk models as well as standardization and correlation with outcomes.
2. Define the role of kidney biopsy in managing AKI.
3. Identify additional endpoints (beyond mortality, chronic kidney disease, and dialysis dependency) for both clinical management and trials. These could include recovery of function, continued need for dialysis, maximum changes in creatinine concentration, stage of AKI, functional renal reserve, biomarkers, and patient experience assessment (patient-reported outcome measures and patient-reported experience measures).
4. Develop a more accurate definition of recovery and its functional (i.e., filtration, tubular, endocrine) and anatomic/structural dimensions.

Fluid management and hemodynamic support

1. Determine the optimal indications and targets for fluid and vasoactive drugs to improve kidney outcomes in acute medical illness and in the perioperative setting.
2. Determine the optimal vasopressor in this context and explore how the indications and targets should be translated to and from resource-limited settings.
3. Investigate the optimal method of administering fluid for preventing or mitigating AKI (route [oral or i.v.]; bolus versus continuous; and rate, volume, and frequency of boluses) and explore whether the optimal methods vary in different contexts where different levels of monitoring are available, including pre-hospital settings and resource-limited settings.
4. Investigate new techniques to detect fluid overload in adults and from this define fluid overload thresholds to guide management decisions; in addition, determine how fluid removal should be optimally accomplished including method, rate, targets, and monitoring.
5. Investigate if there is a confirmed hazard from the use of 0.9% saline compared with balanced solutions on kidney outcomes in adults and identify the mechanism and explore whether there are any subgroups at particular risk.
6. Explore the role for sodium bicarbonate in patients with AKI and metabolic acidosis.

Nephrotoxic agents and drugs that affect kidney function

1. Investigate whether biomarkers for risk prediction, surveillance, or diagnostic evaluation (to discriminate between kidney dysfunction and injury) can affect choice of treatment strategy.
2. Determine the role of electronic clinical decision-support systems to proactively identify risk and injury from drugs.
3. Undertake drug burden assessment to determine which nephrotoxic drugs and drug combinations are associated with increasing risk for dysfunction and injury.
4. Conduct studies to guide timing of ACE-I/ARBs discontinuation and re-initiation in AKI/AKD in different clinical contexts such as heart failure, surgery, and sepsis.
5. Undertake research on the role of statins in preventing contrast-associated AKI in stable and acute settings, and study the dose-dependence of effect.

RRT

1. Investigate the optimal timing, dose, and modality of RRT and identify the indicators that predict successful discontinuation of RRT.
2. Compare different methods of assessing fluid removal goals and rates of fluid removal with RRT.
3. Develop a registry focused on patients receiving ECLS-RRT.
4. Develop a registry of patients receiving combined ECMO/ECCO2R and RRT.
5. Evaluate whether ECCO2R can be efficiently applied in a system combining RRT and ECCO2R.
6. Conduct clinical studies on respiratory dialysis (ECCO2R and ECMO) with modified dialysis solutions.
7. Compare anticoagulation strategies (including citrate) of the RRT circuit during ECMO/ECCO2R.

ACE-I, angiotensin-converting enzyme inhibitors; AKD, acute kidney diseases and disorders; AKI, acute kidney injury; ARB, angiotensin-receptor blockers; ECCO2R, extracorporeal carbon dioxide removal; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; RRT, renal replacement therapy.

changes in creatinine generation due to reduction in muscle mass, among others.

Advances in diagnosis of AKI

Serum creatinine and urine output continue to be the foundational measures for AKI diagnosis even though their limitations are well known. In the future, kidney damage biomarkers, biopsy, and imaging may be useful for staging AKI, classification of cause, prognosis, and treatment. However, currently there is insufficient information about any of these measures to warrant addition to the AKI definition. Given that the global availability of novel biomarkers is limited, incorporating them into definitions will be challenging. Measurements of real-time or kinetic GFR are research tools at present, and more evidence is needed regarding their clinical applicability (Table 2).

Both urine output and serum creatinine level should continue to be used²⁹; ideally, the new AKI guideline would provide further clarification as to the role of these measurements. If possible, both should be ascertained. However, if serum creatinine measurements are not immediately available, urine output criteria should be used.

It remains unclear how to best determine baseline kidney function. What constitutes a baseline serum creatinine level is controversial and inconsistently defined. It would be ideal to have prior serum creatinine or GFR measurements widely available through electronic medical records, but this is not current practice in many parts of the world. Prior serum creatinine or GFR measures may also further elucidate the risk of AKI in patients considered at high risk on the basis of either comorbidity or an intervention. There is controversy about whether an acute decrease in serum creatinine level

indicates AKI that has already occurred, and more research is needed in this area. For example, small declines in serum creatinine level need to be interpreted with caution because they may be the result of acute changes in creatinine production or volume of distribution. After a timed insult (e.g., coronary angiography, elective surgery, nephrotoxic drug exposure), serum creatinine level should be measured at an appropriate time, allowing for AKI to manifest. After AKI onset, serum creatinine level should be measured during follow-up as necessary for clinical management and care transitions (e.g., transfer to and from intensive care) and for determining changes in AKI staging and classification (AKI vs. AKD), including onset of CKD at 90 days.

How urine output should be evaluated is also an area that needs further investigation to avoid variability in reporting of AKI incidence (i.e., use of actual or ideal body weight, strict time period vs. time-averaged values).³⁰ Future guidelines should address how differences in body composition (overweight, fluid overload) affect the interpretation of urine output, and whether these differences need to be considered in regard to the thresholds for AKI. Similarly, fluid status should be considered when evaluating for AKI. Fluid overload is associated with increased mortality and AKI, and it may impact the diagnosis of AKI through its impact on the volume of distribution of serum creatinine. Although there are research methods to define fluid overload, these are not routinely used in clinical practice, and it is unclear whether there is sufficient evidence to define a clinical threshold for fluid overload. In the next AKI guideline, fluid overload should be defined operationally through a rigorous literature review.

AKI RISK STRATIFICATION AND ASSESSMENT

Risk stratification

In community and hospital settings, risk stratification of patients using a combination of baseline risks and acute exposures is important.³¹ In the future, risk stratification could incorporate various clinical contexts: geographic region, onset in community or hospital settings, and location within hospitals. Although the 2012 guideline discussed risk models and clinical scores, these were limited to models for cardiothoracic surgery, contrast exposure, and aminoglycoside administration. Many other clinical scenarios and contexts, such as sepsis and cardiac failure, require guidance for risk assessment. In clinical practice, risk models may be tailored for location and context. Multicenter studies are needed for externally validating models as well as standardization and correlation with outcomes. Furthermore, since 2012, biomarkers for AKI risk stratification have been approved by the US Food and Drug Administration (https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130031.pdf) and integrated in recent guideline recommendations for cardiac surgery.³²

Determining cause and prognosis

Determining the etiology of AKI is essential for management; however, this can be difficult, especially in the presence of

multifactorial mechanisms. Newer developments related to monitoring and evaluating risk progression include e-alert systems, machine-learning algorithms and artificial intelligence for AKI recognition and monitoring,^{20,33–36} as well as models based upon the renal angina index,^{37,38} furosemide stress test (FST),³⁹ or biomarkers.^{40–43} In revisiting the guideline for AKI, severity of AKI should be based not only upon serum creatinine elevation and urine output, but also upon duration, possibly with the inclusion of biomarkers. The need to increase attention for persistent (>48 hours) AKI should also be considered.⁴⁴

The 2012 KDIGO guideline suggests performing a kidney biopsy when the cause of AKI is unclear. Potential benefits for biopsy in AKI are controversial and further research is needed.⁴⁵ Since the 2012 guideline, which recommended ultrasound for assessing kidney size and the presence of an obstruction, new imaging techniques have become available, such as contrast-enhanced ultrasound, doppler ultrasound, and blood oxygenation level–dependent functional magnetic resonance imaging.^{46–48} The role of these techniques in changing outcomes of AKI is yet to be determined.

The 2012 KDIGO guideline recommended urine sediment analysis for differential diagnosis in patients with AKI, especially when glomerular disease is expected. Meeting participants noted that urine sediment analysis is not routinely performed in many centers despite its potential role in the workup of AKI.^{49,50} Additionally, the value of urine biochemistry analysis has been challenged, especially in sepsis.⁵¹

The FST may be useful for identifying patients with AKI who are likely to have progressive disease and need dialysis.⁵² There is also evidence that the FST is useful in predicting delayed graft function following deceased donor kidney transplantation.⁵³ This test was not included in the 2012 guideline but should now be considered. Importantly, unregulated diagnostics tests such as FST or urine sediment analysis require careful standardization and quality control. Their introduction into clinical practice should include local evaluation for correct performance and interpretation.

The traditional approach to classifying AKI as pre-renal, renal, and post-renal is still found in many medical textbooks. A different framework is needed, because these terms are considered unhelpful, especially the term pre-renal, which is often misinterpreted as “hypovolemic” and may encourage indiscriminate fluid administration. For classifying AKI, it may be more beneficial to distinguish between conditions that reduce glomerular function, conditions that result in injury of tubules and/or glomeruli, and conditions that do both.

Endpoints for clinical trials and quality improvement initiatives for AKI include mortality, new onset or progression of CKD, and dialysis dependency. Additional endpoints are needed for both clinical management and research, and these might include recovery of function, maximum changes in creatinine concentration, stage of AKI/AKD, impact on renal reserve, and patient experience. Additionally, there is a need to better define renal recovery and its functional (filtration, tubular, endocrine) and anatomic/structural dimensions.

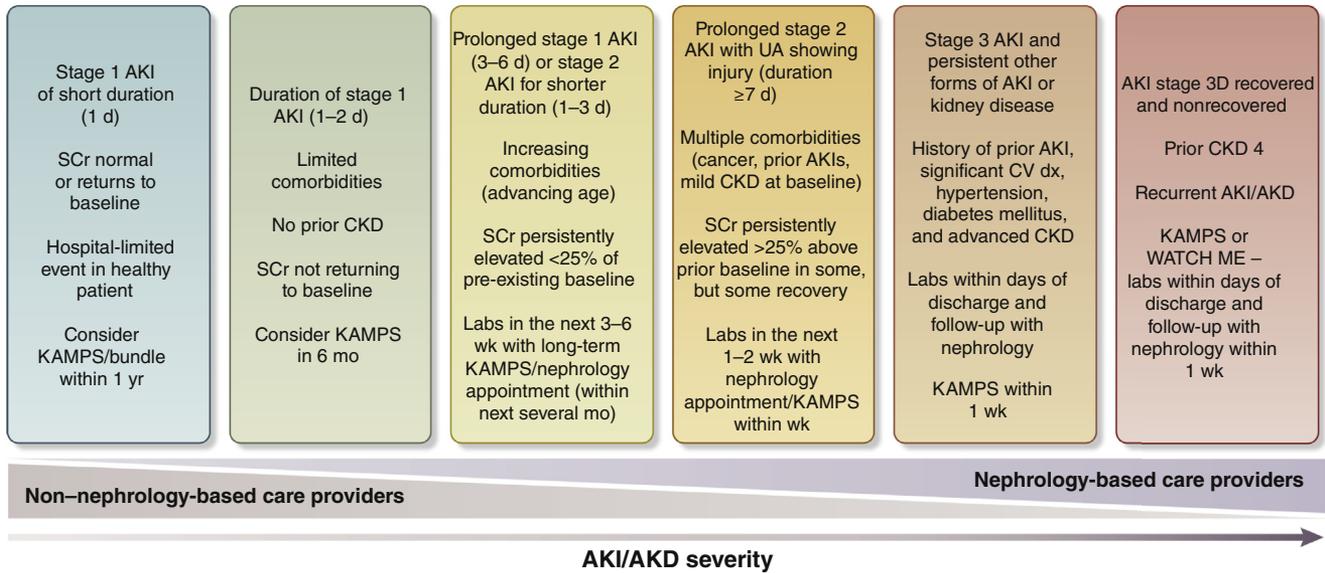


Figure 1 | Schematic for acute kidney injury/acute kidney diseases and disorders (AKI/AKD) follow-up. The figure displays a potential paradigm for the care of patients who experience AKI/AKD. The degree of nephrology-based follow-up increases as the duration and severity of AKI/AKD increases. The timing and nature of follow-up are suggestions, as there are limited data to inform this process. Future research efforts should work to clarify the timing of AKI/AKD follow-up and which specific healthcare providers should provide it. The items in each bucket follow the “OR” rule; therefore, each patient should follow the most-severe bucket even if they meet only 1 criterion in that bucket. For example, a patient with CKD G4, regardless of severity of AKI, should be followed by a nephrologist in 1 week. AKI stage 3D, AKI stage 3 treated by dialysis; CKD, chronic kidney disease; CV, cardiovascular; dx, diagnosis; KAMPS, kidney function–advocacy–medications–pressure–sick day protocol; SCr, serum creatinine; UA, urine analysis; WATCH-ME, weight assessment–access–teaching–clearance–hypotension–medications. Reproduced with permission under a Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>) from Acute Dialysis Quality Initiative. Quality improvement goals for acute kidney injury; ADQI XXII. Available at: https://www.adqi.org/Images_Charts-Call.htm. Accessed June 14, 2020.³¹

Follow-up

Increased risks for mortality, cardiovascular events, and progression of kidney disease are well-documented outcomes of AKI.^{28,54–56} However, not everyone with AKI has a poor outcome, and predictors of poor outcomes have been identified.⁵⁷ Follow-up recommendations (Figure 1)³¹ have been proposed that could be integrated into a KDIGO guideline revision. Although it has been suggested that patients be screened at hospital discharge or seen within 1 month of AKI diagnosis,⁵⁸ there is no consensus on the optimal strategy and duration of follow-up to improve short- and long-term outcomes.

FLUID MANAGEMENT AND HEMODYNAMIC SUPPORT

Timing of fluid administration

Ensuring adequate hydration and volume status is essential in preventing and treating AKI. Oral or i.v. fluid may be administered depending on the local environment and clinical context. The administration of i.v. fluids should be guided by hemodynamic assessment for specific indications and contraindications. When deciding on fluid therapy, consideration for the clinical context and history, including timing of the insult, is critical. Table 3 lists clinical contexts in which indications for fluid administration should be balanced against potential coexisting conditions that require a more cautious approach. Because both the physiological response to fluids and the underlying condition related to AKI are

dynamic over time, fluid administration should be based on repeated assessment of overall fluid and hemodynamic status and dynamic tests of fluid responsiveness.^{59,60}

There continues to be concern about excessive fluid administration for hypotension, and earlier use of vasoactive medications may be appropriate for some patients.^{61,62} The effect of these strategies on kidney function is not clearly defined and likely to be context specific.⁶³ Ongoing major multicenter RCTs examining kidney endpoints are evaluating fluid administration and vasoactive medications, and their results are likely to impact AKI treatment recommendations.

Methods of fluid administration

Significant new evidence from several large multicenter RCTs regarding use of protocolized goal-directed fluid therapy in early septic shock has suggested lack of benefits for survival and kidney outcome.^{64–66} However, there is some evidence to suggest that goal-directed protocols have benefits in perioperative patients.^{67,68} Therefore, recommendations regarding goal-directed fluid therapy for preventing or treating AKI may emerge to become more context specific. Additionally, clinical fluid therapy targets have evolved to include more dynamic indices, including the passive leg-raising test, pulse/stroke volume variation, and parameters derived from ultrasound. However, there is limited evidence that specific physiological targets for fluid therapy improve kidney outcomes.

Table 3 | Clinical contexts for fluid administration in patients with or at risk of AKI

Clinical context	Reasons for fluid administration and potential benefits	Challenges and risks of fluid administration
Age and demographics		
Children	<ul style="list-style-type: none"> • Diseases with volume losses 	<ul style="list-style-type: none"> • Narrow window between hypovolemia and fluid overload
Adults	<ul style="list-style-type: none"> • Indications likely to be context-dependent 	<ul style="list-style-type: none"> • Clear adverse effects of fluid overload • Adverse effects of “one size fits all” approach to fluid management • Uncertain definition of clinically significant fluid overload • In patients with heart disease, poor cardiac reserve to tolerate hypovolemia and hypervolemia • In patients with diastolic dysfunction, risk of potentiating venous hypertension and renal congestion in fluid overload
Setting		
Resource-limited	<ul style="list-style-type: none"> • Specific conditions including diarrheal illness 	<ul style="list-style-type: none"> • Differing spectrum of disease • Potentially delayed presentation to secondary care • Limited range of therapeutic options
Pre-hospital Ward/ICU	<ul style="list-style-type: none"> • Impetus toward early resuscitation • Dynamic phases of illness associated with hypovolemia 	<ul style="list-style-type: none"> • Lack of advanced hemodynamic monitoring • Inappropriate administration of maintenance fluid • Risk of “fluid creep” leading to insidious fluid overload
Comorbid diseases		
CKD	<ul style="list-style-type: none"> • Inability to conserve salt and water 	<ul style="list-style-type: none"> • Risk of hypovolemia • Inability to handle fluid excess • Predisposition to AKI
CHF or severe valvular disease	<ul style="list-style-type: none"> • Poor cardiac reserve to tolerate hypovolemia 	<ul style="list-style-type: none"> • Potentiation of adverse effects of fluid overload • Potentially pre-existing interstitial edema • Higher CVP associated with worsening kidney function
Severe chronic liver disease	<ul style="list-style-type: none"> • Intravascular hypovolemia despite peripheral edema 	<ul style="list-style-type: none"> • Precipitation of fluid accumulation
Acute conditions		
Dehydration	<ul style="list-style-type: none"> • Acute free water deficit 	<ul style="list-style-type: none"> • Challenges of managing relative water and sodium deficits
Hypovolemia	<ul style="list-style-type: none"> • Salt and water deficit 	<ul style="list-style-type: none"> • Need for consensus on optimal endpoints of resuscitation
Hemorrhage	<ul style="list-style-type: none"> • Acutely impaired oxygen delivery 	<ul style="list-style-type: none"> • Dilution of hemoglobin may offset effects of fluid resuscitation on oxygen delivery
Sepsis	<ul style="list-style-type: none"> • Intravascular hypovolemia 	<ul style="list-style-type: none"> • Endothelial dysfunction, capillary leak, fluid losses to interstitium, and vasodilation • Lack of evidence for goal-directed hemodynamic therapy
Cardiogenic shock	<ul style="list-style-type: none"> • Inability to tolerate hypovolemia • Venodilation due to inotropic drugs 	<ul style="list-style-type: none"> • Risk of pulmonary edema • Association between high CVP and adverse kidney outcome
Major surgery	<ul style="list-style-type: none"> • Anesthesia-induced venodilation and vasodilation • Perioperative fluid losses 	<ul style="list-style-type: none"> • Inappropriate administration of maintenance fluid and “fluid creep” leading to insidious fluid overload
Nephrotoxic exposure	<ul style="list-style-type: none"> • Dilution of filtered toxins 	<ul style="list-style-type: none"> • Risk of fluid overload
Abdominal compartment syndrome	<ul style="list-style-type: none"> • Maintenance of visceral and renal perfusion 	<ul style="list-style-type: none"> • Risk of venous hypertension
ARDS	<ul style="list-style-type: none"> • Reduced cardiac preload due to high intrathoracic pressure 	<ul style="list-style-type: none"> • Risk of worsening alveolar edema
Rhabdomyolysis/crush injury	<ul style="list-style-type: none"> • Dilution of myoglobin • Intravascular hypovolemia due to fluid losses to injured muscle 	<ul style="list-style-type: none"> • Development/worsening of compartment syndrome
Timing		
Biomarker-positive states	<ul style="list-style-type: none"> • Prevention of progression to overt AKI 	<ul style="list-style-type: none"> • Presence of early renal injury does not signify need for volume replacement
AKI stage	<ul style="list-style-type: none"> • Reversal of early AKI 	<ul style="list-style-type: none"> • Inappropriate attempts to “reverse” established AKI resulting in fluid overload
Oliguria/anuria	<ul style="list-style-type: none"> • Oliguria as an indication of acute compensated hypovolemia 	<ul style="list-style-type: none"> • Multiple etiologies of oliguria beyond hypovolemia • Vicious cycle of fluid overload resulting in worsening kidney function

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; CVP, central venous pressure; ICU, intensive care unit.

Composition of i.v. fluid preparations

Crystalloids. Evidence of biochemical abnormalities and adverse clinical outcomes associated with 0.9% saline compared with more physiological crystalloids (e.g., lactated Ringer's) has continued to accumulate since 2012.^{11,12} Results from two large ongoing multicenter RCTs (NCT02875873, NCT02721654) are awaited. This evidence will require careful evaluation to provide the community with a new consensus regarding the magnitude of risks associated with 0.9% saline in acute illness and surgery, including considerations for resource-limited settings in which alternatives may be limited.

Synthetic colloids. In recent years, consensus has emerged that due to the increased incidence of kidney dysfunction and mortality, synthetic colloids are harmful in critically ill patients, especially those with sepsis.^{69,70} However, whether these risks also apply to perioperative patients remains controversial, and this question is being examined in ongoing trials.

Albumin. In RCTs, the use of albumin (including hyperoncotic solutions) has not been shown to be harmful to kidney or other outcomes.^{71,72} However, clear evidence of benefit is also lacking, and any benefits may be limited to specific patient populations.^{73–75}

Fluid removal

Physiological and epidemiologic evidence indicates that volume overload and venous congestion have adverse effects on kidney function and outcomes in both acute and chronic illness.^{76–78} In children, there is evidence that >10%–15% fluid overload by body weight is associated with adverse outcomes.^{79,80} However, the method for determining fluid overload and the threshold for clinically significant fluid overload in adults are not well defined, nor is the precise role of timing of fluid removal on kidney function and other outcomes. Therefore, there is a need to develop a consensus around methods and thresholds for fluid overload evaluation in adults and to establish recommendations for its management (Table 2).

NEPHROTOXIC AGENTS AND DRUGS THAT AFFECT KIDNEY FUNCTION

The use of drugs associated with kidney injury or dysfunction is common both in the hospital setting and in the community for patients with chronic illnesses such as hypertension, congestive heart failure, diabetes mellitus, cancer, and CKD. These drugs are often referred to as “nephrotoxic,” although many of them lead to kidney dysfunction without direct glomerular or tubular cell damage. Furthermore, some drugs that may cause a rise in serum creatinine are actually renoprotective and associated with improved outcomes (i.e., angiotensin-converting enzyme inhibitors or sodium-glucose co-transporter-2 inhibitors⁸¹ in diabetic nephropathy). Although it would be ideal to propose a simple yet inclusive term to encompass the various mechanisms by which drugs interface with the kidney, meeting participants were unable to identify one. Thus, here the term “nephrotoxic drugs” is

retained for consistency with the literature. A new classification should also encompass drugs that are not directly harmful to kidney function but are eliminated by the renal route, and where there is concern about harm from accumulation of parent drug or metabolites in the setting of AKI and AKD. Similarly, failure to increase drug doses and intervals in renal recovery or with enhanced elimination via extracorporeal clearance may lead to therapeutic failure.⁸²

In the past 10 years, significant progress has been made regarding susceptibility, management, and preventive strategies to avoid or ameliorate drug- and drug combination-associated kidney injury and dysfunction more broadly.

Overarching nephrotoxic medication management considerations are as follows:

- Patients should receive potentially nephrotoxic medications only if needed and only for as long as needed.
- Potentially nephrotoxic agents should not be withheld in life-threatening conditions, owing to concern for AKI, including i.v. contrast.
- Kidney function must be monitored in patients who are exposed to agents that are associated with kidney injury or dysfunction, to limit the risk and progression of AKI and AKD.
- Patients and clinicians need appropriate and effective education as to the potential for kidney injury and dysfunction from nephrotoxic agents.

Classifying drugs that affect kidney function and/or are nephrotoxic

There are multiple mechanisms by which drugs affect the kidney. They are summarized in 2 major categories: systemic or renal/glomerular hemodynamic effects (i.e., kidney dysfunction); and tubular or structural damage (i.e., kidney injury). Kidney dysfunction can result from drugs that lead to systemic hypotension (e.g., systemic arterial vasodilation) and/or altered intraglomerular hemodynamics (e.g., afferent arteriole constriction, efferent arteriole dilation). As a result, renal perfusion pressure is decreased, and if the decrease is sustained or severe, it can lead to ischemic injury. In comparison, drug-associated kidney injury is characterized by glomerular or tubular cell injury triggered by filtered toxins, tubular obstruction, endothelial dysfunction, or an allergic reaction.^{83–85} Important to note is that a given drug may lead to both dysfunction and injury.

A useful framework for classifying the mechanisms of drug-induced kidney injury or dysfunction is depicted in a 2x2 table to classify functional, structural, and combined functional/structural AKI⁸⁶ (Figure 2). Drugs can affect the kidney by each of these mechanisms, and the figure depicts susceptibilities for AKI, as well as accelerants to develop dysfunction or injury and transition to dysfunction and injury. An important aspect of the framework is consideration of risk-mitigation strategies. Currently, there is sufficient evidence to classify drugs that affect kidney function or are nephrotoxic, in a clinically useful way.^{87,88}

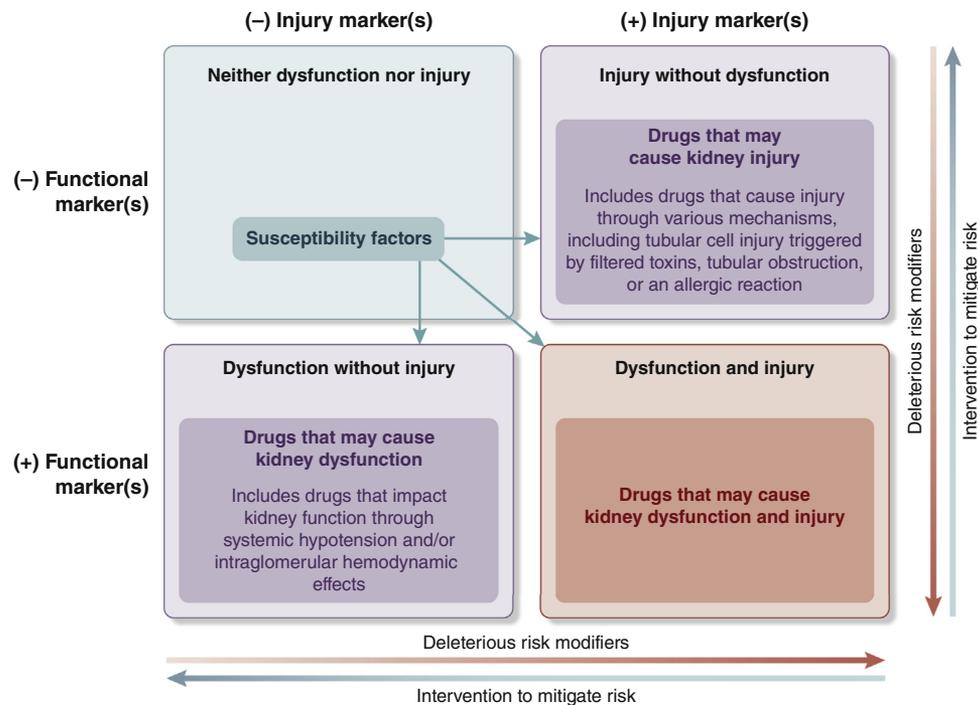


Figure 2 | Classifying drugs that potentially cause acute kidney injury. Iterative classification of agents that have potential to cause kidney dysfunction or kidney injury or both. Functional and injury biomarkers have a role in distinguishing among the different pathophysiological processes. Examples of deleterious risk modifiers are duration of therapy, drug burden, hypotension, and pharmacokinetic/pharmacodynamic interactions. Examples of interventions to mitigate risk are daily dynamic prescribing, kidney monitoring, and patient and provider education. Susceptibility factors include those listed in the 2012 Kidney Disease: Improving Global Outcomes Acute Kidney Injury guideline: dehydration or volume depletion; advanced age; female gender; black race; chronic kidney disease; chronic diseases of the heart, lung, or liver; diabetes mellitus; cancer; and anemia.¹ Any final impact depends on underlying susceptibility, associated risk factors, clinical context, drug management, and modifying factors. Examples of drugs that correspond to the relevant categories above include trimethoprim, cimetidine (neither dysfunction nor injury); angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers (dysfunction without injury); aminoglycoside, acyclovir, vascular endothelial growth factor antagonists (injury without dysfunction); and nonsteroidal anti-inflammatory drugs (dysfunction and injury).

Preventing and mitigating drug-associated AKI

A number of strategies have emerged for preventing or mitigating drug-associated kidney injury or dysfunction. The most important of these is drug stewardship,^{21,89,90} with a primary goal of balancing the changing risks and benefits of drug utilization and dosing in AKI/AKD (Table 4).⁸² Specifically, it is critical to balance the risk of toxicity caused by excessive doses or drug/metabolite accumulation in AKI/AKD versus the risk of therapeutic failure caused by either overly conservative drug avoidance or under-dosing, or the risk of failing to adapt to renal recovery or use of renal replacement therapy (RRT).

Recent literature has demonstrated that certain drug combinations and overall drug burden are associated with AKI.⁹¹ These include the “triple whammy” of renin-angiotensin system inhibitors, diuretics, and nonsteroidal anti-inflammatory drugs, and an increased AKI risk when patients receive 3 or more nephrotoxic drugs daily.⁹² A single center has utilized electronic health records to identify children exposed to 3 or more nephrotoxic drugs, and the approach has led to a sustained decrease in incidence of AKI.²¹

Preventing and managing contrast-associated AKI

The only nephrotoxic agent addressed in any detail by the 2012 KDIGO AKI guideline was iodinated radiocontrast

media.¹ The 2012 guideline included several recommendations to prevent contrast-induced AKI, including use of volume expansion with sodium bicarbonate solutions and oral N-acetylcysteine. Results of the Prevention of Serious Adverse Events Following Angiography (PRESERVE) and POSEIDON trials demonstrated lack of efficacy of these interventions (and instead found improvement using a personalized approach targeting cardiac filling pressures in POSEIDON).^{93,94} Furthermore, recent evidence suggests that the risks associated with i.v. contrast are far fewer with modern agents and practice patterns, and significant kidney injury is unusual in patients with normal or mildly reduced baseline kidney function.⁹⁵ I.v. contrast should not be withheld owing to concern for AKI in life-threatening conditions in which the information gained from the contrast study could have important therapeutic implications.

RENAL REPLACEMENT THERAPY

RRT terminology and initiation

In recent years, the suggestion has been made that the English term “renal” should be replaced by “kidney,” because the latter is more familiar to most English speakers. Additionally, the term “replacement” may not be sufficient, and terms such as “support” or “partial replacement” may be more accurate.

Table 4 | Strategies for a drug stewardship program focused on AKI/AKD

- Include a clinical pharmacist for drug stewardship.
- Identify patients at risk of AKI/AKD and take into account the risk of AKI/AKD when prescribing.
- Assess hydration status.
- Assess chronic drugs and their indication for continuation or discontinuation.
- Perform medication regimen review and evaluate PK/PD interactions.
- Review the use of drugs in patients who develop acute or chronic illnesses that increase the risk of AKI.
- Assess the dynamic impact of AKI/AKD on drug PK/PD.
- Assess the dynamic impact of renal recovery on drug PK/PD.
- Assess concurrent illness on drug PK/PD (e.g., sepsis, heart failure).
- Assess the impact of RRT on drug PK/PD.
- Undertake dynamic prescription and medication reconciliation at transitions of care.

AKD, acute kidney diseases and disorders; AKI, acute kidney injury; PD, pharmacodynamics; PK, pharmacokinetics; RRT, renal replacement therapy.

The implications of changes in nomenclature are not insignificant. Additionally, the distinction between kidney versus renal does not apply in all languages. Accordingly, KDIGO has convened a separate Nomenclature Consensus Conference for the purpose of recommending nomenclature consistent with guidelines for acute and chronic kidney disease.⁹⁶ Above all, patients should be the focus of all communication and care. Whenever possible, all decisions about treatment should be shared with patients, their families and/or next of kin, and if required, all members of the end-of-life care multidisciplinary team. All communication with patients and their supporting families/friends should be provided in simple lay language at regular intervals, with the awareness that patients may be traumatized. “Life support,” “kidney machine,” or similar words are preferred to the term RRT. If RRT becomes permanent, and the patient enters the chronic dialysis pathway, all relevant medical or nursing personnel should change their

language to specify the type of RRT (transplant, hemodialysis, or peritoneal dialysis).

The 2012 KDIGO AKI guideline suggested initiating RRT emergently in the presence of life-threatening changes in fluid, electrolyte, and acid–base balance. Since 2012, data from several RCTs and observational studies have become available.^{13–15,97–104} However, the optimal timing for acute RRT remains unknown. It has been proposed that initiation of RRT should be considered when metabolic and fluid demands exceed the kidney’s capacity to meet them.^{105–107} This concept acknowledges the dynamic nature of acute illness and stresses the importance of regular evaluation of the demand and renal capacity relationship. However, the exact methods for determining demand and capacity are unknown. Existing evidence does not support using biomarkers when deciding whether to initiate RRT.^{13,97,108} Use of a standardized FST can be considered in AKI, to further quantify the likelihood of AKI progression, and integrated into the spectrum of clinical information available when planning for and deciding to initiate RRT.^{39,52,109,110} In determining whether or not to start RRT, risk of complications, global prognosis, potential for recovery, and patient preferences should be considered (Figure 3). Although some regions of the globe have challenges and constraints in providing universal access to RRT,¹¹¹ we recommend a similar approach be undertaken for considering for whom and when to start RRT in all regions.^{112–114} Additionally, a similar approach should be undertaken in both intensive care unit and non-intensive care unit settings.

Providing RRT

Although the timing of RRT initiation is controversial, the provision of RRT itself has become fairly well established. Patients with AKI requiring RRT have an evolving clinical status and should be supported by the appropriate and available modality. Modality choice should also be tailored to

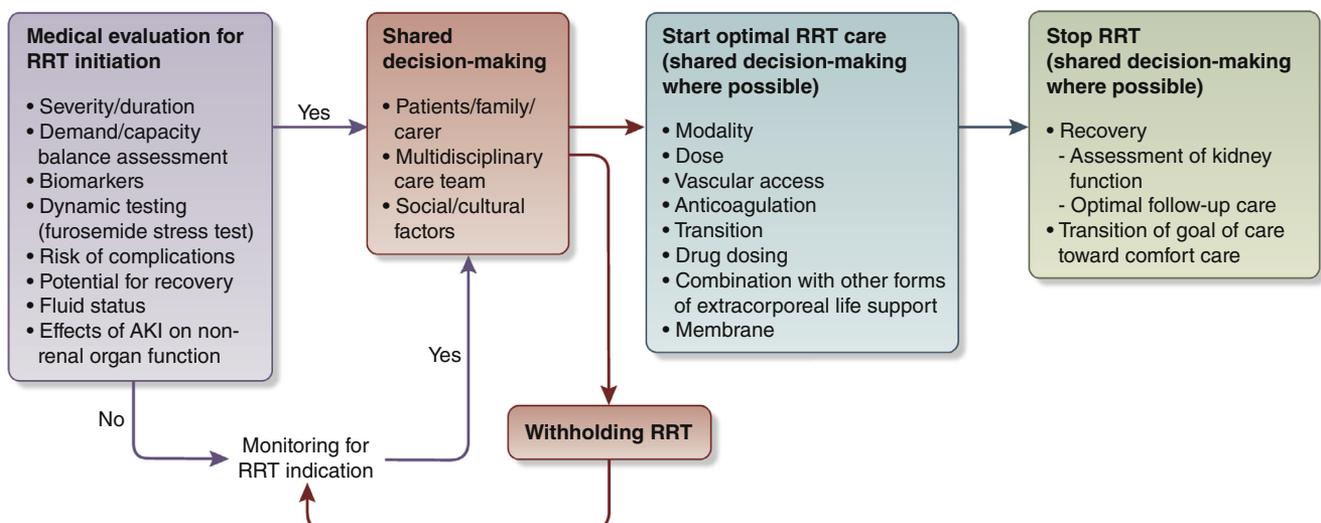


Figure 3 | Schematic diagram of renal replacement therapy (RRT) decisions in acute kidney injury (AKI).

patient clinical status. As suggested in the 2012 KDIGO guideline, in hemodynamically unstable patients, continuous RRT, rather than intermittent hemodialysis, is more physiologically appropriate, but RCTs have not demonstrated better outcomes with continuous RRT.¹ Both continuous and intermittent RRT can lead to changes in intracranial pressure, but the risk is higher with intermittent RRT. Selection of modalities should be considered in the context of available resources and expertise of personnel.

An uncuffed non-tunnelled dialysis catheter of appropriate length and gauge should be used to initiate RRT in AKI patients. In patients with expected prolonged indication for RRT, a cuffed catheter can be considered.¹¹⁵ The first choice for site is the right jugular vein or femoral vein, although the femoral site is inferior in patients with increased body mass. The next choices would be left jugular vein followed by subclavian vein. Anticoagulation type should be selected based on local resources and expertise of personnel. The recommendation from 2012 to use regional citrate anticoagulation for continuous RRT in patients who do not have a contraindication remains supported by existing data.^{116–118} Delivery of RRT must reach the goals of electrolyte, acid–base, solute, and fluid balance for each specific patient.¹¹⁹ When using intermittent or extended RRT, a Kt/V of at least 1.2 per treatment 3 times a week should be delivered.¹²⁰ For peritoneal dialysis, future studies should focus on dosing in AKI, although currently we suggest a dose of 0.3 Kt/V per session. An effluent volume of 20–25 ml/kg per h should be delivered when continuous RRT is used. This will sometimes require a higher prescription of effluent volume.^{121,122} The rate of fluid removal for a given patient with fluid overload is controversial,^{123,124} and more research is needed. Methods to better assess fluid management goals during RRT would also be valuable. Finally, RRT should be discontinued when kidney function has recovered or when RRT becomes inconsistent with shared care goals. Modality transition from continuous RRT to intermittent hemodialysis in intensive care unit patients should be considered when vasopressor support has been stopped, intracranial hypertension has resolved, and positive fluid balance can be controlled by intermittent hemodialysis.

RRT in the context of multi-organ support

The 2012 KDIGO AKI guideline did not address utilization of extracorporeal life support (ECLS) such as extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal (ECCO2R), and left or right ventricular assist device. Several issues remain unresolved: the optimal approach to patient selection, techniques, and timing/indications; circuit integration; and monitoring for ECLS and concomitant blood-purification techniques. Several observational studies on this theme warrant analysis and interpretation.^{125–131}

Decisions regarding how to combine RRT with ECLS devices will depend on local expertise, technology, and human resources. Such combined treatment should be based on a

multidisciplinary approach to patient care and shared decision-making. More studies are needed to define the best strategy for training and practice.

Although different RRT modalities can be used to support patients during ECLS, and comparative studies are not available, because of hemodynamic status, continuous RRT is more appropriate in this setting. It would be useful to develop a registry focused on patients receiving ECLS-RRT, to understand the epidemiology, technology, indications, and complications associated with current practice.

There is no clear evidence that usual RRT indications should vary according to the presence or absence of an ECMO/ECCO2R circuit. Nonetheless, patients for whom ECMO or ECCO2R is required are very sensitive to fluid overload. Therefore, in patients with versus without ECMO/ECCO2R, earlier RRT may be required for preventing and managing fluid overload. A registry of patients combining ECMO/ECCO2R and RRT could improve understanding of current practice for initiating RRT in patients (adults and children) with ECMO/ECCO2R and fluid management. Respiratory dialysis (ECCO2R and ECMO) with modified dialysis solutions is currently limited to *in vitro* and experimental studies,^{132–134} and research focused on this technical aspect is needed.

The anticoagulation of RRT circuits when ECMO/ECCO2R is already running is not standardized. The administration of heparin may depend on patient factors (e.g., risk of bleeding), circuit set-up (e.g., connection to patient or to ECMO), and institutional protocols.^{128,130,135–141} It is possible to have RRT circuits without dedicated heparin in this setting, unless excessively frequent clotting is observed. Studies are needed to compare different anticoagulation strategies in this setting. Citrate anticoagulation during RRT added to ECMO/ECCO2R is possible.^{139,140} Its feasibility and performance compared with other forms of anticoagulation remain untested, and thus comparative studies of citrate anticoagulation are recommended.

RRT long-term outcomes and follow-up

Choice of RRT modality and impact on recovery. The selection of RRT modality does not appear to have a major impact on recovery of kidney function.^{141–143} Selection of modality of RRT should therefore be based on shared decision-making, local expertise, logistic factors, and patient characteristics. Estimated GFR in conjunction with major adverse kidney events has been used for medium- and long-term assessment but has several limitations. There is uncertainty about the best way to measure renal recovery after RRT in both the short- and medium-term. However, proteinuria is associated with worse long-term outcomes and is easy to measure.

Assessment of kidney function for renal recovery. In addition to the development of CKD, patient-centered outcomes (quality of life, functional recovery), along with patient experience after AKI, should be a priority and need to be assessed. Post-AKI proteinuria is associated with future loss of

Table 5 | Summary points from the Acute Kidney Injury Controversies Conference

	Risk assessment	Diagnosis of AKI	Fluid management	Hemodynamic management	Drug stewardship	RRT
Consensus	<ul style="list-style-type: none"> Need for risk models tailored to clinical context 	<ul style="list-style-type: none"> Retention of KDIGO criteria but there is need for refinement (i.e., duration, etiology, course, role of biomarkers, definition and staging of AKD) 	<ul style="list-style-type: none"> Importance of adequate hydration and correction of hypovolemia to prevent and treat AKI 	<ul style="list-style-type: none"> Importance of adequate renal perfusion to prevent and treat AKI 	<ul style="list-style-type: none"> Importance of drug stewardship in preventing and managing AKI Retention of term “nephrotoxic” despite varying effects of drugs on kidney function 	<ul style="list-style-type: none"> Need for patient-centered communication Need to tailor RRT to the condition of the patient
Evidence of importance but lack of consensus	<ul style="list-style-type: none"> Role of new AKI risk models Need for additional endpoints beyond mortality and CKD Impact of renal reserve Follow-up strategy after AKI 	<ul style="list-style-type: none"> Definition of “pre-clinical” AKI Assessment of baseline kidney function Evaluation of urine output Definition of renal recovery Role of kidney biopsy and new imaging techniques 	<ul style="list-style-type: none"> Definition and assessment of fluid overload Impact of saline in different clinical settings Role of goal-directed therapy in different clinical scenarios Strategy of fluid removal 	<ul style="list-style-type: none"> Role of goal-directed therapy in different clinical scenarios Impact of vasopressor type on kidney function 	<ul style="list-style-type: none"> Impact of contrast in different clinical settings Role of ACE-Is/ARBs in AKI 	<ul style="list-style-type: none"> Assessment of recovery after RRT, including kidney function and patient-centered outcomes Combination of RRT and other forms of extracorporeal organ support Identification of quality indicators for acute RRT
Key topics for future research	<ul style="list-style-type: none"> Evaluation of AKI risk models Identification of clinical endpoints 	<ul style="list-style-type: none"> Role of real-time or kinetic GFR Impact of body composition on AKI criteria 	<ul style="list-style-type: none"> Determination of optimal indications, fluid type, administration, and clinical endpoints of fluid therapy in AKI Investigation of fluid-removal strategies 	<ul style="list-style-type: none"> Determination of optimal indications, vasopressor type, and clinical endpoints of fluid therapy in AKI 	<ul style="list-style-type: none"> Development of new classification describing renal effects of drugs Role of biomarkers and electronic clinical decision-support systems Management of ACE-Is/ARBs in AKI 	<ul style="list-style-type: none"> Determination of optimal fluid-removal strategy Integration of RRT and other forms of extracorporeal support

ACE-I, angiotensin-converting enzyme inhibitor; AKD, acute kidney diseases and disorders; AKI, acute kidney injury; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy.

kidney function and is regarded as a valuable risk-stratification tool in the post-AKI period.^{144–146}

Optimal follow-up for AKI patients following RRT

Shared decision-making and communication among caregivers, the patient, and family members is crucial to patient recovery. Patients recovering from critical illness and AKI are often discharged to rehabilitation/skilled nursing facilities and need close monitoring to ensure adequate overall recovery to a baseline state of health and well-being. Such patients should receive multidisciplinary, recovery-focused care. Patients with AKI who continue to require RRT at hospital discharge often receive hemodialysis in outpatient dialysis facilities. Patients with congestive heart failure are less likely to recover kidney function.¹⁴⁷ Higher ultrafiltration rates and more intradialytic hypotensive episodes are associated with higher risk of non-recovery of kidney function.^{148,149} To assess for renal recovery, hemodynamic status, intravascular volume, and urine output during dialysis should be carefully monitored.

Quality indicators for acute RRT

The importance of measuring and monitoring the quality of acute RRT provided to critically ill patients with AKI, including the optimal “benchmarking” for acute RRT programs, is receiving great attention.^{119,150} Quality of acute RRT should be monitored to ensure the effective and safe delivery of care.¹⁵¹ At a minimum, institutions and programs providing RRT should integrate, monitor, and report quality and outcome indicators across all forms of acute RRT therapies.³¹ These outcome measures should comprise a variety of metrics that incorporate patient survival, patient-centered acute RRT outcomes, safety, AKI survivor-related outcomes, and patient experience. Quality indicators should include shared goals that are patient- and clinically centered.

CONCLUSIONS

Although much of the 2012 KDIGO AKI guideline remains state of the art, advances over the past decade have improved our understanding of best practices. Many of these advances are widely accepted (e.g., nephrotoxic medication stewardship, shared decision making for RRT), but others are more controversial (Table 5). Although some centers and specific programs have embraced new technologies and ways of thinking, others have taken a more conservative, or “wait-and-see” approach. Even among conference participants, there was lack of unanimity for various perspectives, and obvious practice variation continues to exist, even among experts. Perhaps more than any new trial or discovery, this fact provides ample rationale for revisiting the AKI guideline in the near future.

APPENDIX

Other conference participants

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DISCLOSURE

MO declared having received consultancy fees from NxStage, speaker honoraria from Fresenius Medical Care, and research support from LaJolla Pharma. RB declared having received speaker honoraria from AbbVie and research support from Baxter. EAB declared having received consultancy fees from AstraZeneca and Fresenius Medical Care, and research support from Fundação de Amparo à Pesquisa do Estado de São Paulo. ZHE declared having received consultancy fees from AstraZeneca, and research support from Health Research Council of New Zealand and National University Hospital Singapore. SLG declared having received stock options from MediBeacon. KDL declared having received consultancy fees from bioMérieux, speaker honoraria from Baxter, and stock options from Amgen. JRP declared having received consultancy fees from MediBeacon, Nikkiso Europe GmbH, and Quark Pharmaceuticals; speaker honoraria from Baxter, Fresenius Medical Care, and Nikkiso Europe GmbH; and research support from bioMérieux. MJ declared having received consultancy fees from Amgen, AstraZeneca, Mundipharma, MSD, and Vifor Fresenius Medical Care Renal Pharma; speaker honoraria from Amgen, Menarini, MSD, and Vifor Fresenius Medical Care Renal Pharma; and research support from Amgen, MSD, and Otsuka. WCW declared having received consultancy fees from Akebia, AstraZeneca, Bayer, Janssen, Merck, Relypsa, and Vifor Fresenius Medical Care Renal Pharma; and research support from the National Institutes of Health. JAK declared having received consultancy fees from Astute Medical, Baxter, bioMérieux, Davita, Fresenius Medical Care, Grifols, NxStage, Potrero, and RenalSense; and research support from Astute Medical, Baxter, bioMérieux, and RenalSense. All the other authors declared no competing interests.

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