Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by Enterobacter, Citrobacter or Serratia species: a systematic review with meta-analysis

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Objectives: This systematic review and meta-analysis compared effects of different antibiotics on mortality in patients with bloodstream infections caused by Enterobacteriaceae with chromosomal AmpC β-lactamase.

Methods: Databases were systematically searched for studies reporting mortality in patients with bloodstream infections caused by AmpC producers treated with carbapenems, broad-spectrum β-lactam/β-lactamase inhibitor (BLBLI) agents, quinolones or cefepime. Pooled ORs for mortality were calculated for cases that received monotherapy with these agents versus carbapenems. Registration: PROSPERO international prospective register of systematic reviews (CRD42014014992; 18 November 2014).

Results: Eleven observational studies were included. Random-effects meta-analysis was performed on studies reporting empirical and definitive monotherapy. In unadjusted analyses, no significant difference in mortality was found between BLBLIs versus carbapenems used for definitive therapy (OR 0.87, 95% CI 0.32–2.36) or empirical therapy (OR 0.48; 95% CI 0.14–1.60) or cefepime versus carbapenems as definitive therapy (OR 0.61; 95% CI 0.27–1.38) or empirical therapy (0.60; 95% CI 0.17–2.20). Use of a fluoroquinolone as definitive therapy was associated with a lower risk of mortality compared with carbapenems (OR 0.39; 95% CI 0.19–0.78). Three studies with patient-level data were used to adjust for potential confounders. The non-significant trends favouring non-carbapenem options in these studies were diminished after adjustment for age, sex and illness severity scores, suggestive of residual confounding.

Conclusions: Despite limitations of available data, there was no strong evidence to suggest that BLBLIs, quinolones or cefepime were inferior to carbapenems. The reduced risk of mortality observed with quinolone use may reflect less serious illness in patients, rather than superiority over carbapenems.

Introduction

Bloodstream infections (BSIs) caused by Gram-negative bacteria are a significant contributor to disease burden worldwide. Many Gram-negative bacteria possess chromosomally encoded and inducible AmpC β-lactamase genes. These include Enterobacter spp., Serratia marcescens, Citrobacter freundii, Providencia spp. and Morganella morganii. These species are sometimes informally referred to as the ‘ESCPM’ group of organisms. Serious infectious due to these organisms pose a challenge for treatment as initial in vitro antibiotic susceptibility may not effectively predict clinical efficacy. Exposure to β-lactam antibiotics may select for derepressed variants expressing high levels of AmpC, through mutations in regulatory genes. This can result in emergent resistance, with a phenotype that is resistant to penicillins, cephalosporins (except cefepime) and β-lactam/β-lactamase inhibitor (BLBLI) agents. This has been generally recognized in the context of the Enterobacter bacteraeia treated...
with third-generation cephalosporins.\textsuperscript{4,5} As such, many consider carbapenems optimal therapy for BSIs caused by these species. One alternative to carbapenems in this context might be piperacillin/tazobactam. Derepressed AmpC variants are usually resistant to piperacillin/tazobactam, yet the risk of selecting for these variants during treatment and the subsequent effect on clinical outcome is not well characterized and cannot be directly extrapolated from experience with third-generation cephalosporins.\textsuperscript{3} Furthermore, it is likely that not all AmpC producers have the same capacity for generating derepressed variants, and levels of AmpC production are highly variable between species.\textsuperscript{2} However, there are few or no randomized data to support the use directly or confirm inferior efficacy of non-carbapenems (such as piperacillin/tazobactam) for ESCPM organisms that otherwise test susceptible. As such, piperacillin/tazobactam is frequently avoided for these infections.

The objectives of this review were to: (i) identify studies that compared antibiotic treatment options for adult patients with BSI caused by AmpC-producing Enterobacteriaceae; and (ii) compare all-cause mortality for patients given either empirical or definitive monotherapy with carbapenems (meropenem, imipenem, ertapenem or doripenem), broad-spectrum BBBLI agents (piperacillin/tazobactam or ticarcillin/clavulanate), cefepime or fluoroquinolones (ciprofloxacin, norfloxacin, levofloxacin or moxifloxacin).

**Methods**

This study is registered with the PROSPERO international prospective registry of systematic reviews (CRD42014014992; registered 18 November 2014, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD 42014014992). This study has been reported in accordance with the PRISMA guidelines on reporting systematic reviews and meta-analyses.\textsuperscript{6}

**Literature search and study selection**

The PICOS criteria used to select studies were as follows:

- **Patient population/problem:** patients with BSIs caused by Gram-negative bacteria with chromosomally encoded AmpC β-lactamase
- **Intervention:** antibiotic therapy, including use of a carbapenem in comparison with non-carbapenem agents
- **Comparison:** to compare the efficacy of broad-spectrum BBBLI agents (e.g. piperacillin/tazobactam), cefepime or fluoroquinolones with carbapenems (standard therapy)
- **Outcome:** all-cause mortality
- **Setting:** hospitalized patients

Studies were considered if they reported data on patients with Gram-negative BSI caused by Enterobacteriaceae with intrinsic chromosomally encoded AmpC β-lactamase, namely, Enterobacter, Serratia, Citrobacter, Providencia and Morganella spp. Any type of study, except case reports, was considered. We selected studies that included carbapenem therapy in comparison with other antibiotic therapies either as empirical or definitive treatment. EMBASE, PubMed, the Cochrane database and Scopus were searched from January 1980 to August 2015. The search protocol used was: (Enterobacter OR Serratia OR Citrobacter OR Providencia OR Morganella) AND (bacteremia OR bacteraemia OR bloodstream infection) AND (piperacillin/tazobactam OR ticarcillin/clavulanate OR cefepime OR carbapenem OR beta-lactam-beta-lactamase inhibitor OR quinolone OR mortality). An additional search was performed in Google Scholar with the same search criteria as that applied to the electronic databases. Additional data were obtained by contacting all authors identified for inclusion, of which six responded with additional data and three with patient-level information such as comorbidity scores. One author supplied data from an, as yet, unpublished study (P. N. Harris, S. Paynter, C. M. Pedersen, A. Vasudevan and J. K. Ferguson, unpublished results) and additional data were obtained from the Australian Group for Antimicrobial Resistance (AGAR) 2013 national survey on Gram-negative bacteraemia.\textsuperscript{7} Studies were excluded if they did not report mortality associated with each class of antibiotic therapy, or if the authors were unable to provide such data on request. Studies that only included non-BSI infections were also excluded.

**Data extraction and management**

Three authors, P. N. A. H., A. W. S. and J. Y. W., independently screened search results according to the PICOS criteria. Details of each study were extracted and tabulated. Data for patient demographics and clinical comorbidity or physiological risk scores were extracted from the original publications. The number of cases treated with each antibiotic, either as empirical or definitive therapy, and the associated all-cause mortality was recorded. All authors of selected studies were contacted for additional patient-level data on comorbidity according to each antibiotic treatment to facilitate the adjustment of treatment effect according to patient disease severity.

**Outcome measures and definitions**

The time to follow-up was taken as defined by each individual study, and 30 day mortality was used as the primary outcome where several follow-up times were reported. Carbapenems were used as the comparator drug against BBBLIs, cefepime or fluoroquinolones when used both as empirical treatment (i.e. agent selected prior to susceptibility testing availability) and definitive treatment (i.e. agent selected once susceptibility testing available).

**Statistical analysis**

The Newcastle–Ottawa Quality Assessment Scale\textsuperscript{8} was used to assess for bias in the included studies, which were all observational studies of either a cohort or case–control design. Unadjusted ORs with 95% CIs for mortality were calculated between BBBLIs versus carbapenems, cefepime versus carbapenems or quinolones versus carbapenems for each individual study. ORs were then pooled using a random-effects model. Heterogeneity between studies was assessed using the $\chi^2$ (P < 0.01 suggesting significant heterogeneity) and I$^2$ tests. For studies where comorbidity data were available, patient-level data were analysed and pooled ORs were estimated using a generalized mixed-effect logistic regression model adjusting for age, sex and illness severity score as fixed effects and study level variability as a random-effects model. The GLIMMIX procedure in the SAS 9.4 version was used for the analysis. Sensitivity analyses were also performed to assess the impact of outlying individual studies on the pooled effect estimate.

**Results**

Figure 1 summarizes the selection process for studies. Eleven studies\textsuperscript{7,8–17} were included in the final meta-analysis, with three study authors\textsuperscript{3,11} providing additional patient-level data to aid calculation of adjusted ORs. Table 1 summarizes the selected study characteristics. Only four studies were multicentre, including 25 different institutions within a single country (Australia),\textsuperscript{14,17} hospitals within a health administrative region of Canada,\textsuperscript{11} three medical centres in north-eastern USA\textsuperscript{13,14} or two centres in a single US city.\textsuperscript{9} One study included patients identified by a single laboratory that served several different regional hospitals, whereas the remainder studied patients from single-centres...
only. There were no randomized controlled trials identified. Only one study made no adjustment for confounding factors such as comorbidity or severity of illness. Most studies adjusted for confounders that potentially affect mortality and two studies used propensity scores to adjust for the likelihood of receiving carbapenem as empirical therapy. Most studies included patients with BSI caused by *Enterobacter* spp. (predominantly *Enterobacter cloacae* or *Enterobacter aerogenes*), but other AmpC-producing species were included in some studies. One study also included a small number of Enterobacteriaceae with plasmid-acquired AmpC β-lactamase. One study included BSI caused by ESBL-producing *E. cloacae*; only patient-level data from the ESBL-negative *E. cloacae* BSI control cases from this study were included in the meta-analysis.

Mortality outcomes were defined with minor differences between studies. Some used all-cause 30 day mortality, 14 day mortality, or in-hospital mortality. Most studies included both community- and hospital/healthcare-acquired BSI, although this was not defined in two studies. Most studies declared conflicts of interest in their acknowledgements, usually in the form of grant support from pharmaceutical companies. Additional funding sources encompassed institutional sources and research funds.

In seven studies, the purpose was to identify risk factors for mortality or other measures of poor outcome in BSI. Five studies reported measures of clinical or microbiological failure in addition to mortality. No study was specifically designed to compare directly the efficacy of BLBLIs such as piperacillin/tazobactam with carbapenems, although in one study the only factor independently associated with improved survival was the empirical use of piperacillin/tazobactam. Siedner et al. reported equivalent efficacy for cefepime when compared with carbapenems for *Enterobacter* BSI, even after adjustment for comorbidities and the propensity to receive carbapenems. Similarly, two studies reported favourable outcomes with cefepime as a potential alternative to carbapenems for BSI caused by *E. cloacae* or other AmpC-producing species.

Factors associated with increased mortality in selected studies included markers of illness severity (such as the McCabe and Jackson category, the presence of septic shock or higher...
<table>
<thead>
<tr>
<th>First author/ year</th>
<th>Study design, period, region</th>
<th>N</th>
<th>Bacterial species</th>
<th>Population characteristics</th>
<th>Bacteraemia characteristics</th>
<th>Isolates with AmpC derepressed phenotype</th>
<th>Comorbidity measures</th>
<th>Adjustments</th>
<th>Outcomes</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcos, 2008</td>
<td>prospective cohort study analysed retrospectively, 1991–2006, Spain</td>
<td>370</td>
<td><em>E. cloacae</em> (72%), <em>E. aerogenes</em> (23%)</td>
<td>adult, cirrhosis (9%), DM (14%), chronic lung (5%), renal failure (7%), malignancy (haem) (15%), SO malignancy (27%), BM transplant (4%), SO transplant (4%), McCabe [non-fatal (26%), ultimately fatal (48%), rapidly fatal (6%)]</td>
<td>vascular catheter (31%), GI and biliary tract (19%), LRT (4%), SSTI (2%), unknown (24%)</td>
<td>20.4%</td>
<td>McCabe and Jackson multivariable regression model</td>
<td>30 day mortality</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Qureshi, 2011</td>
<td>retrospective cohort study, 2005–08, USA</td>
<td>135</td>
<td><em>E. cloacae</em></td>
<td>adult, DM (32%), CRF (16%), liver disease (24%), malignancy (16%), transplant (28%), malignancy (32%), steroids (34%), liver disease (6%)</td>
<td>urine (14%), pneumonia (11%), abdominal (5%), line related (32%), unknown (38%)</td>
<td>27.4%</td>
<td>APACHE II, Charlson, ICU admission</td>
<td>28 day mortality</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>O’Neal, 2012</td>
<td>retrospective cohort study, 2006–08, USA</td>
<td>95</td>
<td><em>E. cloacae</em> (84%), <em>E. aerogenes</em> (16%)</td>
<td>adult, DM (25%), CAD (22%), CVD (13%), renal disease (36%), pulmonary disease (16%), transplant (28%), malignancy (32%), steroids (34%), liver disease (6%)</td>
<td>urine (6%), pulmonary (13%), bone and joint (3%), deep organ space (16%), unknown (62%)</td>
<td>33%</td>
<td>APACHE II, Charlson, ICU admission</td>
<td>multivariate logistic regression</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hilty, 2013</td>
<td>retrospective cohort study, 2008–11, Switzerland</td>
<td>43</td>
<td><em>E. cloacae</em></td>
<td>adult, mean Charlson score 4.3</td>
<td>abdominal (37%), urine (21%), CVC (5%), IV (7%), respiratory (5%), other (5%), unknown (21%)</td>
<td>35.3%</td>
<td>Charlson NA</td>
<td>in-hospital mortality, persistence of presenting signs of infection after 72 h</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Tamma, 2013</td>
<td>prospective propensity-score matched cohort, 2010–12, USA</td>
<td>64 (31 BSI)</td>
<td><em>E. cloacae</em> (53%), <em>E. aerogenes</em> (32%), <em>S. marcescens</em> (15%), <em>C. freundii</em> (1%)</td>
<td>adult, immunocompromised (43%), liver disease (48%), lung disease (18%), renal disease (56%), CVD (33%), neurological disease (23%)</td>
<td>abdominal (52%), pneumonia (47%); note: only BSI cases included in this analysis</td>
<td>24.1%</td>
<td>ICU admission, McCabe score, previous MDRGN propensity-score matched analysis</td>
<td>30 day mortality</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Chaubey, 2014</td>
<td>prospective cohort study, 2000–08, Canada</td>
<td>458</td>
<td>Enterobacter (49%), <em>Serratia</em> (16%), <em>Citrobacter</em> (11%)</td>
<td>adult, malignancy (18%), CHF (14%), DM (16%), dementia (2%), liver disease (8%), renal disease (14%)</td>
<td>urinary (19%), biliary (14%), bowel (7%), pneumonia (7%), SSTI (2%), bone and joint (2%), unknown (49%)</td>
<td>—</td>
<td>Charlson multivariable logistic regression</td>
<td>in-hospital mortality</td>
<td>9</td>
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<tr>
<td>Huh, 2014</td>
<td>retrospective cohort study 2004–11, Seoul, Korea</td>
<td>192</td>
<td>Enterobacter spp.</td>
<td>adults, malignancy (100%), DM (16%), cardiac (5%), liver disease (17%), renal disease (3%), pulmonary disease (3%), neurological disease (3%), SO transplantation (3%)</td>
<td>biliary (24%), abdominal (11%), respiratory (9%), urinary (15%), catheter (6%), skin (6%), GI (3%), unknown (28%)</td>
<td>27.6%</td>
<td>Pitt, ICU admission multivariable logistic regression</td>
<td>30 day mortality</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>AGAR, 2014</td>
<td>prospective cohort study, 2013, Australia</td>
<td>396</td>
<td><em>E. cloacae</em>, <em>E. aerogenes</em>, <em>S. marcescens</em>, <em>C. freundii</em>, <em>M. morganii</em></td>
<td>adults and children</td>
<td>NA</td>
<td>26.0% (E. cloacae only)</td>
<td>NA</td>
<td>NA</td>
<td>30 day mortality</td>
<td>7</td>
</tr>
<tr>
<td>Study design, period, region</td>
<td>Isolates with derepressed AmpC phenotype</td>
<td>Study design, period, region</td>
<td>Isolates with derepressed AmpC phenotype</td>
<td>Study design, period, region</td>
<td>Isolates with derepressed AmpC phenotype</td>
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</table>
| Prospective, from single centres and often with limited numbers of patients and infrequent primary outcomes. However, using pooled mortality from these studies, there does not appear to be a clear signal that non-carbapenems are an inferior option for BSIs caused by AmpC producers (mainly Enterobacter spp.). Although emergent resistance, by augmented AmpC production in variants selected during exposure to β-lactam therapy, is a reasonable concern when using BLBLIs, there is only scant clinical evidence that this translates to poor clinical outcome. There was only one clearly documented case of derepressed AmpC-mediated resistance occurring in the context of treatment with piperacillin/tazobactam for *E. cloacae* BSI.12

This meta-analysis included 232 and 179 observations in patients treated with a BLBLI as empirical or definitive therapy, respectively. There was no significant difference in risk of death for the BLBLIs used either as empirical or definitive therapy than average Charlson scores12), diabetes mellitus10 or an unknown source of infection.14 The presence of expanded-spectrum cephalosporin resistance in Enterobacter BSI was associated with increased mortality in two studies10,12 and clinical failure in one study.13

**Meta-analysis**

Crude mortality rates reported for each study according to the use of carbapenems, BLBLIs, cefepime or fluoroquinolones, either as empirical or definitive therapy, are summarized in Table 2. Using pooled unadjusted ORs for mortality for each antibiotic class compared with carbapenems, only the definitive use of fluoroquinolones was associated with improved outcome (OR 0.39, 95% CI 0.19–0.78). For all other agents, there were no significant differences in ORs for mortality when compared with carbapenems (Table 3). Forest plots are presented in Figures 2–4 for definitive therapy of the BLBLIs, fluoroquinolones and cefepime respectively. In three studies, patient-level comorbidity data were available, from which adjusted ORs could be calculated, to investigate the confounding effect of comorbidity. The results of ORs, unadjusted and adjusted for illness-severity scores, for these three studies are summarized in Table 4. There were insufficient data to calculate meaningful adjusted ORs for empirical therapy.

To assess heterogeneity between studies, we undertook a sensitivity analysis to exclude the effect of outlier studies on outcomes for use of the BLBLIs versus carbapenems as definitive therapy. Of eight studies comparing the BLBLIs with carbapenems, two7,11 had an increased risk of mortality for the BLBLI treatment group while the rest had a decreased risk, causing significant heterogeneity in the estimates between studies. Excluding these outlier studies one at a time dropped the pooled effects estimate, although these remained statistically non-significant. However, dropping both studies resulted in the heterogeneity becoming non-significant and the overall estimate dropped by almost 50% (from 0.87 to 0.46) and was statistically significant (see Figures S1 and S2, available as Supplementary data at JAC Online).

**Discussion**

Evidence from randomized controlled trials is lacking to help define optimal treatment options for resistant Gram-negative bacteria. Studies to date have been observational, usually retrospective, from single centres and often with limited numbers of patients and infrequent primary outcomes. However, using pooled mortality from these studies, there does not appear to be a clear signal that non-carbapenems are an inferior option for BSI caused by AmpC producers (mainly Enterobacter spp.). Although emergent resistance, by augmented AmpC production in variants selected during exposure to β-lactam therapy, is a reasonable concern when using BLBLIs, there is only scant clinical evidence that this translates to poor clinical outcome. There was only one clearly documented case of derepressed AmpC-mediated resistance occurring in the context of treatment with piperacillin/tazobactam for *E. cloacae* BSI.12

This meta-analysis included 232 and 179 observations in patients treated with a BLBLI as empirical or definitive therapy, respectively. There was no significant difference in risk of death for the BLBLIs used either as empirical or definitive therapy...
Table 2. Reported mortality by antibiotic class for empirical and definitive therapy

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Unadjusted mortality [n/N (%)] by antibiotic class when used for empirical or definitive therapy</th>
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<tbody>
<tr>
<td>Marcos, 2008</td>
<td>10/57 (17.5) carbapenems, definitive 10/41 (24.4) carbapenems, empirical 2/19 (10.5) 1/38 (2.6) 8/111 (7.2) 6/48 (12.5)</td>
</tr>
<tr>
<td>Qureshi, 2011</td>
<td>2/9 (22.2) carbapenems, definitive 2/8 (25.0) carbapenems, empirical 0/14 (6.3) 2/32 (5.3) 1/19 (22.2) 2/9 (10.0) 3/30 (11.1)</td>
</tr>
<tr>
<td>O'Neal, 2012</td>
<td>14/30 (46.7) carbapenems, definitive 0/7 (16.7) carbapenems, empirical 2/8 (25.0) 1/19 (5.3) 1/6 (16.7) 1/6 (8.3) 3/16 (18.8)</td>
</tr>
<tr>
<td>Hilty, 2013</td>
<td>NA 1/5 (20.0) carbapenems, definitive 1/4 (25.0) carbapenems, empirical 0/1 (NA) 2/18 (NA)</td>
</tr>
<tr>
<td>Tamma, 2013</td>
<td>4/16 (25.0) carbapenems, definitive 0/16 (NA) carbapenems, empirical 10/22 (45.5) 15/131 (11.5) 30/231 (13.0) 10/76 (25.0) 1/4 (33.3) 1/3 (15.2) 46/302 (25.8) 26/226</td>
</tr>
<tr>
<td>Chaubey, 2014</td>
<td>5/45 (11.1) carbapenems, definitive 0/16 (NA) carbapenems, empirical 10/22 (45.5) 15/131 (11.5) 30/231 (13.0) 10/76 (25.0) 1/4 (33.3) 1/3 (15.2) 46/302 (25.8) 26/226</td>
</tr>
<tr>
<td>Huh, 2014</td>
<td>6/20 (30.0) carbapenems, definitive 4/6 (66.7) carbapenems, empirical 1/18 (5.6) 3/16 (18.8) 1/36 (2.8) 2/5 (40.0) 3/23 (13.0) 3/27 (11.1) 11/97 (11.3) 12/54</td>
</tr>
<tr>
<td>AGAR, 2014</td>
<td>19/265 (7.2) carbapenems, definitive NA 9/50 (5.6) carbapenems, empirical 2/49 (18.0) 2/13 (4.1) 2/13 (15.4) 32/377 (8.5)</td>
</tr>
<tr>
<td>Siedner, 2014</td>
<td>NA 5/19 (26.3) carbapenems, definitive NA 0/3 (NA) carbapenems, empirical NA 0/44 (NA) 7/43 (16.3) 12/109 (11.0)</td>
</tr>
<tr>
<td>Harris, 2015</td>
<td>4/30 (13.3) carbapenems, definitive 0/5 (NA) carbapenems, empirical 1/9 (11.1) 0/13 (0.2) 2/68 (2.9) 1/5 (20.0) 1/5 (0.2) 0/1 (0.0) 0/0 (0.0) 7/108 (6.5) 1/23 (4.3)</td>
</tr>
<tr>
<td>Lin, 2015</td>
<td>4/14 (28.6) carbapenems, definitive NA 8/41 (19.5) carbapenems, empirical NA 1/5 (0.2) 1/5 (0.2) 9/49 (18.4) 9/49 (18.4) 22/109 (20.2)</td>
</tr>
<tr>
<td>Totals</td>
<td>68/486 (14.0) carbapenems, definitive 22/107 (20.6) carbapenems, empirical 32/179 (17.9) 24/245 (9.8) 46/538 (8.6) 22/194 (11.3) 23/147 (15.6) 20/143 (14.0) 169/1350 (12.1) 88/689 (12.8)</td>
</tr>
</tbody>
</table>

FQs, fluoroquinolones; NA, data not reported.

*Studies with patient-level data available for calculating adjusted ORs.*
when compared with carbapenems. In the sensitivity analysis, we
excluded two studies with outlying ORs that contributed to signifi-
cant heterogeneity in the pooled estimate of all studies reporting
outcomes for BLBLIs ($I^2 = 65.5\%$, $P = 0.005$). This resulted in much
less heterogeneity ($I^2 = 0.0\%$, $P = 0.630$) and a significant pooled
effect estimate in favour of the BLBLIs (0.45; 95% CI: 0.21–1.00).
One excluded study carried a large statistical weight but used a
different design (a nationwide survey of Gram-negative BSI) in
comparison with other studies. Treatment allocation was defined
as ‘principal antibiotic’, with no clear distinction between empirical
or definitive therapy or whether combination therapy was
included.\(^7\) The other excluded study in the sensitivity analysis
showed extreme differences in the outcome for piperacillin/tazo-
bactam as an empirical or definitive choice.\(^11\) It was the most
commonly used empirical agent, where it was associated with a
low mortality (15 of 131; 11.5%), yet was only rarely used as
definitive therapy, but showed a markedly different mortality out-
come in this context (10 of 22; 45.5%). However, it is unclear what
may have accounted for these differences and why these out-
comes were inconsistent with other studies.

Use of fluoroquinolones for definitive therapy showed a signifi-
cantly decreased risk of mortality in the unadjusted analysis.

## Table 3. Pooled unadjusted ORs for mortality by antibiotic therapy

<table>
<thead>
<tr>
<th>Antibiotic comparisons</th>
<th>Number of studies, definitive/empirical</th>
<th>Definitive therapy number of patient deaths/number treated (%)</th>
<th>OR (95% CI)</th>
<th>Empirical therapy number of patient deaths/number treated (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLBLIs versus carbapenems</td>
<td>8/8</td>
<td>32/179 (17.9%) versus 64/474 (13.5%)</td>
<td>0.87 (0.32–2.36)</td>
<td>24/232 (10.3%) versus 22/107 (20.6%)</td>
<td>0.48 (0.14–1.60)</td>
</tr>
<tr>
<td>Fluoroquinolones versus</td>
<td>7/8</td>
<td>48/541 (8.9%) versus 64/474 (13.5%)</td>
<td>0.39 (0.19–0.78)</td>
<td>22/195 (11.3%) versus 22/107 (20.6%)</td>
<td>0.66 (0.25–1.75)</td>
</tr>
<tr>
<td>carbapenems</td>
<td></td>
<td></td>
<td>($I^2 = 35.1%$)</td>
<td></td>
<td>($I^2 = 21.3%$)</td>
</tr>
<tr>
<td>Cefepime versus</td>
<td>6/7</td>
<td>17/150 (11.3%) versus 58/433 (13.4%)</td>
<td>0.61 (0.27–1.38)</td>
<td>20/143 (14.0%) versus 12/66 (18.2%)</td>
<td>0.60 (0.17–2.20)</td>
</tr>
<tr>
<td>carbapenems</td>
<td></td>
<td></td>
<td>($I^2 = 31.6%$)</td>
<td></td>
<td>($I^2 = 50.5%$)</td>
</tr>
</tbody>
</table>

Bold text indicates $P<0.05$.
However, using data adjusted for confounders, these beneficial effects were attenuated. Given that fluoroquinolones are the only orally active agent in these comparisons, it is highly likely that bias exists in fluoroquinolones being used as ‘step-down’ therapy in patients with less severe or complex disease, although this cannot be ascertained directly from the data. As such, we would be cautious of adding too much weight to this finding.

There was considerable heterogeneity in the target organisms, outcome measures and study design among the included studies. The majority of studies attempted to adjust for confounders such as illness severity or other comorbid conditions. When crude ORs for mortality were adjusted for a limited number of potential confounders in the three studies for which additional data were available, the non-significant trends favouring non-carbapenems were diminished, suggesting that carbapenems may be more likely to be administered to patients at higher risk of mortality. Such effects may mask any potential benefits of carbapenems on outcome. We attempted to account for this by calculating ORs adjusted for such confounders using patient-level data for a subset of studies. However, small sample sizes and a limited range of variables with which to adjust limited the analysis.

To accurately determine the optimal therapies for BSI caused by ESCPM organisms we require studies with a more robust design, specifically constructed to address these questions in terms of patient-centred outcomes. Ideally, this should be in the form of a randomized controlled trial. A pilot randomized controlled trial comparing piperacillin/tazobactam with meropenem for BSI caused by AmpC producers is actively recruiting (Australia and New Zealand Clinical Trials Registry; ACTRN12614001211651, ‘MERINO-2 Trial’; https://www.anzctr.org.au). We believe such pragmatic, investigator-initiated studies are a pathway to answering such important clinical questions for the future.

Many laboratories restrict the reporting of antibiotic susceptibility results to a limited range of agents for ESCPM organisms, excluding third-generation cephalosporins as well as other β-lactams or BLBLIs. The perceived adverse effect profiles of alternative therapy for ESCPM organisms (e.g. trimethoprim/sulfamethoxazole or aminoglycosides) may encourage a low threshold for carbapenem or fluoroquinolone use. In a recent survey of infectious disease physicians and microbiologists in Australasia, carbapenems were preferred for Enterobacter BSI by 58.3% of respondents.18 Despite their clinical utility, excessive use of carbapenems may drive carbapenem resistance,19 and quinolone overuse has been associated with increased risk of MRSA and Clostridium difficile infections.20,21 Of greatest concern in recent years has been the widespread global dissemination of carbapenemase genes in common Enterobacteriaceae such as *Klebsiella pneumoniae* or *Escherichia coli*.22,23 *Enterobacter* spp. and other AmpC producers may develop carbapenem resistance via acquisition of carbapenemase genes24,25 or via derepression of AmpC in association with changes in outer membrane proteins.26 As such there is an urgent need to re-evaluate current antibiotic use and explore alternative carbapenem-sparing options for these common infections. New BLBLI agents that contain inhibitors of AmpC, such as ceftazidime/avibactam, are now available and have shown utility for a variety of clinical syndromes such as complicated urinary tract infection and intra-abdominal infections.27,28 However, no
studies have yet specifically assessed the efficacy of this agent for BSI. Furthermore, in the trials of ceftazidime/avibactam reported to date, microbiologically proven cases of infection caused by AmpC-producing Enterobacteriaceae have been too infrequent to directly evaluate the clinical efficacy of this agent for this group of organisms.27,28

Several limitations that affect the results of this meta-analysis are acknowledged. Given the retrospective nature of data from sample studies, risk of bias in treatment distribution is highly likely. This would also affect duration, dosage and route of administration. We defined the BLBLI treatment category as including both piperacillin/tazobactam and ticarcillin/clavulanate. Although these are both broad-spectrum agents, to which ESCPM species are usually susceptible, the inhibitor components have different properties with respect to AmpC. Clavulanate is a potent inducer but a poor inhibitor of AmpC, whereas tazobactam is a weaker inducer but not an efficient inhibitor.2 However, in only one study were six patients given ticarcillin/clavulanate as definitive therapy, so this source of heterogeneity is likely to be minimal.

Although this analysis sought to evaluate patients with BSI caused by a range of AmpC-producing Enterobacteriaceae, the number of non-Enterobacter cases were few (Providencia in particular was limited to only one recorded case). The dearth in available data limits the significance of outcome results for non-Enterobacter species. Few studies differentiated ESBL-producing from AmpC derepressed isolates either by phenotypic or molecular testing.

**Figure 4.** Forest plot of unadjusted ORs for mortality in patients given definitive therapy with cefepime versus carbapenems.

**Table 4.** Logistic regression analysis of patient-level data from three studies investigating the confounding effects of age, sex and illness severity on mortality outcomes for comparisons of definitive therapy

<table>
<thead>
<tr>
<th>Comparison by definitive therapy</th>
<th>Number of patient deaths/number treated (%)</th>
<th>Adjusted for age and sex</th>
<th>Adjusted for age, sex and illness severitya</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>adjusted OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>BLBLI versus carbapenem</td>
<td>3/27 (11.1%) versus 10/69 (14.5%)</td>
<td>0.72</td>
<td>0.18–2.93</td>
</tr>
<tr>
<td>Quinolone versus carbapenem</td>
<td>7/104 (6.7%) versus 10/69 (14.5%)</td>
<td>0.39</td>
<td>0.13–1.17</td>
</tr>
<tr>
<td>Cefepime versus carbapenem</td>
<td>3/34 (8.8%) versus 10/69 (14.5%)</td>
<td>0.46</td>
<td>0.11–1.94</td>
</tr>
</tbody>
</table>

aAdjusted for illness severity (either SAPS II or APACHE II scores); study included in the model as a random effect.
In only one study were we able to obtain patient-level data to exclude ESBL producers from our analysis, although a small number of ESBL-producing Enterobacter spp. existed in at least one other study.

Conclusions
No randomized controlled trials have been reported that specifically compare antibiotic treatment options for BSI caused by ESCPM organisms. We urgently need to define ‘carbapenem-sparing’ options for these infections to limit selection pressure for carbapenem resistance in Gram-negative bacilli. Existing studies are few in number, heterogeneous and limited to observational studies, usually from a single centre and of a retrospective design, underpowered to assess the effects of antibiotic choice on mortality outcomes. This meta-analysis attempts to combine mortality data from the existing literature to compare antibiotic choice for empirical or definitive therapy. Crude mortality data would suggest that no significant differences exist between BLBLIs or cefepime when used for empirical or definitive therapy. Fluoroquinolones were associated with reduced risk of death when used for definitive treatment, but this is likely to be confounded by comorbid illness. When compared with carbapenems, non differences in the use of non-carbapenem agents as definitive therapy were found in studies where patient-level data were available to adjust for potential confounders. Given the clear limitations of the current evidence base, we believe randomized controlled trials are warranted to clarify these uncertainties.

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None to declare.

Author contributions
P. N. A. H. and D. L. P. initiated the concept for the study. P. N. A. H., J. Y. W., A. W. S. and A. A. A. performed the literature review, study selection and data extraction, with assistance from S. P. and R. R. H. Additional data was supplied by P. N. A. H., Y. D., C. S. O., T. R. T. and K. H. from their original studies. N. P. and R. R. H. performed the statistical analysis. P. N. A. H., J. Y. W., A. A. A. and A. W. S. wrote the first and final manuscript drafts. All authors contributed to the writing of the manuscript and approved the final submitted version.

Supplementary data
Figures S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


