Section 3. PREVENTION OF ACUTE KIDNEY INJURY

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GUIDELINES

1. Prevention of amino glycoside induced AKI
   
a. After initial therapy with aminoglycoside antibiotics, we suggest using less nephrotoxic therapeutic alternatives when available and still appropriate. (2B)

b. In patients with normal kidney function and in a steady state (stable serum creatinine), we recommend administering aminoglycosides as a single daily dose rather than as multiple doses. (1A)

c. When single daily doses are used for more than 48 hours, we suggest monitoring of aminoglycoside drug levels. (2C)

d. When aminoglycosides are given in multiple daily doses for more than 24 hours, we recommend monitoring of aminoglycoside levels. (1A)

2. Prevention of amphotericin-associated AKI
   
e. We suggest using lipid formulations of amphotericin B rather than conventional preparations of amphotericin B. (2A)

f. In the treatment of systemic fungal infections or relevant parasitic infections, we recommend using azole antifungal agents and/or echinocandins rather than conventional amphotericin B or liposomal amphotericin B, if equal therapeutic efficacy can be assumed. (1A)

3. Other methods of prevention of AKI in the critically ill
   
a. We suggest not using N-acetylcysteine (NAC) to prevent AKI in critically ill patients with hypotension. (2D)

b. We recommend not using N-acetylcysteine (NAC) to prevent post-surgical AKI. (1A)

c. We suggest not using bicarbonate in patients undergoing cardiac surgery with cardiopulmonary bypass with the intent of preventing AKI. (2A)

d. We suggest not selecting off pump coronary artery bypass surgery in preference to the same surgery using cardiopulmonary bypass solely for the purpose of reducing peri-operative AKI or the need for RRT. (2C)
UNGRADED SUGGESTIONS FOR CLINICAL CARE

- We suggest considering both the potential advantages of early aminoglycoside therapy and the limited early risk of aminoglycoside nephrotoxicity when choosing an agent for the initial treatment of infections where aminoglycoside-sensitive organisms may be responsible (Ungraded).

IMPLEMENTATION AND AUDIT

The implementation of these guidelines cannot be easily audited because it involves different patients in different clinical settings. Point prevalence studies of the use of intravenous N-acetylcysteine and bicarbonate in patients receiving cardiac surgery may be possible.

BACKGROUND

Aminoglycoside antimicrobial agents are broad spectrum antibiotics that are widely used, they are effective against multiple Gram-negative and some selected Gram-positive bacterial pathogens. Aminoglycosides have associated dose-dependent and duration side effects which are well established and include nephrotoxicity, ototoxicity and muscular blockade. The KDIGO guideline highlights the risk of overdose of aminoglycosides and that AKI is a known complication.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 21 in the Appendix of the KDIGO guideline) (Kidney International Supplements 2 (2012); 2: 102-113). Additional key papers have been identified by the authors that were published after the KHA-CARI update search.

Databases searched: Medline, Central, Cochrane database of systematic reviews

Date of searches: June 2012

ADEQUACY OF KDIGO SEARCH STRATEGY

The search strategy and evidence provided by KDIGO was comprehensive and included some important randomised controlled trials (RCTs). A number of systematic reviews and RCTs have subsequently been identified in the updated search by KHA-CARI and included in this update.
APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO guidelines are generally applicable to Australia. However, they have been modified in light of recent evidence regarding the use of echinocandins and bicarbonate.

1. PREVENTION OF AKI AND AMPHOTERICIN-ASSOCIATED AKI

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI as part of the adaptation process.

a. After initial therapy, we suggest using less nephrotoxic therapeutic alternatives when available and still appropriate. (2B)

Aminoglycosides are potent antibiotics that have been in use for decades with little emergence of resistance. The risk of AKI is a well-known complication of aminoglycosides and its renal toxicity is related to a number of factors including its dose and duration of administration. This suggests that aminoglycoside can be used early and for a short period of time (e.g. immediate empirical treatment prior to cultures being available) until the offending organism has been identified and other less toxic antibiotics can be used safely and effectively. This approach maximises the potential benefits of aminoglycosides (broad Gram negative organism cover and synergy with beta-lactam antibiotics) and minimises the risks of nephrotoxicity, which are accumulation dependent [1,2].

b. In patients with normal kidney function and in a steady state (stable serum creatinine), we recommend administering aminoglycosides as a single daily dose rather than as multiple doses (1A).

Aminoglycosides are potent antibiotics that have been in use for decades with little emergence of resistance. The risk of AKI is a well-known complication of aminoglycosides and due to accumulation. This suggests that they can be used early and for a short period of time until the offending organism has been identified and other less toxic antibiotics can be used safely and effectively. Single daily dosage is pharmacokinetically logical and optimizes blood level and may minimise toxicity. It is also practically much easier to deliver [3-5].

c. When aminoglycosides are given in multiple daily doses for more than 24 hours, we recommend monitoring of aminoglycoside levels (1A)
The metabolism and volume of distribution of aminoglycosides can vary greatly and monitoring drug levels can help achieve the desired peak and trough levels and help prevent accumulation or toxicity [6-7].

d. When single daily doses are used for more than 48 hours, we suggest monitoring of aminoglycoside drug levels (2C)

The metabolism and volume of distribution of aminoglycosides can vary greatly and monitoring carries risks. It can help achieve the desired peak and trough levels and help prevent accumulation or toxicity. Although single daily dosing is associated with ease of administration, in critically ill patients and in patients with chronic kidney disease, accumulation is possible and may be likely after the second dose and it is safer to monitor levels in such patients [6-7].

e. When feasible, suitable and desirable to achieve high local concentrations, we suggest using topical or local (e.g. aerosol delivery, antibiotic administration into joint) applications of aminoglycosides rather than IV application (2B)

Studies have shown that topical aminoglycoside can be effective in achieving high concentration in situ and also that aerosols containing aminoglycosides can be used to effectively treat cystic fibrosis patients with gram negative lung infections. In such patients local therapy logically decreases the risk of AKI by decreasing systemic exposure [8-10].

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

Amphotericin B is highly nephrotoxic. Lipid preparations have been shown to be less nephrotoxic in multiple RCTs. Although their cost is higher, in developed countries their use has become the standard of care [11, 12].

g. In the treatment of systemic fungal infections or relevant parasitic infections, we recommend using azole antifungal agents and/or echinocandins rather than conventional amphotericin B or liposomal amphotericin B, if equal therapeutic efficacy can be assumed. (1A)

Although liposomal amphotericin B is less nephrotoxic than conventional amphotericin B, it is more nephrotoxic than azole antifungals and echinocandins. In particular for empirical treatment of patients with suspected systemic fungal infections, caspofungin has been shown to be therapeutically equivalent and less nephrotoxic in a large multicentre RCT and of equivalent cost on economic evaluation [13-14].
2. OTHER METHODS OF PREVENTION OF AKI IN THE CRITICALLY ILL

BACKGROUND

Multiple ancillary interventions have been applied and may continue to be applied to the care of patients with or at risk of AKI. These interventions need to be considered when formulating general guidelines for the management of these patients.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI as part of the adaptation process.

a. We suggest not selecting off pump coronary artery bypass (CAB) surgery in preference to the same surgery using cardiopulmonary bypass solely for the purpose of reducing peri-operative AKI or the need for RRT. (2C)

Although indirect observational data suggest that off pump CAB surgery may be associated with decreased risk of AKI, RCTs do not confirm these findings or show limited effects. Moreover, off pump CAB surgery may carry additional risks. Accordingly, the choice of which technique to use should not be conditioned by perceived renal risks or advantages but rather by other more important factors such as the anatomy of the lesions and the perceived risks of aortic cannulation induced thromboembolic events and graft occlusion [15-17].

b. We suggest not using N-acetylcysteine (NAC) to prevent AKI in critically ill patients with hypotension. (2D)

Multiple studies have attempted to demonstrate a possible beneficial kidney-protective effect of NAC administration in critically ill patients. However, outside of the possible effects in radio contrast nephropathy, insufficient data exist to support its use in these patients [18].

c. We recommend not using N-acetylcysteine (NAC) to prevent postsurgical AKI. (1A)

Several studies have investigated the role of NAC as renal protection in patients undergoing cardiac surgery. None of the studies found evidence of renal protection. Similar findings were reported for abdominal surgery [19-23].

d. We suggest not using bicarbonate in patients undergoing cardiac surgery with cardiopulmonary bypass with the intent of preventing AKI. (2A)
An initial single centre study suggested that bicarbonate might be protective to the kidney in patients undergoing open heart surgery with cardiopulmonary bypass. However in a much larger multicenter study, these initial observations were not confirmed [24, 25].

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcome Quality Initiative (2013):
No change to KDIGO guidelines

UK Renal Association (2011):
No change to KDIGO guidelines

Canadian Society of Nephrology (2013): [26]
Canadian Society of Nephrology commentary agrees with the 2012 KDIGO AKI recommendations on prevention of AKI.

European Renal Best Practice Guidelines (2012): [27]

2.2.5 Prevention of AKI and amphotericin-associated AKI

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

2.2.5.2 We recommend that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single-dose daily rather than multiple-dose daily treatment regimens. (1B)
An exception to this recommendation can be patients with endocarditis, where inconsistent evidence on non-inferiority of single versus multiple daily dosing is reported. (1D)

2.2.5.3 We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24 h. (1A)

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

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

2.2.5.6 We recommend that patients receiving whatever formulation of amphotericin B should receive adequate sodium loading and potassium supplementation (1B).
We suggest balancing the presumed lower nephrotoxicity of lipid formulations against their higher cost. (2D)
2.2.5.7 We suggest balancing the need for adequate antimycotic treatment against the potential risk of nephrotoxicity in selecting the most suitable antimycotic agent. (Ungraded statement)

**SUGGESTIONS FOR FUTURE RESEARCH**

Future research should continue to explore novel prophylactic interventions aimed at minimising the risk of AKI in all patients, including in patients receiving cardiac surgery. The development of less nephrotoxic and effective antifungal agents needs to be encouraged. Finally, the assessment of whether long-term aminoglycoside therapy is needed in any condition would be desirable.

**CONFLICT OF INTEREST**

R Bellomo has received consultancy fees from Gambro Pty Ltd & Baxter Pty Ltd, for consultation regarding acute dialysis and fluid market. An Honorarium has been provided by BBraun Pty Ltd for consultation regarding fluid management, Gambro Pty Ltd additionally paid for R Bellomo travel to a dialysis meeting.
REFERENCES


