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Short Communication

Clinical outcomes following treatment of Enterobacter species pneumonia with piperacillin/tazobactam compared to cefepime or ertapenem

Maya R. Holsen, PharmD[a], Lynn C. Wardlow, PharmD, BCPS, AQ-ID[a], Jose A. Bazan, DO[b], Lynn A. Fussner, MD[c], Kelci E. Coe, MPH[b], Jessica L. Elefritz, PharmD, BCCCP[a,*]

[a] Department of Pharmacy, The Ohio State University Wexner Medical Center, 410 West 10th Avenue, Columbus, Ohio 43210, United States of America
[b] Division of Infectious Diseases, The Ohio State University College of Medicine, 370 West 9th Avenue, Columbus, OH 43210, United States of America
[c] Division of Pulmonary, Critical Care, and Sleep Medicine, The Ohio State University College of Medicine, 370 West 9th Avenue, Columbus, OH 43210, United States of America

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ABSTRACT

Background: Enterobacter spp. are a common cause of nosocomial pneumonia and treatment can be complicated by AmpC resistance. Carbapenems are the treatment of choice; however, alternatives are needed. Cefepime has been shown to be non-inferior to carbapenems. There are limited data to support the use of piperacillin/tazobactam. The objective of this study was to determine if piperacillin/tazobactam is non-inferior to cefepime or ertapenem for Enterobacter pneumonia treatment.

Objectives: To compare the rate of clinical cure in patients with Enterobacter pneumonia receiving definitive treatment with piperacillin/tazobactam, cefepime, or ertapenem. Secondary outcomes included hospital mortality, infection-related length of stay, duration of mechanical ventilation, recurrent pneumonia, and resistance.

Methods: Retrospective, single-center study.

Results: Of 114 patients included, 59 received definitive treatment with piperacillin/tazobactam and 55 received cefepime or ertapenem. There was no difference in the proportion of patients who achieved clinical cure in the piperacillin/tazobactam group compared to the cefepime or ertapenem group (76.3% vs. 87.3%, $P = 0.13$). Treatment group was not associated with clinical cure when controlling for confounders in multivariable logistic regression (adjusted odds ratio [OR] 0.59, 95% confidence interval [CI] 0.15-2.37). The rate of recurrent pneumonia was 11.4% in the piperacillin/tazobactam group and 6.7% in the cefepime or ertapenem group ($P = 0.48$). Other secondary outcomes did not differ between the groups.

Conclusions: In this retrospective study of patients with Enterobacter pneumonia, clinical cure with piperacillin/tazobactam was comparable to that with cefepime or ertapenem; however, a prospective trial with a larger population is needed to determine if definitive treatment with piperacillin/tazobactam is non-inferior to definitive treatment with cefepime or ertapenem.

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1. Introduction

Enterobacter spp. are the third most common cause of hospital-acquired pneumonia and can be difficult to treat, as they may possess an AmpC beta-lactamase gene that can be either actively expressed or repressed [1–3]. The chromosomally-induced expression of AmpC beta-lactamases can develop following exposure to certain antibiotics [3]. When AmpC is repressed, bacterial isolates may be initially susceptible to antibiotics; however, antibiotic exposure may induce production of AmpC beta-lactamase, resulting in development of antibiotic resistance [3]. Awareness of this resistance mechanism is crucial to optimize clinical outcomes [4].

Induction and/or mutant subpopulation selection of AmpC beta-lactamases has been documented with ceftriaxone; this led some prescribers to prefer carbapenems as they maintain stability in the presence of these enzymes [3]. In the context of global health trends in antibiotic resistance with use of broad-spectrum antibiotics, carbapenem-sparing options are needed [3,5]. Cefepime is a

* Corresponding author: Jessica Elefritz, A1166 460 W 10th Ave, Columbus, OH 43210 USA, Phone: 614-293-8475, Fax: 614-293-2513.
E-mail address: jessica.elefritz@osumc.edu (J.L. Elefritz).

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weak inducer of AmpC beta-lactamases and is weakly hydrolyzed by the AmpC beta-lactamase [3,6,7]. Cefepime has been shown to have similar efficacy as carbapenems for Enterobacter infections, with no differences in bacteremia duration, length of stay (LOS), or mortality [3,6,7].

Piperacillin/tazobactam is also a weak inducer of AmpC beta-lactamases and is commonly used to treat Enterobacter infections [8]. Studies comparing the clinical efficacy of piperacillin/tazobactam with that of cefepime and/or carbapenems are lacking. One study compared the use of piperacillin/tazobactam to meropenem or cefepime and two studies compared carbapenem to non-carbapenem treatment options and found no difference in mortality or clinical cure in patients with Enterobacter blood stream and urinary tract infections (UTI) [3,9,10]. No studies to date have evaluated the clinical efficacy of piperacillin/tazobactam for treatment of Enterobacter pneumonia. Therefore, the objective of this study was to determine whether piperacillin/tazobactam is non-inferior to cefepime or ertapenem in patients with Enterobacter pneumonia.

2. Material and Methods

2.1. Study Design and Patient Population

This was a single-center, retrospective cohort study in patients with Enterobacter pneumonia treated definitively with piperacillin/tazobactam or treated with cefepime or ertapenem for at least 72 h. Patients aged 18-89 years with Enterobacter pneumonia admitted to The Ohio State University Wexner Medical Center (OSUWMC) between November 1, 2011 and September 30, 2017 were eligible for inclusion in the study. Exclusion criteria were: (1) switch to cefepime, ertapenem, or piperacillin/tazobactam more than 72 h after positive Enterobacter culture; (2) treatment with Enterobacter-targeted combination therapy for more than 72 h; (3) extended-spectrum beta-lactamase (ESBL)-producing isolates; (4) concomitant respiratory infection with Pseudomonas, Acinetobacter, Stenotrophomonas, or Burkholderia spp; (5) concomitant endocarditis; (6) any concomitant infection not appropriately treated; (7) pregnancy; and (8) incarceration.

The primary endpoint was clinical cure at day 7 after respiratory culture obtainment or at time of patient discharge if prior to day 7. Secondary endpoints included incidence of recurrent pneumonia, development of resistance, duration of mechanical ventilation (MV), infection-related LOS, and in-hospital mortality. The study was Institutional Review Board-approved.

All patients received extended infusions of piperacillin/tazobactam and cefepime. Bolus doses were infused over 30 min followed by 4-h infusions. The dosing for piperacillin/tazobactam was 4.5 g every 8 h and for cefepime was 2 g every 8 h with renal function adjustments. During the study period, isolates were tested by a single microbiology laboratory within the healthcare system utilizing MicroScan Walkaway® (Siemens Diagnostics) broth microdilution technology. The piperacillin/tazobactam susceptibility breakpoints applied in the study align with current CLSI M100 recommendations, and remained constant throughout the study period: $\leq$ 16 μg/mL as susceptible, 32-64 μg/mL as intermediate, and $>$ 64 μg/mL as resistant. The panels used for susceptibility testing were breakpoint-only panels, and specific minimum inhibitory concentration (MIC) dilutions under 16 μg/mL could not be determined.

2.2. Definitions

Enterobacter pneumonia was defined as a positive Enterobacter respiratory culture (bronchoalveolar lavage [BAL], blind bronchial sampling, or sputum) and documented infiltrate on chest radiograph, with at least one clinical sign or symptom of pneumonia, including leukocytosis (white blood cell count [WBC] $\geq 12 \times 10^3$/μL), fever ($>$37.8°C), initiation of MV or increase in settings as follows: positive end-expiratory pressure (PEEP) increase $\geq$3 cmH_2O (where 0 and 5 are equivalent) or fraction of inspired oxygen (FiO_2) increase $\geq$0.20, sustained for 48 h after a 48-h period of decreased or stable requirements. Diagnosis was confirmed by provider documentation or expert review by an infectious diseases or pulmonary physician. Empirical therapy was defined as the antibiotic(s) the patient was started on or was maintained on at the time of respiratory culture obtainment. Definitive therapy was defined as the antibiotic the patient received after identification of the bacteria and the susceptibility result. Screening of ESBL was performed using Microscan panels containing ceftazidime and cefotaxime, with and without clavulanate. Any bacterial growth identified in both the individual drug and beta-lactamase inhibitor-containing wells was manually confirmed via Kirby Bauer disks with the same antibiotics. A measured zone of inhibition difference of at least 5 mm was considered positive for ESBL production.

The primary endpoint of clinical cure required two of the following three criteria for a period of 24 h on day 7 or at time of discharge: (1) WBC decrease ($\geq 2 \times 10^3$/μL); (2) temperature $\leq$37.8°C; and/or (3) extubation or improvement in ventilator settings (PEEP decrease $\geq$3 cmH_2O or FiO_2 decrease $>$0.20). Infection-related LOS was time from culture obtainment to time of discharge. Recurrent pneumonia was defined as the presence of a positive Enterobacter spp. respiratory culture within 30 days after completion of treatment and meeting the definition of pneumonia previously described. Development of resistance was defined as a subsequent respiratory culture obtained within 30 days after antibiotic completion that showed a more resistant susceptibility profile to piperacillin/tazobactam, cefepime, or ertapenem based on MICs.

2.3. Data Collection

Demographic and clinical outcomes data were collected. On the day of culture obtainment, the Sequential Organ Failure Assessment (SOFA) score and Charlson Comorbidity Index were collected in addition to severity of illness markers. Microbiological and antibiotic data were collected and isolate resistance to cefoxitin on initial respiratory culture was a surrogate marker of AmpC beta-lactamase production [11].

2.4. Statistical Analysis

Descriptive statistics were used to compare outcomes based on treatment group. Continuous variables were reported as median (interquartile range [IQR]) with Student's T-tests or Wilcoxon rank sum tests used to test association, as appropriate. Categorical variables were reported as frequency (%) with chi-square or Fisher's Exact test. A one-sided a priori power calculation showed a 20% difference in the primary endpoint at a significance level of 0.05 and power of 80% requiring a total of 78 patients per group. As no comparative cure rates were available for this specific population, a 20% difference in the primary outcome was deemed clinically significant by investigators. Simple and multivariate logistic regression models were used to estimate the crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) assessing the strength of the association between antibiotic treatment group and confounders. Severity of illness variables with the potential to impact the primary outcome were selected for inclusion in the model by investigators in addition to variables found to be statistically significant on univariate analysis. All statistical analysis was performed using SAS (SAS Intuition, version 9.3, Cary, NC).

Table 1
Comparison of demographic and clinical characteristics between antibiotic treatment groups

	Piperacillin/Tazobactam (n = 59)	Cefepime or Ertapenem (n = 55)	*P*-value
Age (years), median [IQR]	64 [52-70]	56 [49-68]	0.53
Male, n (%)	38 (64.4)	43 (78.2)	0.11
Weight (kg), median [IQR]	81.8 [62.6-96.6]	84.4 [70.9-102.5]	0.39
Height (m), median [IQR]	1.7 [1.7-1.8]	1.8 [1.7-1.8]	0.004
ICU, n (%)	38 (64.4)	46 (83.6)	0.02
MV, n (%)	46 (77.8)	49 (89.1)	0.11
Initiation of MV, n (%)	22 (37.3)	14 (24.5)	0.17
PaO_2/FiO_2 <300, n (%)	30 (90.9)	33 (89.2)	0.81
Shock, n (%)	21 (35.6)	15 (27.3)	0.34
ANC <500, n (%)	1 (1.7)	2 (3.6)	0.61
Enterobacter bacteremia, n (%)	0 (0)	0 (0)	–
SOFA Score, median [IQR]	6 [2-9]	5 [3-7]	0.94
Charlson Comorbidity Score, median [IQR]	6 [2-9]	5 [2-7]	0.56
White Blood Cells (12×10^3/μL), median [IQR]	13.9 [9.2-16.5]	13.8 [8.8-18.3]	0.40
Source of Culture BAL/Blind Bronchial Sampling, n (%)	41 (69.5)	44 (80.0)	0.20
Culture Quantity Count >10 000 cfu, n (%)	32 (54.2)	32 (58.2)	0.73
Enterobacter cloacae, n (%)	37 (62.7)	35 (66.0)	0.71
Enterobacter aerogenes, n (%)	20 (33.9)	18 (32.7)	0.71
Cefoxitin Resistance, n (%)	58 (98.3)	55 (98.2)	0.95
Ertapenem Susceptibilities			0.95
Susceptible	59 (100%)	54 (98.2%)	
Intermediate	0 (0%)	1 (1.8%)	
Resistant	0 (0%)	0 (0%)	
Cefepime Susceptibilities			0.95
Susceptible	59 (100%)	48 (87.3%)	
Intermediate	0 (0%)	4 (7.3%)	
Resistant	0 (0%)	3 (5.5%)	
Piperacillin/Tazobactam Susceptibilities			0.002
Susceptible	56 (94.9%)	38 (69.1%)	
Intermediate	3 (5.1%)	8 (14.5%)	
Resistant	0 (0%)	9 (16.4%)	
Time to Appropriate Therapy			<0001
Less than 24 h	57 (96.6)	40 (72.7)	
At least 24 h	2 (3.4)	15 (27.3)	

ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; cfu, colony-forming units; IQR, interquartile range; MV, mechanical ventilation; PaO_2/FiO_2, ratio of partial pressure arterial oxygen and fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment

Table 2
Comparison of secondary outcomes between antibiotic treatment groups

	Piperacillin/Tazobactam (n = 59)	Cefepime or Ertapenem (n = 55)	*P*-value
Clinical Cure, n (%)	45 (76.3%)	48 (87.3%)	0.13
Duration of MV (days), median [IQR]	3 [1-8]	7 [3-16]	0.74
Infection-related LOS, median [IQR]	9 [6-16]	18 [9-29]	0.92
In-Hospital Mortality, n (%)	14 (23.7)	13 (23.6)	0.99
Recurrent Pneumonia, n (%)	5/44 (11.4)	3/45 (6.7)	0.48

IQR, interquartile range; LOS, length of stay; MV, mechanical ventilation

3. Results

Over the 6-year study period, 256 patients were assessed for inclusion, and 142 patients were excluded. The most common reasons for exclusion were switch to definitive therapy after 72 h (n = 48) and ESBL-producing isolates (n = 46). A total of 114 patients were included in the final analysis: 59 patients in the piperacillin/tazobactam treatment group and 55 patients in the cefepime or ertapenem treatment group (26 patients received cefepime and 29 patients received ertapenem).

The median age of patients in the overall cohort was 61 years (IQR 50.3-69) and the majority were male (n = 82, 71%). Baseline patient characteristics, including severity of illness markers, were statistically similar in the two treatment groups; however, there were more ICU patients in the cefepime or ertapenem group (Table 1).

The Enterobacter spp. isolated in the majority of patients was *Enterobacter cloacae* (n = 72, 63.2%) and 98.2% of Enterobacter spp. isolates were resistant to cefoxitin on initial culture (n = 112). More Enterobacter spp. isolates had resistant or intermediate sensitivity to piperacillin/tazobactam on initial culture compared with cefepime or ertapenem. A larger number of patients were retained on initial therapy for definitive treatment in the piperacillin/tazobactam group compared with the cefepime or ertapenem group (n = 56, 95% vs. n = 18, 32.7%; $P<0.01$). Thirty-six patients (31.6%) had positive respiratory cultures with bacteria isolated in addition to Enterobacter. Any patient with concomitant bacterial isolates received treatment with an antibiotic to which it was susceptible. The duration of treatment in the piperacillin/tazobactam group was similar to that in the cefepime or ertapenem group (median 7 days [IQR 7-10] vs. 8 days [IQR 7-9]; $P = 0.57$).

Clinical cure was achieved in 45 (76.3%) patients in the piperacillin/tazobactam group and 48 (87.3%) patients in the cefepime or ertapenem group ($P = 0.13$). Other secondary efficacy outcomes were not statistically different between the two groups (Table 2). Within the total cohort, 10 patients had respiratory cultures within 30 days of clinical cure, of which 8 were determined to meet the criteria for recurrent pneumonia. Subsequent resistance to one of the studied antibiotics (piperacillin/tazobactam, cefepime or ertapenem) was found in 6 of all repeat isolates. Resistance was found in 4 of 7 repeat isolates (57.1%) in the

Table 3
Multivariable logistic regression model for clinical cure of Enterobacter pneumonia

	OR (95% CI)	[1]Adjusted OR (95% CI)
Piperacillin/Tazobactam	0.47 (0.17-1.27)	0.59 (0.15-2.37)
ICU	1.98 (0.73-5.41)	0.93 (0.26-3.40)
MV	3.38 (1.13-10.05)	5.56 (1.29-24.07)
Shock	0.91 (0.33-2.48)	0.51 (0.15-1.70)
WBC (12×10^3/μL)	1.10 (1.01-1.20)	1.14 (1.04-1.25)
Initially on Appropriate Therapy	0.98 (0.20-4.92)	1.30 (0.22-7.97)
Initially on Definitive Therapy	1.93 (0.65-5.73)	1.21 (0.26-5.77)

CI, confidence interval; MV, mechanical ventilation; OR, odds ratio; WBC, white blood cells

[1] Adjusted OR was obtained by fitting a logistic model with clinical cure as the outcome and all variables in the table as covariates.

piperacillin/tazobactam group and in 2 of 3 repeat isolates (66.7%) in the cefepime or ertapenem group ($P = 1.00$).

Treatment group did not impact achievement of clinical cure after controlling for potential confounders in multivariable logistic regression (Table 3). The factors significantly associated with achievement of cure were MV and WBC count.

4. Discussion

There were no differences in the achievement of clinical cure or secondary outcomes for patients with Enterobacter pneumonia receiving definitive treatment with piperacillin/tazobactam compared to cefepime or ertapenem; however, this study was not adequately powered. Duration of MV was shorter in the piperacillin/tazobactam group (3 days) compared with in the cefepime or ertapenem group (7 days) but this was not statistically significant. More patients in the cefepime or ertapenem group were admitted to the ICU compared with in the piperacillin/tazobactam group; this may be due to prescribing practices rather than severity of illness as there were no differences between the groups in other severity indicators, including shock and SOFA score. Additionally, in multivariable logistic regression, treatment group was not associated with achievement of clinical cure when controlling for ICU admission and other variables. The association of MV with clinical cure indicates a protective effect of this respiratory support for patients infected with Enterobacter pneumonia, although the proportion of patients with a PaO_2/FiO_2 ratio less than 300 was similar in the two groups. Lower WBC were associated with clinical cure but the difference may not be clinically significant [12 vs. 14.5 (12×10^3/μL)]. Time to appropriate antibiotic administration in the cefepime or ertapenem group was statistically significantly longer than that in the piperacillin/tazobactam group due to more isolates with intermediate susceptibility or resistance to piperacillin/tazobactam requiring a therapy change from piperacillin/tazobactam to cefepime or ertapenem. This may have affected clinical cure rates in this treatment group; however, this was controlled for in the multivariable logistic regression and determined not to affect the primary outcome.

To our knowledge, this is the only study exploring the efficacy of piperacillin/tazobactam for treatment of Enterobacter pneumonia, and findings are consistent with other studies investigating the use of piperacillin/tazobactam for infections with AmpC-producing organisms. In 2008, Marcos et al. evaluated 30-day mortality in patients with Enterobacter bacteremia [10]. The mortality rate in the piperacillin/tazobactam group (10.5% [n = 2/19]) was not different from other treatment groups; however, only a small number of patients were treated with piperacillin/tazobactam in this study. A retrospective cohort study from Moy et al. assessed clinical response with carbapenem vs. non-carbapenem treatment in patients with bacteremia (n = 67) or UTI (n = 78) caused by Serratia spp., Pseudomonas spp., Proteus spp., Citrobacter spp., or Enterobacter spp. [9]. Results showed no difference in clinical response between the carbapenem group (80%, n = 16/20) vs. the non-carbapenem group (90.3%, n = 112/124; $P = 0.24$). Piperacillin/tazobactam was used for treatment in 35.9% of patients (n = 52/145). Cheng et al. recently compared cefepime or meropenem with piperacillin/tazobactam in adult patients with Enterobacter spp., Serratia spp., or Citrobacter spp. blood stream infections [3]. The rate of treatment failure did not differ between the groups (15%, n = 6/41 vs. 15%, n = 6/41; $P = 0.96$). The MERINO trial demonstrated that piperacillin/tazobactam is inferior to meropenem for the treatment of blood stream infections with Enterobacteriaceae that are not susceptible to third-generation cephalosporins [13]. Although this is an important finding, the study has several key differences compared with the present study. The MERINO trial focused on *Escherichia coli* and *Klebsiella pneumonia*, which may have different resistance mechanisms compared with Enterobacter spp., including a majority of ESBL-producers (86.0%), and were excluded from the present study. Furthermore, the MERINO trial focused on blood stream infections, with pneumonia the identified source in less than 5% of patients, whereas the present study focused exclusively on pneumonia.

These published studies have several differences compared with the present study; most notably they did not assess patients with pneumonia. As pneumonia has different underlying pathophysiology, there may be differences in clinical outcomes. Additionally, as hospital-acquired infections are common in patients with infections caused by AmpC-producing organisms, mortality as a primary endpoint is difficult because patients may have other comorbid conditions. The present study included only infections caused by Enterobacter spp. whereas two of the previous studies included Serratia spp. and Citrobacter spp., which differ in expression of AmpC beta-lactamase [12]. Nevertheless, previous findings of clinical response were consistent with those in our study, further supporting treatment of a variety of types of Enterobacter spp. infections with piperacillin/tazobactam. Note, after the study period, *Enterobacter aerogenes* was renamed *Klebsiella aerogenes*.

In our study the rate of recurrent pneumonia within 30 days of treatment completion was 11.4% (n = 5/44) in the piperacillin/tazobactam group and 6.7% (n = 3/45) in the cefepime or ertapenem group. Of the 6 isolates with new resistance in the 8 patients with recurrent pneumonia, resistance to piperacillin/tazobactam was noted in 5/6 isolates, to cefepime in 1/6 isolates, and all isolates remained susceptible to ertapenem regardless of antibiotic treatment group. This trend in resistance development is a concern for treatment of both initial and recurrent Enterobacter spp. pneumonia infections with piperacillin/tazobactam and warrants further investigation.

Many patients in the cefepime or ertapenem group were initially on appropriate therapy but few were initially on definitive therapy. This was not the case in the piperacillin/tazobactam group and may be explained by the lower initial isolate susceptibility to piperacillin/tazobactam (82%) requiring a change to either cefepime (94%) or ertapenem (99%) as susceptibility information resulted. Unfortunately, there is no commercially available laboratory test to reliably detect the presence of AmpC in clinical practice. Some literature suggests surrogate markers of AmpC, such as resistance to cefoxitin; however, utilizing a surrogate marker has limitations and may not correlate with in vitro antibiotic resistance [11,14]. A study conducted in 2005 described AmpC prevalence in 4275 Enterobacter isolates in the United States and Europe [12]. The study showed approximately 80% of isolates possessed inducible resistance, 15% derepressed activity, and 5% ESBL production, which may co-harbor the AmpC gene. Clinicians must use available information, such as a positive culture with Enterobacter spp., previously described prevalence of resistance,

and piperacillin/tazobactam susceptibilities for Enterobacter spp. within their institution, to determine if cefepime or ertapenem should be preferentially prescribed empirically for Enterobacter infections.

Our study has several limitations. This was a small, retrospective, single-center study and did not include enough patients to meet statistical power. Also, as it is not possible to assess isolates for AmpC resistance in the laboratory, it is unknown which of the isolates possessed this resistance mechanism. Almost all isolates possessed resistance to cefoxitin, which indicates potential AmpC expression. As the presence of the AmpC gene is not readily known in practice, it is clinically relevant to conduct a treatment outcome study with Enterobacter spp. regardless of AmpC genetic activity. Conducting pneumonia studies can be challenging due to the difficulty with retrospective diagnosis verification. The definitions of pneumonia and clinical cure in this study were rigorous and required multiple objective signs as well as documentation or physician review to confirm the diagnosis.

5. Conclusion

In summary, our study findings indicate piperacillin/tazobactam may be considered a treatment option for patients with Enterobacter pneumonia, while continuing to evaluate institutional susceptibility patterns for empirical treatment options. The primary outcome of clinical cure did not differ between patients treated with piperacillin/tazobactam and cefepime or ertapenem and rates of recurrent pneumonia were similar, although the study was not adequately powered to detect a difference between groups. Larger, prospective studies are necessary to confirm that piperacillin/tazobactam is a non-inferior treatment option.

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