CONCISE COMMUNICATION

Carbapenems Versus Piperacillin-Tazobactam for Bloodstream Infections of Nonurinary Source Caused by Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae

Hadas Ofer-Friedman, MD;[1,*] Coral Shefler, BS;[2,*] Sarit Sharma, MD;[3] Amit Tirosh, MD;[4] Ruthy Tal-Jasper, BS;[2] Deepthi Kandipalli;[3] Shruti Sharma;[3] Pradeep Bathina;[3] Tamir Kaplansky, BS;[1] Moran Maskit, BS;[1] Tal Azouri, BS;[1] Tsilia Lazarovitch, PhD;[5] Ronit Zaidenstein, MD;[4] Keith S. Kaye, MD, MPH;[3] Dror Marchaim, MD[1,2]

A recent, frequently quoted study has suggested that for bloodstream infections (BSIs) due to extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL) *Escherichia coli,* treatment with β-lactam/β-lactamase inhibitors (BLBLIs) might be equivalent to treatment with carbapenems. However, the majority of BSIs originate from the urinary tract. A multicenter, multinational efficacy analysis was conducted from 2010 to 2012 to compare outcomes of patients with non-urinary ESBL BSIs who received a carbapenem (69 patients) vs those treated with piperacillin-tazobactam (10 patients). In multivariate analysis, therapy with piperacillin-tazobactam was associated with increased 90-day mortality (adjusted odds ratio, 7.9, $P=.03$). For ESBL BSIs of a non-urinary origin, carbapenems should be considered a superior treatment to BLBLIs.

Infect Control Hosp Epidemiol 2015;36(8):981–985

Extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL) are prevalent human pathogens that inflict a serious burden on individual patients and on public health.[1] ESBL bloodstream infections (BSIs) are now common in healthcare and community settings,[2] and they are associated with frequent delays in initiation of appropriate antimicrobial therapy and with devastating outcomes.[3] No randomized controlled trials have been conducted to establish the safest and the most efficacious treatment for ESBL-producing Enterobacteriaceae infections.

ESBLs are Ambler A enzymes, which are inhibited by β-lactamase inhibitors.[4] This feature is frequently used to phenotypically diagnose the production of ESBLs among strains (ie, the ESBL test).[5] However, when β-lactam-β-lactamase inhibitor combinations (BLBLIs) were used and tested in trials among patients with ESBL infections, clinical failures were noted.[6,7] These results were speculated to stem from the inoculum effect.[8] Carbapenems are not considerably hydrolyzed by ESBL enzymes,[9] and due to their excellent safety profile and established efficacy, they were considered for years as the agents of choice for ESBL infections, particularly for invasive infections such as BSIs.[6,10]

In 2012 in Spain, Rodriguez-Bano et al[11] meticulously conducted a multicenter, post hoc, prospective observational trial to examine the efficacy of BLBLIs vs carbapenems for *E. coli* ESBL BSIs.[11] Outcomes of patients treated with BLBLIs were equivalent to those treated with carbapenems. Moreover, a trend for favorable outcomes of BLBLIs over carbapenems was observed in the definitive treatment arm. Rodriguez-Bano et al concluded that BLBLIs should be considered legitimate alternatives to carbapenems for *E. coli* ESBL BSIs. Some might have extrapolated these results to all ESBL-producing Enterobacteriaceae (not solely *E. coli*) and to all clinical infectious syndromes.[12] However, as noted in the editorial that accompanied this publication,[13] this generalization has several limitations: (1) Nearly 70% of BSIs originated from the urinary (or biliary) tract. Tazobactam, the only active ingredient in the piperacillin-tazobactam combination, is excreted almost exclusively unchanged in the urine.[14] In addition, urinary tract infections (UTIs) are relatively low-inoculum infections.[15] Therefore, a reverse inoculum effect might be expected in ESBL UTIs, that is, the inoculum of infection is relatively low and the concentration of the antibiotic is high enough to suffice in these circumstances. (2) Nearly 90% of ESBL *E. coli* BSIs are caused in this region by $bla_{\text{CTX-M}}$-producing pathogens.[11] These enzymes are known to be hydrolyzed more efficiently by tazobactam compared with other ESBLs, such as bla_{TEM} and bla_{SHV}, which are more prevalent among other Enterobacteriaceae (eg, *Klebsiella pneumoniae* and *Proteus mirabilis*). (3) Piperacillin-tazobactam was administered in relatively higher doses compared with the common practice in other locations worldwide, which might have contributed to their overall enhanced efficacy. (4) The investigators found an obvious and significant correlation between the piperacillin-tazobactam minimal inhibitory concentration (MIC) and clinical outcomes: mortality increased when the MIC was >4 mg/L.[11,16] Many ESBL isolates in multiple locations worldwide, particularly non–*E. coli* and non–$bla_{\text{CTX-M}}$-producing strains, possess higher MICs to piperacillin-tazobactam.[17] (5) Notably, bla_{CMY}-producing *E. coli* strains, which are not inhibited by tazobactam, are as common as ESBL-producing strains in certain areas.[13] (6) Specifically in *E. coli*, recent spread of a single clone (designated ST [sequence type] -131 per MLST [multi-locus sequence typing]), which is known to have lower MICs to BLBLIs, has been reported.[18] This strain was also prevalent in the Spanish region where the study by Rodriguez-Bano et al was conducted.[19] Therefore, considering all of these factors, it is difficult to generalize the results of this study to all ESBL-producing Enterobacteriaceae infections and for all infectious clinical syndromes. Interestingly, as Rodriguez-Bano et al pointed out, the sickest patients were treated with carbapenems instead of BLBLIs.[11]

https://doi.org/10.1017/ice.2015.101 Published online by Cambridge University Press

This finding might imply that carbapenems are still more trusted, even in this region. Moreover, the authors forced a prediction score into the mortality model to appropriately control for this potential confounder.

A meta-analysis published later in 2012 reported the overall superiority of carbapenems over noncarbapenem regimes, including BLBLIs.[12] The debate pertaining to the superiority of carbapenem is still relevant and clinically applicable because ESBL infections are common worldwide. Therefore, it is important to establish the most superior regimen for these infections. Moreover, piperacillin-tazobactam might exert broader selective pressure than group 1 carbapenems[13]; thus, this issue might be important in terms of stewardship efforts as well. In this study, we conducted an efficacy analysis comparing carbapenems to piperacillin-tazobactam among patients with ESBL-producing BSIs originating from a nonurinary source.

A retrospective cohort analysis was conducted at 2 locations endemic for ESBL infections:[20,21] Assaf Harofeh Medical Center (AHMC, an 813-bed tertiary center in southern-central Israel) and Detroit Medical Center (DMC, a 2,200-bed tertiary center in Detroit, Michigan, USA). Adult patients (>18 years of age) with ESBL BSIs of nonurinary origin were enrolled at AHMC from 2008 to 2012 and at DMC from 2010 to 2012. The infectious clinical syndrome was determined by experienced infectious disease specialists at each center (DM and KSK) based on established criteria.[22] Monomicrobial blood isolations of ESBL-producing *E. coli*, *K. pneumonia*, and *P. mirabilis* were considered for inclusion, and all patients had "true BSIs" based on established criteria.[23] Patients were enrolled only once, and only the first isolation per patient was included. The study was approved by the ethics committee of both institutions.

A carbapenem case was defined as a patient who was treated with ≥2 doses of a carabapenem (eg, ertapenem, imipenem, meropenem, or doripenem) from 3 days prior to 14 days following the culture date. A piperacillin-tazobactam case was defined as a patient who was treated with ≥2 doses of piperacillin-tazobactam from 3 days prior to 14 days following the culture date. Patients who had received ≥1 dose of both agents or of a different agent with activity against the offending ESBL isolate (eg, aminoglycosides, fluoroquinolones, trimethoprim/sulfamethoxazole, fosfomycin, nitrofurantoin) were excluded. Piperacillin-tazobactam cases in patients with an isolate that was nonsusceptible to piperacillin-tazobactam were excluded. Empiric treatment was defined as a regimen administered 3 days (72 hours) prior to 3 days (71 hours) following the ESBL culture date. The main definitive consolidative regimen was defined as a regimen administered 3 days (72 hours) to 14 days following culture. ESBL production was determined by the automated identification systems at both centers (Vitek-2® at AHMC and MicroScan® at DMC) and were confirmed phenotypically by disc diffusion tests.[5] ESBL-positive pathogens that were not susceptible to any carbapenem or produced any carbapenemase, according to phenotypic (ie, Modified Hodge Test) or genotypic (eg, bla_{KPC} PCR) test results, were excluded.

The outcomes considered included in-hospital mortality, 30-day mortality, and 90-day mortality. These data were obtained from the Israeli Interior Ministry records for AHMC patients and from the Social Security death index (SSDI) for DMC patients. For patients who survived the hospitalization, additional outcomes were reviewed: (1) length of hospital stay (LOS) from culture to discharge, (2) total days in the intensive care unit (ICU) from culture to discharge, (3) functional status deterioration (according to Katz criteria[24]), (4) discharge to a long-term care facility (LTCF) after being admitted from home, and (5) invasive procedures (or surgeries) in the following 3 months.

IBM-SPSS software (version 21.0, 2013) was used for all statistical analyses. Logistic regression was used to construct a multivariate model for each outcome and to analyze the risk of being a piperacillin-tazobactam case. The risk of being a piperacillin-tazobactam case was analyzed to control for the possibility that patients in the piperacillin-tazobactam group might have had less severe acute disease states, or vice versa.[11] In addition to examining statistical significance and confounding for each model, effect modification between variables was evaluated by testing appropriate interaction terms for statistical significance. When effect modification was detected, subgroup analyses were performed. Separate subanalyses were conducted for empiric and definitive regimens.

Of the 1,974 adult patients with Enterobacteriaceae BSI during the study period (1,002 from DMC and 972 from AHMC), 79 patients met the strict inclusion criteria for a ESBL BSI of nonurinary origin treated with either a carbapenem or piperacillin-tazobactam and were enrolled: 49 patients were from AHMC and 30 patients were from DMC. A total of 69 patients were treated with carbapenems and 10 were treated with piperacillin-tazobactam as the only active drug vs the ESBL pathogen. Of these patients, 42 (53%) were men. The mean age of the entire cohort was 70.2 ± 16 years, and 67% were older than 65 years. Among this cohort, 42 patients (54%) had resided in an LTCF in the 6 months prior to their index hospitalization and 58 (74%) had been hospitalized in an acute-care facility in the preceding 3 months. Of all BSI patients enrolled, 57% were diagnosed upon admission, ie, <72 hours following admission. Sources of BSIs were determined according to the following infections clinical syndromes: 27 patients (34%) had pneumonia, 22 (28%) had skin and soft-tissue infections, 13 (17%) had biliary infections, 7 (9%) had other intra-abdominal infections. In addition, 6 patients (8%) had primary BSIs, and 4 patients (5%) had a BSI with undetermined origin. Of the offending ESBL-producing isolates, 42 isolates (53%) were *E. coli*, 22 isolates (28%) were *K. pneumoniae*, and 15 isolates (19%) were *P. mirabilis*. In addition, 20 isolates (28%) were resistant to piperacillin-tazobactam (all were carbapenem cases), and 77 isolates (98%) were resistant to cefepime. The median MIC to piperacillin-tazobactam was 8 g/ml (range, 2–256 g/ml) among the carbapenem patients, and this MIC was 4 g/ml (range, 2–4 g/ml) among the piperacillin-tazobactam patients ($P = .09$).

https://doi.org/10.1017/ice.2015.101 Published online by Cambridge University Press

The median Charlson's combined condition score was 6 (interquartile range [IQR], 0–21);[25] 31 patients (39%) had a rapidly fatal condition per McCabe score;[26] 22 patients (28%) were immunosuppressed; 58 patients (73%) were partially or fully dependent upon admission;[24] and 37 patients (47%) had deteriorated cognition and/or consciousness upon admission. The mean Pitt bacteremia score was calculated among DMC patients only and was 3.1 ± 3.5.[6] Overall, 70 patients (89%) had received prior antibiotics in the preceding 3 months. The median time to initiation of appropriate therapy (determined according to the in vitro laboratory report) was 1 day (IQR, 0–7 days). A total of 24 patients (31%) had received an empiric regimen containing a carbapenem, and 9 patients (12%) had received an empiric regimen containing piperacillin-tazobactam.

A multivariate analysis of carbapenem cases vs piperacillin-tazobactam cases was conducted. The 2 variables in the final model were having pneumonia as the infectious clinical syndrome, which was independently associated with being a piperacillin-tazobactam case (adjusted odds ratio [aOR], 7.9; 95% confidence interval [CI], 1.5–40.8; $P = .01$), and having a permanent foreign device (eg, tracheotomy, gastrostomy, tunneled central line, chronic urinary catheter, external fixator, implanted defibrillator, pacemaker), which was independently associated with being a carbapenem case (aOR, 0.005; 95% CI, 0.005–0.4; $P = .007$). These parameters were forced into outcome models.

A total of 28 patients (37%) died within 30 days of their respective culture dates: 21 of these patients (43%) were from AHMC and 7 (23%) were from DMC (odds ratio [OR], 2.1; $P = .03$ between these groups). However, patients from AHMC were significantly older (mean age 76 ± 12.3 years at AHMC vs 61 ± 17.4 years at DMC; $P < .001$) and more often had a rapidly fatal condition:[26] 24 patients (49%) at AHMC had fatal conditions vs 7 patients (23%) at DMC ($P = .02$). A total of 27 patients (34%) died during their hospitalization, and 39 patients (53%) died within 90 days of their respective culture dates. Of the patients who survived hospitalization, the median total LOS for the entire cohort from infection onset (culture date) to discharge was 11 days (range, 1–187 days). The median LOS at AHMC was 13 days (range, 2–187 days) and the median LOS at DMC was 7 days (range, 1–27 days, $P < .001$). The mean ICU LOS from ESBL culture to discharge was 3.8 ± 10.9 days (4.1 ± 13 days at AHMC and 3.4 ± 6.6 days at DMC). In addition, 16 of the patients (30%) who survived the hospitalization had a deterioration in their functional status (15 patients [50%] at AHMC and 1 patient [4%] at DMC, $P < .001$); 16 patients (30%) were discharged to an LTCF (of any sort) after being admitted from home (14 patients [61%] at AHMC and 18 patients [75%] at DMC, $P = .05$); and 45 patients (57%) had an invasive procedure (including surgeries) in the 3 months following their respective culture dates (15 patients [31%] at AHMC and all 30 patients from DMC; $P < .001$).

Overall, being a piperacillin-tazobactam case was associated with relatively worse outcomes. The odds ratio was >1 among all the univariate outcomes analyses conducted (ie, various mortality outcomes). Among survivors only, being a piperacillin-tazobactam case was associated with increased LOS from culture to discharge, increased ICU LOS, and deterioration in functional status. However, only 90-day mortality was significantly different between groups per univariate analysis: 8 patients (80%) among the piperacillin-tazobactam cases died within 90 days of their respective culture dates vs 31 patients (48%) among the carbapenem cases (OR, 4.5; 95% CI, 1.01–34; $P = .05$). In addition, 30-day mortality was nearly significantly different between groups according to univariate analysis as well: 6 patients (60%) among the piperacillin-tazobactam cases died within 30 days of their respective culture dates vs 22 patients (34%) among the carbapenem cases (OR, 3; $P = .10$).

Because only 90-day mortality was significantly different between groups, we present the multivariate model for this outcome parameter only, per our a priori criteria (Table 1). Being a piperacillin-tazobactam case remained an independent significant predictor for 90-day mortality (OR, 7.9, $P = .03$). A multivariate analysis for independent factors associated with 30-day mortality was constructed as well, but as in the univariate analysis, although the same trend was clearly evident, the correlation between piperacillin-tazobactam therapy and mortality was weaker compared to 90-day mortality (data not shown). Due to the low number of patients in each arm, separate subanalyses for empiric regimens and for definitive regimens are not displayed. To more appropriately compare

TABLE 1. Multivariate Analysis of 90-Day Mortality of Patients with BSIs Due to ESBL-Producing *Enterobacteriaceae* at Assaf Harofeh Medical Center and Detroit Medical Center, 2008–2012

	90-Day Mortality	
Variable	Odds Ratio (95% CI)	*P* Value
Piperacillin-tazobactam case[a]	7.9 (1.2–53)	.03
Time at risk[b]	1.1 (1.008–1.13)	.03
Fatal McCabe score[26]	26 (6–115)	<.001

[a]A patient who had received ≥2 doses of piperacillin-tazobactam and had not received any carbapenem from 3 days prior to 14 days following the culture date.

[b]Number of days from admission to ESBL culture.

NOTE. Variables enforced into the primary model were the following: (1) having pneumonia as the infectious clinical syndrome (vs other infectious syndromes) which was associated with being a piperacillin-tazobactam case and (2) presence of permanent foreign device (eg, tracheotomy, gastrostomy, tunneled central line, chronic urinary catheter, external fixator, implanted defibrillator, pacemaker), which was independently associated with being a carbapenem case. In addition, variables inserted into the primary model but did not remain independently significantly associated with 90-day mortality were the following: (1) patients hospitalized at AHMC, (2) advanced age, (3) deteriorated functional status at admission, and (4) severe level of SIRS (ie, severe sepsis and/or septic shock and/or multiple organ failure per established definitions[23]).

https://doi.org/10.1017/ice.2015.101 Published online by Cambridge University Press

the results from the Spanish study by Rodriguez-Bano et al,[11] in which no significant association between piperacillin-tazobactam treatment and outcome was identified, to the findings from this study, additional analyses were conducted. Because BSIs were primarily from urinary and biliary sources in this prior publication, bivariate analyses were re-run in the current study (which included only BSIs of non-urinary origin) after excluding the 13 patients with BSIs from a biliary source. The association between piperacillin-tazobactam and mortality remained unchanged (data are not shown).

To conclude, in this small retrospective cohort study among adults, receiving piperacillin-tazobactam as opposed to carbapenems was independently associated with 90-day mortality, following an ESBL BSI of nonurinary origin. This finding implies that the study published previously,[11] pertaining to this aspect of using BLBLIs for ESBL BSIs, should be interpreted cautiously and that its results should not be generalized to all ESBL-producing Enterobacteriaceae infections or to all infectious clinical syndromes. Furthermore, a recent meta-analysis[12] demonstrated that carbapenems should still be considered as the agents of choice for ESBL BSIs. Group 1 carbapenems, which are active against ESBL BSIs,[27] has the potential advantage over group 2 carbapenems and over piperacillin-tazobactam, in terms of reduced selective antimicrobial pressure vs certain nosocomially significant pathogens (eg, *P. aeruginosa* and *A. baumannii*).[28] BLBLIs might be suitable alternatives for certain *E. coli* ESBL BSIs, mainly BSIs originating from the urinary tract, as long as the isolate is susceptible to piperacillin-tazobactam. BLBLIs might also be particularly effective for treatment of the piperacillin-tazobactam–susceptible ESBL-producing *E. coli* endemic clone ST-131.[19]

It was challenging to enroll patients as piperacillin-tazobactam cases for this study. Even though the study lasted for several years at 2 large endemic centers, only 10 patients met our strict case definition. Therefore, although this study lacked the statistical power to conduct extensive analyses pertaining to all of the outcomes parameters that were captured, it seems that a strong and a stable signal was identified in this analysis: all outcomes were worse among piperacillin-tazobactam cases. Also, 30-day mortality was nearly significantly worse among the piperacillin-tazobactam cases, and after 90 days, the difference became independently and significantly worse according to multivariate analysis (ie, controlling for parameters signifying the risk of being a piperacillin-tazobactam or a carbapenem case). Thus far, this small analysis provides the best available data pertaining to this common and debatable issue, but larger prospective trials are definitely warranted. Future efforts should focus on identifying ESBL infections more rapidly by creating reliable prediction tools for attending clinicians and by improving rapid diagnostic tools. Tight regulation and monitoring of food products are warranted to decrease the rate of ESBL emergence and spread in community settings. Staff should adhere to proper standard precautions and infection control measures to curb the rate of patient-to-patient transmission of offending strains in healthcare settings.

ACKNOWLEDGMENTS

This work was performed in partial fulfillment of the M.D. thesis requirements of the Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel.

Financial support: This study was not supported directly by any source. K.S.K is supported in part by the National Institute of Health (protocol no. 10-0065).

Potential conflicts of interest: In the past KSK and DM received research support from Merck, Inc., unrelated to this study.

Affiliations: 1. Unit of Infectious Diseases, Assaf Harofeh Medical Center, Zerifin, Israel; 2. Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; 3. Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Detroit, Michigan, USA; 4. Department of Medicine A, Assaf Harofeh Medical Center, Zerifin, Israel; 5. Clinical Microbiology Laboratory, Assaf Harofeh Medical Center, Zerifin, Israel.

Address correspondence to Dror Marchaim, MD, Unit of Infectious Diseases, Assaf Harofeh Medical Center, Zerifin, 70300, Israel (drormarchaim@gmail.com).

*Hadas Ofer-Friedman and Coral Shefler contributed equally to this publication.

Received January 8, 2015; accepted April 5, 2015; electronically published May 20, 2015

 0899-823X/2015/3608-0019. DOI: 10.1017/ice.2015.101

REFERENCES

1. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev* 2005;18:657–686.
2. Ben-Ami R, Rodriguez-Bano J, Arslan H, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. *Clin Infect Dis* 2009;49:682–690.
3. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:913–920.
4. Bush K. Extended-spectrum beta-lactamases in North America, 1987–2006. *Clin Microbiol Infect* 2008;14(Suppl 1):134–143.
5. Clinical and Laboratory Standards Institute. Performance standards for antimibrobial susceptibility testing. Nineteenth informational supplement. Approved standard M100-S19. Wayne, PA: CLSI, 2009.
6. Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. *Clin Infect Dis* 2004; 39:31–37.
7. Zimhony O, Chmelnitsky I, Bardenstein R, et al. Endocarditis caused by extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae*: emergence of resistance to ciprofloxacin and piperacillin-tazobactam during treatment despite initial susceptibility. *Antimicrob Agents Chemother* 2006;50:3179–3182.
8. Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. *Clin Microbiol Rev* 2010;23:160–201.
9. Bush K. Bench-to-bedside review: The role of beta-lactamases in antibiotic-resistant Gram-negative infections. *Crit Care* 2010;14:224.
10. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. *N Engl J Med* 2010;362:1804–1813.
11. Rodriguez-Bano J, Navarro MD, Retamar P, Picon E, Pascual A. Beta-lactam/beta-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum

beta-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. *Clin Infect Dis* 2012;54:167–174.
12. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. *J Antimicrob Chemother* 2012;67:2793–2803.
13. Perez F, Bonomo RA. Can we really use ss-lactam/ss-lactam inhibitor combinations for the treatment of infections caused by extended-spectrum ss-lactamase-producing bacteria? *Clin Infect Dis* 2012;54:175–177.
14. Wooley M, Miller B, Krishna G, Hershberger E, Chandorkar G. Impact of renal function on the pharmacokinetics and safety of ceftolozane-tazobactam. *Antimicrob Agents Chemother* 2014;58: 2249–2255.
15. Sobel JD. Pathogenesis of urinary tract infection. Role of host defenses. *Infect Dis Clin North Am* 1997;11:531–549.
16. Retamar P, Lopez-Cerero L, Muniain MA, Pascual A, Rodriguez-Bano J. Impact of the MIC of piperacillin-tazobactam on the outcome of patients with bacteremia due to extended-spectrum-beta-lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2013;57:3402–3404.
17. Marchaim D, Sunkara B, Lephart PR, et al. Extended-spectrum beta-lactamase producers reported as susceptible to piperacillin-tazobactam, cefepime, and cefuroxime in the era of lowered breakpoints and no confirmatory tests. *Infect Control Hosp Epidemiol* 2012;33:853–855.
18. Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum beta-lactamase-producing *Escherichia coli* infection in the United States. *Clin Infect Dis* 2013;56:641–648.
19. Lopez-Cerero L, Navarro MD, Bellido M, et al. *Escherichia coli* belonging to the worldwide emerging epidemic clonal group O25b/ST131: risk factors and clinical implications. *J Antimicrob Chemother* 2014;69:809–814.
20. Marchaim D, Gottesman T, Schwartz O, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by Enterobacteriaceae producing extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2010;54:5099–5104.
21. Chopra T, Marchaim D, Veltman J, et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae and *Escherichia coli*. *Antimicrob Agents Chemother* 2012;56:3936–3942.
22. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332.
23. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327.
24. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. the index of ADL: a standardized measure of biological and psychosocial function. *JAMA* 1963;185:914–919.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
26. Bion JF, Edlin SA, Ramsay G, McCabe S, Ledingham IM. Validation of a prognostic score in critically ill patients undergoing transport. *Br Med J* (*Clin Res Ed*) 1985;291:432–434.
27. Collins VL, Marchaim D, Pogue JM, et al. Efficacy of ertapenem for treatment of bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2012;56:2173–2177.
28. Carmeli Y, Lidji SK, Shabtai E, Navon-Venezia S, Schwaber MJ, The effects of group. 1 versus group 2 carbapenems on imipenem-resistant *Pseudomonas aeruginosa*: an ecological study. *Diagn Microbiol Infect Dis* 2011;70:367–372.

https://doi.org/10.1017/ice.2015.101 Published online by Cambridge University Press