β-Lactam/β-lactamase inhibitors versus carbapenems for the
treatment of sepsis: systematic review and meta-analysis of randomized controlled trials

Shachaf Shiber1†, Dafna Yahav2,3*†, Tomer Avni4, Leonard Leibovici3,4 and Mical Paul3,5

1Emergency Department, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; 2Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; 3Sackler Faculty of Medicine, Tel-Aviv University, Ramat Aviv, Israel; 4Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; 5Unit of Infectious Diseases, Rambam Health Care Center, Haifa, Israel

*Corresponding author. Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel. Tel: +972-50-4065475; Fax: +972-3-9376512; E-mail: dafna.yahav@gmail.com
†Equal contribution.

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Background: Data on the relative efficacy of β-lactam/β-lactamase inhibitors (BL/BLIs) versus carbapenems are scant.

Methods: This is a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing any BL/BLI versus any carbapenem for the treatment of sepsis. The primary outcome was all-cause mortality. A broad search was conducted with no restrictions on language, publication status or date. Two reviewers independently applied the inclusion criteria and extracted the data. Assessment of risk of bias was performed using the domain-based approach. Subgroup analyses were used to investigate heterogeneity and focus on patient groups more likely to harbour ESBL-positive bacteria. Risk ratios (RRs) with 95% CIs were calculated and pooled.

Results: Thirty-one RCTs were included. There was no difference between BL/BLIs and carbapenems in terms of mortality (RR 0.98, 95% CI 0.79–1.20), without heterogeneity. No differences were observed with regard to clinical or microbiological failure and bacterial superinfections. The results were not affected by risk of bias. No differences were detected in the subgroups of patients with nosocomial infections, Gram-negative infections and neutropenic fever. Adverse events requiring discontinuation were more common with BL/BLIs, on account of an increased incidence of diarrhoea. However, Clostridium difficile-associated diarrhoea (RR 0.29, 95% CI 0.10–0.87) was more frequent with carbapenems and seizures were more frequent with imipenem (RR 0.21, 95% CI 0.05–0.93).

Conclusions: No differences in efficacy between BL/BLIs and carbapenems exist in RCTs including patient populations with a certain, albeit unknown, rate of ESBL-positive bacteria causing infections.

Keywords: antibiotic treatment, BL/BLIs, ESBLs

Introduction

β-Lactam/β-lactamase inhibitors (BL/BLIs) and carbapenems are often considered for the treatment of sepsis when the main suspected pathogens are Gram-negative bacteria, because of their broad spectrum of coverage. These infections include most healthcare-associated infections, intra-abdominal infections, urinary tract infections and febrile neutropenia.

A special consideration within this comparison is that of ESBL-producing bacteria, which are found increasingly more frequently among such infections. The European Antimicrobial Resistance Surveillance Network reported in 2010 that 8.5% of Escherichia coli and 27.5% of Klebsiella pneumoniae isolates were resistant to third-generation cephalosporins, with ESBL positivity rates among these bacteria of 65%–100% for E. coli and 75%–100% for K. pneumoniae. In the community, ESBL rates reported among Enterobacteriaceae, mainly E. coli, were 30% in children in Guinea-Bissau, 11.3% in the UK, 10% in the Netherlands, 7.3% in Tunisia and 3% in Sweden in 2010.2–5 Between 2008 and 2010, 25% of E. coli and 34% of K. pneumoniae clinical isolates were ESBL positive in Latin America.6
Systematic review

The decision to choose between BL/BLIs and carbapenems depends on their comparative efficacy, side effects, induction of resistance and costs. Comparative data for their use in infections caused by ESBL-producing bacteria are based on observational studies alone. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that compared BL/BLIs versus carbapenems for the treatment of sepsis. We attempted to examine infections caused by ESBL producers specifically through subgroup analyses.

Methods

We included RCTs comparing any BL/BLI versus any carbapenem for the treatment of sepsis, including all sources of infection or febrile neutropenia, among adults and children. Study drugs could be administered in combination with other antibiotics only if the same antibiotic/treatment schedules were applied to both study arms.

The primary outcome was all-cause mortality, preferably at 30 days. If these data were unavailable, we extracted all-cause mortality at the end of the follow-up, and if this was not reported, at end of treatment. Mortality at 30 days or at the end of follow-up, and at end of treatment, were also analysed separately. Secondary outcomes included: clinical failure, defined as the persistence of fever or other symptoms or signs of infection beyond the protocol-defined period for clinical response in the study, a need for antibiotic modification or death; microbiological failure, examined per patient and per isolate including only patients with microbiologically documented infections; bacterial superinfections; clinical failure regardless of antibiotic modifications; colonization by bacteria resistant to study interventions; the development of complications of infection that were not initially present; fever duration and hospitalization duration; and adverse events (any adverse event, adverse events requiring treatment discontinuation and specific adverse events).

We searched the Cochrane Central Register of Controlled Trials, PubMed, Embase and Lilacs databases. Unpublished trials were sought in references of included studies, relevant conference proceedings, trial registries and ongoing trial databases, and new drug application documents in the FDA and European Medicines Agency databases and through personal contact with the investigators and sponsoring pharmaceutical companies of the included studies. No language or date restrictions were imposed. The last search was done on 1 June 2014. We searched for: (tazobactam OR clavulanate OR sulbactam OR avibactam OR any others?) AND (carbapenem* OR doripenem OR Meropenem OR Merrem OR anypenem), using the Cochrane highly sensitive filter for RCTs in PubMed.7

Two reviewers independently performed the search, applied the inclusion criteria and extracted the data. For the outcomes of mortality and clinical failure, data were extracted for the largest patient population evaluated (ITT). Whenever mortality data or randomization methods were not reported we contacted the authors and the sponsor requesting these data.

Assessment of risk of bias was performed using the domain-based approach, examining the generation of the allocation sequence, allocation concealment, blinding, assessment of incomplete outcome data, selective outcome reporting, early conclusion of the trial and extreme imbalance at baseline. Allocation concealment and generation were graded as having a low, high or unknown risk of bias by the use of criteria suggested in the Cochrane handbook.7 The effects of each domain on outcomes were examined through sensitivity analyses.

Risk ratios (RRs) for individual studies were calculated with 95% CIs and pooled using the Mantel–Haenszel fixed-effects method. Heterogeneity in the results of the trials were assessed using a X^2 test of heterogeneity (P<0.1) and the I^2 measure of inconsistency8 and was investigated using subgroup analyses. The planned subgroups included patients with documented ESBL infection; patients with healthcare-associated or hospital-acquired infections, infections caused by K. pneumoniae, urinary tract infections; and patients with bacteraemia. In addition, we examined separately the effects for specific BL/BLIs and carbapenems. Meta-regression of the effects against the study years was performed using fixed-effect regression. Analyses were conducted using RevMan 5.2 and Comprehensive Meta-Analysis 2.2 software. A funnel plot was used to assess small-studies effects.

Results

Thirty-one RCTs (32 comparisons) that compared a BL/BLI with a carbapenem fulfilled the inclusion criteria for the review9–39 (Figure 1). The trials’ location, types of infection, interventions, number of participants and methods are detailed in Table S1 (available as Supplementary data at JAC Online). The infections addressed by descending order of frequency were abdominal or pelvic infections (11 trials), febrile neutropenia (8), lower respiratory tract infections (7), complicated skin and soft tissue infections (4) and urinary tract infections (2). Piperacillin/tazobactam was the most frequently studied BL/BLI (22 trials) followed by cefoperazone/sulbactam (3), ticarcillin/clavulanate (2), ampicillin/sulbactam (3) and ceftazidime/avibactam (1). Imipenem was the most frequent carbapenem (18 trials, with 2 trials allowing imipenem or meropenem), followed by ertapenem (8), meropenem (2) and doripenem (1). Additional antibiotics, most commonly vancomycin, were permitted equally in both arms in 15 trials (Table S1).

Allocation concealment was classified as having a low risk of bias in 17 trials, allocation generation a low risk of bias in 18 trials and both a low risk of bias in 10 trials. Ten trials were double-blinded, 1 trial was single-blinded, 1 trial was outcome assessor blinded and 19 trials were open (Table S1).

All-cause mortality

Overall, the mortality at any timepoint (preferentially extracting data at 30 days or the end of the follow-up) was reported in 26 trials, with no difference between BL/BLIs and carbapenems (RR 0.98, 95% CI 0.79–1.20, 6471 patients, without heterogeneity,
The funnel plot was symmetrical, suggesting that there was no small-studies effect. There were no significant differences between BL/BLIs and carbapenems at 30 days or at the end of follow-up (usually 2–6 weeks post therapy) (RR 1.06, 95% CI 0.84–1.32, 20 trials, 4990 patients) or at end of treatment (7–21 days) (RR 0.96, 95% CI 0.64–1.34, 11 trials, 2952 patients), without significant heterogeneity in either analysis. There was no difference between BL/BLIs and carbapenems with a different risk of bias [Figure 2 (by allocation concealment) and Table 1]. Given the lack of data reported on patients with infections caused by ESBL-producing bacteria, we analysed the results for nosocomial infections and patients with neutropenic fever, groups of patients who might harbour a higher rate of ESBL-positive infections than others (Table 2). No differences between BL/BLIs and

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>BL/BLI Total</th>
<th>Carbenem Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>RR M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.5.1 Low risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eklund 1993 PT-I</td>
<td>0 55 4</td>
<td>58</td>
<td>2.7%</td>
<td>0.12 [0.01, 2.12]</td>
<td></td>
</tr>
<tr>
<td>Erasmo 2004 PT-I</td>
<td>3 149 0</td>
<td>144</td>
<td>0.3%</td>
<td>6.77 [0.35, 129.85]</td>
<td></td>
</tr>
<tr>
<td>Jaccard 1998 ABD PT-I</td>
<td>1 76 2</td>
<td>83</td>
<td>1.2%</td>
<td>0.55 [0.05, 5.90]</td>
<td></td>
</tr>
<tr>
<td>Jaccard 1998 PNU PT-I</td>
<td>2 75 6 79</td>
<td>79</td>
<td>3.7%</td>
<td>1.23 [0.43, 3.49]</td>
<td></td>
</tr>
<tr>
<td>Lipsky 2005 PT-E</td>
<td>0 285 0</td>
<td>289</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marr 1998 PT-I</td>
<td>12 127 12</td>
<td>75</td>
<td>7.5%</td>
<td>1.00 [0.48, 2.08]</td>
<td></td>
</tr>
<tr>
<td>Namias 2007 PT-E</td>
<td>12 247 9 247</td>
<td>247</td>
<td>5.6%</td>
<td>1.33 [0.57, 3.11]</td>
<td></td>
</tr>
<tr>
<td>Niimokoshi 1993 PT-I</td>
<td>2 47 1</td>
<td>39</td>
<td>0.7%</td>
<td>1.66 [0.16, 17.62]</td>
<td></td>
</tr>
<tr>
<td>Reich 2005 PT-M</td>
<td>1 116 0</td>
<td>116</td>
<td>0.3%</td>
<td>3.00 [0.12, 72.89]</td>
<td></td>
</tr>
<tr>
<td>Schmitt 2006 PT-I</td>
<td>17 107 11</td>
<td>110</td>
<td>6.8%</td>
<td>1.59 [0.78, 3.23]</td>
<td></td>
</tr>
<tr>
<td>Solomkin 2003 PT-E</td>
<td>11 310 20</td>
<td>323</td>
<td>12.3%</td>
<td>0.57 [0.28, 1.18]</td>
<td></td>
</tr>
<tr>
<td>Yellin 2007 TC-E</td>
<td>0 24 0</td>
<td>81</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1566</td>
<td>1644</td>
<td>41.1%</td>
<td>1.03 [0.75, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>66</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: **Chi² = 9.03, df = 8 (P = 0.43); I² = 0%**
Test for overall effect: Z = 0.21 (P = 0.84)

| **1.5.2 Unclear** |             |                |        |                   |                      |
| Demir 2011 CS-C | 2 104 1 | 104             | 0.6%   | 2.00 [0.18, 21.72] |                      |
| Figueria 2001 PT-I | 6 69 6 | 68              | 3.8%   | 0.99 [0.33, 2.90] |                      |
| Graham 2002 PT-E | 2 258 1 | 271             | 0.6%   | 2.10 [0.19, 23.03] |                      |
| Ito 2010 PT-I | 12 81 20 | 82              | 12.4%  | 0.61 [0.32, 1.16] |                      |
| Joshi 2006 PT-I | 23 222 17 | 215            | 10.8%  | 1.31 [0.72, 2.38] |                      |
| Naber 2002 PT-I | 2 161 2 | 166             | 1.2%   | 1.03 [0.15, 7.23] |                      |
| Oztunk 2010 PT-C | 6 43 12 | 41              | 7.7%   | 0.48 [0.20, 1.15] |                      |
| Rea-Neto 2008 PT-D | 31 212 30 | 217         | 18.6%  | 1.06 [0.66, 1.68] |                      |
| Roy 2003 PT-E | 0 196 0      | 216             | Not estimable |                  |                      |
| Saltoglu 2010 PT-I | 0 31 0 | 33              | Not estimable |                  |                      |
| Vural 2010 PT-I | 0 33 0      | 30              | Not estimable |                  |                      |
| Winston 1998 CS-I | 6 101 5 | 102             | 3.1%   | 1.21 [0.38, 3.84] |                      |
| **Subtotal (95% CI)** | 1511         | 1545           | 58.9%  | 0.96 [0.73, 1.25] |                      |
| Total events | 90          | 94             |        |                   |                      |

Heterogeneity: **Chi² = 6.49, df = 8 (P = 0.59); I² = 0%**
Test for overall effect: Z = 0.32 (P = 0.75)

Total (95% CI) 3077 3189 100.0% 0.99 [0.80, 1.22]
Total events 156 159
Heterogeneity: **Chi² = 15.75, df = 18 (P = 0.61); I² = 0%**
Test for overall effect: Z = 0.11 (P = 0.92)
Test for subgroup differences: **Chi² = 0.13, df = 1 (P = 0.72); I² = 0%**

Figure 2. All-cause mortality at the end of follow-up for BL/BLIs versus carbapenems, stratified by risk of bias in allocation concealment. Studies are identified by the name of the first author, the year of publication and the interventions and are sorted by year of publication. PT, piperacillin/tazobactam; TC, ticarcillin/clavulanate; CS, ceftazidime/subactam; AS, ampicillin/subactam; E, ertapenem; I, imipenem; M, meropenem; C, carbapenem (study allowed more than one carbapenem); PNU, pneumonia; ABD, abdominal infection (peritonitis).
carbapenems were observed in these subgroups. Most studies were conducted in countries where ESBLs are prevalent (Table S1). The exclusion of three studies conducted in Finland, Switzerland and Sweden, where ESBLs are rarer, resulted in a similar effect estimate (RR 1.01, 95% CI 0.81–1.25). The meta-regression of RRs against study years was non-significant, showing a ratio of 1, and limiting the analyses to studies published between 2006 and 2011 resulted in an RR of 1.03 and 95% CI 0.80–0.33 (10 trials, 2264 patients), without significant heterogeneity.

Analysis by specific drugs was limited due to the scarcity of studies using BL/BLIs other than piperacillin/tazobactam. Twenty-two studies using this drug compared with any carbapenem demonstrated no significant difference between study arms (RR 0.96, 95% CI 0.78–1.19). A separate analysis for ertapenem (seven studies) versus any BL/BLI demonstrated an RR of 0.86 and a 95% CI of 0.52–1.43, and for other carbapenems (19 studies) versus any BL/BLI values of RR 1.00 and 95% CI 0.80–1.26. Thus, we could not identify differences between individual drugs in the same class.

Secondary efficacy outcomes

There were no significant differences between BL/BLIs and carbapenems with regard to failure at the end of treatment (RR 0.99, 95% CI 0.89–1.11, 25 trials, 4947 patients) or at end of the follow-up (RR 1.01, 95% CI 0.92–1.11, 22 trials, 4392 patients), with no significant heterogeneity in either analysis. Subgroup analyses by trial methods are shown in Table 1. There were no significant differences between the subgroups for all analyses.

Clinical subgroup analyses were conducted on the outcome of clinical failure at the end of treatment (Table 2). There were no significant differences between BL/BLIs and carbapenems among patients with documented Gram-negative infections (RR 1.06, 95% CI 0.84–1.34, 13 trials, 1379 patients), nosocomial infections (RR 0.98, 95% CI 0.86–1.12, 9 trials, 1844 patients) and neutropenic fever (1.01, 95% CI 0.89–1.14, 11 trials, 2509 patients). A subgroup of patients with ESBL-producing bacteria was not reported.

There were no significant differences between BL/BLIs and carbapenems in terms of microbiological failure (RR 0.94, 95% CI 0.82–1.07, 19 trials, 2788 patients) and bacterial superinfections (RR 0.94, 95% CI 0.69–1.28, 15 trials, 2678 patients), with no significant heterogeneity for either outcome (Table 1).

Other protocol-defined efficacy outcomes were usually not reported and hence could not be assessed. Development of resistance was reported in only five trials (1275 patients), with no differences between the groups (RR 1.10, 95% CI 0.66–1.83) and moderate heterogeneity ($I^2=56$%). Analyses by specific BL/BLIs and carbapenems did not reveal significant differences or trends (data not shown), although larger CIs were seen.
Table 3. Adverse events for BL/BLIs versus carbapenems

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>27</td>
<td>6837</td>
<td>1.02 (0.95–1.08)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>14</td>
<td>4194</td>
<td>0.89 (0.73–1.08)</td>
</tr>
<tr>
<td>Requiring discontinuation</td>
<td>16</td>
<td>5304</td>
<td>1.36 (1.03–1.79)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>18</td>
<td>4371</td>
<td>0.87 (0.69–1.11)</td>
</tr>
<tr>
<td>CDAD</td>
<td>6</td>
<td>2002</td>
<td>0.29 (0.10–0.87)</td>
</tr>
<tr>
<td>Diarrhoea, any</td>
<td>21</td>
<td>6579</td>
<td>1.46 (1.25–1.70)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>17</td>
<td>4659</td>
<td>0.68 (0.55–0.85)</td>
</tr>
<tr>
<td>Seizures</td>
<td>10</td>
<td>3147</td>
<td>0.43 (0.19–0.98)</td>
</tr>
</tbody>
</table>

Adverse events

The frequencies of any adverse events (RR 1.02, 95% CI 0.95–1.08, 27 trials, 6837 patients) and serious adverse events (RR 0.89, 95% CI 0.73–1.08, 14 trials, 4194 patients) were similar for BL/BLIs versus carbapenems (Table 3). The rate of adverse events requiring discontinuation of the study drug was significantly higher with BL/BLIs compared with carbapenems (1.36, 95% CI 1.03–1.79, 15 trials, 5304 patients). In terms of specific adverse events, diarrhoea was significantly more common with BL/BLIs (RR 1.46, 95% CI 1.25–1.70, 21 trials, 6579 patients), with similar RRs for piperacillin/tazobactam and other BL/BLIs. However, *Clostridium difficile*-associated diarrhoea (CDAD) was significantly more common in the carbapenem group (RR 0.29, 95% CI 0.10–0.87, 6 trials, 2002 patients). Seizures were significantly more common in the carbapenem group (RR 0.43, 95% CI 0.19–0.98, 10 trials, 3147 patients), the difference originating from studies using imipenem (RR 0.21, 95% CI 0.05–0.93, 4 trials, 822 patients).

Discussion

We pooled outcome data from RCTs comparing BL/BLIs with carbapenems for patients with sepsis. We found no differences between BL/BLIs and carbapenems in all-cause mortality (RR 0.98, 95% CI 0.79–1.20) or clinical failure at the end of treatment (RR 0.99, 95% CI 0.89–1.11). Subgroup analyses of patients more likely to have had infections caused by ESBL-producing bacteria did not reveal an advantage from using carbapenems. Adverse events requiring discontinuation were more common with BL/BLIs (RR 1.36, 95% CI 1.03–1.79), most probably related to diarrhoea, which was significantly more common with BL/BLIs (RR 1.46, 95% CI 1.25–1.70). Seizures, vomiting and CDAD were significantly more common with carbapenems. The RR of 0.29 (0.10–0.87) for CDAD denotes a 71% lower incidence with BL/BLIs, with 95% CIs ranging from a decrease of 90% to a decrease of 13%.

Previous studies examining the question of using BL/BLIs versus carbapenems specifically for infections caused by ESBL-producing bacteria were observational. For many years carbapenems were considered preferable. This was based on a multicentre prospective cohort study conducted between 1996 and 1997 that evaluated 71 patients with ESBL-producing *K. pneumoniae* bacteraemia receiving covering antibiotics, of whom 10 died. Treatment with carbapenems was associated with a significantly lower 14 day mortality than was seen with other active antibiotics on an adjusted analysis. A recent study re-examined this question, including patients with bloodstream infections due to ESBL-producing *E. coli* from six prospective cohorts. There was no significant difference in the mortality and length of hospital stay for patients treated with amoxicillin/clavulanic acid or piperacillin/tazobactam versus carbapenems. Infections originated mainly in the urinary and biliary tract in this study and the 14 day mortality was low (17/174, 9.8%). Vardakas et al. summarized the unadjusted results from all observational studies examining outcomes associated with treatment with carbapenems or other antibiotics for the treatment of bacteraemia due to ESBL-positive Enterobacteriaceae. The crude RR for death with empirical treatment was 0.91 (95% CI 0.66–1.25, 13 studies, 647 patients; RR <1 favouring carbapenems) and with definitive treatment was 0.52 (95% CI 0.23–1.13, 11 studies, 516 patients), with a large heterogeneity ($I^2 = 71\%$) that was not explained in this analysis. The differences between the studies of *K. pneumoniae* and *E. coli* bacteraemia and the heterogeneity in the meta-analysis might have arisen from a true variability in the response to antibiotics of different bacteria or in the different sources of infection associated with these pathogens.

Our analysis focused on RCTs, which is the only design that allows the testing of interventions with minimum bias, and included ~4000–5000 patients in different analyses. The main limitation is that these studies do not specifically address the core patient population with severe infections caused by ESBL-positive bacteria. The crude mortality of patients included in these RCTs at the end of follow-up was 6% (275/4581) while in the observational studies it was 19% (99/516). No subgroup analyses of ESBL-positive infections were reported. We did not identify a difference between BL/BLIs and carbapenems with different sources of infection (data not shown), but a per pathogen analysis was not possible since only a small percentage of patients had a microbiological documentation and analysis by pathogen was not performed. Finally, an important outcome and the reason to prefer BL/BLIs over carbapenems, namely the development of resistance following treatment, was reported in only a few RCTs.

A large RCT comparing a BL/BLI with a carbapenem should and can be conducted. The trial could recruit patients with severe sepsis and a high likelihood of ESBL infection using a risk score for empirical treatment, or include patients with documented bacteraemia caused by ESBL-positive bacteria, randomizing patients for a covering BL/BLI versus carbapenem. The sample size calculation should allow for showing an advantage of carbapenems as well as any equivalence of the two regimens and subgroup analyses for the main bacteria, particularly *E. coli* and *K. pneumoniae*. Paterson and colleagues are planning to initiate such a study. If our analysis can be used to predict its results, we expect no significant differences in the 30 day mortality.

Our analysis joins that of the overview of all observational studies, showing no advantage of carbapenems over BL/BLIs in the treatment of sepsis. The increased rate of CDAD with carbapenems and the dread of losing the efficacy of carbapenems as drugs of last resort speak in favour of using BL/BLIs. Further research should examine whether the decision to use carbapenems or a covering BL/BLI should be directed by pathogen, MIC,
source of infection or other factors. RCTs including patients with ESBL-positive bacteria or a high likelihood of such bacteria are necessary.

Funding
This study was carried out as part of our routine work.

Transparency declarations
None to declare.

Author contributions
M. P. and L. L. designed and planned the study, S. S. and T. A. conducted the literature search, D. Y., T. A. and S. S. extracted the data. M. P., S. S., D. Y. and L. L. analysed the data and wrote the manuscript. L. L. and M. P. supervised the study. All authors have seen and approved the final version of the manuscript.

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

References
19. Naber KG, Savov O, Salmen HC. Piperacillin 2 g/tazobactam 0.5 g is as effective as imipenem 0.5 g/clindamycin 0.5 g for the treatment of acute uncomplicated pyelonephritis and complicated urinary tract infections. Int J Antimicrob Agents 2002; 19: 95–103.


