(0.87 ± 0.43 and 0.24 ± 0.43 mg/L at 12 h and 24 h, respectively). The concentration at the site of action is also a key determinant in the activity of an antimicrobial agent. Arrigucci et al. have shown that peritoneal concentrations at 3 h after a 1 g intravenous infusion of ertapenem in scheduled surgery patients were 83% of the plasma concentration. In our study, the ability to assay the unbound fraction was limited because of the low total plasma and peritoneal concentrations and the high protein-bound level of this antimicrobial agent. Even if the free fraction exceeded 50%, the C_{min} of free ertapenem would not exceed the breakpoint in these patients.

In most of our patients, total ertapenem plasma and peritoneal concentrations did not reach the target recommended for critically ill patients. At 12 h after infusion, concentrations in peritoneal fluid were above the breakpoint for ertapenem susceptibility against Enterobacteriaceae and anaerobes, but at 24 h, concentrations were frequently below these thresholds. We found good peritoneal ertapenem diffusion, with concentrations equivalent to those measured in plasma, but they remained insufficient with regards to the breakpoints for susceptibility against causative bacteria. Despite the low total-plasma and peritoneal concentrations, a lack of efficacy to cure our patients could not be concluded, but the impact of such findings on clinical outcomes and the risk of selecting multiresistant bacteria are of concern. In conclusion, at a fixed dose of 1 g/day, total plasma and peritoneal C_{min} of ertapenem in patients who have severe secondary peritonitis were low with regards to breakpoint susceptibilities of this antimicrobial agent for the main bacterial types recovered in these infections. These findings suggest that dosing ertapenem at 1 g twice daily would be more suitable.

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Transparency declarations
None to declare.

References

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Gentamicin and acute kidney injury requiring renal replacement therapy in the context of a restrictive antibiotic policy

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Sir,
Acute kidney injury affects up to 20% of hospitalized patients and is associated with increased mortality.1,2 Gentamicin is an important cause of acute kidney injury as a result of a complex interaction of renal tubular dysfunction, tubular obstruction and reduced glomerular filtration.3 Reported incidence varies due to differences in study design and patient risk factors.

In August 2008, following a rise in Clostridium difficile infection, antibiotic guidelines in Greater Glasgow and Clyde Health Board were revised, restricting cephalosporins, co-amoxiclav and quinolones and promoting narrow-spectrum agents and short-term gentamicin. As a consequence, gentamicin use doubled from ~20 to 40 defined daily doses/1000 bed days.
We investigated whether this change resulted in any effect on the incidence of, or mortality from, acute kidney injury. A retrospective audit of all patients requiring emergency renal replacement therapy within Glasgow hospitals before the change in antibiotic guidelines from 1 August 2007 to 31 January 2008 (period 1) and after the change in antibiotic guidelines 1 August 2008 to 31 January 2009 (period 2) was performed. The audit periods were separated by 6 months allowing a ‘run in’ period, and minimizing seasonal bias. Case notes were reviewed for co-morbidity, causes of acute kidney injury, dates of gentamicin use, duration of renal replacement therapy, mortality and extent of renal recovery. All intensive therapy units (ITUs) and renal units in Greater Glasgow and Clyde were included. Patients excluded were those transferred from hospitals outside Glasgow, post-cardiac surgery and with documented stage 5 chronic kidney disease or already requiring dialysis.

Modes of emergency renal replacement therapy used in Glasgow are haemodialysis and continuous veno-venous haemofiltration depending on local expertise and resources. The indications for emergency renal replacement therapy are well recognized, being refractory hyperkalaemia, metabolic acidosis, fluid overload resistant to medical therapy, symptoms or signs of uremia and toxicity with certain poisonous substances.

There is no accepted definition of gentamicin-associated acute kidney injury. For the purposes of this audit, we have defined it as acute kidney injury associated with the initiation of gentamicin between 1 and 10 days prior to the requirement for renal replacement therapy.

In time period 1, recommended gentamicin dosing was based on a 24 or 48 hourly dosing system (~5 mg/kg) utilizing body weight with creatinine clearance (CL\textsubscript{CR}) estimated using the Cockcroft–Gault calculation. After auditing compliance with these guidelines, and estimating pharmacokinetic profiles, the gentamicin dosing regimen was simplified prior to period 2, to 180 mg every 48 h to 400 mg every 24 h, with 2.5 mg/kg maximum dose, 180 mg recommended for patients with a CL\textsubscript{CR} of <20 mL/min. This ensured either 24 or 48 hourly dosing and uniformity of prescribing guidance across all hospitals. An intranet-based gentamicin dosage calculator was introduced to further simplify dosing.\textsuperscript{a}

The data from period 1 and period 2 were compared. Following this, those with gentamicin-associated acute kidney injury from either time period were compared with the rest of the cohort. A univariate binary logistic regression analysis, to identify factors associated with a higher risk of death, was performed using the entire cohort. Those with \(P < 0.15\) were entered into multivariate analysis using a backwards selection model. The Mann–Whitney \(U\)-test, binomial comparison of two distributions and binary logistic regression analysis were utilized where appropriate using Minitab 13.1 software.

There were 191 patients identified as having received emergency renal replacement therapy during period 1, and 184 during period 2.

There was no significant difference in patient age, length of hospital stay, incidence of sepsis and mortality between the two periods. In both populations 43% of patients received gentamicin at any time during their admission. Overall, 40.5% (61 patients) of patients who received gentamicin were classified as having gentamicin-associated acute kidney injury, having started gentamicin therapy between 1 and 10 days prior to requiring renal replacement therapy. The gentamicin-associated acute kidney injury group was more likely to have undergone surgery, be immunosuppressed and to have been admitted to an ITU reflecting the use of gentamicin in severe sepsis and multiorgan dysfunction.

In a multivariate analysis of all patients requiring emergency renal replacement therapy, gentamicin exposure prior to renal replacement therapy was not associated with increased risk of death. ITU admission and increasing age were associated with increased risk of death, whereas angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) use prior to renal replacement therapy was associated with decreased risk of death (Table 1).

In summary, we have found no evidence of an increase in gentamicin-associated acute kidney injury requiring renal replacement therapy despite doubling of gentamicin use in the hospital population. Our concern that increased gentamicin use may result in a significant increase in acute kidney injury requiring emergency renal replacement therapy was unfounded. It is recognized that lesser degrees of acute kidney injury are associated with significant morbidity and mortality and so further audit into acute kidney injury not requiring dialysis is necessary. Continued vigilance is required to ensure that gentamicin is used safely and appropriately, particularly through careful therapeutic drug monitoring.

### Table 1. Binary logistic regression analysis of factors associated with in-hospital mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis odds ratio</th>
<th>95% CI</th>
<th>(P) value</th>
<th>Multivariate analysis odds ratio</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITU admission</td>
<td>3.81</td>
<td>2.32, 6.27</td>
<td>0.000</td>
<td>4.87</td>
<td>2.65, 8.23</td>
<td>0.000</td>
</tr>
<tr>
<td>Age</td>
<td>1.16\textsuperscript{a}</td>
<td>1.01, 1.32</td>
<td>0.03</td>
<td>1.44\textsuperscript{a}</td>
<td>1.22, 1.70</td>
<td>0.000</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.53</td>
<td>0.90, 2.61</td>
<td>0.116</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.46</td>
<td>0.27, 0.79</td>
<td>0.004</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>2.28</td>
<td>1.07, 4.86</td>
<td>0.028</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Gentamicin use at any time</td>
<td>1.60</td>
<td>1.05, 2.43</td>
<td>0.028</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Prior ACE-I/ARB</td>
<td>0.49</td>
<td>0.31, 0.78</td>
<td>0.002</td>
<td>0.45</td>
<td>0.24, 0.82</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CI, confidence interval; NS, not significant.

\textsuperscript{a}Per 10 year increase in age.
avoidance of other co-administered nephrotoxic agents and restriction in duration of therapy.

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Preliminary data from this audit have been presented at the Scottish Renal Association Meeting, November 2010. In addition, an abstract has been submitted to the Renal Association and British Renal Society Joint Conference, June 2011.

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Y. G. and R. A. S. are members of the NHS Greater Glasgow Clyde antimicrobial management team and were responsible for introducing the infection management guidelines including those relating to gentamicin use. A. H. and C. D. have nothing to declare.

**References**