Surgical prophylaxis with gentamicin and acute kidney injury: a systematic review and meta-analysis

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Background: Gentamicin has been increasingly used instead of cephalosporins for surgical prophylaxis in an attempt to reduce the rate of "*Clostridium difficile*" infection. There are limited data regarding nephrotoxicity related to gentamicin in these patients.

Methods: We have conducted a systematic review and meta-analysis to evaluate the risk of acute kidney injury (AKI) in gentamicin-containing surgical prophylactic regimens, compared to regimens without gentamicin, in several types of surgery. Electronic searches were performed using PubMed and Embase, including terms for "AKI, gentamicin, and surgical prophylaxis" with and without MeSH/EMTREE functions. Statistical analysis was then performed using a random-effect model; risk ratios (RR), risk differences (RD) and heterogeneity (I^2) were calculated. Funnel plot was used for assessment of publication bias.

Results: Eleven studies with fifteen cohorts with 18,354 patients were included in the analysis. Subgroup analysis was performed according to surgery type. We have found that antibiotic prophylaxis with gentamicin containing regimen has significant risk for developing postoperative AKI in orthopedic surgery (RR 2.99; 95% CI: 1.84, 4.88). The results were inconclusive in other types of surgery. Funnel plot indicates potential publication bias.

Conclusions: Gentamicin-induced AKI is significant in patients undergoing orthopedic surgery. Physicians should consider risks and benefits of using this regimen in individual patients.

Keywords: Acute kidney injury (AKI); antibiotic prophylaxis; surgical prophylaxis; gentamicin

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Introduction

Surgical site infections accounted for 17% of healthcare associated infections and were found in 2–5% of patients undergoing inpatient surgery. These infections are estimated to cost up to $10 billion annually (1). Prophylactic antibiotics have been found to reduce the incidence of postoperative wound infections (2). According to clinical practice guidelines for antimicrobial prophylaxis in surgery, antimicrobials from the cephalosporin class are recommended as the first-line agents for the majority of procedures. However, studies have found that cephalosporins are among the common antimicrobials associated with *Clostridium difficile*-associated diarrhea (CDAD). Other agents associated with CDAD include clindamycin, fluoroquinolones, and extended-spectrum penicillins (3). Given this concern over the increasing incidence of CDAD, alternative regimens with decreased

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risk of CDAD, including ones containing gentamicin, have been increasingly used in current practice (2,4).

Gentamicin has been in use for more than 40 years and remains popular not only because its effectiveness but also because of its low rate of antimicrobial resistance, low cost, and low risk of CDAD (5). It belongs to the aminoglycoside class of drugs; its main bactericidal mechanism is inhibition of protein synthesis in susceptible organisms. Gentamicin has activity against a wide range of aerobic gram-negative bacteria, including *Escherichia coli*, Proteus species, *Pseudomonas aeruginosa*, species of the Klebsiella-Enterobacter-Serratia group, and Citrobacter species. It is also active against methicillin-susceptible *Staphylococcus aureus* (MSSA) but not methicillin-resistant *Staphylococcus aureus* (MRSA) or Streptococci (6).

The major disadvantages of gentamicin are its requirement for drug level monitoring and the risks of ototoxicity and nephrotoxicity. The pathogenesis of gentamicin-induced nephrotoxicity is related to tubular necrosis and glomerular injury through the induction of mesangial cell contraction, proliferation, and apoptosis.

Studies have shown that the rate of nephrotoxicity secondary to therapeutic use of gentamicin is between 8% and 26%. Patients at risk include patients with elevated gentamicin trough level, elevated area under the plasma drug concentration-time curve, prolonged duration of treatment, concomitant use of vancomycin, flucloxacillin or furosemide, elevated baseline serum creatinine, or volume depletion (5). Most data on gentamicin-induced nephrotoxicity have been obtained in patients who had received therapeutic doses of this drug. The data on kidney injury associated with prophylactic use of gentamicin have been reported in small studies. We, therefore, wanted to systematically review the association between the risk of acute kidney injury (AKI) and prophylactic use of gentamicin in the setting of different types of surgery in adult patients.

Methods

Identification of studies

Two main authors performed electronic searches in January 2016 on PubMed and Embase. First, MeSH terms (PubMed) and Emtree terms (Embase) were used to search for available articles. Subsequently, to broaden the search results, the authors repeated the search without using the MeSH/EMTREE functions. The search strategy included terms for AKI, gentamicin, and surgical prophylaxis. The authors then reviewed all titles and abstracts for subsequent selection of articles.

Inclusion and exclusion criteria

Studies were included if: the incidence of AKI was reported; a control group was included; they were published in English.

Studies were excluded if: the study did not report all incidence of AKI; the study was performed in pediatric patients; the study was published in languages other than English; a full text was not available. There were no limitations in the publication dates.

Data extraction

All titles and abstracts were reviewed by two reviewers independently. In abstracts which information was insufficient, the full text was also reviewed. Any discrepancies were resolved through consensus.

Quality assessment

All included studies are either prospective or retrospective cohort studies. No randomized controlled trials were found during the electronic search. We used the risk of bias assessment tool for observational studies recommended in GRADE working group to assess the quality of each study. The assessment tool addressed the following four aspects: failure to develop and apply appropriate eligibility criteria, flawed measurement of both exposure and outcome, failure to adequately control confounding and incomplete or inadequately short follow-up (7). The risk of bias for each domain was categorized into three levels: low, high and unclear.

Statistical analysis

The authors used the Review Manager 5.3 software (The Cochrane Collaboration, Oxford, UK) for data analysis as well as quality of evidence assessment. The risk ratios (RR), risk differences (RD) and 95% confidence intervals were calculated using a random-effect model. Pooled RR was then calculated and Forest plots were drawn. I^2 was calculated to measure heterogeneity across studies.

Funnel plot was utilized to allow for visual assessment of publication bias.

Since the included studies reported the incidence of AKI related to gentamicin-containing surgical prophylactic regimen in several types of surgery, subgroup analysis was performed according to the types of surgery (orthopedic, cardiac, and urologic surgery).

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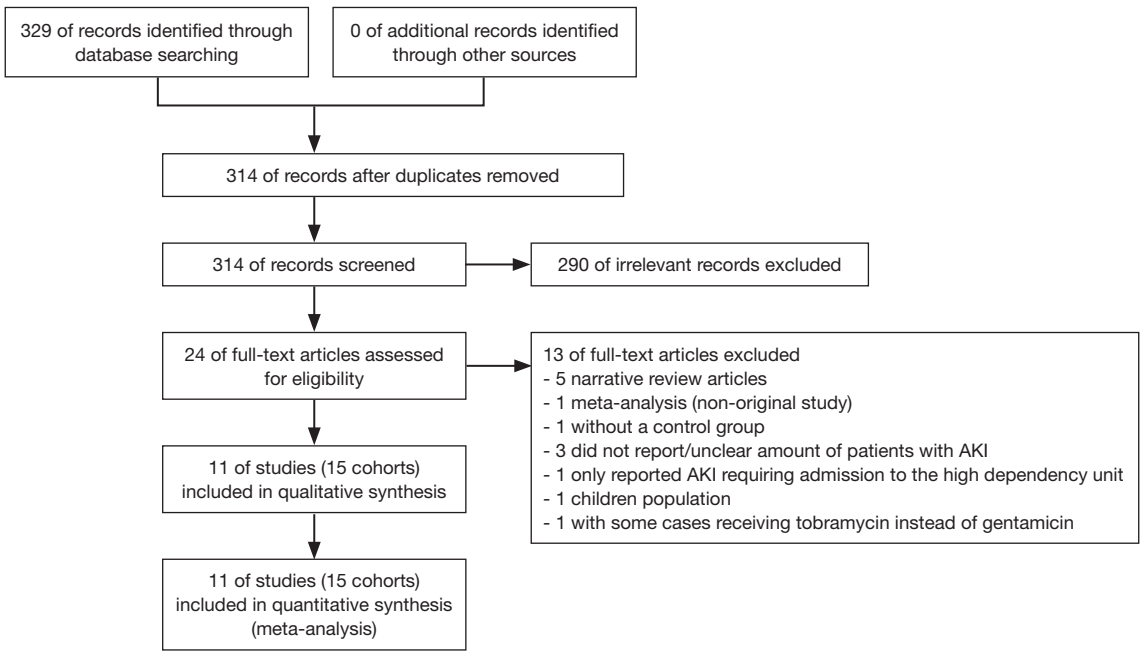

Figure 1 Demonstrates the flow diagram of the study selection process.

Results

Three hundred and fourteen articles were identified using our search strategy. Two hundred and ninety studies were excluded after title and abstract review as they were not relevant to the study question. The authors then reviewed the remaining 24 studies in full length to evaluate their study designs, patient cohorts, and outcomes. After full-length review, 13 studies were excluded as they met exclusion criteria. Finally, 11 studies (15 cohorts) with 18,354 patients were included in the statistical analysis. *Figure 1* demonstrates the flow diagram of the study selection process. *Table 1* contains the characteristics of the included studies. The study conducted by Bell *et al.* consisted of 5 cohorts, with each cohort representing one surgical subspecialty (15). There were 4 study groups in each of the studies done by Challagundla *et al.* (9) and Schneider *et al.* (8), so we coupled each 2 study groups together in order to simplify the comparisons.

Figure 2 demonstrates the analysis with all studies included, regardless of surgery type. The pooled RR of all studies regardless of surgery type was found to be 1.66 (1.32, 2.09), whereas the pooled RD of this analysis was found to be 0.05 (0.03, 0.07). The calculated heterogeneity value (I^2) was 75%.

Figure 3 demonstrates the subgroup analysis according to surgery type. The pooled RR of orthopedic surgery only was found to be 2.99 (1.84, 4.88), whereas the pooled RD of this analysis was found to be 0.07 (0.04, 0.11) with I^2 of 61%. The pooled RR of cardiac surgery only was found to be 1.29 (0.77, 2.17), whereas the pooled RD of this analysis was found to be 0.05 (–0.03, 0.13) with I^2 of 83%. The pooled RR of urologic surgery only was not applicable as one study (13) had zero AKI events thus RR was not estimable.

Figure 4 illustrates the funnel plot of all studies included in this meta-analysis which is used to visually assess the publication bias. *Figure 5* and *Figure 6* show the risk of bias assessment. These trials had methodological limitations mainly in failure to control confounding factors since all of them were observational studies and most did not take possible confounding factors into account i.e., pre- or perioperative medications, perioperative hypotension or blood loss. One study had high risk of bias in terms of appropriateness of eligibility criteria due to lack of exclusion criteria (11). In another study, only 47% and 52% of patients undergoing gynecologic and urologic operations respectively, were able to document postoperative renal function which raised a major concern over incomplete follow-up (15).

Discussion

The included studies reported the incidence of AKI

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Table 1 Characteristics and descriptions of the included studies

Study ID	Gentamicin-containing therapy			Control group			Mean age (range/SD)	Subjects/ operations
	Agents	AKI	Total	Agents	AKI	Total	(Gentamicin *vs.* control)	
Schneider 1996 (8)								
A *vs.* B	Gentamicin 1.5 mg/kg ×4 + flucloxacillin 3 g then 1 g ×4	28	91	Cephalothin 3 g then 1 g ×4	9	72	62 (7) *vs.* 63 (7)	CABG
C *vs.* D	Gentamicin 1.5 mg/kg ×4 + flucloxacillin 3 g then 1 g ×4	4	57	Cephalothin 3 g then 1 g ×4	1	47	63 (9) *vs.* 64 (9)	CABG
Solgaard 2000 (10)	Dicloxacillin 2 g + gentamicin 240 mg	17	87	No antibiotic prophylaxis	4	76	82 *vs.* 81	Intertrochanteric hip fracture
Craig 2012 (11)	Coamoxiclav 1.5 g + gentamicin 240 mg	8	100	Cefuroxime 1.5 g ×3	5	100	80.3 *vs.* 83.6	Fracture neck of femur
Challagundla 2012 (9)								
Cef1 *vs.* LD	Flucloxacillin 1 g ×4 + gentamicin 120-160 mg	10	46	Cefuroxime 1.5 g then 750 mg ×2	4	48	69.9 [50–85] *vs.* 71.1 [52–86]	THR or TKR
Cef2 *vs.* HD	Flucloxacillin 2 g ×4 + gentamicin 120–160 mg	27	52	Cefuroxime 1.5 g then 750 mg ×2	7	52	71.1 [47–95] *vs.* 69.7 [39–85]	THR or TKR
White 2013 (12)	Flucloxacin 1 g ×2 (or teicoplanin 400 mg ×1–2) + gentamicin 2 mg/kg	57	1,695	Cefuroxime 1.5 g × 3–5 (or vancomycin 1.5 g ×4 if resternotomy or MRSA risk or PCN allergy)	74	1,725	64.8 (10.8) *vs.* 64.3 (10.9)	Cardiac surgery
Abboud 2013 (13)	Gentamicin 2 mg/kg ×2 + cefuroxime 1.5 g ×1 then 750 mg ×4	0	21	Cefuroxime 1.5 g ×1 then 750 mg ×4	0	24	47.5 *vs.* 46.4	Renal transplant
Ross 2013 (14)	Gentamicin 4 mg/kg + flucloxacillin 1 g (or clindamycin 600 mg if PCN allergy) up to ×4	9	149	Cefuroxime 1.5 g then 750 mg up to ×3	2	124	72.5 *vs.* 72.3	THR or TKR
Bell 2014 (15)								
Ortho	Flucloxacillin 1 g ×2 + gentamicin 4 mg/kg	361	3,372	Cefuroxime 1.5 g	186	2,981	70.7 (13.9) *vs.* 71.2 (13.5)	Orthopedics
Uro	Gentamicin 4 mg/kg	63	402	Coamoxiclav 1.2 g	49	421	70.0 (13.1) *vs.* 71.4 (12.5)	Urology
Vas	Flucloxacillin 1 g ×2 + metronidazole 500 mg +/– gentamicin 4 mg/kg	91	362	Coamoxiclav 1.2 g	83	358	69.0 (12.9) *vs.* 70.0 (11.3)	Vascular surgery
GI	Metronidazole 500 mg + gentamicin 4 mg/kg	204	1,672	Coamoxiclav 1.2 g	118	1,599	61.8 (16.3) *vs.* 62.1 (15.9)	Gastrointestinal surgery
GYN	Metronidazole 500 mg + gentamicin 4 mg/kg	9	227	Coamoxiclav 1.2 g	8	176	53.5 (13.7) *vs.* 54.9 (13.7)	Gynecology
Craxford 2014 (16)	Gentamicin 3 mg/kg + flucloxacillin 2 g then 1 g ×3	16	200	Cefuroxime 1.5 g then 750 mg ×2	2	200	68.2 *vs.* 68.3	THR or TKR
Bailey 2014 (4)	Flucloxacillin 2 g + a height- & gender-determined dose of gentamicin	24	254	Cefuroxime 1.5 g	4	238	64.4 *vs.* 66.1	THR or TKR
Nielsen 2014 (17)	Gentamicin 240 mg + teicoplanin 400 mg + dicloxacillin 1 g ×2	145	668	Teicoplanin 400 mg + dicloxacillin 1 g ×2	110	668	64.1 (13.8) *vs.* 64.0 (13.8)	Cardiac surgery

MRSA, methicillin-resistant Staphylococcus aureus; PCN, penicillin; CABG, coronary artery bypass graft; THR, total hip replacement; TKR, total knee replacement.

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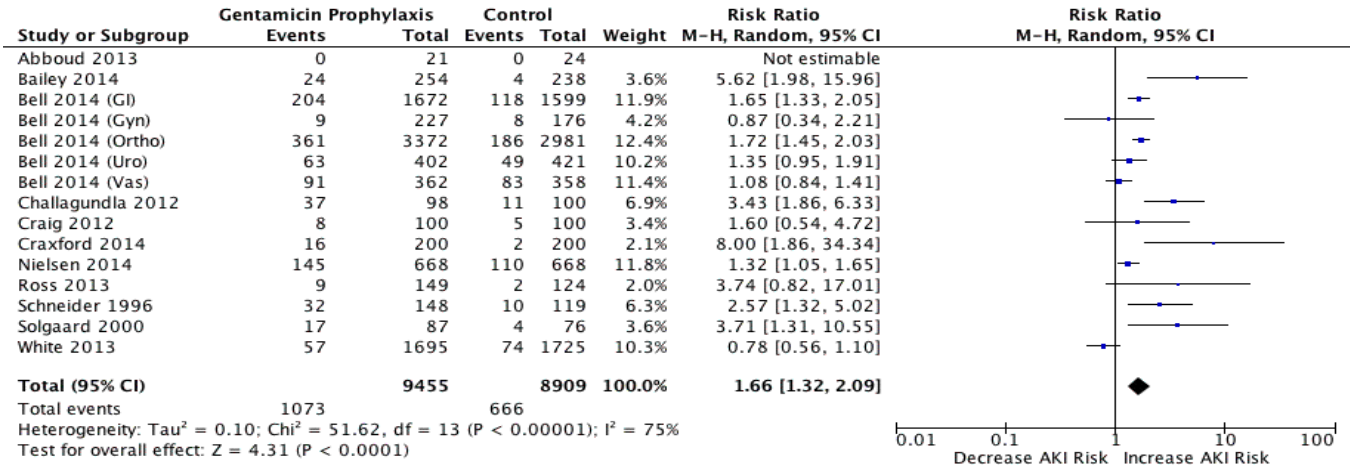

Figure 2 Demonstrates the analysis with all studies included, regardless of surgery type.

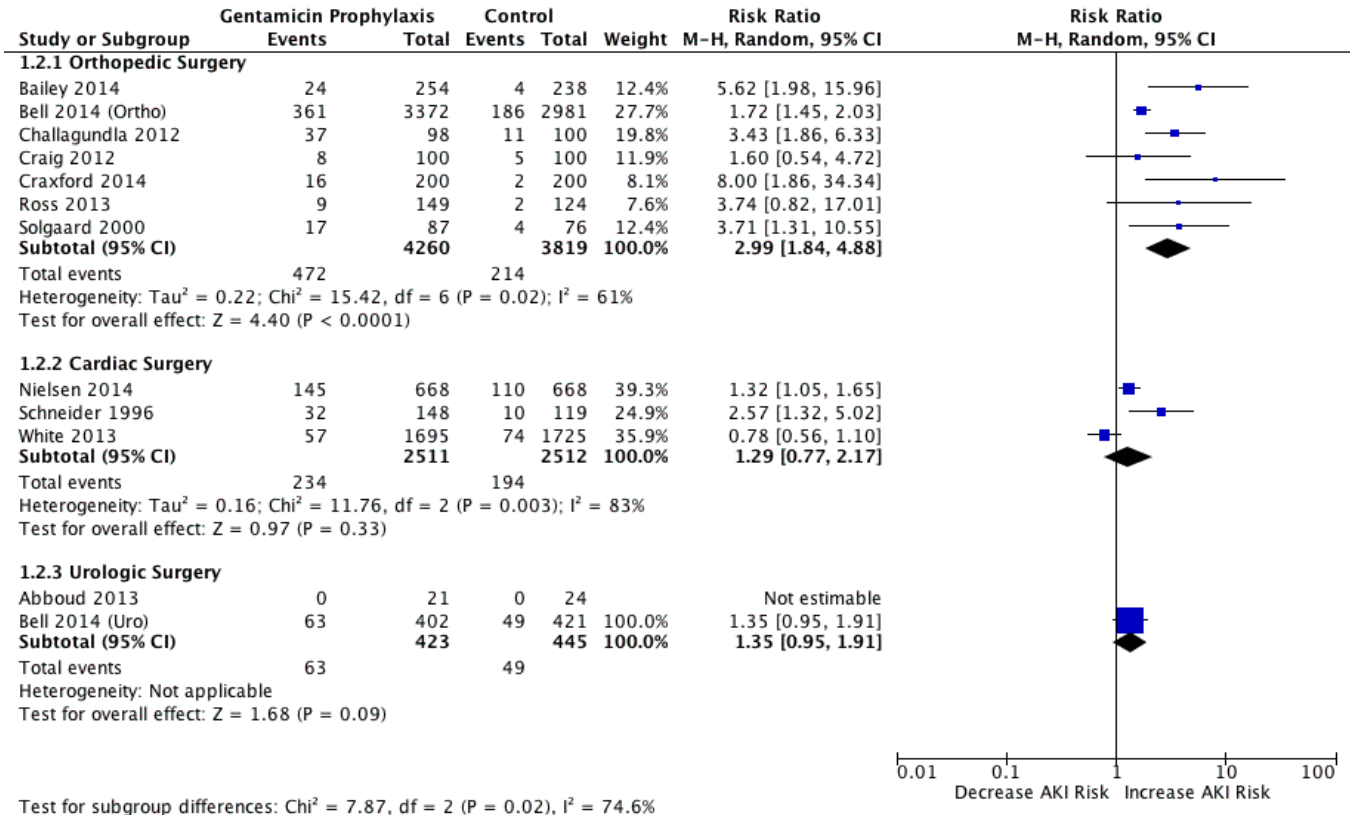

Figure 3 Demonstrates the subgroup analysis according to surgery type.

secondary to gentamicin prophylaxis in several types of surgery. Studies in orthopedic surgery were the most frequent (7 cohorts). The characteristics of the gentamicin-containing arm and the control arm were the most homogeneous in the orthopedic studies, with penicillin antibiotic (mostly flucloxacillin) and gentamicin in the exposure arm and cefuroxime in the control arm, except for one study (10) in which the control group used no antibiotic

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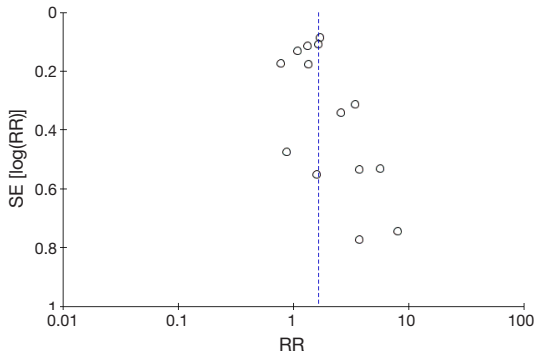

Figure 4 Illustrates the funnel plot of all studies included in this meta-analysis. RR, risk ratio.

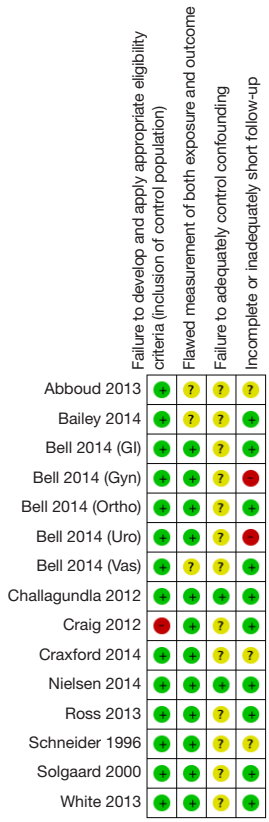

Figure 5 Demonstrates the result of risk of bias assessment of each study.

prophylaxis.

The second most frequent type of surgery in the included studies was cardiac surgery. With three cohorts, the characteristics of the gentamicin-containing arm and the control arm were less homogeneous compared to the orthopedic surgery studies. Gentamicin and flucloxacillin were the main regimen in the exposure arm, whereas the control arm mainly used beta-lactam antibiotics (with or without teicoplanin).

Two urologic studies were included here; the exposure arm and the control arm were not as homogeneous as in the orthopedic studies.

It is noteworthy that dosing, frequency, and timing of antibiotic administrations were different across studies. Most studies defined AKI as a rise in serum creatinine of greater than 50% of the baseline (4,9,11,14,16), while two studies used the aforementioned criteria or an increase in serum creatinine of >0.3 mg/dl (or >26.5 μmol/L) (17), and >26.4 μmol/L (15). One study not only defined AKI as an increase of >50% in the serum creatinine but the serum creatinine value must also be >120 μmol/L on the first postoperative day (8). Solgaard *et al.* defined a reversible nephrotoxicity as an increase of serum creatinine above the upper standard 95% limit, and irreversible kidney damage as uremia leading to death (10). White *et al.* defined renal impairment as serum creatinine >200 μmol/L (or 2.26 mg/dL) or requirement for renal replacement therapy (12). Abboud *et al.* did not define AKI in their study, however, the investigated patients did not have worsening renal function in that study—most likely because the study was done in renal transplantation (13).

Most studies reported the mean preoperative creatinine values which ranged between 71–98 μmol/L in the control groups and 65–98 μmol/L in the gentamicin groups. Bailey *et al.* excluded patients with baseline glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 (4). Craxford *et al.* also excluded patients with abnormal baseline renal function although the cutoff GFR was not mentioned (16). Five studies did not mention the use or requirement of renal replacement therapy. The requirement rates of renal

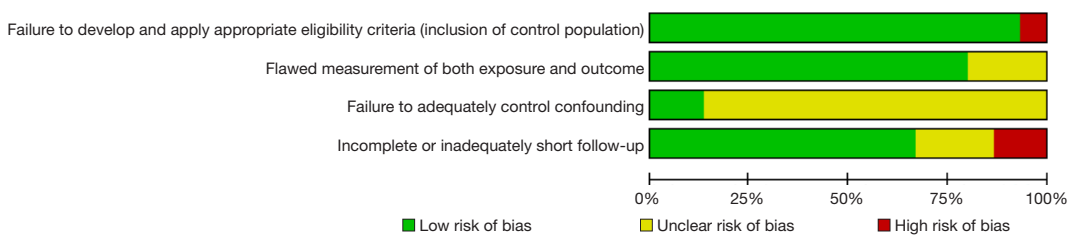

Figure 6 Demonstrates the pooled risk of bias assessment of studies included in this meta-analysis.

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replacement therapy ranged between 0–2.2% in the control groups and 0–2.88% in the gentamicin groups.

Our meta-analysis showed that there was a significant increase in risk of AKI related to gentamicin therapy used as a surgical prophylaxis. The analysis of orthopedic studies had the largest effect size and the greatest degree of homogeneity. Gentamicin and penicillin-antibiotic therapy as a surgical prophylaxis carries more risk for the development of AKI for patients undergoing orthopedic surgery as compared to cefuroxime therapy. In a subtype of orthopedic surgery, Craxford *et al.* showed that total knee replacement (TKR) had a significantly higher rate of kidney injury than total hip replacement (THR) (16). They suggested that using pneumatic tourniquet in TKR produced ischemic metabolites and further increased risk of AKI when combined with gentamicin use.

Although, gentamicin-containing regimen was associated with higher risk of developing AKI, the degree and severity of AKI in these studies were mild and transient. Bell *et al.* showed that the majority of affected patients had transient stage1 AKI by Kidney Disease Improving Global Outcomes (KDIGO) classification and the median length of stay in patients with AKI was 8 days compared to 7 days in patients without AKI (15).

Our meta-analysis showed that gentamicin-containing therapy slightly increased risk of AKI compared to the control group treated with beta-lactam antibiotics (with or without teicoplanin) in cardiac surgery patients, but this did not reach statistical significance. In one cardiac surgery study, gentamicin had a protective effect compared to cefuroxime. The author suggested that gentamicin might protect against perioperative infection, but this did not reach statistical significance (12). Gentamicin-containing therapy as a surgical prophylaxis in urologic surgery also had an increased risk of AKI compared to the beta-lactam prophylaxis but this did not reach statistical significance.

The combination of gentamicin and flucloxacillin was used in most studies, and these drugs had a significant increase in risk of AKI. However, it is difficult to determine whether gentamicin, flucloxacillin, or both increase the risk of AKI development. Gentamicin is a common cause of tubular injury, whereas flucloxacillin is an uncommon cause of interstitial nephritis. Challagundla *et al.* reported a significant decrease in the incidence of AKI after reducing the dose of flucloxacillin from 8 to 4 g (9).

AKI in postsurgical patients is probably multifactorial (hypotension, medication, infection, etc.). It may be hard to blame one factor, but gentamicin has definite nephrotoxicity and could have a role in patients who are at risk for AKI and prolong the renal function recovery period. Despite the increased risk of AKI in gentamicin-containing regimens compared to beta-lactam regimens, the benefits of gentamicin over beta-lactam antibiotics need to be considered. The rate of *Clostridium difficile* infection with the use of beta-lactam antibiotics is an important concern. Further analysis of this outcome should be conducted in the future.

Limitations exist for our study. First, all studies included were retrospective/prospective cohort studies which could have confounding factors affecting the results. A randomized controlled trial could eliminate these biases. Second, the heterogeneity of regimen across studies (types of regimen and dosage) might lead to difficulty in interpretation. Additionally, the calculated heterogeneity values (I^2) in all analysis were considered high. Third, the definition of AKI, the change in creatinine, and length of creatinine monitoring varied among studies. Fourth, the sample sizes of cardiac and urologic studies were not large enough to reflect any statistical significance. Finally, the asymmetrical funnel plot may suggest some degree of publication bias.

Conclusions

Our meta-analysis demonstrates that antibiotic prophylaxis with gentamicin containing regimen has significant risk for developing postoperative AKI in orthopedic surgery, and therefore should be avoided if possible especially in patients with pre-existing risks of AKI. The results were inconclusive in other types of surgery. Physicians should consider risks and benefits of using this regimen in individual patients. To confirm the outcome, prospective randomized control trial needs to be conducted in the future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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