British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 396–403 396

SHORT REPORT

Drug management in acute kidney disease – Report of the Acute Disease Quality Initiative XVI meeting

Correspondence Marlies Ostermann, King's College London, Guy's and St Thomas' Foundation Hospital, Department of Critical Care, London SE1 7EH, UK. Tel.: +44 207 1883038; E-mail: marlies.ostermann@gstt.nhs.uk

Received 5 June 2017; **Revised** 9 September 2017; **Accepted** 20 September 2017

Marlies Ostermann[1], Lakhmir S. Chawla[2], Lui G. Forni[3], Sandra L. Kane-Gill[4], John A. Kellum[5], Jay Koyner[6], Patrick T. Murray[7], Claudio Ronco[8], Stuart L. Goldstein[9] and ADQI 16 workgroup*

[1]Department of Intensive Care, King's College London, Guy's & St Thomas' NHS Foundation Hospital, London, UK, [2]Department of Medicine, Veterans Affairs Medical Center, Washington, DC, USA, [3]Intensive Care Unit, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK, [4]University of Pittsburgh School of Pharmacy, Pittsburgh, USA, [5]Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, USA, [6]Department of Medicine, University of Chicago, Chicago, USA, [7]UCD School of Medicine, Health Sciences Centre, University College Dublin, Dublin, Ireland, [8]Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, International Renal Research Institute of Vicenza, Vicenza, Italy, and [9]Cincinnati Children's Hospital Medical Center, Division of Nephrology and Hypertension, Cincinnati, USA

*ADQI 16 workgroup: Zoltan Endre, Ravindra Mehta, Rinaldo Bellomo, Sean M. Bagshaw, Azra Bihorac, Dinna Cruz, Eric Hoste, Kathleen D. Liu, Etienne Macedo, Neesh Pannu, Edward D. Siew, Ron Wald, Alexander Zarbock, Mitra Nadim, Paul M. Palevsky, Mitchell Rosner, David Bittleman and Robert L. Fitzgerald.

Keywords acute kidney disease, acute kidney injury, drug management, drugs

AIMS

To summarize and extend the main conclusions and recommendations relevant to drug management during acute kidney disease (AKD) as agreed at the 16th Acute Disease Quality Initiative (ADQI) consensus conference.

METHODS

Using a modified Delphi method to achieve consensus, experts attending the 16th ADQI consensus conference reviewed and appraised the existing literature on drug management during AKD and identified recommendations for clinical practice and future research. The group focussed on drugs with one of the following characteristics: (i) predominant renal excretion; (ii) nephrotoxicity; (iii) potential to alter glomerular function; and (iv) presence of metabolites that are modified in AKD and may affect other organs.

RESULTS

We recommend that medication reconciliation should occur at admission and discharge, at AKD diagnosis and change in AKD phase, and when the patient's condition changes. Strategies to avoid adverse drug reactions in AKD should seek to minimize adverse events from overdosing and nephrotoxicity and therapeutic failure from under-dosing or incorrect drug selection. Medication regimen assessment or introduction of medications during the AKD period should consider the nephrotoxic potential, altered renal and nonrenal elimination, the effects of toxic metabolites and drug interactions and altered pharmacodynamics in AKD. A dynamic monitoring plan including repeated serial assessment of clinical features, utilization of renal diagnostic tests and therapeutic drug monitoring should be used to guide medication regimen assessment.

CONCLUSIONS

Drug management during different phases of AKD requires an individualized approach and frequent re-assessment. More research is needed to avoid drug associated harm and therapeutic failure.

DOI:10.1111/bcp.13449

© 2017 The British Pharmacological Society

Introduction

Drug dosing in critically ill patients is challenging due to altered pharmacokinetics and pharmacodynamics, multiple drug interactions and limited evidence to guide accurate prescribing [1]. Patients with impaired kidney function are particularly at risk for under- and over-dosing [2–4]. Guidelines are available for the drug management in patients with acute kidney injury (AKI) [5] but little is known for patients with acute kidney disease (AKD). The term AKD refers to a condition in which the renal pathophysiological processes are still ongoing and AKI stage 1 or greater [as defined by the Kidney Disease Improving Global Outcome (KDIGO) criteria] is present ≥7 days after an AKI initiating event [6]. AKD that persists beyond 90 days is considered to be chronic kidney disease (CKD). Often, there is a continuum from AKI to AKD and CKD [6]. Typical scenarios are cases where AKI is observed and the patient remains in AKI stage 1 or greater for >7 days. Another option is a patient who develops AKI during hospitalization and their serum creatinine improves before discharge but the AKD pathophysiological processes continue leading to CKD at 90 days [7]. There may also be instances where the onset of AKI was not directly observed (i.e., community acquired AKI) and patients present with impaired renal function that has been present for ≥7 days but <90 days. Conceptually, AKD consists of three phases: *deteriorating phase* when kidney function is actively worsening; *maintenance phase* when the injury has ended but kidney function has yet to recover; and *improvement phase* where renal function begins to recover, ideally towards the preinjury baseline [8]. (Figure 1) The duration of these individual phases varies and not every patient progresses through all three phases. Renal function often fluctuates with a variable rate of renal recovery and it can be difficult to determine when sustained recovery has occurred. As a result, patients are at high risk for over-dosing, under-dosing and nephrotoxicity [3, 4, 9]. Finally, AKI and AKD are syndromes comprising multiple different aetiologies. They rarely occur in isolation but usually in the context of other dynamic acute illnesses and on the background of profound chronic comorbidities, all of which impact the selection of drugs and their pharmacokinetics and pharmacodynamics.

The 16th Acute Disease Quality Initiative (ADQI) consensus conference focused on clinically important aspects during the period of AKD [6]. The key recommendations related to the definition of renal recovery, criteria for AKD, assessment of renal function and clinical management were published in early 2017. In this report, we summarize and extend the main conclusions and recommendations relevant to drug management.

Methods

The 16th ADQI conference was held over 2.5 days in San Diego, USA, and included a diverse panel of clinicians and researchers representing relevant disciplines – internal medicine, paediatrics, primary care, nephrology, critical care,

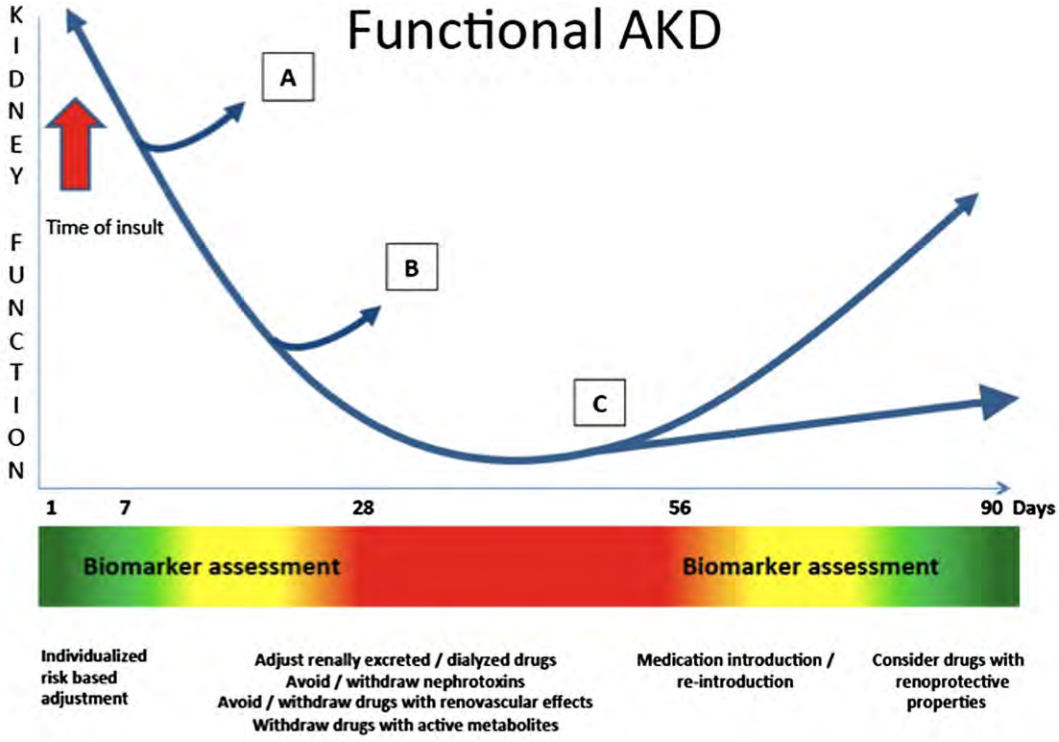

Figure 1

Drug management during different phases of acute kidney disease [6]. AKD = acute kidney disease. (A) AKD begins to improve early in the clinical course; (B) AKD persists for longer and renal function improves only after a considerable decline; (C) AKD is severe; after an extended period of AKD, renal function may recover fully to baseline or only partially or progress to chronic dialysis dependence

pharmacy, epidemiology, health-services research, biostatistics, bioinformatics and data analytics – from Europe, North America and Australia [8]. The meeting followed the established ADQI process, and used a modified Delphi method to achieve consensus [10]. Members of the work groups performed reviews of the literature in a systematic manner and developed a consensus of opinion, backed by evidence where possible, to distil the available literature and identify recommendations for clinical practice and future research.

While the considerations for drug dosing during AKD are relevant to any medication, it was decided to focus on main principles and specific issues related to drugs with one of the following characteristics: (i) predominant renal excretion; (ii) nephrotoxicity; (iii) potential to alter glomerular function; and (iv) presence of metabolites that are modified in AKI/AKD and may affect other organs.

Results

General principles of drug selection, dosing and monitoring during AKD

The disposition and effects of drugs given to the patient with AKD are modulated by several factors, including changes in drug clearance (glomerular and tubular kidney function; nonrenal drug metabolism), and altered pharmacokinetic parameters as a result of decreased kidney function (volume overload, metabolic acidosis etc.). Understanding how a particular drug or metabolite is handled is essential to formulate a therapeutic plan for a specific agent across every phase of AKD (deteriorating, maintenance or improvement phase; Figure 1). Depending on the drug, renal elimination may occur through glomerular filtration, tubular secretion or tubular reabsorption (following glomerular filtration). In addition, the kidney may oxidize, reduce, hydrolyse and/or conjugate a particular drug or its metabolite leading to drug activation/inactivation [1]. There may also be additional contribution to drug metabolism through the action of renal tubular cytochrome P450 (CYP450) [11]. It is crucial to know what phase of AKD (deteriorating, maintenance or improvement) a patient is in and whether changes in function (e.g. glomerular filtration) and/or structural injury to the renal tubules have occurred and the specific site of injury (as measured by damage biomarkers) [12, 13]. These details are vital to understand how the different phases of AKD may impact drug dosing.

In conclusion, drug selection and dosing in AKD requires multiple and regular re-assessment considering patient risk profile, baseline and actual renal function and trajectories, drug mechanisms, biomarkers predicating injury and recovery, nonrenal dysfunction affecting drug clearance, indications and alternative therapies, genetic susceptibility and potential availability of therapeutic drug monitoring [6].

Assessment of renal function during AKD

Functional markers of glomerular filtration (e.g. serum creatinine or cystatin C) are good biomarkers during steady states, but are not ideally suited for acute changes [14–16]. Other methods to assess filtration include timed urinary collection(s) in order to estimate creatinine and urea clearances [17, 18]. Multiple kinetic algorithms have been proposed to predict glomerular filtration rate (GFR) in the nonsteady-state [19–23], but none is universally accepted. Several models of real-time GFR have also been investigated including real-time plasma elimination kinetics of fluorescein isothiocyanate (FITC)-sinistrin and fluorescence based measures of filterable (inulin) and nonfilterable (500 kDa dextrans) molecules [24, 25]. While real-time GFR measurement may be the ideal biological measure in the setting of AKD, these techniques have yet to be approved for use following validation in humans.

Potential non-GFR based imaging modalities as measures of renal function in AKD include contrast enhanced ultrasound, positron emission tomography (PET), and blood oxygenation level-dependent magnetic resonance imaging [26]. Similarly, renal blood flow and renal tissue oxygenation assessments have been suggested as potential indicators of underlying intrinsic kidney function [27] but the role of these new techniques outside the research setting remains uncertain.

Novel biomarkers of renal tubular injury have been approved for clinical use around the globe [28–35]. They predict both short and long-term outcomes after AKI [12, 13, 33–45] and have also been shown to direct clinical management [46–48]. Although their role in guiding drug dosing remains unclear, it is easy to imagine clinical scenarios where changes in nephron segment-specific damage biomarkers alert the prescriber that dose adjustments, including drug discontinuation, are needed for drugs handled by specific nephron segments [49]. Examples of biomarkers and drugs specific to nephron segments are provided in Table 1.

Current care algorithms rely on imperfect functional markers of glomerular filtration. Incorporation of newer damage biomarkers may decrease exposure to nephrotoxins, facilitate more accurate dosing of drugs cleared by the kidney, and lead to a decreased incidence and severity of AKI. For example, risk stratification with a novel biomarker to employ an AKI risk reduction bundle (including nephrotoxic medication avoidance) led to less AKI after cardiac surgery [46]. In another study, a damage biomarker was able to predict supra-therapeutic concentrations of tobramycin in patients with cystic fibrosis [50]. Ideally, dosing of drugs with renal excretion in any AKD phase (deteriorating *versus* maintenance *versus* improvement) should prioritize the most dynamic and feasible functional assessments possible. The ADQI expert group recommended that further research related to assessment of renal function during AKD, including the utilization of renal biomarkers was urgently needed [6].

Nephrotoxin management during AKD

Drug-associated AKI occurs in approximately 25% of critically ill patients, making drugs a common cause of AKI in the intensive care unit [51, 52]. The prevalence of drug associated AKI is 2–3 times higher in elderly patients [53–55]. The consequences are severe, with rates of nonrecovery, dialysis dependence and/or mortality similar to AKI from other aetiologies (40–50%) [52].

Table 1

Examples of biomarkers and drugs specific to nephron segments

Nephron segment	Segment specific biomarker	Drugs handled by relevant nephron segment
Glomerulus	Albumin Cystatin C	Doxrubicin Gold Penicillamine
Proximal tubules	Albumin Clusterin IGFBP7 KIM-1 L-FABP NAG NGAL Osteropontin TIMP-2 Cystatin C	Amikacin Cisplatin Colistin Cyclosporine Gentamicin Hydroxyetheyl starch Tacrolimus Tobramycin Vancomycin
Loop of Henle	Osteopontin	Analgesics (chronic)
Distal tubules	Clusterin NAG NGAL Osteopontin	Amphotericin B Cyclosporine Sulfadiazine Tacrolimus
Collecting duct	Calbindin D28	Ampotericin B Acyclovir Lithium (acute)

IGFBP7, insulin-like growth factor-binding protein 7; KIM-1, Kidney injury molecule-1; L-FABP, Liver-type fatty acid binding protein; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, Tissue inhibitor of metalloproteinase 2

Table 2

Considerations for nephrotoxin management during AKD

When to avoid starting a nephrotoxic drug
Patient has known risk factors for kidney injury (i.e. advanced age, previous AKI episode, CKD, diabetes mellitus, proteinuria, hypertension)
A suitable and less nephrotoxic drug is available
Nephrotoxin is considered nonessential
Patient is already receiving a nephrotoxic drug and there is concern for a pharmacokinetic or pharmacodynamic drug interaction
Intended duration of the drug therapy is chronic and the initiation of the drug can be delayed until after the AKD episode
Biomarker indicates renal tubular injury is impending
Biomarker predicts risk of drug accumulation
There is a concern for a lack of appropriate follow up of serum creatinine and/or therapeutic drug concentration monitoring
When to discontinue a nephrotoxin
An evaluation of causal relationship indicates that the nephrotoxin is the potential cause of AKI/AKD
A suitable and less nephrotoxic drug is available
Nephrotoxin is considered nonessential
Biomarker indicates renal tubular injury has occurred
Other considerations for nephrotoxin management
Regular monitoring of functional status while on a nephrotoxin- either dose increase or decrease may be necessary
Minimizing the duration and dose of nephrotoxin exposure, if possible
Using evidence dosing guidelines
When nephrotoxin administration is essential – monitor for and manage subsequent adverse drug events

AKI, acute kidney injury; AKD, acute kidney disease; CKD, chronic kidney disease

Evaluation of nephrotoxins as a plausible cause for AKI is the first consideration in medication management and includes assessment of the temporal sequence between administration and event and alternative explanations [56]. In general, in all phases of AKD, selection of the least nephrotoxic drug and/or avoidance of a nephrotoxin should be the goal. This approach is supported by the fact that each nephrotoxin administration presents a 53% greater odds of developing AKI [57], and is compounded when patients receive more than one nephrotoxin [58].

Combining drugs can also result in important pharmacodynamic drug interactions [55, 56]; for instance, the administration of some macrolide antibiotics (clarithromycin/erythromycin) with a 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitor (statin) may lead to a greater number of hospitalizations for AKI (from rhabdomyolysis), compared to the administration of azithromycin (a macrolide that does not powerfully inhibit CYP450 enzyme CYP 3A4 and affect clearance of a HMG-CoA reductase inhibitor) [59].

Drug selection, dosing and monitoring in AKI and AKD should be guided by personalized clinical decision making, including considerations for nephrotoxin initiation and discontinuation and the impact of starting alternative medications (Table 2). Factors to consider when starting a nephrotoxin include patient age, history of diabetes mellitus with proteinuria, hypertension, volume depletion, baseline kidney function, trauma, circulatory shock, sepsis, degree of fluid overload and concomitant administration of nephrotoxins [57, 60, 61]. In the future, risk assessment is likely to include the detection of kidney damage using novel techniques before a functional change is observed [60].

The maintenance phase of AKD necessitates continued consideration of nephrotoxin avoidance (Figure 1). During the improvement phase of AKD, caution is still applied to nephrotoxin initiation, to prevent re-injury. An evaluation of the appropriate timing to start or re-start a drug assumes that a nephrotoxin is essential for the patient. The treatment of an infection with an antibiotic that is necessary for survival should begin immediately, and may even prevent deterioration of renal function. Further thought is given to the best time to restart a chronic therapy, or to increase the dose of renally excreted drugs to avoid a therapeutic failure in the renal recovery phase [62]. Also, the interplay with augmented renal clearance during the recovery phase of AKD is unclear [63, 64].

A general statement cannot be made about a functional threshold to avoid or discontinue nephrotoxins. Ideally, nephrotoxic medications or combinations should be avoided in patients with AKD. When nephrotoxic medications are needed for clinically compelling reasons, efforts should be made to mitigate their nephrotoxic effects. The recommendations provided in package inserts or guidelines specific to a drug or drug class may offer guidance. At present there is a significant gap in knowledge to support drug management in AKD as outlined in the research agenda provided in Table 3.

Management of angiotensin-converting enzyme inhibitor and angiotensin II receptor blockers

The therapeutic options for supporting transition from AKI to renal recovery are limited and the decision to restrict certain therapies may reflect their nephrotoxic potential. A clinically relevant example is the use of angiotensin converting enzyme inhibitor (ACEi) and angiotensin II receptor blockers (ARB), which are associated with renal functional impairment, particularly in the setting of acute hypovolaemia [65–67]. The indications for this group of medications are broad and include heart failure with documented left ventricular dysfunction, CKD with proteinuria, and hypertension. Consequently, they are frequently prescribed, particularly in the elderly [68]. A recent study using routinely-collected national hospital administrative data showed while ACEi and ARB prescribing increased by 16%, hospital admissions complicated by AKI rose by 50% in the same time period [69]. Despite the clear benefits of these drugs in the chronic setting, the risk–benefit ratio during AKD is uncertain.

It has been suggested to routinely stop ACEi and ARBs during any intercurrent illness, despite the lack of any evidence supporting these recommendations [70]. This could potentially lead to worsening in hypertension or deterioration in symptoms of congestive cardiac failure. It is not known if withholding or re-starting these drugs during AKD results in better outcomes, and at what stage they are ideally re-started post AKI/AKD. Two studies evaluating nonresumption of ACEi after surgery demonstrated an increase in 30-day mortality [71, 72]. Although re-introduction of such therapies is often part of a multidisciplinary approach to AKI care, it is usually considered when the GFR has stabilized and volume status is optimized. ACEi- or ARB- associated hypotension and decreased filtration fraction are recognized as adverse effects that can cause or exacerbate AKI. The risk–benefit ratio for their use in AKD must be carefully considered to personalize therapy. While chronic tolerance to reversible decrements in filtration fraction and GFR caused by ACEi and ARB may be desirable in congestive cardiac failure and CKD, such effects may not be tolerable and beneficial in AKD.

Similarly, there is a significant risk of potential therapeutic failure caused by under-dosing or avoidance of the most effective drugs in patients with AKD (particularly in the recovery phase) but this is rarely recorded [62]. A recent single-centre observational study including 396 patients highlighted that 7.5% of patients had a therapeutic failure defined as subtherapeutic drug levels and underdosing of medications, with 30% of events being life threatening and primarily related to antibiotics [73]. Underdosing of antibiotics in particular, is a serious problem during periods of fluctuating renal function. More than most other drug classes, antibiotics have a clear concentration-effect relationship where effect can be defined as time-dependent or concentration-dependent killing. Maintaining drug concentrations according to pharmacodynamics and antibiotic characteristics is essential. Numerous factors contribute to subtherapeutic concentrations, including inappropriate drug dosing, unrecognized recovery of native renal function, and changes in pharmacodynamics and nonrenal clearance [74].

In patients with AKD, the decision to discontinue, introduce and/or re-introduce medications with important effects on other organs needs to be individualized and discussed with the appropriate interdisciplinary care providers. This

Table 3

Consensus recommendations of ADQI 16

Drug management in clinical practice

1) We recommend medication assessments at the following instances during the AKD period:

a) medication reconciliation should occur at ICU/hospital admission and discharge
b) medication regimen assessment at AKD diagnosis and change in AKD stage
c) reassessment when patient condition changes

2) Strategies to avoid adverse drug reactions in AKD should seek to minimize both adverse events from overdosing or nephrotoxicity and therapeutic failure from under-dosing or incorrect drug selection.

3) Medication regimen assessment or consideration of medication introduction during the AKD period should consider:

a) nephrotoxic potential
b) altered drug disposition including renal or hepatic elimination, toxic metabolites and drug interactions
c) altered pharmacodynamics in AKD

4) Medication regimen assessment should be guided by a dynamic monitoring plan to include repeated serial assessment of:

a) clinical features (adverse drug reaction or therapeutic failure)
b) currently available renal diagnostic tests (eg biochemistry, imaging)
c) currently available therapeutic drug monitoring (parent drugs +/− metabolites)

Advocacy and future research

1) We advocate for a clinical pharmacist to undertake medication regimen assessment throughout the AKD period.

2) We advocate for a clinical pharmacist to undertake a formal medication reconciliation and AKD education at hospital discharge

3) We recommend a research agenda that prioritizes federal and industry funding to:

a) develop better drug specific damage markers and therapeutic monitoring assays
b) validate better biomarkers of kidney injury, including imaging
c) undertake trials for drug management in AKD

ADQI, Acute Disease Quality Initiative; AKD, acute kidney disease; ICU, intensive care unit

also includes the effects of AKD on drug metabolites, including nonrenal metabolism.

Effects of AKD on drug pharmacokinetics

The effects of CKD on drug metabolism are relatively well established but little is known with regard to the impact of AKD. The extrapolation of data from CKD is flawed given that the time course of disease progression is different and renal function may be fluctuant in AKD. During critical illness, organ cross-talk may also influence drug metabolism, particularly if involving the liver and the kidney [10, 75]. This may reflect the impact of AKD on hepatic blood flow, changes in protein binding and drug distribution, and the increasingly recognized effects on CYP450 activity [75, 76]. Impairment of CYP450 activity, as well as effects on drug transporters, may also account for some of the pharmacodynamic effects during AKD. Many critically ill patients have AKI with varying volumes of distribution and protein concentrations that affect a drug's pharmacokinetics. The volume of distribution for hydrophilic drugs such as β-lactams is typically increased in critically ill patients who have an increase in total body water, especially patients with AKI. As the patient recovers from their critical illness and AKI, the fluid shifts and volume decreases, but the extent and the speed of improvement vary, thus making dosing during AKD a challenge. Further, in patients with renal disease, volume of distribution is increased as a result of reduced protein binding and increased tissue binding. Exact prediction of the effects of AKD on the pharmacokinetics of drugs remains challenging and further in-depth research is urgently required.

Conclusions

Drug management during the phases of AKD requires an individualized approach using general principles as outlined in Table 3. More research is urgently needed to avoid therapeutic failure and mitigate drug associated harm affecting chances of renal recovery during important phases of acute renal disease.

Competing Interests

There are no competing interests to declare.

We would like to thank R. Bellomo, A. Bihorac, E.D. Siew, S.M. Bagshaw, D. Bittleman, D. Cruz, Z. Endre, R.L. Fitzgerald, E. Hoste, K.D. Liu, E. Macedo, R. Mehta, M. Nadim, P.M. Palevsky, N. Pannu, M. Rosner, R. Wald and A. Zarbock for their invaluable suggestions and contributions towards the document.

References

1 Eyler RF, Mueller BA, Medscape. Antibiotic dosing in critically ill patients with acute kidney injury. Nat Rev Nephrol 2011; 7: 226–35.

2 Lewis SJ, Mueller BA. Antibiotic dosing in patients with acute kidney injury: "enough but not too much". J Intensive Care Med 2016; 31: 164–76.

3 Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, *et al*. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014; 58: 1072–83.

4 Roberts DM, Roberts JA, Roberts MS, Liu X, Nair P, Cole L, *et al*. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. Crit Care Med 2012; 40: 1523–8.

5 Matzke GR, Aronoff GR, Atkinson AJ Jr, Bennett WM, Decker BS, Eckardt KU, *et al*. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from kidney disease: improving global outcomes (KDIGO). Kidney Int 2011; 80: 1122–37.

6 Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew E, Bagshaw SM, *et al*. On behalf of the acute disease quality initiative workgroup 16. Acute kidney disease and renal recovery: guideline report of the acute disease quality initiative (ADQI) 16 workgroup. Nat Rev Nephrol 2017; 13: 241–57.

7 Pannu N, James M, Hemmelgarn B, Klarenbach S, Alberta Kidney Disease Network. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. Clin J Am Soc Nephrol 2013; 8: 194–202.

8 Acute Dialysis Quality Initiative 16 (www.adqi.org)

9 Hug BL, Witkowski DJ, Sox CM, Keohane CA, Seger DL, Yoon C, *et al*. Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. Kidney Int 2009; 76: 1192–8.

10 Kellum JA, Bellomo R, Ronco C. Acute dialysis quality initiative (ADQI): methodology. Int J Artif Organs 2008; 31: 90–3.

11 Philips BJ, Lane K, Dixon J, Macphee I. The effects of acute renal failure on drug metabolism. Expert Opin Drug Metab Toxicol 2014; 10: 11–23.

12 Murray PT, Mehta RL, Shaw A, Ronco C, Endre Z, Kellum JA, *et al*. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th acute dialysis quality initiative consensus conference. Kidney Int 2014; 85: 513–21.

13 Endre ZH, Kellum JA, Di Somma S, Doi K, Goldstein SL, Koyner JL, *et al*. Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workgroup statements from the tenth acute dialysis quality initiative consensus conference. Contrib Nephrol 2013; 182: 30–44.

14 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med 1999; 130: 461–70.

15 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–12.

16 Waikar SS, Betensky RA, Emerson SC, Bonventre JV. Imperfect gold standards for kidney injury biomarker evaluation. J Am Soc Nephrol 2012; 23: 13–21.

17 Chrymko MM, Schentag JJ. Creatinine clearance predictions in acutely ill patients. Am J Hosp Pharm 1981; 38: 837–40.

18 Hellerstein S, Berenbom M, Erwin P, Wilson N, DiMaggio S. Timed-urine collections for renal clearance studies. Pediatr Nephrol 2006; 21: 96–101.

19 Chen S. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. J Am Soc Nephrol 2013; 24: 877–88.

20 Jelliffe RW, Jelliffe SM. Estimation of creatinine clearance from changing serum-creatinine levels. Lancet 1971; 2: 710.

21 Chiou WL, Hsu FH. A new simple and rapid method to monitor the renal function based on pharmacokinetic consideration of endogeneous creatinine. Res Commun Chem Pathol Pharmacol 1975; 10: 315–30.

22 Moran SM, Myers BD. Course of acute renal failure studied by a model of creatinine kinetics. Kidney Int 1985; 27: 928–37.

23 Yashiro M, Ochiai M, Fujisawa N, Kadoya Y, Kamata T. Evaluation of estimated creatinine clearance before steady state in acute kidney injury by creatinine kinetics. Clin Exp Nephrol 2012; 16: 570–9.

24 Schock-Kusch D, Sadick M, Henninger N, Kraenzlin B, Claus G, Kloetzer HM, *et al*. Transcutaneous assessment of renal function in conscious rats with a device for measuring FITC-sinistrin disappearance curves. Kidney Int 2011; 79: 1254–8.

25 Wang E, Meier DJ, Sandoval RM, Von Hendy-Willson VE, Pressler BM, Bunch RM, *et al*. A portable fiberoptic ratiometric fluorescence analyzer provides rapid point-of-care determination of glomerular filtration rate in large animals. Kidney Int 2012; 81: 112–7.

26 Ostermann M, Joannidis M. Acute kidney injury in 2016: diagnosis and diagnostic workup. Crit Care 2016; 20: 299.

27 Evans RG, Gardiner BS, Smith DW, O'Connor PM. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. Am J Physiol Renal Physiol 2008; 295: F1259–70.

28 Okusa MD, Jaber BL, Doran P, Duranteau J, Yang L, Murray PT, *et al*. Physiological biomarkers of acute kidney injury: a conceptual approach to improving outcomes. Contrib Nephrol 2013; 182: 65–81.

29 Chen LX, Koyner JL. Biomarkers in acute kidney injury. Crit Care Clin 2015; 31: 633–48.

30 Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int 2008; 73: 1008–16.

31 Koyner JL, Parikh CR. Clinical utility of biomarkers of AKI in cardiac surgery and critical illness. Clin J Am Soc Nephrol 2013; 8: 1034–42.

32 Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant 2013; 28: 254–73.

33 Coca SG, Garg AX, Thiessen-Philbrook H, Koyner JL, Patel UD, Krumholz HM, *et al*. Urinary biomarkers of AKI and mortality 3 years after cardiac surgery. J Am Soc Nephrol 2014; 25: 1063–71.

34 Koyner JL, Garg AX, Coca SG, Sint K, Thiessen-Philbrook H, Patel UD, *et al*. Biomarkers predict progression of acute kidney injury after cardiac surgery. J Am Soc Nephrol 2012; 23: 905–14.

35 Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, *et al*. Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol 2011; 22: 1748–57.

36 Parikh CR, Thiessen-Philbrook H, Garg AX, Kadiyala D, Shlipak MG, Koyner JL, *et al*. Performance of kidney injury molecule-1 and liver fatty acid-binding protein and combined biomarkers of AKI after cardiac surgery. Clin J Am Soc Nephrol 2013; 8: 1079–88.

37 Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, *et al*. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med 2014; 189: 932–9.

38 Hoste EA, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, *et al*. Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. Nephrol Dial Transplant 2014; 29: 2054–61.

39 Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, *et al*. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013; 17: R25.

40 Koyner JL, Shaw AD, Chawla LS, Hoste EA, Bihorac A, Kashani K, *et al*. Tissue inhibitor metalloproteinase-2 (TIMP-2)IGF-binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI. J Am Soc Nephrol 2015; 26: 1747–54.

41 Nejat M, Hill JV, Pickering JW, Edelstein CL, Devarajan P, Endre ZH. Albuminuria increases cystatin C excretion: implications for urinary biomarkers. Nephrol Dial Transplant 2011; 27 (Suppl): iii96–103.

42 Nejat M, Pickering JW, Devarajan P, Bonventre JV, Edelstein CL, Walker RJ, *et al*. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. Kidney Int 2012; 81: 1254–62.

43 Ralib AM, Pickering JW, Shaw GM, Devarajan P, Edelstein CL, Bonventre JV, *et al*. Test characteristics of urinary biomarkers depend on quantitation method in acute kidney injury. J Am Soc Nephrol 2012; 23: 322–33.

44 Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: the light and the dark sides. Nephrol Dial Transplant 2016; 31: 16–22.

45 Pianta TJ, Buckley NA, Peake PW, Endre ZH. Clinical use of biomarkers for toxicant-induced acute kidney injury. Biomark Med 2013; 7: 441–56.

46 Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, *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. https://doi.org/10.1007/s00134-016-4670-3.

47 Ronco C, Rizo-Topete L, Serrano-Soto M, Kashani K. Pro: prevention of acute kidney injury: time for teamwork and new biomarkers. Nephrol Dial Transplant 2017; 32: 408–13.

48 Rizo-Topete LM, Rosner MH, Ronco C. Acute kidney injury risk assessment and the nephrology rapid response team. Blood Purif 2017; 43: 82–8.

49 Bonventre JV, Vaidya VS, Schmouder R, Feig P, Dieterle F. Next-generation biomarkers for detecting acute kidney injury. Nat Biotechnol 2010; 28: 436–40.

50 Downes KJ, Dong M, Fukuda T, Clancy JP, Haffner C, Bennet MR, *et al*. Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: a population pharmacokinetic analysis. J Antimicrob Chemother 2017; 72: 254–60.

51 Hoste E, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, *et al*. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41: 1411–23.

52 Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, *et al*. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int 2004; 66: 1613–21.

53 Kohli HS, Bhaskaran MC, Muthukumar T, Thennarasu K, Sud K, Jha V, *et al*. Treatment-related acute renal failure in the elderly: a hospital-based prospective study. Nephrol Dial Transplant 2000; 15: 212–7.

54 Abdel-Kader K, Palevsky PM. Acute kidney injury in the elderly. Clin Geriatr Med 2009; 25: 331–58.

55 Handler SM, Cheung PW, Culley CM, Perera S, Kane-Gill SL, Kellum JA, *et al*. Determining the incidence of drug-associated acute kidney injury in nursing home residents. J Am Med Dir Assoc 2014; 15: 719–24.

56 Kane-Gill SL, Forsberg EA, Verrico MM, Handler SM. Comparison of three pharmacovigilance algorithms in the ICU setting: a retrospective and prospective evaluation of ADRs. Drug Saf 2012; 35: 645–53.

57 Cartin-Ceba R, Kashiouris M, Plataki M, Kor DJ, Gajic O, Casey ET. Risk factors for development of acute kidney injury in critically ill patients: a systematic review and meta-analysis of observational studies. Crit Care Res Pract 2012; 2012: 691013.

58 Rivosecchi R, Dasta J, Kellum J, Kane-Gill S. 975: a unique application of the grade criteria: drug-combination associated Aki. Crit Care Med 2015; 43 (12 Suppl 1): 245.

59 Patel AM, Shariff S, Bailey DG, Juurling DN, Gandhi S, Mamdani M, *et al*. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. Ann Intern Med 2013; 158: 869–76.

60 Kane-Gill SL, Goldstein SL. Drug-induced acute kidney injury: a focus on risk assessment for prevention. Crit Care Clin 2015; 31: 675–84.

61 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.

62 Cox ZL, McCoy AB, Matheny ME, Bhave G, Peterson NB, Siew ED, *et al*. Adverse drug events during AKI and its recovery. Clin J Am Soc Nephrol 2013; 8: 1070–8.

63 Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics. Pharmacotherapy 2015; 35: 1063–75.

64 Udy AA, Roberts JA, Lipman J. Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol 2011; 7: 539–43.

65 Chao CT, Tsai HV, Wu CY, Lin YF, Hsu NC, Chen JS, *et al*. Cumulative cardiovascular polypharmacy is associated with the risk of acute kidney injury in elderly patients. Medicine 2015; 94: e1251.

66 Ftouh S, Thomas M, Acute Kidney Injury Guideline Development Group. Acute kidney injury: summary of NICE guidance. BMJ 2013; 347: f4930.

67 Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ 2013; 346: e8525.

68 Smets HL, De Haes JF, De Swaef A, Jorens PG, Verpooten GA. Exposure of the elderly to potential nephrotoxic drug combinations in Belgium. Pharmacoepidemiol Drug Saf 2008; 17: 1014–9.

69 Tomlinson LA, Abel GA, Chaudhry AN, Tomson CR, Wilkinson IB, Roland MO, *et al*. ACE inhibitor and angiotensin receptor-II antagonist prescribing and hospital admissions with acute kidney injury: a longitudinal ecological study. PLoS One 2013; 8: e78465.

70 Whiting P, Morden A, Tomlinson LA, Caskey F, Blakeman T, Tomson C, *et al*. What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis. BMJ Open 2017; 7: e012674.

71 Mudumbai SC, Takemoto S, Cason BA, Au S, Upadhyay A, Wallace AW. Thirty-day mortality risk associated with the postoperative nonresumption of angiotensin-converting enzyme inhibitors: a retrospective study of the veterans affairs healthcare system. J Hosp Med 2014; 9: 289–96.

72 Lee SM, Takemoto S, Wallace AW. Association between withholding angiotensin receptor blockers in the early postoperative period and 30-day mortality: a cohort study of the veterans affairs healthcare system. Anesthesiology 2015; 123: 288–306.

73 Roberts JA, Kumar A, Lipman J. Right dose, right now: customized drug dosing in the critically ill. Crit Care Med 2017; 45: 331–6.

74 De Waele JJ, Lipman J, Akova M, Bassetti M, Dimopoulos G, Kaukonen M, *et al*. Risk factors for target non-attainment during empirical treatment with β-lactam antibiotics in critically ill patients. Intensive Care Med 2014; 40: 1340–51.

75 Dixon J, Lane K, Macphee I, Philips B. Xenobiotic metabolism: the effect of acute kidney injury on non-renal drug clearance and hepatic drug metabolism. Int J Mol Sci 2014; 15: 2538–53.

76 Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000; 85: 599–610.