Original Article
Prophylactic use of gentamicin/flucloxacillin versus cefuroxime in surgery: a meta analysis of clinical studies

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Abstract: Purpose: To conduct meta-analyses of all available studies comparing efficacies of prophylactic cefuroxime and prophylactic gentamicin/flucloxacillin (Gen/Flu) in preventing post-operative wound infections and their association with risks of Clostridium difficile infections and post-operative renal impairment. Methods: Published studies including both prophylactic cefuroxime and prophylactic Gen/Flu used in surgery were included for meta analysis. Outcomes were analyzed using a random-effect model or a fixed-effect model depending on the heterogeneity across the included studies. Results: Gen/Flu prophylaxis showed similar efficacy as cefuroxime prophylaxis in preventing post-operative wound infections and was associated with a significantly lower risk of Clostridium difficile infection, but it was associated with a higher risk of post-operative renal impairment, especially in orthopedic surgery. Conclusions: Our findings that Gen/Flu prophylaxis was associated with significantly higher risk of post-operative renal impairment dictate that benefits and risks of Gen/Flu prophylaxis should be carefully assessed and balanced, and each patient should be evaluated individually so that a proper antibiotic prophylaxis regimen could be chosen.

Keywords: Cefuroxime, gentamicin, flucloxacillin, prophylaxis, surgery, infection, meta-analysis

Introduction

Prophylactic antibiotics have been shown to reduce the incidence of post-operative wound infection and are routinely administered to patients undergoing surgery. [1, 2]. Cephalosporin antibiotics such as cefuroxime have often been used because of their broad spectrum [3]. However, their use has been associated with increased risk of Clostridium difficile infection [4]. As a result, in order to reduce rates of Clostridium difficile infection, prophylactic gentamicin in combination with flucloxacillin has recently been widely used to replace prophylactic cefuroxime [2, 3, 5-8]. Gentamicin was chosen because it has good antibiotic activity against gram-negative bacteria and is also potent against Staphylococcus aureus, especially in combination with a beta-lactam antibiotic such as flucloxacillin [9]. Therefore, gentamicin in combination with flucloxacillin was considered proper prophylactic antibiotic regimen and is currently used by many surgical teams around the world.

Despite the advantage of the broad spectrum of antibacterial coverage provided by the combination of gentamicin and flucloxacillin, there are concerns about the risk of renal impairment associated with their use as prophylactic antibiotics because both gentamicin and flucloxacillin are known to be nephrotoxic in some patients [10, 11]. Coincidentally, there are reports of a probable increase in the incidence of acute kidney injury (AKI) after arthroplasty and of nephrotoxicity associated with gentamicin and dicloxacillin in 163 patients with intertrochanteric hip fracture [12, 13]. It remains inconsistent whether prophylactic gentamicin and flucloxacillin is associated with an increased risk...
of renal impairment compared to prophylactic cefuroxime [2, 3, 5, 6, 8].

There has been no meta-analysis comparing the efficacies of prophylactic cefuroxime and prophylactic gentamicin and flucloxacillin (Gen/Flu) in preventing post-operative wound infections, and their association with risk of Clostridium difficile infection and renal impairment. The main aim of the current study was to perform meta-analyses of all available studies comparing the efficacies of prophylactic cefuroxime and prophylactic Gen/Flu in preventing post-operative wound infections and their association with the risks of Clostridium difficile infections and post-operative renal impairment in order to assess the relative advantages and disadvantages of prophylactic Gen/Flu when compared with prophylactic cefuroxime, such assessment could potentially help surgeons choose a proper prophylactic antibiotic regimen based on different patients' needs.

Materials and methods

Search strategy


Inclusion and exclusion criteria

Published studies (criterion 1) reporting efficacies of prophylactic cefuroxime and prophylactic Gen/Flu in preventing post-operative wound infections, or their associations with the risks of Clostridium difficile infection or renal impairment (criterion 2) on all ethnic groups were all considered eligible for inclusion in the meta-analyses. Reviews and meeting abstracts were excluded.

Two of the participating authors (JZ and JF) selected studies for possible inclusion in the current meta-analyses independently by reviewing titles and abstracts identified from the search independently followed by examining independently the full text of all studies considered to be possibly relevant. Any disagreement regarding whether a particular study should be included was resolved by discussion participated by all authors followed by a consensus reached by all.

Data extraction

Two authors (JF and XL) extracted data independently and any disagreement between the two authors were resolved by discussion. The following information was extracted: author(s), year of publication, methodology details such as sample size for both prophylactic cefuroxime and prophylactic Gen/Flu, diagnostic tools for renal impairment and Clostridium difficile infections whenever the information was available, types of post-operative wound infections, and sample characteristics including gender ratio, mean age and the numbers of patients having and not having post-operative wound infections, Clostridium difficile infections, and/or post-operative renal impairment in both groups whenever the information was available.

Quality of studies

Quality of each studies included in the current meta-analyses was assessed by two methods. First, we evaluated the adequacy of each study in three key areas: methodological, clinical and statistical; we then screened each study with the Newcastle-Ottawa Scale [14].

Statistical analysis

The efficacies of prophylactic cefuroxime and prophylactic Gen/Flu in preventing post-operative wound infections, and their associations with the risk of Clostridium difficile infection and post-operative renal impairment were compared by calculating their respective Odds Ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) as the effect size measurement for the analyses. The ORs with their corresponding 95% CIs were calculated with the Cochrane Review Manager (RevMan, version 5.2). Because heterogeneity among the studies was expected, pooled ORs with their corresponding 95% CIs were calculated first using a random-effect model that assumes a genuine diversity in the results of the included
Prophylactic use of gen/flu vs. cefuroxime in surgery and therefore incorporates a between-study variance into the calculation [15]. Z test was used to assess the statistical significance of the pooled ORs, further, between-studies heterogeneity was assessed using chi-square (χ²) test based on Cochran Q statistic [16]. I² index was used to quantify the between-studies heterogeneity, wherein a I² value around 25%, 50% or 75% indicated low, moderate or large heterogeneity, respectively [17]. When there was no between-studies heterogeneity, data was analyzed using a fixed-effect model. A P value <0.05 was considered to be statistically significant except for the Q statistics wherein a P<0.10 was considered to be statistically significant.

Sub-population analyses were performed for orthopedic surgery on efficacies of prophylactic cefuroxime and prophylactic Gen/Flu in preventing post-operative wound infections, and their associations with the risk of Clostridium difficile infection and post-operative renal impairment. Sensitivity analysis examining the effect of excluding a particular study was also performed which used a stepwise process, wherein a single study included in the meta-analysis was excluded each time to assess its influence on the pooled OR. Funnel plots were used to assess publication bias in the meta-analyses.

Results
Eligible studies and study characteristics

Figure 1 described the search process flow and results. From a total of 15 potentially eligible studies, 9 were excluded because they were not relevant to the study questions, [18-24] or review [25]. From the 7 studies eligible for inclusion, 1 was excluded because no detailed numbers of patients having or not having post-operative wound infection, Clostridium difficile infections, or post-operative renal impairment were given [26]. A total of 6 studies were included in the current meta-analyses and their data were extracted, [2, 3, 5-8] among them, 4 were included in the meta-analysis of prophylactic antibiotic regimens and post-operative wound infections, [2, 3, 5, 7] were included in the meta-analysis of prophylactic antibiotic regimens and Clostridium difficile infections, [2, 3, 5, 7, 8] and 5 were included in the meta-analysis of prophylactic antibiotic regimens and post-operative renal impairment [2, 3, 5, 6, 8]. All eligible studies were of adequately high quality.

Table 1-4, including name of the first author, year of publication, sample sizes in each group (prophylactic cefuroxime and prophylactic Gen/Flu), gender ratio, mean age, numbers of subjects developing or not developing post-operative wound infections in each group (for the 4 studies included in the meta-analysis of prophylactic antibiotic regimens and post-operative wound infections), numbers of subjects developing or not developing Clostridium difficile infection in each group (for the 5 studies included in the meta-analysis of prophylactic antibiotic regimens and Clostridium difficile infection); and number of subjects developing or not developing post-operative renal impairment in each group (for the 5 studies included...
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Table 1. Characteristics of studies included in the meta-analyses

<table>
<thead>
<tr>
<th>First author</th>
<th>Subjects receiving prophylactic cefuroxime</th>
<th>Subjects receiving prophylactic gentamicin and flucloxacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total sample (N)</td>
<td>Male/Female</td>
</tr>
<tr>
<td>Al-Obaydi 2010 [7]</td>
<td>625 (231 in trauma group; and 394 in elective group)</td>
<td>196/429 (55/176 for trauma group; 141/253 for elective group)</td>
</tr>
<tr>
<td>Challagundla 2012 [5]</td>
<td>100</td>
<td>36/64</td>
</tr>
<tr>
<td>Craxford 2013 [3]</td>
<td>200 (100 total hip replacement [THR] and 100 total knee replacement [TKR])</td>
<td>-</td>
</tr>
<tr>
<td>Ross 2013 [6]</td>
<td>124 (74 for THR; 50 for TKR)</td>
<td>55/69</td>
</tr>
<tr>
<td>Vooght 2013 [8]</td>
<td>202</td>
<td>-</td>
</tr>
<tr>
<td>White 2013 [2]</td>
<td>1725</td>
<td>1275/450</td>
</tr>
</tbody>
</table>

Table 2. Studies included in the meta-analysis of prophylactic antibiotic regimens and post-operative wound infections

<table>
<thead>
<tr>
<th>First author</th>
<th>Subjects receiving prophylactic cefuroxime</th>
<th>Subjects receiving prophylactic gentamicin and flucloxacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects developing post-operative wound infections (N)</td>
<td>Number of subjects not developing post-operative wound infections (N)</td>
</tr>
<tr>
<td>Al-Obaydi 2010 [7]</td>
<td>12 (6 for trauma group; 6 for elective group)</td>
<td>613 (225 for trauma group; 388 for elective group)</td>
</tr>
<tr>
<td>Challagundla 2012 [5]</td>
<td>10 (all superficial wound infection)</td>
<td>90</td>
</tr>
<tr>
<td>Craxford 2013 [3]</td>
<td>3 (2 SSI and 1 RTT)</td>
<td>197</td>
</tr>
<tr>
<td>White 2013 [2]</td>
<td>56</td>
<td>1669</td>
</tr>
</tbody>
</table>
### Table 3. Studies included in the meta-analysis of prophylactic antibiotic regimens and Clostridium difficile infection

<table>
<thead>
<tr>
<th>First author</th>
<th>Subjects receiving prophylactic cefuroxime</th>
<th>Subjects receiving prophylactic gentamicin and flucloxacillin</th>
<th>P value</th>
<th>Diagnostic tool of Clostridium difficile infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Obaydi 2010 [2]</td>
<td>23 (19 for trauma group; 4 for elective group)</td>
<td>602 (212 for trauma group; 390 for elective group)</td>
<td>0.004 (0.02 for trauma group; 0.27 for elective group)</td>
<td>Examination of diarrhoeal faecal specimens</td>
</tr>
<tr>
<td>Challagundla 2012 [5]</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>Clostridium difficile associated diarrhoea (CDAD)</td>
</tr>
<tr>
<td>Craxford 2013 [3]</td>
<td>11 developed any form of AKI by RIFLE criteria</td>
<td>89</td>
<td>100</td>
<td>Acute kidney injury (AKI) classified according to the risk, injury, failure, loss of function and end stage renal disease (RIFLE criteria) [33]</td>
</tr>
<tr>
<td>Ross 2013 [6]</td>
<td>Total AKI: 2 (2 for THR; 0 for TKR)</td>
<td>198 (98 for THR; 100 for TKR)</td>
<td>0.058</td>
<td>AKI was defined by a 50 % increase in serum creatinine over baseline and graded as per the RIFLE classification [34]</td>
</tr>
<tr>
<td>Vooght 2013 [8]</td>
<td>3 (all with hip fracture)</td>
<td>199</td>
<td>202 (80 hip fracture)</td>
<td>0.04</td>
</tr>
<tr>
<td>White 2013 [2]</td>
<td>9</td>
<td>1716</td>
<td>1725</td>
<td>0.24</td>
</tr>
</tbody>
</table>

### Table 4. Studies included in the meta-analysis of prophylactic antibiotic regimens and post-operative renal impairment

<table>
<thead>
<tr>
<th>First author</th>
<th>Subjects receiving prophylactic cefuroxime</th>
<th>Subjects receiving prophylactic gentamicin and flucloxacillin</th>
<th>P value</th>
<th>Diagnostic tool of renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Challagundla 2012 [5]</td>
<td>11 developed any form of AKI by RIFLE criteria</td>
<td>89</td>
<td>100</td>
<td>Acute kidney injury (AKI) classified according to the risk, injury, failure, loss of function and end stage renal disease (RIFLE criteria) [33]</td>
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<td>0.058</td>
<td>AKI was defined by a 50 % increase in serum creatinine over baseline and graded as per the RIFLE classification [34]</td>
</tr>
<tr>
<td>Ross 2013 [6]</td>
<td>2</td>
<td>122</td>
<td>9</td>
<td>Each patient was also categorised RIFLE classification</td>
</tr>
<tr>
<td>Vooght 2013 [8]</td>
<td>10</td>
<td>192</td>
<td>23</td>
<td>AKI classified by severity (AKI Network Criteria)</td>
</tr>
<tr>
<td>White 2013 [2]</td>
<td>90</td>
<td>1635</td>
<td>73</td>
<td>0.24</td>
</tr>
</tbody>
</table>
in the meta-analysis of prophylactic antibiotic regimens and incidence of post-operative renal impairment). The pooled population was 2,650 subjects receiving prophylactic cefuroxime and 2,699 subjects receiving prophylactic Gen/Flu for the meta-analysis of prophylactic antibiotic regimens and post-operative wound infections; 2,852 subjects receiving prophylactic cefuroxime and 2,909 subjects receiving prophylactic Gen/Flu for the meta-analysis of prophylactic antibiotic regimens and Clostridium difficile infection; and 2,351 subjects receiving prophylactic cefuroxime and 2,352 subject receiving prophylactic Gen/Flu for the meta-analysis of prophylactic antibiotic regimens and post-operative renal impairment.

Meta-analysis comparing efficacies of prophylactic Gen/Flu and prophylactic cefuroxime in preventing post-operative wound infections

A meta-analysis comparing efficacies of prophylactic Gen/Flu and prophylactic Cefuroxime in preventing post-operative wound infections was first performed using a random-effect model and it did not reveal a significant difference between the two regimens (OR=0.87; 95% CI= [0.63, 1.20]; P=0.39; I²=0). Sub-population analysis for Orthopedic surgery including 3 of the 4 studies [3, 5, 7] yielded similar result (OR=0.95; 95% CI= [0.53, 1.65]; P=0.82; I²=0). Because there was no between-studies heterogeneity, a fixed-effect model was then used to perform the meta-analysis and it yielded similar result (OR=0.86; 95% CI= [0.63, 1.20]; P=0.38; I²=0) (Figure 2A). Sub-population analysis for Orthopedic surgery including 3 of the 4 studies [3, 5, 7] using a fixed-effect model also produced similar result (OR=0.94; 95% CI= [0.53, 1.65]; P=0.82; I²=0) (Figure 2A). The results demonstrated that No significant difference in efficacies between the two prophylactic antibiotic regimens.

Sensitivity analysis, between-studies heterogeneity and publication bias

No study altered the results when removed individually from the meta-analysis during the
sensitivity analysis with overall $P$ value remaining insignificant (data not shown). There was no between-studies heterogeneity (Figure 2A). Further, the funnel plot used to assess publication bias is symmetrical, indicating presence of very little or none publication bias in the meta-analysis (Figure 2B).

**Meta-analysis comparing associations of prophylactic Gen/Flu and prophylactic cefuroxime with post-operative clostridium difficile infection**

A meta-analysis comparing the associations of prophylactic Gen/Flu and prophylactic cefuroxime with Clostridium difficile infection was first performed using a random-effect model, and it revealed that compared with prophylactic cefuroxime, prophylactic Gen/Flu was associated with significantly lower risk of post-operative Clostridium difficile infection ($OR=0.28; 95\% CI= [0.14, 0.57]; P=0.0005; I^2=0$). Sub-population analysis for Orthopedic surgery yielded similar result ($OR=0.32; 95\% CI= [0.15, 0.68]; P=0.003; I^2=0$). Because there was no between-studies heterogeneity, a fixed-effect model was then used to perform the meta-analysis and it produced similar result ($OR=0.26; 95\% CI= [0.13, 0.53]; P=0.0002; I^2=0$) (Figure 3A). Sub-population analysis for Orthopedic surgery using a fixed-effect model also produced similar result ($OR=0.31; 95\% CI= [0.15, 0.66]$. 

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**Figure 3.** A. Forest plot of comparison of associations of Gen/Flu prophylaxis and cefuroxime prophylaxis with post-operative Clostridium difficile infection: overall effect for dichotomous outcome (fixed-effect model). The diamond stood for pooled effect. Gen/Flu prophylaxis was associated with significantly lower risk of post-operative *Clostridium difficile* infection. B. Funnel plot of studies included in the meta-analysis of associations of Gen/Flu prophylaxis and cefuroxime prophylaxis with post-operative Clostridium difficile infection. The symmetrical funnel suggested little or no publication bias in the analysis.
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P=0.002; I²=0 (% Figure 3A). These results suggested that prophylactic Gen/Flu was associated with significantly lower risk of Post-Operative Clostridium difficile Infection.

Sensitivity analysis, between-studies heterogeneity and publication bias

Only one study [7] altered the results for sub-population analysis for Orthopedic surgery when removed individually from the meta-analysis during the sensitivity analysis (OR=0.14; 95% CI= [0.01, 2.64]; P=0.19). The remaining studies did not alter the result of the analysis when removed individually from the meta-analysis with overall P value remaining significant (data not shown). There was no between-studies heterogeneity (Figure 3A). Further, the funnel plot used to assess publication bias is symmetrical, indicating presence of very little or none publication bias in the meta-analysis (Figure 3B).

Meta-analysis comparing associations of prophylactic gen/flu and prophylactic cefuroxime with post-operative renal impairment

A meta-analysis comparing associations of prophylactic Gen/Flu and prophylactic cefuroxime with post-operative renal impairment was performed using a random-effect model, and it revealed that compared with prophylactic cefuroxime, prophylactic Gen/Flu was associated with significant higher risk of post-operative renal impairments (OR=2.85; 95% CI= [1.06, 7.70]; P=0.04; I²=87) (Figure 4A). Sub-population analysis for Orthopedic surgery including 4 of the 5 studies [3, 5, 6, 8] yielded
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similar result (OR=3.85; 95% CI= [2.35, 6.30]; P<0.00001; I²=4). (Figure 4A). Therefore, we concluded that prophylactic Gen/Flu was associated with significantly higher risk of post-operative renal impairment.

Sensitivity analysis, between-studies heterogeneity and publication bias

4 of the 5 included studies [3, 5, 6, 8] altered the results for the overall analysis when removed individually from the meta-analysis during the sensitivity analysis (OR=2.29; 95% CI=[0.82, 6.39]; P=0.11; I²=88) with [3] removed, (OR=2.40; 95% CI=[0.84, 6.86]; P=0.10; I²=83] with [5] removed, (OR=2.70; 95% CI=[0.89, 8.17]; P=0.08; I²=90) with [6] removed, and (OR=3.11; 95% CI=[0.84, 11.59]; P=0.09; I²=90) with [8] removed. The remaining study [2] did not alter the result of the analysis when removed from the analysis with overall P value remaining significant (data not shown).

There was high degree of between-studies heterogeneity for the overall analysis with I²=87 and low degree of between-studies heterogeneity for the sub-population analysis for Orthopedic surgery with I²=4 (Figure 4A). Further, the funnel plot used to assess publication bias is symmetrical, indicating presence of very little or none publication bias in the meta-analysis (Figure 4B).

Discussion

In this first meta-analysis in literature, we analyzed and compared the efficacy of cefuroxime prophylaxis and gentamicin/flucloxacillin prophylaxis in preventing post-operative wound infections and their associations with post-operative Clostridium difficile infection and renal impairment. Our meta-analyses revealed that although prophylactic Gen/Flu was associated with a significantly lower risk of Clostridium difficile infection compared with prophylactic cefuroxime, it was associated with a significantly higher risk of post-operative renal impairment than prophylactic cefuroxime, further there was no significant difference in their efficacy in preventing post-operative wound infection.

Surgical teams around the world moved away from cefuroxime prophylaxis and chose gentamicin/flucloxacillin prophylaxis due to reports of association of cefuroxime prophylaxis with Clostridium difficile infection [2, 3, 5-8] and our meta-analysis confirmed that prophylactic Gen/Flu did significantly reduce the risk of post-operative Clostridium difficile infection, since Clostridium difficile infections such as Clostridium difficile associated diarrhea (CDAD) confers mortality, especially in frail elderly people wherein CDAD confers a mortality of up to 25%, [27] by reducing the risk of Clostridium difficile infection while having similar efficacy in preventing post-operative wound infections, Gen/Flu prophylaxis does have obvious advantages over cefuroxime prophylaxis.

On the other hand, the advantage of Gen/Flu prophylaxis comes with a cost, our meta-analysis showed that Gen/Flu prophylaxis was associated with significantly increased risk of renal impairment such as AKI, since AKI is associated with increased morbidity and mortality, [9] said cost needs careful consideration. Flucloxacillin-related renal impairment is not common, there are only a couple of case reports that linked flucloxacillin specifically to acute interstitial nephritis [28-30]. Gentamicin is more often associated with acute tubular necrosis [31]. Challagundla et al. reported that renal impairment induced by Gen/Flu prophylaxis implicated flucloxacillin because 6 our of the 7 patients with AKI RIFLE Class F were taking high-dose flucloxacillin and also because when the dose of flucloxacillin is reduced by half, the incidence of AKI dropped significantly [5].

Further the sub-population analysis for renal impairment associated with Gen/Flu prophylaxis and cefuroxime prophylaxis showed that the increased risk of renal impairment associated with Gen/Flu prophylaxis only happened in Orthopedic surgery, while in cardiac surgery, there was no significant difference between the two prophylactic regimens (OR=0.82; 95%=[0.60, 1.12]; P=0.21) (Figure 4A), this, coupled with the fact that Gen/Flu prophylaxis in cardiac surgery had similar efficacy in preventing post-operative wound infections (OR=0.83; 95% CI=[0.56, 1.24]; P=0.36) (Figure 2A) and was associated with significantly lower risk of Clostridium difficile infection (OR=0.11; 95% CI=[0.01, 0.89]; P=0.04) (Figure 3A), suggested that Gen/Flu prophylaxis was clearly preferable over cefuroxime prophylaxis in cardiac surgery, however, since there is only one relevant study comparing cefuroxime prophylaxis and
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Gen/Flu prophylaxis in cardiac surgery and it is a retrospective study, [2] it is clear that more studies are needed to confirm this finding.

In addition, one of the included studies, Craxford et al. [3] showed that when the subjects were further divided into separate groups for total hip replacement (THR) and total knee replacement (TKR), the significantly higher risk of renal impairment associated with Gen/Flu prophylaxis remained the same in TKR (P<0.01) while in THR, there was no significant difference between the two regimens (P=0.44) and they hypothesized that ischaemic metabolites production from the use of a pneumatic tourniquet in the TKR group in combination with gentamicin might induce AKI in some patients. Obviously, more studies are needed to confirm this finding.

Our meta-analyses could provide some guidance for surgeon in choosing a proper prophylactic regimen. Since our meta-analyses showed that compared with cefuroxime prophylaxis, although Gen/Flu had the advantage of lowering the risk of Clostridium difficile infection while at the same time having similar efficacy in preventing post-operative wound infections, it was associated with significantly increased risk of renal impairment especially when it is used in orthopedic surgery, therefore its use must be carefully considered and its dosage should also be carefully determined so that the risk of renal impairment is minimized without compromising its ability to prevent post-operative wound infections. Further, based on the findings of Craxford et al., [3] it is possible that Gen/Flu prophylaxis is more suitable for THR than TKR. In addition, White et al. suggests that Gen/Flu prophylaxis is clearly preferable than cefuroxime prophylaxis in cardiac surgery since there was no significant difference between their association with risk of renal impairment [2]. Finally, as part of the effort to choose a proper prophylactic antibiotic regimen for a particular patient, patients at high risk of developing significant renal impairment should be identified by identifying factors such as high body mass index, hypertension, chronic obstructive pulmonary disease and congestive cardiac failure prior to admission [6, 32] and Gen/Flu prophylaxis should not be used on these patients.

Our meta-analyses have some limitation. First, the number of available relevant studies eligi-


[28] Pusey CD, Saltissi D, Bloodworth L, Rainford DJ, Christie JL. Drug associated acute intersti-
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