Long-term adherence to a 5 day antibiotic course guideline for treatment of intensive care unit (ICU)-associated Gram-negative infections

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Objectives: To determine long-term adherence to a 5 day antibiotic course guideline for treating intensive care unit (ICU)-acquired Gram-negative bacteria (GNB) infections.

Methods: Descriptive analysis of patient-level data on all GNB-active antibiotics prescribed from day 3 and all GNB identified in clinical samples in 5350 patients admitted to a 30 bed general ICU between 2002 and 2009.

Results: Four thousand five hundred and eleven of 5350 (84%) patients were treated with one or more antibiotics active against GNB commenced from day 3. Gentamicin was the most frequently prescribed antibiotic (92.2 days of therapy/1000 patient-days). Only 6% of courses spanned 6 days of therapy and 89% of antibiotic therapy days were with a single antibiotic active against GNB. There was no significant difference between gentamicin and meropenem in the number of first courses in which a resistant GNB was identified in blood cultures [11/1177 (0.9%) versus 5/351 (1.4%); P = 0.43] or respiratory tract specimens [59/951 (6.2%) versus 17/246 (6.9%); P = 0.68] at the time of starting therapy.

Conclusions: This study demonstrates long-term adherence to a 5 day course antibiotic guideline for treatment of ICU-associated GNB infections. This guideline is a potential antibiotic-sparing alternative to currently recommended dual empirical courses extending to ≥7 days.

Keywords: aminoglycosides, antibiotic resistance, Gram-negative bacteria

Introduction

There are concerns about increasing antimicrobial resistance, particularly among Gram-negative bacteria (GNB) in the intensive care unit (ICU).1,2 This has led to the introduction of stewardship programmes promoting guideline adherence to reduce unnecessary antimicrobial prescribing.3 Writing antibiotic guidelines for ICU infections is challenging because of the need to balance making recommendations that ensure appropriate empirical therapy for likely pathogens against restricting unnecessary antibiotic use that selects for resistance.4 Many studies show a benefit associated with early appropriate empirical therapy,5–10 although some do not.11–14 International guidelines for ICU-acquired infections, such as ventilator-associated pneumonia, usually, but not always, favour two empirical antibiotics active against GNB to ensure appropriate therapy.15–17 The benefit of a dual empirical therapy approach is the focus of many studies but remains controversial.18–23

One approach to reducing unnecessary therapy when two empirical antibiotics are used is to de-escalate to a single active agent once susceptibility patterns are known;24,25 however, once two agents have been started de-escalation may be difficult for a variety of reasons, including uncertainty as to the causative organism.26 There is also limited evidence to guide recommendations on the length of therapy and the extent to which this should be influenced by the focus, degree of sepsis or causative organism. Guidelines for pneumonia and sepsis frequently recommend 7–10 days,15,26 whereas guidelines for catheter-related bloodstream infection point out there are no compelling data to support specific recommendations.27 Few studies have provided information on actual prescribing practice.28–31

Our ICU guideline has recommended a 5 day single antibiotic course for ICU-acquired GNB infections for many years.12 The objectives here were to determine adherence over an extended period of time and to assess the susceptibility of GNB identified at clinical sites to the prescribed antibiotics.
Methods

This work was conducted in the Centre for Clinical Infection and Diagnostic Research (CIDR) and the ICU at Guy’s and St Thomas’ NHS Foundation Trust.

Study design and setting

Guy’s and St Thomas’ NHS Foundation Trust is a 1150 bed, dual-site central London teaching hospital with a 30 bed mixed medical and surgical ICU on the St Thomas’ Hospital site. Patient-level clinical, demographic, microbiological culture and antimicrobial prescribing data on patients admitted to the ICU between January 2002 and December 2009 were extracted from clinical information systems (Intellivue, clinical information portfolio (Philips), ISOFT and the in-house microbiology computer system) with local ethics committee approval (10/H1102/80) as recently published. Prior to any linking and analysis, data were processed, cleaned and corrected using patient names, ICU location and hospital number identifiers. Fewer than 100 patients had identification inconsistencies or missing data.

Definitions and statistics

The day of admission was defined as day 1. The longest ICU stay for each patient extending at least until day 3 was analysed, with two episodes <2 days apart being collapsed into a single episode. Only systemic antibiotic therapy commenced from day 3 was analysed. Antibiotic course length was defined as the number of continuous days of therapy on which at least one dose of antibiotic was received, apart from gentamicin and amikacin, for which a gap of 1 day between doses was called continuous therapy. Comparisons between inappropriate therapies were made using the two-sided $\chi^2$ test for the null hypothesis of equality of proportions, with a modified Bonferroni procedure to adjust the level of significance for multiple testing. Two-sided $P$ values are reported.

Antimicrobial prescribing guidelines and practice

An antibiotic guideline developed by intensivists, microbiologists and pharmacists was in place throughout the 8 years. The guideline recommended gentamicin, administered with an extended-duration dosing protocol (5 mg/kg lean body weight; maximum 500 mg), as first-line empirical or targeted therapy for all GNB infections. Ceftazidime was recommended as an alternative first-line agent in renal failure or at the intensivist’s discretion. Ciprofloxacin and piperacillin/tazobactam were recommended for suspected resistance or allergy to other first-line antibiotics. Meropenem or amikacin was reserved for subsequent episodes of sepsis (second-line) or suspected resistance. All patients with severe sepsis or septic shock were recommended to receive a single dose of gentamicin if a non-aminoglycoside antibiotic course was selected. These recommendations for ICU-acquired GNB infections remained in place throughout the 8 years. The guideline recommended initial electronic prescription of a 5 day course regardless of suspected focus. All antibiotic prescriptions were reviewed daily at the bedside by microbiologists, pharmacists and intensivists together. The clinical response and microbiological culture results were used to decide on the need to deviate from the guideline. De-escalation to a narrower-spectrum antibiotic was not generally undertaken when bacterial susceptibility results became available because of the short time to stop date.

Microbiological culture

Microbiological culture results were analysed from all clinical site samples taken on the ICU. Throat and rectal screening swabs were also collected on admission and every Monday to identify gentamicin-resistant GNB. Ten percent of patients had a positive gentamicin resistance screen on admission but results from these screening swabs are not included in the analysis. All GNBs were identified and had antimicrobial susceptibility determined using standard laboratory techniques. Before August 2008, susceptibility patterns were determined using agar disc diffusion according to BSAC standards. Thereafter the VITEK system (bioMérieux, Marcy-l’Étoile, France) was used.

Results

Five thousand three hundred and fifty patients admitted to the ICU between 2002 and 2009 had at least one ICU episode extending beyond the third day of admission and comprised the study cohort. The median age was 65 (IQR 51.5–74.8) years and 62.6% were males. Their median admission APACHE II score was 18 (IQR 14–22), the median ICU length of stay was 8 days (IQR 5–17) and ICU mortality was 25.5%.

Eighty-four percent (4511) of cohort patients received 6793 courses of any systemic antibiotic active against GNB (average 1.5 courses/patient), of which 5709 (84%) were with the six guideline-recommended antibiotics (Table 1). Further analysis predominantly focused on these six antibiotics.

Gentamicin and then ceftazidime were the most frequently prescribed antibiotics in terms of number of courses, days of therapy and number of treated patients, consistent with the guideline (Table 1). Thirty-one percent of all cohort patients received gentamicin and 17% received ceftazidime, whereas <10% received each of the other antibiotics (Table 1). Median time to starting a course of gentamicin and ceftazidime for ICU-acquired infections was less than that for ciprofloxacin, piperacillin/tazobactam, meropenem or amikacin (5 and 6 versus 9–11 days) (Figure S1, available as Supplementary data at JAC Online).

Data on the longest course of each antibiotic administered to each patient are presented in Figure 1. The mode of the longest course length for gentamicin and amikacin was 1 day, compared with 6 days for other anti-Gram-negative agents. Only 6% (342/5709) of courses with the six guideline-directed antibiotics spanned >6 days. The median length of continuous active antibiotic therapy commenced at the time of identifying a GNB in blood cultures was also 6 days (IQR 4–7; n = 383). Overall, 75.1% (3120/4151) of first courses of the six guideline-directed antibiotics ended whilst the patient remained alive and on the ICU.

The number of prescription days with one or two antibiotics active against GNB is presented in Table S1 (available as Supplementary data at JAC Online). Of 21248 days of therapy with GNB-active antibiotics commenced from day 3, 18614 (88%) were with a single agent. Sixty-one percent (1616/2634 days) of dual therapy days included gentamicin and 25% (1629/6298) of gentamicin therapy days were in combination with another agent.

Of the 5350 patients, 3254 (61%) had a GNB cultured from one or more clinical site samples during their ICU stay (Table 2). There was significant variation in the percentage of patients identified with a GNB resistant to the different antibiotics (range 9%–27%). Percentages were higher if the number of patients in whom a GNB was identified for microbiological analysis was used as the denominator (14%–44%) (Table 2). The time to first detection of a GNB resistant to each antibiotic is shown in Figure 2. Days 1 and 2 were the most frequent days for first detection of resistance to all six antibiotics, indicating a significant burden of importation of
The median time to first detection of resistance was longer for amikacin and meropenem (9 and 10 days, respectively) compared with other antibiotics (5–6 days). The percentage of antibiotic courses for which a resistant GNB was identified at a clinical site at the time of starting antibiotic therapy (+1 day of first dose) was used as a measure of resistance at clinical sites. The median time to first detection of resistance was longer for amikacin and meropenem (9 and 10 days, respectively) compared with other antibiotics (5–6 days).

### Table 1. Antimicrobials with activity against GNB prescribed for ICU-acquired infections and the frequency of resistance of GNB identified at clinical sites at the time of starting therapy

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of courses</th>
<th>Number of treated patients</th>
<th>DOT per 1000 patient-days&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Number (%) of patients with GNB at clinical sites&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Number with resistant GNB at clinical sites</th>
<th>GNB resistance/therapy course (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>2580</td>
<td>1648</td>
<td>92.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>922 (74)</td>
<td>264</td>
<td>10.2</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1165</td>
<td>932</td>
<td>74.1</td>
<td>541 (76)</td>
<td>211</td>
<td>18.1</td>
</tr>
<tr>
<td>Meropenem</td>
<td>611</td>
<td>476</td>
<td>45.3</td>
<td>271 (66)</td>
<td>52</td>
<td>8.5</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>492</td>
<td>425</td>
<td>33.0</td>
<td>220 (65)</td>
<td>59</td>
<td>11.9</td>
</tr>
<tr>
<td>Amikacin</td>
<td>485</td>
<td>342</td>
<td>21.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>214 (70)</td>
<td>47</td>
<td>9.7</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>376</td>
<td>328</td>
<td>25.4</td>
<td>193 (70)</td>
<td>74</td>
<td>19.6</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>366</td>
<td>335</td>
<td>21.8</td>
<td>121 (50)</td>
<td>40</td>
<td>10.9</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>365</td>
<td>347</td>
<td>16.7</td>
<td>129 (53)</td>
<td>53</td>
<td>14.5</td>
</tr>
<tr>
<td>Others&lt;sup&gt;d&lt;/sup&gt;</td>
<td>353</td>
<td>297</td>
<td>22.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Antimicrobials are listed in descending order of the number of courses with each antibiotic starting from day 3 of admission. NA, not applicable. DOT, (total number of antibiotic therapy days for all courses that started from day 3/total patient-days on ICU from day 3) × 1000.<sup>a</sup> Only clinical samples collected ±1 day of first antibiotic dose of each course were included.<sup>b</sup> Percentage of cases in which a resistant organism was identified at any clinical site ±1 day of first antibiotic dose of each course.<sup>c</sup> A 1 day gap between administration of gentamicin and amikacin consumption was defined as continuous therapy.<sup>d</sup> Other antibiotics with activity against GNB were co-trimoxazole, ceftriaxone, colistin, cefotaxime, amoxicillin and ampicillin.

Figure 1. Length of antibiotic courses. The longest continuous therapy course commenced from day 3 of admission for each antibiotic for each patient is included. Gaps of 1 day between doses of gentamicin or amikacin were considered continuous therapy days. The numbers shown in each panel are the median (IQR) length of therapy.
inappropriate therapy (Table 1). For positive blood cultures this ranged from 0.9% of gentamicin courses to 3.3% of ceftazidime and piperacillin/tazobactam courses, and for respiratory tract samples this ranged from 6.2% of gentamicin courses to 16.5% for piperacillin/tazobactam courses. Some differences reached statistical significance (Table 3).

Table 2. Prevalence of resistance of GNB identified at clinical sites to guideline-directed antibiotics

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Number of patients</th>
<th>GEN</th>
<th>AMK</th>
<th>CAZ</th>
<th>MEM</th>
<th>TZP</th>
<th>CIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1368</td>
<td>266</td>
<td>56</td>
<td>83</td>
<td>85</td>
<td>24</td>
<td>103</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>981</td>
<td>158</td>
<td>72</td>
<td>161</td>
<td>4</td>
<td>123</td>
<td>199</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>850</td>
<td>157</td>
<td>43</td>
<td>204</td>
<td>6</td>
<td>187</td>
<td>183</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>632</td>
<td>98</td>
<td>18</td>
<td>484</td>
<td>8</td>
<td>451</td>
<td>86</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>363</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>361</td>
<td>20</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>256</td>
<td>191</td>
<td>107</td>
<td>220</td>
<td>71</td>
<td>183</td>
<td>197</td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>254</td>
<td>14</td>
<td>14</td>
<td>175</td>
<td>3</td>
<td>171</td>
<td>15</td>
</tr>
<tr>
<td>Stenotrophomonas maltophiliaa</td>
<td>182</td>
<td>167</td>
<td>167</td>
<td>159</td>
<td>165</td>
<td>151</td>
<td>170</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>141</td>
<td>14</td>
<td>3</td>
<td>93</td>
<td>2</td>
<td>81</td>
<td>16</td>
</tr>
<tr>
<td>Any GNB</td>
<td>3254</td>
<td>949</td>
<td>510</td>
<td>1441</td>
<td>464</td>
<td>1271</td>
<td>983</td>
</tr>
</tbody>
</table>

GEN, gentamicin; AMK, amikacin; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin/tazobactam; CIP, ciprofloxacin; NA, not applicable.

For each bacterium the number of patients with a resistant isolate is presented with the percentage given in parentheses (the denominator for each percentage being the number of patients with any isolate of that bacteria identified at a clinical site). For the row 'Any GNB', n(%)% is presented, where n is the number of patients with any GNB resistant to the indicated antibiotic. The first percentage uses a denominator of only those patients identified with a GNB at a clinical site (n=3254) and the second percentage uses a denominator of all cohort patients (n=5350).

* Susceptibility testing for these antibiotics against S. maltophilia is unreliable and was not used as a measure of clinical efficacy to guide treatment decisions.

Figure 2. Time from ICU admission to first detection of a GNB at clinical sites that was resistant to guideline-directed antibiotics. Numbers are median in days from admission (IQR).
Table 3. Presence and resistance of GNB in blood and respiratory tract samples taken at the time of commencing the first course of each antibiotic

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of coursesa</th>
<th>Number (%) with a cultured GNB</th>
<th>Number (%) with a resistant GNBb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>1177</td>
<td>118 (10.0)</td>
<td>11 (0.9)</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>693</td>
<td>78 (11.2)</td>
<td>23 (3.3)</td>
</tr>
<tr>
<td>meropenem</td>
<td>351</td>
<td>64 (18.2)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>242</td>
<td>31 (12.8)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>289</td>
<td>37 (12.8)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>amikacin</td>
<td>246</td>
<td>49 (19.9)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>951</td>
<td>527 (55.4)</td>
<td>59 (6.2)</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>579</td>
<td>355 (61.3)</td>
<td>86 (14.8)</td>
</tr>
<tr>
<td>meropenem</td>
<td>246</td>
<td>157 (63.8)</td>
<td>17 (6.9)</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>194</td>
<td>136 (70.1)</td>
<td>32 (16.5)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>225</td>
<td>136 (60.4)</td>
<td>21 (9.3)</td>
</tr>
<tr>
<td>amikacin</td>
<td>184</td>
<td>113 (61.4)</td>
<td>19 (10.3)</td>
</tr>
</tbody>
</table>

aFirst patient courses for which at least one sample was collected +1 day of the first dose.
bNumber (%) of antibiotic courses in which a resistant GNB was identified in at least one blood culture or respiratory tract specimen taken +1 day of first antibiotic dose.

Significant differences between antibiotics in courses started in the presence of resistant GNB were as follows. Blood cultures: gentamicin versus ceftazidime, \( P = 0.005 \); ceftazidime versus meropenem, \( P = 0.008 \). Respiratory tract cultures: gentamicin versus ceftazidime, \( P = 0.0017 \); gentamicin versus piperacillin/tazobactam, \( P = 0.003 \); meropenem versus ceftazidime, \( P = 0.0067 \); meropenem versus piperacillin/tazobactam, \( P = 0.01 \). All other antibiotic comparisons were not statistically significant.

Discussion

This study demonstrated long-term adherence to a 5 day single-antibiotic course guideline for ICU-associated GNB infections. An average of 1.5 courses of GNB-active antibiotics were prescribed per treated patient, with course length spanning ≤6 days of therapy in 94% of cases and 88% of therapy days being with a single GNB-active antibiotic. This implies that the multidisciplinary team considered a 5 day course to be adequate for the majority of ICU-acquired GNB infections. This likely includes those at the more severe end of the spectrum, given that a similar course length was also prescribed when local infections were associated with a bacteraemia. There was infrequent practice of prescribing multi-day combination courses of anti-GNB therapy or immediate commencement of further courses with different antimicrobials at the end of 5 days, both of which would have led to a much higher proportion of dual-therapy days or courses per patient.

Antibiotics started on days 1 and 2 were excluded because they are often started prior to arrival, for a different spectrum of bacteria causing infections that often require longer courses, such as endocarditis, osteomyelitis or meningitis. This study focused on therapy for infections acquired on the ICU that are predominantly due to breach of an epithelial surface following insertion of a catheter, drain or knife, or bypassing of other surface defences following insertion of endotracheal or urinary catheters. The rationale for recommending a 5 day course was that iatrogenic breach of epithelial surfaces can be considered as a homogeneous process, independent of site or bacterial species, even though the clinical response may differ significantly. Thus, a single course length and antibiotic choice could be recommended, assuming that attention is given to early source control. Corona et al highlighted the large variation in duration of therapy for ICU bloodstream infections from <7 to >14 days, indicating that the course length recommended here is at the lower end of that range. There is some evidence that longer courses are required for ventilator-associated pneumonia due to environmental Gram-negative bacteria. The course length may have been extended for such infections, given that 6% of courses spanned >6 days, but this was not specifically assessed.

Another aspect of this guideline requiring comment is the recommendation of a single empirical antibiotic course. There are probably three reasons why this recommendation had a high level of adherence despite significant unit-level resistance. Firstly, the guideline recommended an adjunctive single dose of gentamicin for patients with severe sepsis if other antibiotic classes were selected. Secondly, culture results from admission clinical samples and gentamicin-resistance screens would become available to guide therapy choices from the third day of admission. This may help explain why the frequency of inappropriate therapy was similar for gentamicin and meropenem (Table 3) despite gentamicin having higher unit-level resistance (18% and 9% respectively; Table 2). Finally, the proportion of treatment courses resulting in inappropriate initial therapy based on the antibiogram was comparable to other studies.

A dominant role for aminoglycosides in critically ill patients, even as short courses or single doses, may be controversial. Aminoglycosides penetrate relatively poorly into tissues, require careful monitoring to reduce the risk of nephrotoxicity and ototoxicity, and are difficult to dose in renal failure. However, they have advantages such as low rates of allergy and less disturbance of bowel flora and potentially Clostridium difficile infection compared with other antibiotics. Aminoglycosides have been prescribed as first-line treatment on our ICU for over 40 years and the policy remained in place in 2013, apart from changing ceftazidime to piperacillin/tazobactam as an alternative first-line antibiotic.

There are limitations to this study. It was performed at a single centre and so resistance rates and guideline implementation will differ hugely between units and countries. We did not determine whether bacterial culture represented infection versus colonization, or determine the association between appropriateness of antibiotic choice and patient outcomes. Such considerations are important and have been the focus of many observational studies with conflicting results. Finally, the laboratory had an expert rule advising all Citrobacter freundii and Enterobacter, Serratia, Morganella and Providencia species to be reported as resistant to cephalosporins and piperacillin/tazobactam regardless of test result. This rule was controversial and not implemented rigorously; nevertheless some resistant isolates will have been reported rather than measured as resistant, which would falsely increase resistance to ceftazidime and piperacillin/tazobactam.

In summary, balancing the potentially conflicting objectives of ensuring appropriate therapy for bacterial infections with preventing unnecessary antibiotic use is a challenge in patients with...
a new septic episode in the ICU. This paper demonstrates high long-term multidisciplinary team adherence to a guideline for all ICU-acquired GNB infections that recommends a 5 day single antibiotic course combined with the option of a single initial aminoglycoside dose in patients with severe sepsis. Further studies are needed to determine whether this antibiotic-sparing approach is an acceptable alternative to currently recommended longer dual-therapy course guidelines.

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Transparency declarations

J. D. E. has sat on advisory panels for Basilea. In the last 3 years, D. W. has received consultancy fees and or honoraria for speaking from Astellas, Baxter, Bioproducts, Biova, Covidien, Convatec, Eli Lilly, Johnson & Johnson, Sage Products, Iskus, Pfizer and Portex. C. A. M. has delivered educational sessions and sat on advisory panels for Pfizer UK, Drager, Orion Pharma and Basilea. I. C. S. and M. S.-H.: none to declare.

Supplementary data

Figure S1 and Table S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


