Healthcare Resource Utilization of Ceftolozane/Tazobactam Versus Meropenem for Ventilated Nosocomial Pneumonia from the Randomized, Controlled, Double-Blind ASPECT-NP Trial

Thomas Lodise · Joe Yang · Laura A. Puzniak · Ryan Dillon ·
Marin Kollef

ABSTRACT

Introduction: Hospital-acquired and ventilator-associated bacterial pneumonia (HABP and VABP) are associated with significant healthcare resource utilization (HCRU). This a priori, exploratory, secondary analysis from the ASPECT-NP clinical trial evaluated resource utilization among patients with ventilated HABP (vHABP)/VABP treated with ceftolozane/tazobactam or meropenem.

Methods: This analysis used data from the randomized, double-blind, noninferiority phase 3 ASPECT-NP trial of patients with vHABP/VABP randomized to receive

T. Lodise
Albany College of Pharmacy and Health Sciences, Albany, NY, USA

J. Yang · L. A. Puzniak (✉) · R. Dillon
Merck & Co., Inc., Kenilworth, NJ, USA
e-mail: Laura.puzniak@merck.com

M. Kollef
Washington University School of Medicine, St. Louis, MO, USA

ceftolozane/tazobactam 3 g (ceftolozane 2 g/tazobactam 1 g) or meropenem 1 g for 8–14 days. Day 28 outcomes included hospital length of stay (LOS), intensive care unit (ICU) LOS, and time to mechanical ventilation extubation in the microbiological intention-to-treat (mITT) population and in an HCRU population. The HCRU population, a subset of patients from the mITT population that were alive at day 28, was used to remove resource use bias influenced by mortality rates.

Results: Ceftolozane/tazobactam-treated versus meropenem-treated patients, respectively, had fewer deaths (20.1% vs. 25.5%), fewer hospital discharges (30.7% vs. 32.4%), and higher ICU discharges (60.0% vs. 58.3%) and extubations (51.9% vs. 48.2%) by day 28. In the HCRU population, adjusted LOS differences (95% confidence intervals) for ceftolozane/tazobactam compared with meropenem were 0.1 (− 1.4 to 1.6) hospitalization days, − 1.4 (− 2.9 to 0.2) ICU days, and − 0.9 (− 2.4 to 0.7) mechanical ventilation days. Patterns were similar among the VABP and *Pseudomonas aeruginosa* subgroups.

Conclusion: Similar 28-day resource utilization outcomes were observed between ceftolozane/tazobactam and meropenem in the mITT population of patients from ASPECT-NP with vHABP/VABP due to gram-negative pathogens. ASPECT-NP was not powered to detect differences in resource utilization outcomes between treatment groups; however,

numerical differences in ICU LOS and duration of mechanical ventilation were noted. Further study is needed to assess resource utilization in the real-world practice setting, especially among patients excluded from ASPECT-NP, including those with resistant *P. aeruginosa* infections.

DIGITAL FEATURES

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Key Summary Points

Why carry out this study?

Hospital-acquired and ventilator-associated bacterial pneumonia (HABP and VABP) are associated with significant healthcare resource utilization.

In this exploratory secondary analysis of the ASPECT-NP noninferiority registration trial, we hypothesized that participants treated with ceftolozane/tazobactam or meropenem would have similar resource utilization.

What was learned from the study?

Similar 28-day HCRU outcomes were observed between ceftolozane/tazobactam and meropenem in the microbiological intention-to-treat (mITT) population of participants with ventilated HABP (vHABP) or VABP due to gram-negative pathogens.

Although ASPECT-NP was a noninferiority study and not powered to detect differences in outcomes between treatment groups, there were numerical differences in resource utilization outcomes, specifically for intensive care unit (ICU) hospital length of stay (LOS) and duration of mechanical ventilation.

If a reduction of these costly resources (ICU days and mechanical ventilation) can be realized in a real-world setting, the use of ceftolozane/tazobactam could potentially minimize the economic burden associated with the management of patients with VABP or vHABP due to gram-negative pathogens. Further evaluations of resource utilization especially in key subpopulations are needed.

INTRODUCTION

Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are infections of the lower respiratory tract that occur after at least 48 h of hospitalization or mechanical ventilation, respectively [1]. Although regional variation exists, *Pseudomonas aeruginosa* is the leading gram-negative pathogen responsible for HABP/VABP in the USA, Europe, and Latin America, followed by Enterobacterales (mainly *Escherichia coli* and *Klebsiella* spp.) [2–4]. HABP and VABP are both associated with significant healthcare resource utilization (HCRU), morbidity, and mortality [5, 6]. The attributable mortality of nosocomial pneumonia is high, with rates ranging from 20% to 55% [1, 7–10]. A US national database study evaluated the economic burden, as measured by median hospitalization cost and hospital length of stay (LOS), for patients with community-acquired pneumonia, healthcare-associated pneumonia, HABP, and VABP. The highest median cost ($64,639; interquartile range [IQR], $36,979–$108,391) and longest median LOS (21 days; IQR, 13–33 days) were among patients with VABP, followed by

patients with HABP at a median cost of $27,422 (IQR, $15,075–$52,469) and a median LOS of 14 days (IQR, 9–22 days). These hospital-acquired infections have a greater economic burden compared with patients with healthcare-associated pneumonia, at a median cost of $16,505 (IQR, $8706–$32,681) and a median LOS of 9 days (IQR, 6–15 days), and community-acquired pneumonia, with the lowest cost at $11,440 (IQR, $6345–$23,352) and the shortest LOS of 7 days (IQR, 5–12 days). This hierarchical economic burden remained even after adjusting for age and disease severity [11].

The burden of HABP/VABP is further complicated by the increased ubiquity of antibacterial-resistant pathogens [12]. Bacterial susceptibility to available first-line empiric treatments has diminished over time [13]. Patients with serious infections due to antibacterial-resistant pathogens have considerably worse outcomes relative to their susceptible counterparts [14]. In a US national database study, patients with multidrug-resistant *P. aeruginosa* respiratory infections had higher mortality, an approximately 7-day longer LOS, $20,000 excess costs, higher readmission rates, and more than $10,000 excess net loss per case for the hospital relative to those with non-multidrug-resistant *P. aeruginosa* infections [15]. Infections caused by antibacterial-resistant pathogens also increase the likelihood that a patient will not receive a microbiologically active antibacterial agent for several days after infection onset [16–18], further exacerbating the deleterious outcomes observed among patients with antibacterial-resistant infections [19].

Ceftolozane/tazobactam is a novel combination of ceftolozane, a potent antipseudomonal cephalosporin, and tazobactam, a β-lactamase inhibitor [20–22]. Ceftolozane/tazobactam has demonstrated in vitro activity against many pathogens that cause nosocomial pneumonia, including multidrug-resistant *P. aeruginosa* and extended-spectrum β-lactamase-producing Enterobacterales [23], and was recently approved by the US Food and Drug Administration and European Medicines Agency for the treatment of adult patients with HABP and VABP due to gram-negative

pathogens [22]. These approvals were based on the randomized, controlled, double-blind, phase 3 noninferiority ASPECT-NP (nosocomial pneumonia) trial, conducted at 263 hospitals in 34 countries, that established the efficacy and safety of ceftolozane/tazobactam 3 g (ceftolozane 2 g/tazobactam 1 g) relative to meropenem 1 g for patients with VABP or ventilated HABP (vHABP). In ASPECT-NP, day 28 all-cause mortality (primary endpoint) and clinical response at the test-of-cure visit (key secondary efficacy endpoint) were similar between treatment groups, and noninferiority was demonstrated for both endpoints [24].

While these endpoints provide critical information on the safety and efficacy of ceftolozane/tazobactam, it is also crucial to evaluate the impact of new treatment modalities on the quality and efficiency of healthcare delivery. The emphasis on efficiency is also congruent with antibacterial stewardship efforts in the hospital setting, which seek to improve patient outcomes, reduce the development of antimicrobial resistance, and minimize unnecessary costs without negatively impacting quality of care [25]. Given the increased focus on value and efficiency of care across healthcare systems worldwide, an a priori secondary exploratory analysis was included in the ASPECT-NP protocol to evaluate the differences in hospital LOS, intensive care unit (ICU) LOS, and duration of mechanical ventilation between patients treated with ceftolozane/tazobactam or meropenem. Although this study was not powered to detect differences between treatment groups, we anticipated that patients treated with ceftolozane/tazobactam or meropenem would have similar resource utilization in this secondary exploratory analysis due to the ASPECT-NP study meeting its noninferiority endpoint.

METHODS

Study Design

This a priori, secondary, exploratory resource utilization analysis was based on data from the randomized, double-blind, noninferiority

phase 3 ASPECT-NP trial of patients at least 18 years of age with VABP or vHABP. Details on inclusion and exclusion criteria of the randomized controlled trial are described elsewhere [24] and listed in the supplemental material. Patients were randomized to receive ceftolozane/tazobactam 3 g (ceftolozane 2 g and tazobactam 1 g) or meropenem 1 g via 1-h intravenous infusion every 8 h for 8–14 days. Treatment duration was at the investigator's discretion, although a minimum of 14 days of therapy was recommended for patients with *P. aeruginosa* infection. Patients were stratified by the study design into VABP or vHABP groups. The VABP group required the addition of at least 48 h of mechanical ventilation and either acute changes in ventilator support to enhance oxygenation or the presence of hypoxemia before the infection. The vHABP group required hospitalization for at least 48 h (or previous discharge within the past 7 days) and had at least one of the following criteria within 24 h before intubation or within 48 h after intubation: worsening cough, tachypnea, dyspnea, respiratory rate greater than 30 breaths per minute, and/or hypoxemia [24]. The ASPECT-NP study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the appropriate institutional review boards and regulatory agencies. All patients or legally acceptable representatives provided informed consent.

Resource Utilization Outcomes

Resource utilization metrics analyzed in this study were the proportion of patients that were discharged from the hospital, discharged from the ICU, or extubated within 28 days of randomization, along with hospital/ICU LOS and duration of mechanical ventilation. Resource utilization duration was measured as the number of days between the date of randomization and either the date of resource utilization termination (i.e., hospital discharge, ICU discharge among patients in the ICU at baseline, and extubation) or the date of truncation (death or day 28, whichever came first). Although there were patients who exceeded a 28-day stay

within the trial, the 28-day endpoint was chosen to align with the trial's primary and secondary efficacy endpoints and because follow-up beyond 28 days was variable.

Analysis Populations

This analysis included two study populations: the microbiological intention-to-treat (mITT) population and the HCRU population. The mITT population included patients who received any amount of study drug and had at least one bacterial respiratory pathogen (excluding *Staphylococcus aureus*) isolated from the baseline lower respiratory tract culture that was susceptible to at least one of the study drugs. The mITT population ($n = 511$) was a subset of the intention-to-treat population ($n = 726$) and was chosen as the main analysis population to assess resource utilization because it required receipt of the study drugs and a pathogen against which the study drugs were active. The HCRU population was a subset of the mITT population and comprised patients who were alive at day 28 and achieved the outcome of interest by day 28 (i.e., hospital discharge, ICU discharge among patients in the ICU at baseline, and extubation). The HCRU population was created to mitigate the influence of death on resource utilization. The high mortality rate seen in vHABP and VABP can bias the true effect of resource utilization because patients who die tend to have a much shorter LOS relative to those who do not. Because the HCRU population is dependent on outcome of interest, the sample size varies by outcome. For example, the HCRU population for hospital discharge is less than one-third of the mITT population.

Statistical Analysis

We report the numbers and percentages of patient characteristics, the proportion of patients that achieved each outcome of interest (i.e., hospital discharge, ICU discharge among patients in the ICU at baseline, and extubation) by day 28 after enrollment, and the duration of resource utilization including number of patients, arithmetic mean, and standard

deviation (SD). To address possible imbalances in characteristics of discharged/extubated patients in the two groups, we used the generalized linear model (GLM) to calculate adjusted differences in LOS. The GLM is a preferred statistical method for LOS analyses where skewness and truncation are often present [26–28]. We used the GLMs with log-link function and tested three residual distributions, namely gamma, negative binomial, and Poisson. The selection between the residual distributions was made by analyzing the scale parameter to determine the presence of overdispersion [29]. In the total 24 GLM regressions, overdispersion (i.e., scale parameter > 1.0) was detected in 20 regressions, suggesting that the negative binomial was the most appropriate distribution specification. Covariates in the GLMs included age (< 65 vs. ≥ 65 years), sex, baseline Acute Physiology and Chronic Health Evaluation II score (< 20 or ≥ 20), baseline pathogen type (*P. aeruginosa* vs. Enterobacterales), infection type (polymicrobial vs. monomicrobial), pneumonia type (vHABP vs. VABP), country of treatment, prior antibacterial failure, bacteremia, comorbidities (diabetes, congestive heart failure, chronic obstructive pulmonary disease, emphysema, and pleural effusion), and log-transformed pre-randomization resource utilization duration of the corresponding resource type (e.g., for ICU LOS, pre-randomization ICU stay was used). Selection of covariates was based on clinical meaningfulness and relevancy. We did not implement any variable selection procedure based on predictive power, which is often used for outcome prediction but not for effect estimation. The average LOS difference attributable to treatment was calculated as the difference in least-squares means between the two treatment groups. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA), primarily PROC GENMOD and LIFETEST functions.

RESULTS

A total of 726 patients were enrolled and randomly assigned to ceftolozane/tazobactam (*n* = 362) or meropenem (*n* = 364). The mITT population comprised 264 patients treated with ceftolozane/tazobactam and 247 treated with meropenem. Baseline and clinical characteristics of the mITT population were comparable between both treatment groups (Table 1). However, more patients who received ceftolozane/tazobactam had prior antibacterial therapy failure (ceftolozane/tazobactam, *n* = 39/264 [14.8%]; meropenem, *n* = 24/247 [9.7%]) and bacteremia (ceftolozane/tazobactam, *n* = 43/264 [16.3%]; meropenem, *n* = 26/247 [10.5%]) at baseline. In the mITT population, the mean (SD) duration of hospitalization before randomization was 12.0 (60.4) days in the ceftolozane/tazobactam group versus 7.0 (7.0) days in the meropenem group. Mean (SD) duration of mechanical ventilation before randomization was 11.2 (26.4) days for patients treated with ceftolozane/tazobactam versus 9.8 (7.6) days for those treated with meropenem. Clinical cure was observed in 193 (73.1%) ceftolozane/tazobactam-treated patients and 168 (68.0%) meropenem-treated patients in the mITT population.

Table 2 reports 28-day mortality and hospital/ICU discharge and mechanical ventilation extubation rates among the mITT population. Mortality within 28 days occurred in 53 (20.1%) of 264 ceftolozane/tazobactam-treated patients and 63 (25.5%) of 247 meropenem-treated patients. Within 28 days, 81 (30.7%) of 264 ceftolozane/tazobactam-treated patients and 80 (32.4%) of 247 meropenem-treated patients were discharged from the hospital, 153 (60.0%) of 255 ceftolozane/tazobactam-treated patients and 140 (58.3%) of 240 meropenem-treated patients were discharged from the ICU, and 137 (51.9%) of 264 ceftolozane/tazobactam-treated patients and 119 (48.2%) of 247 meropenem-treated patients were extubated.

Resource utilization durations for hospitalization, ICU stay, and mechanical ventilation are shown in Table 3. In the mITT population, the patient characteristic-adjusted LOS differences (95% confidence interval [CI]) for ceftolozane/tazobactam compared with meropenem were 1.1 (− 0.4 to 2.7) hospitalization days, − 0.6 (− 2.3 to 1.0) ICU days, and − 0.6 (− 2.1 to 0.9) mechanical ventilation days. Of note, mortality (ceftolozane/tazobactam,

Table 1 Patient demographics and clinical characteristics of the mITT population ($N = 511$)

	Ceftolozane/tazobactam ($n = 264$)	Meropenem ($n = 247$)
VABP, n (%)	209 (79.2)	176 (71.3)
vHABP, n (%)	55 (20.8)	71 (28.7)
Age, years, n (%)		
< 65	152 (57.6)	131 (53.0)
≥ 65	112 (42.4)	116 (47.0)
Male sex, n (%)	198 (75.0)	177 (71.7)
APACHE II score, median (IQR)	17 (15–20)	17 (15–21)
Prior antibacterial failure, n (%)	39 (14.8)	24 (9.7)
Bacteremia, n (%)	43 (16.3)	26 (10.5)
Baseline *P. aeruginosa* pathogen, n (%)	63 (23.9)	65 (26.3)
Duration of hospitalization before randomization, mean (SD), days	12.0 (60.4)	7.0 (7.0)
Duration of mechanical ventilation before randomization, mean (SD), days	11.2 (26.4)	9.8 (7.6)

APACHE II Acute Physiology and Chronic Health Evaluation II, *IQR* interquartile range, *mITT* microbiological intention-to-treat, *SD* standard deviation, *VABP* ventilator-associated bacterial pneumonia, *vHABP* ventilated hospital-acquired bacterial pneumonia

20.1%; meropenem, 25.1%) had an influence on the duration of resource utilization in the mITT population, as deceased patients had, on average, a 4-day reduction in hospital LOS and a 2-day reduction in ICU LOS and time spent on mechanical ventilation. Within the HCRU population in which the influence of mortality was removed, adjusted LOS differences (95% CIs) for ceftolozane/tazobactam compared with meropenem were 0.1 (− 1.4 to 1.6) hospitalization days ($n = 161$), − 1.4 (− 2.9 to 0.2) ICU days ($n = 284$), and − 0.9 (− 2.4 to 0.7) mechanical ventilation days ($n = 269$).

Duration of resource utilization was further analyzed by subgroups of interest (Table 4). In general, the subgroup of patients with VABP and *P. aeruginosa* within the mITT population showed some numerical reductions in all three

types of resource utilization for ceftolozane/tazobactam compared with meropenem. Similar results were also observed in the HCRU subgroups in which patients were alive and achieved the outcome of interest by day 28. More specifically, in the HCRU population among patients with VABP, the adjusted LOS differences (95% CIs) for ceftolozane/tazobactam compared with meropenem were − 1.1 (− 2.6 to 0.6) hospitalization days, − 1.5 (− 3.1 to 0.3) ICU days, and − 1.3 (− 3.0 to 0.8) mechanical ventilation days; the corresponding metrics for patients with infections due to *P. aeruginosa* were − 2.1 (− 5.1 to 1.8) days, − 3.0 (− 5.3 to − 0.2) days, and − 4.5 (− 8.1 to 0.7) days for duration of hospitalization, ICU stay, and mechanical ventilation, respectively. However, in the vHABP subgroup within the

Table 2 Day 28 mortality and termination of hospital resource use in the mITT population

	Ceftolozane/tazobactam, n/N (%)	Meropenem, n/N (%)
Day 28—mortality		
mITT total	53/264 (20.1)	63/247 (25.5)
vHABP subgroup[a]	10/55 (18.2)	24/71 (33.8)
VABP subgroup[a]	43/209 (20.6)	36/176 (20.5)
Baseline *P. aeruginosa* subgroup	16/63 (25.4)	12/65 (18.5)
Day 28—patients achieving respective outcome of interest[b]		
Hospital discharge		
mITT total	81/264 (30.7)	80/247 (32.4)
vHABP subgroup[a]	20/55 (36.4)	23/71 (32.4)
VABP subgroup[a]	61/209 (29.2)	57/176 (32.4)
Baseline *P. aeruginosa* subgroup	18/63 (28.6)	19/65 (29.2)
ICU discharge[c]		
mITT total	153/255 (60.0)	140/240 (58.3)
vHABP subgroup[a]	33/53 (62.3)	34/68 (50.0)
VABP subgroup[a]	115/202 (56.9)	98/172 (57.0)
Baseline *P. aeruginosa* subgroup	35/59 (59.3)	39/63 (61.9)
Mechanical ventilator extubation		
mITT total	137/264 (51.9)	119/247 (48.2)
vHABP subgroup[a]	35/55 (63.6)	36/71 (50.7)
VABP subgroup[a]	108/209 (51.7)	90/176 (51.1)
Baseline *P. aeruginosa* subgroup	34/63 (54.0)	40/65 (61.5)

HCRU healthcare resource utilization, *ICU* intensive care unit, *mITT* microbiological intention-to-treat, *VABP* ventilator-associated bacterial pneumonia, *vHABP* ventilated hospital-acquired bacterial pneumonia

[a] Percentage of *P. aeruginosa* was comparable in both VABP ($n = 100/385$ [26%]) and vHABP ($n = 28/126$ [22%])

[b] Patients achieving respective outcome of interest were defined as those who were alive and experienced, respectively, hospital discharge, ICU discharge, or mechanical ventilator extubation within 28 days of enrollment. These patients constituted the HCRU population

[c] Although all patients were receiving mechanical ventilation, not all patients were admitted to the ICU at trial enrollment

HCRU population, differences were in a reverse direction for hospitalization days (adjusted LOS difference, 5.7 [95% CI − 0.4 to 13.6] days) and mechanical ventilation (adjusted ventilation difference, 0.4 [95% CI − 1.5 to 3.1] days) but similar for ICU stay (adjusted ICU LOS, − 1.3 [95% CI − 4.8 to 3.1] days).

DISCUSSION

Phase 3 international, multicenter, randomized, double-blind, comparative noninferiority clinical trials are the current gold standard for establishing the efficacy and safety profiles of new antibacterial agents for the treatment of

Table 3 Duration of resource utilization for hospitalization, ICU stay, and mechanical ventilation for the overall mITT and HCRU populations

	Ceftolozane/tazobactam	Meropenem	Unadjusted difference (95% CI)	Adjusted difference[a] (95% CI)
mITT population				
Hospital LOS, *n*	264	247		
Median (IQR)	28 (16–28)	24 (15–28)		
Mean (SD)	21.9 (7.6)	21.1 (7.9)	0.8 (− 0.5 to 2.1)	1.1 (− 0.4 to 2.7)
ICU LOS, *n*	255	240		
Median (IQR)	16 (9–25)	17 (11–25)		
Mean (SD)	16.3 (8.5)	17.0 (8.3)	− 0.7 (− 2.2 to 0.8)	− 0.6 (− 2.3 to 1.0)
Mechanical ventilator use, *n*	264	247		
Median (IQR)	12 (5–28)	13 (6–28)		
Mean (SD)	14.3 (10.0)	14.8 (10.0)	− 0.5 (− 2.2 to 1.2)	− 0.6 (− 2.1 to 0.9)
HCRU population (patients achieving respective outcome of interest[b] within 28 days)				
Hospital LOS, *n*	81	80		
Median (IQR)	17 (14–22)	17 (14–22)		
Mean (SD)	17.8 (5.4)	17.8 (5.5)	− 0.0 (− 1.7 to 1.7)	0.1 (− 1.4 to 1.6)
ICU LOS, *n*	148	136		
Median (IQR)	13 (9–18)	15 (10–22)		
Mean (SD)	13.3 (6.5)	15.1 (6.8)	− 1.8 (− 3.3 to − 0.3)	− 1.4 (− 2.9 to 0.2)
Mechanical ventilator use, *n*	143	126		
Median (IQR)	7 (4–12)	8 (3–15)		
Mean (SD)	8.8 (6.5)	9.9 (7.4)	− 1.1 (− 2.8 to 0.6)	− 0.9 (− 2.4 to 0.7)

CI confidence interval, *HCRU* healthcare resource utilization, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *mITT* microbiological intention-to-treat, *SD* standard deviation, *VABP* ventilator-associated bacterial pneumonia, *vHABP* ventilated hospital-acquired bacterial pneumonia

[a] Adjusted difference is based on a generalized linear model with log-link function and negative binomial distribution. Covariates included treatment (ceftolozane/tazobactam vs. meropenem), age (< 65 vs. ≥ 65 years), sex (male vs. female), baseline Acute Physiology and Chronic Health Evaluation II score (< 20 vs. ≥ 20), pneumonia type (vHABP vs. VABP), baseline pathogen type (*P. aeruginosa* vs. Enterobacterales), infection type (polymicrobial vs. monomicrobial), country of treatment, prior antibacterial failure, bacteremia, comorbidities (diabetes, congestive heart failure, chronic obstructive pulmonary disease, emphysema, and pleural effusion), and log-transformed pre-randomization resource utilization duration of the corresponding type (e.g., for total hospital LOS, pre-randomization hospital LOS was used); adjusted difference is based on estimate of average marginal effect for ceftolozane/tazobactam

[b] Patients achieving respective outcome of interest were defined as those who were alive and experienced, respectively, hospital discharge, ICU discharge, or mechanical ventilator extubation within 28 days of enrollment. These patients constituted the HCRU population

Table 4 Duration of resource utilization including hospitalization, ICU stay, and mechanical ventilation for the overall mITT population and among the HCRU population (discharged patients in the mITT population)

	Ceftolozane/tazobactam		Meropenem		Difference (95% CI)	
	n	**Mean (SD)**	**n**	**Mean (SD)**	**Unadjusted**	**Adjusted[a]**
VABP						
Hospital LOS						
mITT population	209	21.7 (7.8)	176	22.1 (7.2)	− 0.4 (− 1.9 to 1.1)	0.2 (− 1.3 to 1.9)
HCRU population	61	16.9 (5.1)	57	18.1 (5.4)	− 1.2 (− 3.1 to 0.7)	− 1.1 (− 2.6 to 0.6)
ICU LOS						
mITT population	202	16.4 (8.5)	172	18.0 (8.1)	− 1.6 (− 3.3 to 0.1)	− 1.1 (− 2.6 to 0.7)
HCRU population	115	13.3 (6.4)	98	15.6 (7.0)	− 2.3 (− 4.1 to 0.5)	− 1.5 (− 3.1 to 0.3)
Mechanical ventilator use						
mITT population	209	14.8 (10.1)	176	16.3 (10.0)	− 1.5 (− 3.5 to − 0.5)	− 0.8 (− 2.5 to 1.3)
HCRU population	108	8.8 (6.5)	90	10.7 (7.8)	− 1.9 (− 3.9 to 0.1)	− 1.3 (− 3.0 to 0.8)
vHABP						
Hospital LOS						
mITT population	55	22.7 (7.1)	71	18.6 (9.0)	4.1 (1.2 to 7.0)	5.2 (1.3 to 9.9)
HCRU population	20	13.8 (7.7)	23	10.5 (7.5)	3.3 (− 1.4 to 8.0)	5.7 (− 0.4 to 13.6)
ICU LOS						
mITT population	53	16.1 (8.7)	68	14.6 (8.4)	1.5 (− 1.6 to 4.6)	2.0 (− 1.2 to 6.1)
HCRU population	33	13.2 (6.7)	34	13.7 (6.3)	− 0.5 (− 3.7 to 2.7)	− 1.3 (− 4.8 to 3.1)
Mechanical ventilator use						
mITT population	55	12.6 (9.6)	71	10.8 (9.1)	1.8 (− 1.5 to 5.1)	3.2 (− 0.4 to 8.1)
HCRU population	35	8.9 (6.7)	36	7.8 (5.9)	1.1 (− 1.9 to 4.1)	0.4 (− 1.5 to 3.1)
Pseudomonas aeruginosa						
Hospital LOS						
mITT population	63	21.7 (7.7)	65	23.2 (7.2)	− 1.5 (− 4.1 to 1.1)	− 1.7 (− 4.0 to 1.0)
HCRU population	18	18.4 (5.8)	19	21.4 (4.5)	− 3.0 (− 6.5 to 0.5)	− 2.1 (− 5.1 to 1.8)
ICU LOS						
mITT population	59	15.6 (8.2)	63	18.5 (7.7)	− 2.9 (− 5.8 to − 0.0)	− 3.1 (− 5.3 to − 0.5)
HCRU population	35	14.0 (6.8)	39	18.3 (6.5)	− 4.3 (− 7.3 to − 1.3)	− 3.0 (− 5.3 to − 0.2)
Mechanical ventilator use						
mITT population	63	13.2 (10.0)	65	14.5 (9.4)	− 1.3 (− 4.7 to 2.1)	− 2.1 (− 4.8 to 0.4)

Table 4 continued

	Ceftolozane/tazobactam		Meropenem		Difference (95% CI)	
	n	Mean (SD)	*n*	Mean (SD)	Unadjusted	Adjusted[a]
HCRU population	34	7.2 (6.3)	40	11.9 (7.8)	− 4.7 (− 8.0 to − 1.4)	− 4.5 (− 8.1 to 0.7)

CI confidence interval, *HCRU* healthcare resource utilization, *ICU* intensive care unit, *LOS* length of stay, *mITT* microbiological intention-to-treat, *SD* standard deviation, *VABP* ventilator-associated bacterial pneumonia, *vHABP* ventilated hospital-acquired bacterial pneumonia

[a] Adjusted difference is based on a generalized linear model with log-link function and negative binomial distribution; covariates included treatment (ceftolozane/tazobactam vs. meropenem), age (< 65 vs. ≥ 65 years), sex (male vs. female), baseline Acute Physiology and Chronic Health Evaluation II score (< 20 vs. ≥ 20), baseline pathogen type (*P. aeruginosa* vs. Enterobacterales), infection type (polymicrobial vs. monomicrobial), pneumonia type (vHABP vs. VABP), country of treatment, prior antibacterial failure, bacteremia, comorbidities (diabetes, congestive heart failure, chronic obstructive pulmonary disease, emphysema, and pleural effusion), and log-transformed pre-randomization resource utilization duration of the corresponding type (e.g., for total hospital LOS, pre-randomization hospital LOS was used); adjusted difference is based on estimate of average marginal effect for ceftolozane/tazobactam

HABP/VABP. Although efficacy and safety are established in such a design setting for the purposes of regulatory approval, it is challenging to infer meaningful economic or comparative effectiveness. The consideration of economic endpoints and the magnitude of these differences is key to making value judgments [30]. Given the increased focus on value and efficiency of care across healthcare systems worldwide, an a priori, secondary, exploratory analysis was included in the ASPECT-NP protocol to evaluate the differences in hospital LOS, ICU LOS, and duration of mechanical ventilation between patients treated with ceftolozane/tazobactam or meropenem. Overall, similar 28-day resource utilization outcomes were observed between ceftolozane/tazobactam and meropenem in the mITT population of patients from ASPECT-NP with vHABP/VABP due to gram-negative pathogens. Although ASPECT-NP was a noninferiority study and not powered to detect differences in outcomes between treatment groups, several numerical differences in resource utilization outcomes were noted between groups, and most favored ceftolozane/tazobactam relative to meropenem. In conjunction with the clinical efficacy and safety data shown in the randomized trial, these

results support the overall value of ceftolozane/tazobactam for the treatment of patients with vHABP and VABP [24].

Despite numerical differences in key outcomes, including duration of ICU and mechanical ventilation use, most results were nonsignificant, reflected in most 95% CIs including the null value. This could be related to several facets of the trial design. First and foremost, the trial was not adequately powered for these resource utilization endpoints. Further, the inclusion criteria required that patients have a susceptible infection. Since meropenem has been shown to be an effective agent for patients with susceptible HABP/VABP, the benefit of ceftolozane/tazobactam among patients with antibacterial-resistant infections, such as meropenem-resistant or multidrug-resistant *P. aeruginosa*, could not be assessed in this study. In addition, the average hospital LOS before infection was 12 days for ceftolozane/tazobactam-treated patients compared with 7 days for meropenem-treated patients. Previous hospitalization and the patient's underlying condition could also influence subsequent outcomes that are not attributable to treatment or the infection. As an international study, variable local clinical practice and healthcare

reimbursement policies may influence duration of ICU and hospital stay for study participants that could lead to unmeasurable bias. Lastly, like most phase 3 trials, ASPECT-NP had fixed therapy duration requirements, lacked oral stepdown therapy, and lacked predefined criteria for hospital discharge, which could also impact overall ICU and hospital stay.

Although the resource utilization measures were constrained by study design limitations, time to extubation is an important effectiveness metric for clinicians treating patients with VABP and vHABP. Mechanical ventilation is one of the primary drivers of resource utilization for patients with VABP and vHABP. There are considerable efforts, irrespective of healthcare system or country, exerted to minimize patients' time spent on mechanical ventilation due to long-term complications and healthcare costs. Although no definitive conclusions can be drawn from these data, the observed differences in extubation between treatment groups highlight the need for additional real-world comparative effectiveness and quality assurance initiatives between ceftolozane/tazobactam and meropenem. Furthermore, the results of this study highlight the need for further resource utilization assessment in high-risk patient populations (i.e., patients with VABP, infections due to *P. aeruginosa* and resistant pathogens) as they represented the groups with the largest numerical differences in resource utilization treatment outcomes.

This study is not without limitations. First, this study only evaluated a portion of the patient's experience during their hospitalization, specifically from the time of randomization to day 28. Although the 28-day window is consistent with the primary endpoints of the randomized clinical trial, some patients continued to accrue resources past 28 days. Moreover, there were differences in prior resource utilization before randomization. Resource utilization before infection may impact a patient's future resource utilization after infection that is not necessarily attributed to the infection.

Secondly, challenges exist with resource utilization studies, particularly when there is a high underlying mortality rate. In this analysis, patients who died did not have the opportunity for discharge or extubation, which violates an assumption of future occurrence. Patients who died during this study had, on average, a 4-day reduction in hospital LOS and a 2-day reduction in ICU LOS and time spent on mechanical ventilation. As these data suggest, most patients who die consume less resources, which can underestimate the burden of mortality on resource utilization, especially for conditions that generally have high mortality levels. There are multiple methods described in the literature to account for the deleterious effects of mortality in a resource utilization study. In this study, we analyzed those patients who were alive at day 28 to minimize the impact of mortality on resource utilization [31]. Furthermore, these patients had significant underlying issues independent of the infection that could have also impacted resource utilization duration. Overall hospitalization was the most similar endpoint between the two treatment groups in this study and had the largest truncation due to the 28-day window. However, the 28-day observation period represents a reasonable time from infection to account for resource utilization associated with the acute event of the infection as opposed to other underlying reasons for hospitalization.

CONCLUSIONS

Similar 28-day resource utilization outcomes were observed between ceftolozane/tazobactam and meropenem in the mITT and HCRU populations, a subset of patients included within ASPECT-NP that had vHABP/VABP due to gram-negative pathogens. Although ASPECT-NP was a noninferiority study and not powered to detect differences in outcomes between treatment groups, several numerical differences in resource utilization outcomes were noted between treatment groups, particularly with respect to ICU LOS and duration of mechanical ventilation. If a reduction for these costly resources (ICU days and mechanical ventilation use) can be realized in a real-world setting, the use of ceftolozane/tazobactam could potentially minimize the economic burden associated with the management of patients with VABP or

vHABP due to gram-negative pathogens. In addition, from both the hospital and patient perspective, decreased hospital LOS minimizes the transmission of resistant pathogens and reduces the need for additional treatment regimens. Resource utilization measures and the sequential benefits of reduced hospital exposure are important considerations in determining the overall value of novel antibacterial agents and are included in the principles of antimicrobial stewardship.

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