

Beta-Lactam/Beta-Lactamase Inhibitor Therapy for Potential AmpC-Producing Organisms: A Systematic Review and Meta-Analysis

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The optimal treatment for potential AmpC-producing *Enterobacteriaceae*, including *Serratia*, *Providencia*, *Citrobacter*, *Enterobacter*, and *Morganella* species, remains unknown. An updated systematic review and meta-analysis of studies comparing beta-lactam/beta-lactamase inhibitors with carbapenems in the treatment of bloodstream infections with these pathogens found no significant difference in 30-day mortality (OR, 1.13; 95% CI, 0.58 – 2.20).

Key words. *ampC*; bacteremia; beta-lactamase; Beta-Lactam; carbapenem.

Widespread use of third-generation cephalosporins has resulted in the emergence of organisms that possess broad spectrum beta-lactamases. These enzymes are classified according to their amino acid structure and display variable affinity to different beta-lactams. Certain *Enterobacteriaceae*, including *Serratia*, *Providencia*, *Citrobacter*, *Enterobacter*, and *Morganella* species, can carry a gene, *ampC*, which encodes a broad-spectrum beta-lactamase that most beta-lactamase inhibitors cannot inactivate. When exposed to the selective pressure of beta-lactam antibiotics, these organisms have the potential to express this enzyme 10- to 100-fold above baseline levels [1].

The most recent Clinical and Laboratory Standard Institute (CLSI) guidelines suggest reporting susceptibility data for *Enterobacter spp.*, *Citrobacter spp.*, and *Serratia spp.* based on phenotypic testing. Although these organisms may become resistant after initiation of therapy, the CLSI guidelines do not recommend initial supplemental investigations for inducible resistance [2]. Yet, some studies suggest that hydrolysable beta-lactam therapy, including third-generation cephalosporins and beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, may be associated with an increased risk of treatment failure in cases of infections caused by potential AmpC-producing organisms [3]. Consequently, their use is often discouraged in clinical practice [4] and many clinical laboratories either directly edit susceptibility reports or issue warning messages favoring the use of other antibiotics. For this reason, clinicians may prescribe alternate therapies, including carbapenems, which may favor the emergence of other multidrug resistant organisms.

Previous studies evaluating BL/BLIs in the treatment of potential AmpC-producing organisms are of relatively small sample size and have had varying results. To further contribute to our knowledge on this topic, we updated a previous systematic review and meta-analysis of studies on this issue [5] and included results from a retrospective chart review of cases in our institution. The goal was to update the estimated risk of 30-day mortality among patients who received BL/BLIs as definitive therapy compared to those who received carbapenem therapy.

METHODS

This meta-analysis was performed according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [6]. We updated a previously published study comparing carbapenems to BL/BLIs for the definitive therapy [5] of bloodstream infections (BSIs) involving potential AmpC-producing *Enterobacteriaceae*. We extended the authors' original search strategy, which ended in August 2015, up to October 2018 and included the results from our own unpublished retrospective cohort (described in the [Supplementary Appendix](#)). We queried electronic databases, including EMBASE, PubMed, the Cochrane database, and Scopus for articles of interest. The search protocol used was the following: (*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). Searches were limited to human studies published in English or French. Additional articles were identified from references of included studies.

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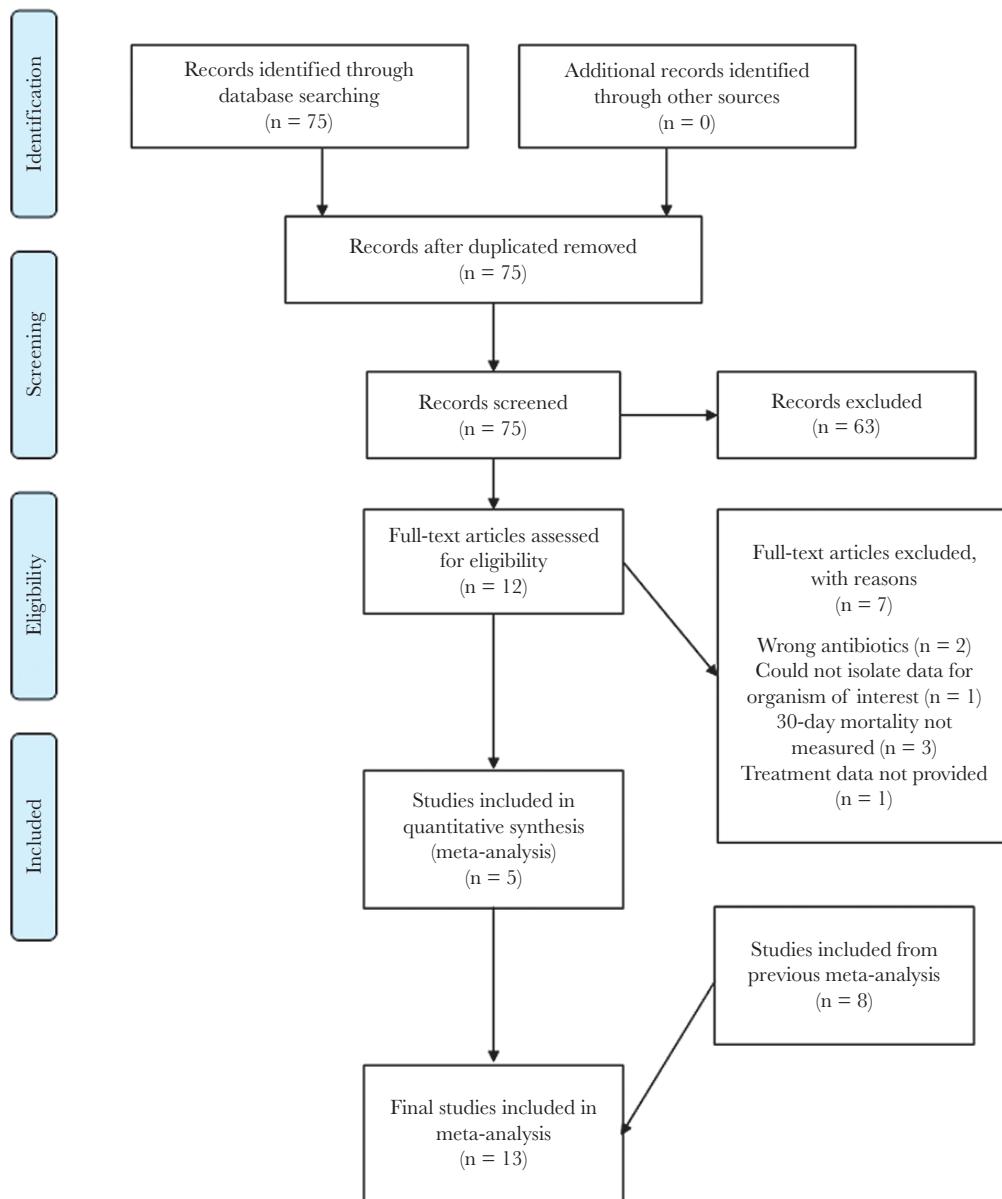
Study Selection and Data Extraction

Studies were included if they reported on patients with BSIs caused by organisms that may harbor inducible AmpC resistance (*Serratia*, *Providencia*, *Citrobacter*, *Enterobacter*, or *Morganella* species), where patients were definitively treated with either a carbapenem or a BL/BLI, and where mortality was the primary outcome. There were no specific study selection criteria based on study design or study quality. Two reviewers (M.P.C. and T.C.L.) screened the potentially relevant studies by title and abstract, and then M.P.C. assessed their eligibility and quality by full-text review. Two authors (M.P.C. and K.D.) then independently extracted data from

each relevant study. Data on mortality by treatment assignment was extracted from each source paper. When this was unavailable, the corresponding authors were contacted for additional data for inclusion. There were no discrepancies in extraction. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale [7], but there was no quality threshold to be included.

Outcome Measures and Statistical Analysis

Unadjusted odds ratios (ORs) for mortality within 30 days were calculated between BL/BLIs versus carbapenems as definitive therapy in the treatment of BSI with potential AmpC-producing



- Wrong antibiotics (n = 2) Could not isolate data for organism of interest (n = 1) 30-day mortality not measured (n = 3) Treatment data not provided (n = 1)

Figure 1. Flowchart of the Identification, Screening, and Inclusion and Exclusion of Studies

Table 1. Study Characteristics

First Author/ Year	Study Design, Period, Region	N	Bacterial Genus	Population Characteristics	Bacteremia Characteristics	Isolates With AmpC Phenotype	Comorbidity Measures	Adjustments	Outcomes Included in the Meta-analysis	NOS
Cheng L, 2017	Retrospective, case-control study, 2009–15, USA	165	<i>Enterobacter</i> , (62%) <i>Citrobacter</i> , (10%) <i>Serratia</i> (27%)	Adult, male (59%), neutropenia (6%), immune suppression (26%), RRT (6%), ICU admis- sion (40%), septic shock (24%)	Urinary (24%), IAI (20%), LRT/WAP (17%), cath- eter related (13%), SST/surgical (9%), gut translocation (8%), multiple (2%), un- known (12%)	152 isolates available for testing, of which 140 (92.1%) are resistant to ceftioxi- m and 129 (84.9%) were genotype positive	CCI, ICU ad- mission, Pitt bac- teremia score	Propensity- score matched analysis	30-day mortality and persistent bac- teremia at ≥72 h from the time of treatment initi- ation	8
Erlanger, 2017	Retrospective case-control study, 1997–2014, Israel	136	<i>Morganella</i> (100%)	Adult, male (48%), community- acquired infection (32%), HCF acquired (68%), admis- sion to medical ward (69%), debilitative state (62%), sur- gical (24%), ICU (7%), mean Charlson score 7.3	Soft tissue (30.1%), Primary bacteremia (25.7%), GI/ hepatobiliary 19.9%, urinary (19.9%), CLABSI (2.9%), respi- ratory (1.5%)	20% resistant to 3 rd generation cephalosporins	CCI	Multivariate logistic re- gression	30-day mortality	7
Harris, 2017 (includes data from Harris 2015)	Retrospective case-control study, 1998–2015, Australia	159	<i>Enterobacter</i> (80%), <i>Klebsiella</i> (20%)	Adult, male (59%), immune sup- pression (40%), community- acquired (19%) vs healthcare (81%); admission to med/ surg (58%), hematology and oncology (28%), ICU (21%) and renal (14%)	Line-associated (43%), non-line associated (55%)	48% ampC phenotype	SAPS II score	Multivariate logistic re- gression	Persistence or relapse of bacteremia de- fined as repeated positive blood cultures collected between 72 hours and up to 28 days post initial positive blood culture	6
Moy, 2017	Retrospec- tive cohort study, 2011–2014, USA	145	<i>Enterobacter</i> (39%), <i>Pseudomonas</i> (34%), <i>Citrobacter</i> (15%), <i>Serratia</i> (12%), <i>Proteus</i> (1%)	Adult, male (48%), mean age 69 years, median length of stay 14 days	Infected catheter (31%), pneumonia (15%), urine (12%), intra- abdominal (10%)	Not described	SAPS ^d II	Logistic re- gression	In-hospital mortality	7
Noguichi 2017	Retrospective case-control study, 2011–2012, Japan	111	<i>Escherichia</i> (43%), <i>Enterobacter</i> (24%), <i>Klebsiella</i> (22%), <i>Serratia</i> (5%), <i>Citrobacter</i> (3%), <i>Proteus</i> (3%)	Adult, male (59%), nosocomial or HCF acquisition (85%), solid organ malignancy (37%), CKD (36%), cardiac disease (36%), DM (25%), liver disease (24%), lung disease (18%), transplant (14%), hematological cancer (13%), CTD (11%)	BSI (36%), IAI (23%), urinary (22%), respiratory (4%)	33% non- susceptible to ceftriaxone	CCI, SOFA	Cox hazard model	30-day mortality	8
Cheng MP (unpub- lished)	Retrospective, case-control study, 2010– 15, Canada	91	<i>Enterobacter</i> (66%), <i>Serratia</i> (17%), <i>Citrobacter</i> (14%), <i>Morganella</i> (3%)	Adult, male (62.6%), median CCI 3, IQR (2, 6), Pittsburgh bacte- remia ≥ 4 (16.5%), qSOFA ≥ 2 (12.1%), ICU at time of culture (16.5%)	Urinary source, 7.7%; non- urinary source, 92.3%	17.6% non- susceptible to ceftriaxone	CCI, ICU ad- mission, Pitt bac- teremia score	Multivariate logistic re- gression	30-day mortality	8

Table 1. Continued

First Author/Year	Study Design, Period, Region	N	Bacterial Genus	Population Characteristics	Bacteremia Characteristics	Isolates With AmpC Phenotype	Comorbidity Measures	Adjustments	Outcomes Included in the Meta-analysis	NOS
Studies included in the original meta-analysis										
Marcos, 2008	Prospective cohort study analysed retrospectively, 1991–2006, Spain	370	<i>Enterobacter</i> (100%)	Adult, cirrhosis (9%), DM (14%), chronic lung (5%), renal failure (7%), malignancy (haem) (15%), solid organ malignancy (27%), bone marrow transplant (4%), solid organ transplant (4%), McCabe Inon-fatal (26%), ultimately fatal (48%), rapidly fatal (6%)	Vascular catheter (31%), GI and biliary tract (19%), LRT (4%), SSTI (2%), unknown (24%)	20.4%	McCabe and Jackson	multivariable regression model	30-day mortality	7
Qureshi, 2011	Retrospective cohort study, 2005–08, USA	135	<i>Enterobacter</i> (100%)	DM (32%), CKD (16%), liver disease (24%), malignancy (16%), transplant (27%), CVD (14%), immunocompromised (68%)	Urine (14%), pneumonia (11%), abdominal (5%), line-related (32%), unknown (38%)	27.4%	APACHE II, Charlson, ICU admission	multivariate logistic regression	28-day mortality	7
O'Neal, 2012	Retrospective cohort study, 2006–08, USA	95	<i>Enterobacter</i> (100%)	Adult, DM (25%), CAD (22%), CVD (13%), renal disease (16%), pulmonary disease (16%), transplant (28%), malignancy (32%), steroids (34%), liver disease (6%)	Urine (6%), pulmonary (13%), bone and joint (3%), deep organ space (16%), unknown (62%)	33%	APACHE II, Charlson, ICU admission	multivariate logistic regression	In-hospital mortality, persistence of presenting signs of infection after 72 h	8
Chaubey, 2014	Prospective cohort study, 2000–08, Canada	458	<i>Enterobacter</i> (49%), <i>Serratia</i> (16%), <i>Citrobacter</i> (11%)	Adult, malignancy (18%), CHF (14%), DM (16%), dementia (2%), liver disease (8%), renal disease (14%)	Urinary (19%), biliary (14%), bowel (7%), pneumonia (7%), SSTI (2%), bone and joint (2%), unknown (49%)	Not described	Charlson	multivariable logistic regression	In-hospital mortality	9
Huh, 2014	Retrospective cohort study 2004–11, Seoul, Korea	192	<i>Enterobacter</i> (100%)	Adults, malignancy (100%), DM (16%), cardiac (5%), liver disease (17%), renal disease (3%), pulmonary disease (3%), neurological disease (3%), solid organ transplantation (3%)	Biliary (24%), abdominal (11%), respiratory (9%), urinary (15%), catheter (6%), skin (6%), GI (3%), unknown (28%)	27.6%	Pitt, ICU admission	multivariable logistic regression	30-day mortality	7
AGAR, 2014	Prospective cohort study, 2013, Australia	396	<i>Enterobacter</i> , <i>Klebsiella</i> , <i>Serratia</i> , <i>Citrobacter</i> , <i>Morganella</i>	Adults and children	Not described	26.0% (E. cloacae only)	Not described	Not described	30-day mortality	7
Lin, 2015	Prospective cohort study, 2003–2012, Taiwan	109	<i>Morganella</i> (100%)	Adult, liver cirrhosis (6%), solid malignancy (27%), haematological malignancy (3%), hypertension (62%), DM (39%), cerebrovascular accident (39%), CKD (30%), COPD (6%)	Biliary (28%), urinary (41%), SSTI (21%), unknown (10%)	1.8%	Not described	Multivariable logistic regression	14-day mortality	7

Abbreviations: BSI, bloodstream infection; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; CKD, chronic kidney disease; CLABSI, central-line associated bloodstream infection; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; CVD, cardiovascular disease; DM, diabetes mellitus; HCF, healthcare facility; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; LRT/IVAP, lower respiratory tract infection/Ventilator associated pneumonia; NOS, Newcastle-Ottawa Quality Assessment Scale; RRT, Renal replacement therapy; SAPS, Simplified Acute Physiology Score; SOFA, Sequential organ failure assessment; SSTI, skin and soft-tissue infection.

organisms. These ORs were pooled using a random effects model. Heterogeneity was assessed using I^2 . All calculations were performed in Stata version 15 (StataCorp, College Station, TX) using the “metan” command [8].

RESULTS

The search strategy yielded 75 potential studies for inclusion (see Figure 1 in the Supplementary Appendix). A complete review of the articles yielded 5 new studies [9–13], which were used to update the previous meta-analysis of 8 studies [5] comprising 665 patients. One study included patients who were already reported in the previous meta-analysis [11] and so to avoid double counting we only included those patients in the later group. In total, 13 studies (including our unpublished data) and 1021 patients were included in the meta-analysis.

Characteristics of Studies from the Updated Search Strategy

All identified studies were observational in nature. Study characteristics, including design, time-period, bacterial species, population characteristics, bacteremia characteristics, and outcome measures are summarized in Table 1, which also includes the 8 studies from the previous meta-analysis. Five of the 6

studies from the expanded search, including our patient cohort, reported the proportion of isolates with an AmpC phenotype, which varied from 18% to 92%. The study quality and risk of selection bias were moderate for all studies, as all were single center.

Outcome Measures

One study was excluded from the final analysis due to the absence of events in either treatment arm [13]. Meta-analysis of the 12 remaining studies yielded a pooled OR for death within 30 days for patients receiving a BL/BLI as definitive therapy of 1.04 (95% CI 0.54–2.02). There was moderate heterogeneity within the studies ($I^2 = 56.0%$, $P = .009$) mainly due to studies published in 2014 where carbapenem use was favourable. The Forrest plot is presented in Figure 2.

DISCUSSION

We updated a previous systematic review and meta-analysis and were able to increase the number of included patients by 54%. Although the results of this updated analysis substantiate the hypothesis that a BL/BLI may be a reasonable alternative to carbapenems in the definitive treatment of BSI with

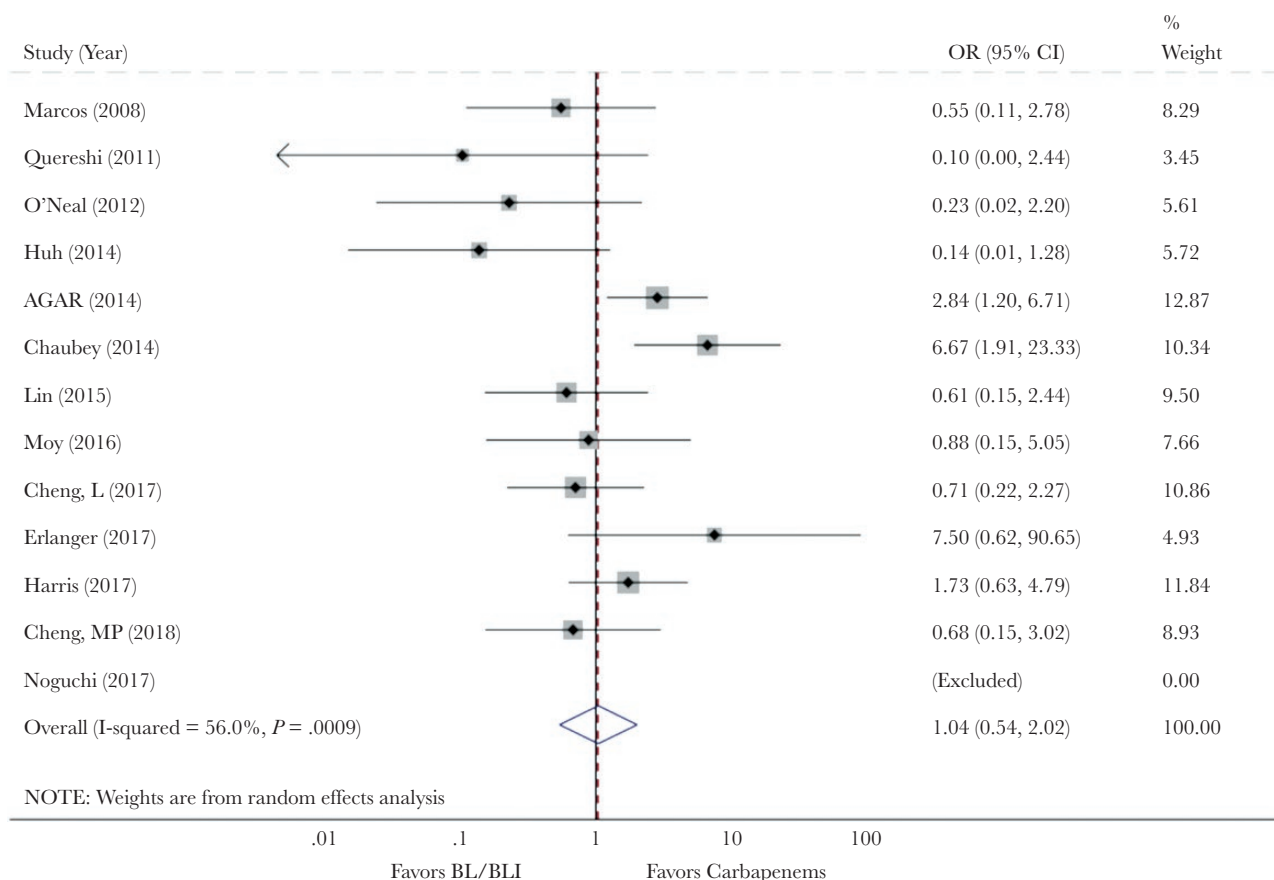


Figure 2. Forrest Plot of Definitive Therapy with Beta-Lactamase/Beta-Lactamase Inhibitors Versus Carbapenems for Outcome of Mortality Within 30 Days [11].

potential AmpC-producing *Enterobacteriaceae*, some uncertainty remains. This is largely because the proportion of isolates that harbor the AmpC gene, and the degree to which the enzyme becomes expressed during treatment, remains largely unknown. Third-generation cephalosporins have previously been associated with adverse patient outcomes in the treatment of potential AmpC-producing organisms [14]; however, this was prior to the revision of the ceftriaxone breakpoints and may no longer be true. These conservative breakpoints may now label organisms with a greater propensity to fail hydrolysable beta-lactam therapy as resistant at the onset of treatment. Moreover, piperacillin-tazobactam, because it is a relatively weak inducer of AmpC [15], may be more likely than ceftriaxone to have favorable outcomes.

Our results must be interpreted with caution, as the published studies were all retrospective in nature and conducted using available clinical data. As the CLSI guidelines do not recommend routine genotypic and phenotypic testing for AmpC production, we were unable to determine what portion of the included isolates were hyperproducing AmpC enzymes. However, our findings remain generalizable as many centers do not routinely test for AmpC production. Different studies had unequal organism representation: *Enterobacter spp.* was the most common organism studied and also has one of the higher potentials for AmpC enzyme expression [16]. As such, our findings presumably are generalizable to other organisms with lesser potential for enzyme expression. Because our results may have over-estimated any negative effect of AmpC production, our results suggest that BL/BLIs may remain a reasonable carbapenem-preserving strategy in the treatment of potential AmpC-producing organisms. However, given that the 95% confidence limits do not exclude a potentially higher mortality rate with BL/BLI, this may be limited outside of a clinical trial to those patients who have had source control and already demonstrated a clinical response to antibiotics.

The strength of this systematic review and meta-analysis is that it now includes many patients with BSIs with potential AmpC-producing *Enterobacteriaceae* arising after the CLSI breakpoint revision [5]. It also comprises many studies from different countries with a sizable number of patients treated with BL/BLIs to compare this treatment strategy with carbapenems. In the absence of randomized clinical trial data comparing BL/BLI to carbapenems, we believe this study is an important contribution to our limited knowledge on this issue.

Based on our meta-analysis, and accounting for all the limitations of observational studies, including confounding by severity or indication, we were not able to demonstrate that BL/BLIs result in inferior outcomes for BSIs with potential AmpC-producing organisms. Although there are theoretical advantages to using a carbapenem, we do not know if this advantage is attenuated by the selective pressure on other carbapenem-resistant

organisms [17] or the development of *de novo* carbapenem resistance via porin mutations in AmpC hyperproducers. As we await the results of an ongoing pilot randomized noninferiority trial on this subject [18], our results provide additional clinical equipoise for a future multicenter, randomized controlled trial to address the issue of whether BL/BLIs present a valid definitive treatment option for these bacteria.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

M.P.C., S.D.M., E.G.M., C.Y., P.N.H., and T.C.L. conceived and designed the study. A.P.C., S.D.M., K.D., and M.P.C. performed data extraction for the cohort study. M.P.C., K.D., and T.C.L. updated the systematic review and meta-analysis. R.S.L. and T.C.L. performed the statistical analysis for both parts of the study. M.P.C. and R.S.L. wrote the draft manuscript. T.C.L. was responsible for trainee supervision. All authors revised the draft for intellectual content and reviewed and approved the submitted version. Members of the writing team had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication, but all authors agree to be held accountable for its integrity.

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