Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

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Summary

Background Nosocomial pneumonia due to antimicrobial-resistant pathogens is associated with high mortality. We assessed the efficacy and safety of the combination antibacterial drug ceftolozane–tazobactam versus meropenem for treatment of Gram-negative nosocomial pneumonia.

Methods We conducted a randomised, controlled, double-blind, non-inferiority trial at 263 hospitals in 34 countries. Eligible patients were aged 18 years or older, were undergoing mechanical ventilation, and had nosocomial pneumonia (either ventilator-associated pneumonia or ventilated hospital-acquired pneumonia). Patients were randomly assigned (1:1) with block randomisation (block size four), stratified by type of nosocomial pneumonia and age (<65 years *vs* ≥65 years), to receive either 3 g ceftolozane–tazobactam or 1 g meropenem intravenously every 8 h for 8–14 days. The primary endpoint was 28-day all-cause mortality (at a 10% non-inferiority margin). The key secondary endpoint was clinical response at the test-of-cure visit (7–14 days after the end of therapy; 12·5% non-inferiority margin). Both endpoints were assessed in the intention-to-treat population. Investigators, study staff, patients, and patients' representatives were masked to treatment assignment. Safety was assessed in all randomly assigned patients who received study treatment. This trial was registered with ClinicalTrials.gov, NCT02070757.

Findings Between Jan 16, 2015, and April 27, 2018, 726 patients were enrolled and randomly assigned, 362 to the ceftolozane–tazobactam group and 364 to the meropenem group. Overall, 519 (71%) patients had ventilator-associated pneumonia, 239 (33%) had Acute Physiology and Chronic Health Evaluation II scores of at least 20, and 668 (92%) were in the intensive care unit. At 28 days, 87 (24·0%) patients in the ceftolozane–tazobactam group and 92 (25·3%) in the meropenem group had died (weighted treatment difference 1·1% [95% CI −5·1 to 7·4]). At the test-of-cure visit 197 (54%) patients in the ceftolozane–tazobactam group and 194 (53%) in the meropenem group were clinically cured (weighted treatment difference 1·1% [95% CI −6·2 to 8·3]). Ceftolozane–tazobactam was thus non-inferior to meropenem in terms of both 28-day all-cause mortality and clinical cure at test of cure. Treatment-related adverse events occurred in 38 (11%) of 361 patients in the ceftolozane–tazobactam group and 27 (8%) of 359 in the meropenem group. Eight (2%) patients in the ceftolozane–tazobactam group and two (1%) in the meropenem group had serious treatment-related adverse events. There were no treatment-related deaths.

Interpretation High-dose ceftolozane–tazobactam is an efficacious and well tolerated treatment for Gram-negative nosocomial pneumonia in mechanically ventilated patients, a high-risk, critically ill population.

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Introduction

Nosocomial pneumonia, which is often associated with mechanical ventilation, is one of the most common hospital-acquired infections and is associated with high mortality.[1,2] Crude mortality estimates range from 20% to 50%;[3] infections caused by multidrug-resistant bacteria are associated with a particularly high mortality risk.[4] Rising multidrug resistance among Gram-negative pathogens, including *Pseudomonas aeruginosa* and Enterobacteriaceae (Enterobacterales), is widely recognised as a major public health issue globally.[5–7] Resistant pathogens are especially problematic in critically ill patients, who are at high risk of adverse clinical outcomes,[7] and in whom up to 20–30% of cases of ventilator-associated pneumonia due to *P aeruginosa* are caused by multidrug-resistant strains.[8] New treatment options for nosocomial pneumonia are therefore urgently needed.

Previous large phase 3 trials[9–11] in patients with nosocomial pneumonia have been unable to show non-inferiority of several novel drugs (eg, tigecycline, doripenem, and ceftobiprole) to established therapies. However, underdosing of these novel drugs might have contributed to the negative results.[12–14] Many patients with nosocomial pneumonia are critically ill, and the pharmacokinetic and pharmacodynamic profiles for antimicrobials in such patients are frequently complex,

Research in context

Evidence before this study

Nosocomial pneumonia is one of the most common and serious hospital-acquired infections (crude mortality 20–50%). We searched PubMed with terms including "hospital-acquired pneumonia", "ventilator-associated pneumonia", "phase 3", and "randomised" for randomised, controlled trials published in any language between July 1, 2009, and July 1, 2019, that assessed antibacterial agents for the treatment of nosocomial pneumonia. Full details of the search are provided in the appendix (p 33). Previous clinical trials showed higher mortality at 28 days in patients with ventilated hospital-acquired pneumonia than in those with ventilator-associated pneumonia. Nosocomial pneumonia is frequently caused by Gram-negative pathogens, including *Pseudomonas aeruginosa* and Enterobacteriaceae. Selection of appropriate antibacterial therapy is increasingly complicated by the rising incidence of multidrug resistance among these key causative pathogens, and this problem is widely recognised as a major, global public health issue. New safe and effective antibacterial drugs are thus urgently needed, but phase 3 trials of novel drugs tigecycline, doripenem, and ceftobiprole were unsuccessful.

Ceftolozane–tazobactam, a novel combination of a potent anti-pseudomonal cephalosporin and a β-lactamase inhibitor, is approved for complicated urinary tract and intra-abdominal infections. Its profile suggests that it would also be an efficacious treatment for Gram-negative nosocomial pneumonia.

Added value of this study

This trial is the first randomised, controlled study to assess the efficacy and safety of ceftolozane–tazobactam for nosocomial pneumonia, an infection for which additional treatment options are urgently needed. Unlike most non-inferiority studies of other novel antibacterial agents in the same clinical setting, we enrolled only mechanically ventilated patients—specifically, those with ventilator-associated pneumonia or ventilated hospital-acquired pneumonia, who have higher mortality than non-ventilated patients with nosocomial pneumonia. Notably, on the basis of pharmacokinetic–pharmacodynamic modelling, we selected a dose of ceftolozane–tazobactam that was twice that approved for other indications. Ceftolozane–tazobactam was non-inferior to meropenem in both the primary endpoint of 28-day all-cause mortality and the key secondary endpoint of clinical response at the test-of-cure visit, irrespective of causative pathogens (most commonly Enterobacteriaceae and *P aeruginosa*). It also seemed to be well tolerated in this critically ill population, with a low incidence of treatment-related adverse events.

Implications of all the available evidence

High-dose ceftolozane–tazobactam can be used to treat nosocomial pneumonia caused by *P aeruginosa* (including multidrug-resistant strains), Enterobacteriaceae (including producers of extended-spectrum β-lactamases), and other Gram-negative pathogens.

potentially leading to rapid drug elimination and changes in volume of distribution.[12] Additionally, drug concentrations in the lungs are often lower than those in plasma,[12] and causative pathogens in nosocomial pneumonia often have reduced antibacterial susceptibility.[15–17] The combination of these factors could lead to insufficient drug concentrations at the infection site, and thus antibacterial dosing regimens in patients with nosocomial pneumonia should be carefully optimised.[12]

Ceftolozane–tazobactam is a novel combination antibacterial consisting of ceftolozane (a potent anti-pseudomonal cephalosporin) and tazobactam (a β-lactamase inhibitor).[18] It is approved for complicated urinary tract and intra-abdominal infections at a dose of 1·5 g (ie, 1 g ceftolozane and 0·5 g tazobactam) every 8 h.[19] Ceftolozane–tazobactam is active in vitro against many important pathogens associated with nosocomial pneumonia, including multidrug-resistant pseudomonal species and Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBLs),[15,19] and had good lung penetration in two phase 1 trials[20,21] (one of which was done in critically ill patients undergoing mechanical ventilation). These findings suggest that the combination would be efficacious against Gram-negative nosocomial pneumonia.

We therefore aimed to assess the efficacy and s of ceftolozane–tazobactam compared with merope (an established, broad-spectrum, first-line treatr in patients with nosocomial pneumonia. To e sufficient drug concentrations in patients' lungs, we a new dosing regimen for ceftolozane–tazob (ie, double the dose approved for other indications)

Methods

Study design and participants

Protocol MK-7625A-008 (ASPECT-NP) was a rando controlled, double-blind, phase 3, non-inferiorit done at 263 hospitals in 34 countries. Eligible p were aged 18 years or older, were intubate mechanically ventilated, and had ventilator-ass pneumonia or ventilated hospital-acquired pneu Pneumonia was diagnosed if patients had the fo clinical and radiographic criteria within 24 h bef first dose of study drug: purulent tracheal secretio at least one other clinical criterion (ie, fever [≥ hypothermia [≤35°C], ≥10 000 or ≤4500 white blo per μL, or ≥15% of white blood cells being in neutrophils) and chest radiographs or CTs shov presence of a new or progressive infiltrate sugg bacterial pneumonia. Diagnosis of ventilator-as pneumonia additionally required at least 4

mechanical ventilation, and either the presence of hypoxaemia or acute changes in the ventilator support system to enhance oxygenation. Ventilated hospital-acquired pneumonia was diagnosed in mechanically ventilated patients who met the clinical and radiographic criteria for pneumonia diagnosis, had been in hospital for at least 48 h (or had been discharged from hospital within the past 7 days), and had at least one of the following: new or worsening cough, dyspnoea, tachypnoea, respiratory rate greater than 30 breaths per min, and hypoxaemia, either within 24 h before intubation or within 48 h after intubation.

Exclusion criteria included a baseline Gram stain with only Gram-positive pathogens and more than 24 h of treatment within the past 72 h with active, systemic, or inhaled antibacterials with Gram-negative activity (although such patients were eligible for inclusion if they had persistent, worsening, or new nosocomial pneumonia despite ≥48 h of active antibacterial therapy). Additionally, patients were excluded if they had more than 24 h of carbapenem therapy in the past 7 days, growth of a Gram-negative pathogen resistant to meropenem or ceftolozane–tazobactam from a respiratory or blood culture (not including the baseline lower respiratory tract culture) obtained within the past 15 days, diagnoses or comorbidities that could potentially interfere with assessment or interpretation of outcomes (eg, pneumonia caused by a non-bacterial pathogen, known or suspected community-acquired pneumonia, or lung cancer), active immunosuppression (including patients with HIV with a CD4 count <200 cells per µL, patients receiving any immunosuppressive therapy, and solid organ or bone marrow transplant recipients), neutropenia, continuous renal replacement therapy, or end-stage renal disease requiring haemodialysis. Detailed inclusion and exclusion criteria are listed in the appendix (pp 92–96).

The study was done in accordance with principles of Good Clinical Practice and was approved by the institutional review boards at each participating centre and regulatory agencies in each participating country. All patients (or legally acceptable representatives) provided informed consent. The study protocol is available in the appendix (pp 36–138).

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either ceftolozane–tazobactam or meropenem. Block randomisation (block size four) was done via a centralised, interactive voice and integrated web-response system, and was stratified by diagnosis (ventilator-associated pneumonia *vs* ventilated hospital-acquired pneumonia) and age (<65 years *vs* ≥65 years), with geographical region as a blocking factor. The study pharmacist, who could not be masked to treatment assignment, prepared all infusions and was responsible for necessary dose adjustments based on patients' renal function (appendix p 90).

The study sponsor (except for certain drug supply, quality assurance, and monitoring personnel), investigators, study staff involved in patient care or clinical assessments, patients, and patient representatives were masked to treatment assignment until study completion and database lock. All infusion bags, including drip chambers, were obscured with an amber bag cover to maintain the blinding. If dose adjustments necessitated a change in the dosing schedule, dummy infusions were given to maintain the interval between doses. Treatment assignment could be unblinded only in case of urgent medical necessity, so that appropriate therapy for nosocomial pneumonia could be prescribed or adverse events could be managed.

Procedures

Patients received either 3 g ceftolozane–tazobactam (ie, 2 g ceftolozane and 1 g tazobactam) or 1 g meropenem as 1-h intravenous infusions every 8 h for 8–14 days. Treatment duration was at the discretion of investigators, but 14 days' therapy was recommended for patients infected with *P aeruginosa*. Adjunctive empirical linezolid (600 mg as an intravenous infusion over 30–120 min every 12 h) or an acceptable alternative was given to all patients until lower respiratory tract cultures taken at baseline showed the absence of *Staphylococcus aureus*. Adjunctive empirical therapy with 15 mg/kg amikacin was permitted for up to 72 h after the first dose of study drug at sites where at least 15% of *P aeruginosa* isolates were resistant to meropenem (according to the site's most recent institutional antibiogram). Other aminoglycosides could be used (when approved by the sponsor) if they were standard of care at the site, the patient could not tolerate amikacin, or amikacin was contraindicated. Other non-study antibacterial drugs could not be used for nosocomial pneumonia unless clinical failure was documented with the study drug, in which case the study drug was discontinued.

See Online for appendix

A lower respiratory tract specimen was taken for Gram staining at most 36 h before randomisation. To obtain this sample, we used bronchoalveolar lavage or non-bronchoscopic bronchoalveolar lavage, or took protected brush specimens or endotracheal aspirates. Pathogen identification and susceptibility testing were done at local site laboratories and confirmed at a central laboratory with standard methods.[24] Once baseline culture results were available, if all Gram-negative isolates were non-susceptible to both ceftolozane–tazobactam and meropenem, study treatment was discontinued and appropriate non-study therapy initiated. If Gram-negative isolates were non-susceptible to only one of the study treatments or there was no growth of Gram-negative pathogens, investigators were encouraged to base decisions about continuation of study drug on the patient's clinical response and all available clinical and laboratory data. Susceptibility to ceftolozane–tazobactam was based on provisional

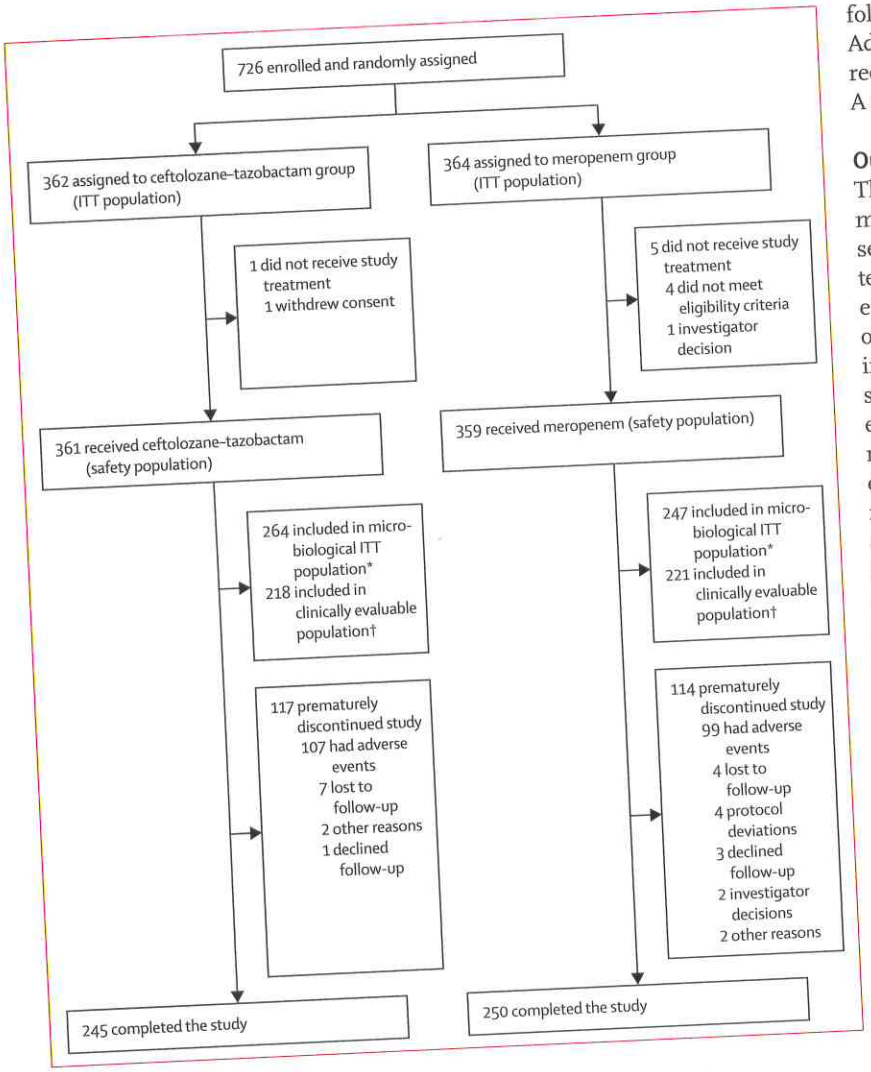


Figure 1: **Trial profile**
ITT=intention-to-treat. *Reasons for exclusion from this population are in the appendix (p 13). †Reasons for exclusion from this population are in the appendix (p 15).

break-points for the nosocomial pneumonia indication (mini-mum inhibitory concentration [MIC] ≤4 μg/mL for Enterobacteriaceae and ≤8 μg/mL for *P aeruginosa* and all other pathogens); susceptibility to meropenem was based on Clinical & Laboratory Standards Institute breakpoints.[25] Multidrug resistance was defined according to consensus criteria.[26]

Post-baseline quantitative lower respiratory tract cultures were collected from intubated patients on days 1, 2, 3, and 8, and, if indicated, at the end-of-therapy and at the test-of-cure visit (which was 7–14 days after the end of therapy). Clinical assessments of pneumonia symptoms (presence and severity of cough, tachypnoea, dyspnoea, rigours or shaking chills, and pleuritic chest pain, as applicable and feasible), temperature, vital signs, and the pulmonary system (through a focused examination) were done daily while patients received study therapy and at end-of-therapy, test-of-cure, and late follow-up (ie, 28–35 days after end of treatment) visits. Adverse events were monitored from when patients received the first dose of study drug until late follow-up. A detailed assessment schedule is in the appendix (p 112).

Outcomes

The primary efficacy endpoint was 28-day all-cause mortality in the intention-to-treat population. The key secondary efficacy endpoint was clinical response at the test-of-cure visit in the same population. Other secondary efficacy endpoints included clinical response at the test of-cure visit in the clinically evaluable population (which included those who received study drug, adhered to the study protocol up to the test-of-cure visit, and had evaluable clinical outcomes at that timepoint), clinical response at the late follow-up visit in the clinically evaluable population, per-pathogen and per-patient microbiological responses at the test-of-cure visit and 28-day all-cause mortality in the microbiologic intention-to-treat population (which included patients who received at least one dose of study treatment and from whom at least one Gram-negative or streptococcal respiratory pathogen susceptible to at least one study drug was cultured from baseline lower respiratory tract samples).

Clinical response at the test-of-cure visit was categorised as cure (ie, resolution of baseline signs and symptoms of nosocomial pneumonia, with no new signs or symptoms and no need for additional antibacterial therapies to treat nosocomial pneumonia), treatment failure (ie, progression, relapse, or recurrence of nosocomial pneumonia; insufficient resolution of baseline signs and symptoms to discontinuation of study drug because of resistant lower respiratory tract pathogens; or death from nosocomial pneumonia), or indeterminate (ie, death from non-attributable causes, discontinuation of study drug because no Gram-negative or streptococcal isolate could be identified in baseline samples, or missing data). In patients with clinical cure at test-of-cure only, clinical response was also assessed at the late follow-up visit, and was classified as either sustained cure, relapse (ie, recurrence of signs or symptoms of pneumonia, new radiological evidence of pneumonia, or receipt of antibacterial therapy for treatment of pneumonia after the test-of-cure visit), or indeterminate (appendix p 126).

Microbiological response was categorised at the test-of-cure visit as eradication (ie, a lower respiratory tract culture showing a ≥1-log reduction in baseline pathogenic bacterial burden, with a maximum per-pathogen count of 10^4 colony forming units [CFU] per mL for endotracheal aspirate specimens, 10^3 CFU per mL for bronchoalveolar lavage specimens, and 10^2 CFU per mL for protected specimen specimens), presumed eradication (ie, no microbiological culture available in a patient with clinical cure), persistence (appendix p 136), or presumed persistence (ie, no microbiological culture available in patients with clinical failure). Consistent with the study objective

microbiological data are presented for the microbiological intent-to-treat population. Detailed definitions of analysis populations and endpoints are in the appendix (p 118).

Safety was a secondary endpoint and was assessed according to actual treatment received in all randomly assigned patients who received at least one dose of study treatment. Adverse events and safety laboratory assessments were assessed throughout the study (appendix p 85). Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 17.0). Adverse event severity was graded according to standard definitions (appendix p 112).

Statistical analysis

The study was designed to show non-inferiority for the primary endpoint in the intention-to-treat population, with a 10% non-inferiority margin to achieve 90% power at a one-sided significance level of 0·025 (based on regulatory agency guidance)[27] and assuming a 28-day all-cause mortality rate of 20% in both groups. We used a sequential testing approach to control this α level to show non-inferiority in the key secondary endpoint. Ceftolozane–tazobactam was non-inferior to meropenem for the primary endpoint if the lower bound of the 95% CI for the weighted treatment difference (meropenem minus ceftolozane–tazobactam) did not cross –10% and for the key secondary endpoint if the lower bound for the treatment difference (ceftolozane–tazobactam minus meropenem) did not cross –12·5%. For per-patient primary and secondary efficacy endpoints that were dichotomous, treatment differences (which were stratified by diagnosis and age, if appropriate) were calculated as weighted proportional differences with Mehrotra-Railkar continuity-corrected minimum risk stratum weights.[28] Associated 95% CIs were calculated as stratified Newcombe CIs.[29] Within-group 95% CIs were calculated as stratified Wilson CIs.[29]

In addition to the populations already described, the primary and key secondary efficacy endpoints were also assessed in predefined subgroups that reflected patients' baseline characteristics. These subgroup analyses and other secondary endpoints were not powered for non-inferiority testing. Analyses that were done post hoc are clearly indicated. For subgroup analyses with reduced sample sizes, no stratification was applied. Depending on the analysis, missing responses (including indeterminates) were either considered to represent treatment failure or were excluded from analyses. Safety data were analysed descriptively. All statistical analyses were done in SAS (versions 9.3 and 9.4). This trial is registered with ClinicalTrials.gov, NCT02070757.

Role of the funding source

Employees of the study funder, including several authors, were involved in study design, data collection, data analysis, data interpretation, and writing of the manuscript.

	Ceftolozane–tazobactam group (n=362)	Meropenem group (n=364)
Sex		
Male	262 (72%)	255 (70%)
Female	100 (28%)	109 (30%)
Age		
<65 years	202 (56%)	204 (56%)
≥65 years	160 (44%)	160 (44%)
Mean, years	60·5 (16·7)	59·5 (17·2)
Median, years	63 (50–72)	62 (49–73)
Weight, kg	80 (70–90)	80 (70–90)
Body-mass index, kg/m²	27 (24–30)	26 (24–30)
Creatinine clearance, mL/min		
≥150	67 (19%)	64 (18%)
≥80	227 (63%)	236 (65%)
>50 to <80	82 (23%)	77 (21%)
≥30 to ≤50	35 (10%)	26 (7%)
≥15 to <30	17 (5%)	21 (6%)
<15	0	1 (<1%)
Missing	1 (<1%)	3 (1%)
Admitted to intensive care unit		
Yes	334 (92%)	334 (92%)
No	28 (8%)	30 (8%)
APACHE II score		
≤14	89 (25%)	93 (26%)
15–19	148 (41%)	154 (42%)
≥20	124 (34%)	115 (32%)
Missing	1 (<1%)	2 (1%)
Mean	17·5 (5·2)	17·4 (5·7)
Median	17 (15–21)	17 (14–21)
Sequential Organ Failure Assessment score		
≤7	261 (72%)	237 (65%)
>7	101 (28%)	125 (34%)
Missing	0	2 (1%)
Mean	6·5 (2·4)	6·8 (2·5)
Median	6 (5–8)	6 (5–8)
Previous antibacterial use*		
Yes	318 (88%)	323 (89%)
No	44 (12%)	41 (11%)
Primary diagnosis		
Ventilator-associated pneumonia	263 (73%)	256 (70%)
Ventilated hospital-acquired pneumonia	99 (27%)	108 (30%)
Clinical Pulmonary Infection Score		
≤6	25 (7%)	32 (9%)
7	29 (8%)	35 (10%)
8	45 (12%)	42 (12%)
>8	263 (73%)	254 (70%)
Missing	0	1 (<1%)
Mean	9·7 (2·0)	9·5 (2·1)
Median	10 (1–13)	10 (2–13)

(Table 1 continues on next page)

	Ceftolozane–tazobactam group (n=362)	Meropenem group (n=364)
(Continued from previous page)		
Duration of hospitalisation, days†		
<5	80 (22%)	81 (22%)
≥5	278 (77%)	279 (77%)
Missing	4 (1%)	4 (1%)
Mean	10·9 (23·1)	9·9 (10·5)
Median	8 (5–12)	7 (5–12)
Duration of mechanical ventilation, days†		
<5 days	178 (49%)	184 (51%)
≥5 days‡	182 (50%)	176 (48%)
Missing	2 (1%)	4 (1%)
Mean	10·3 (51·8)	7·0 (9·0)
Median	5 (3–8)	5 (3–9)
Previous unsuccessful antibacterial therapy for current episode of nosocomial pneumonia§		
Yes	53 (15%)	40 (11%)
No	309 (85%)	323 (89%)
Missing	0	1 (<1%)
Bacteraemia (Gram-negative respiratory pathogen)		
Yes	25 (7%)	19 (5%)
No	337 (93%)	345 (95%)

Data are n (%), mean (SD), or median (IQR). APACHE II=Acute Physiology and Chronic Health Evaluation II. *Antibacterial therapy received in the 14 days before the first dose of study drug. †Before randomisation. ‡Some of these patients might have been unsuccessfully treated with antibacterial therapy for the current episode of nosocomial pneumonia before randomisation, and the denominator includes patients with ventilated hospital-acquired pneumonia; thus, this number is not an exact substitute for late ventilator-associated pneumonia. §Persistent or worsening signs or symptoms of nosocomial pneumonia after at least 48 h of antibacterial therapy active against Gram-negative pathogens.

Table 1: Baseline demographics and clinical characteristics in the intention-to-treat population

All authors had full access to all the data in the study and had joint final responsibility for the decision to submit for publication.

Results

Between Jan 16, 2015, and April 27, 2018, 726 patients were enrolled and randomly assigned, 362 to the ceftolozane–tazobactam group and 364 to the meropenem group (intention-to-treat population; figure 1). Patients were enrolled at 119 of the 263 participating hospitals in 29 countries (appendix p 3). Premature unblinding occurred in six patients in each group (ie, one instance of protocol-allowed unblinding in the meropenem group and 11 instances of accidental unblinding that involved site-level personnel).

Baseline demographic and clinical characteristics were similar between treatment groups in the intention-to-treat population (table 1). The majority of patients had ventilator-associated pneumonia and were in the intensive care unit. Characteristics by treatment group in the subpopulations of patients with ventilator-associated pneumonia and ventilated hospital-acquired pneumonia, the microbiological intention-to-treat population, and the clinically evaluable population are in the appendix (pp 8–15); notably, 65% of patients with ventilator-associated pneumonia had at least 5 days of mechanical ventilation directly before randomisation. 151 (42%) of 362 patients in the ceftolozane–tazobactam group and 168 (46%) of 364 in the meropenem group received vasopressors (ie, adrenergic or dopaminergic drugs) concurrently with study therapy. Adjunctive Gram-negative therapy was given to 103 (28%) patients in the ceftolozane–tazobactam group and 112 (31%) in the meropenem group. All but four of these patients received amikacin (one patient in the ceftolozane–tazobactam group and three in the meropenem group received tobramycin). A protocol deviation was noted for one patient in the ceftolozane–tazobactam group, who received more than 72 h of adjunctive Gram-negative therapy.

Lower respiratory tract pathogens identified in the 511 patients who made up the microbiological intention-to-treat population (including 264 in the ceftolozane–tazobactam group and 247 in the meropenem group) were mostly Enterobacteriaceae (largely *Klebsiella pneumoniae* and *Escherichia coli*), which were isolated in 380 (74%) patients, and *P aeruginosa*, which was isolated in 128 (25%; appendix p 34). ESBL-producing Enterobacteriaceae were isolated from 157 (31%) patients. Among all baseline isolates of the microbiological intention-to-treat population pooled, four (3%) of the 127 *P aeruginosa* isolates were resistant to ceftolozane–tazobactam and 16 (13%) were resistant to meropenem. Overall, 58 (13%) of 456 Enterobacteriaceae isolates were resistant to ceftolozane–tazobactam and one (<1%) of 457 was resistant to meropenem (the corresponding frequencies for ESBL-producing Enterobacteriaceae were 54 [32%] of 171 and none of 171, respectively). The MIC ranged from less than 0·064 µg/mL to 256 µg/mL or more for ceftolozane–tazobactam (MIC that inhibited 50% of isolates 0·5 µg/mL; MIC that inhibited 90% of isolates 16 µg/mL) and from less than 0·064 µg/mL to 256 µg/mL or more for meropenem (MIC that inhibited 50% of isolates <0·064 µg/mL, MIC that inhibited 90% of isolates 1 µg/mL). 210 (80%) of 264 patients in the ceftolozane–tazobactam group and 219 (89%) of 247 in the meropenem group had lower respiratory tract pathogens at baseline that were susceptible to the study drug they were assigned to.

Duration of study therapy was similar in both groups (median 7·7 days [IQR 7·3–9·7] in the ceftolozane–tazobactam group and 7·7 days [7·5–10·7] in the meropenem group). Treatment duration was similar between treatment groups irrespective of the causative pathogen and whether patients had polymicrobial or monomicrobial infections (appendix p 16).

At 28 days, 87 (24·0%) of 362 patients in the ceftolozane-tazobactam group and 92 (25·3%) of 364 in the meropenem group had died (weighted proportional difference 1·1% [95% CI −5·1 to 7·4]; table 2). Ceftolozane–tazobactam thus met the prespecified non-inferiority criterion. In patients with ventilated hospital-acquired pneumoni

	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
28-day all-cause mortality (ITT population)†			
Overall	87/362 (24·0%)	92/364 (25·3%)	1·1 (–5·1 to 7·4)‡
Ventilator-associated pneumonia	63/263 (24·0%)	52/256 (20·3%)	–3·6 (–10·7 to 3·5)§
Ventilated hospital-acquired pneumonia	24/99 (24·2%)	40/108 (37·0%)	12·8 (0·2 to 24·8)§
28-day all-cause mortality (microbiological ITT population)†	53/264 (20·1%)	63/247 (25·5%)	4·4 (–2·8 to 11·8)‡
Clinical cure at test of cure (ITT population)†			
Overall	197/362 (54·4%)	194/364 (53·3%)	1·1 (–6·2 to 8·3)‡
Ventilator-associated pneumonia	147/263 (55·9%)	146/256 (57·0%)	–1·1 (–9·6 to 7·4)§
Ventilated hospital-acquired pneumonia	50/99 (50·5%)	48/108 (44·4%)	6·1 (–7·4 to 19·3)§
Clinical cure at test of cure (clinically evaluable population)¶			
Overall	139/218 (63·8%)	143/221 (64·7%)	–1·3 (–10·2 to 7·7)‡
Ventilator-associated pneumonia	105/159 (66·0%)	111/172 (64·5%)	1·5 (–8·7 to 11·6)§
Ventilated hospital-acquired pneumonia	34/59 (57·6%)	32/49 (65·3%)	–7·7 (–25·0 to 10·6)§
Microbiological eradication at test of cure (microbiological ITT population)†	193/264 (73·1%)	168/247 (68·0%)	4·5 (–3·4 to 12·5)‡

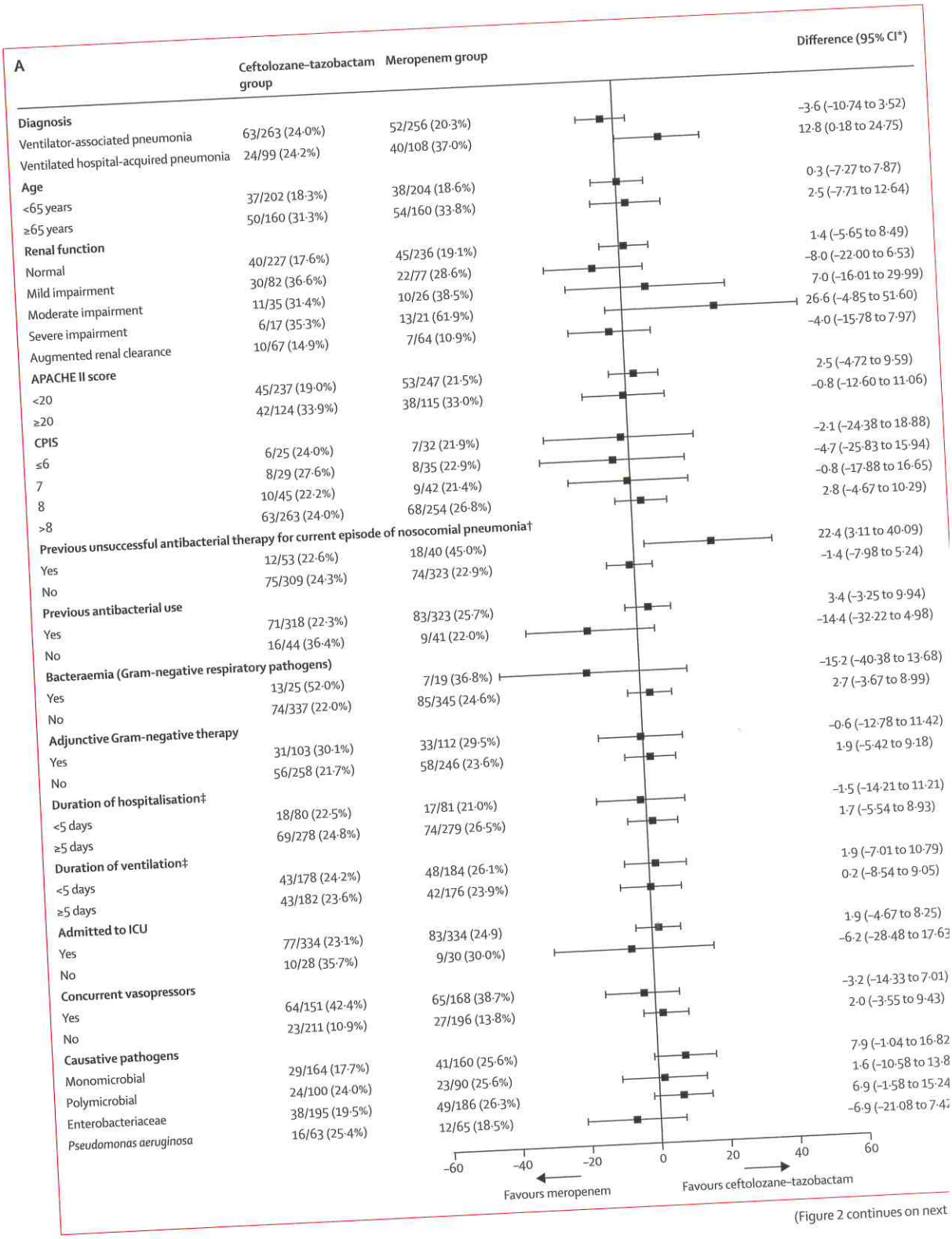
Data are n/N (%). ITT=intention-to-treat. *Differences in mortality were calculated as the meropenem group minus the ceftolozane–tazobactam group, whereas differences in the other outcomes were calculated as the ceftolozane–tazobactam group minus the meropenem group. †Patients with missing or indeterminate data were reported as deceased or not meeting the criteria for clinical cure or microbiological eradication (depending on the endpoint). ‡Weighted proportional difference stratified by diagnosis (ventilator-associated pneumonia *vs* ventilated hospital-acquired pneumonia) and age (<65 years *vs* ≥65 years), with stratified Newcombe CIs. §Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible. ¶Data were reported as observed—ie, patients with missing or indeterminate responses were excluded.

Table 2: **Primary and secondary efficacy outcomes in various analysis populations**

(table 2), and in those in whom previous antibacterial therapy for the current episode of nosocomial pneumonia was unsuccessful before study entry (figure 2A), the 95% CI for the between-group difference did not cross zero, with lower mortality in the ceftolozane–tazobactam group than in the meropenem group. In patients with ventilator-associated pneumonia, there was no difference between groups in mortality (table 2). Mortality was generally similar in both treatment groups in all geographical regions (appendix p 17) and in patient subgroups (figure 2A), including patients with augmented renal clearance and patients who received adjunctive Gram-negative therapy. A post-hoc sensitivity analysis of mortality in patients in the intention-to-treat population who did not receive adjunctive therapy or previous Gram-negative therapy also supported the results noted for the primary and key secondary outcomes (appendix pp 18–19). An additional post-hoc analysis showed that among patients with infections caused by ESBL-producing Enterobacteriaceae, 18 (21%) of 84 in the ceftolozane–tazobactam group and 21 (29%) of 73 in the meropenem group had died by 28 days (point difference 7·3% [95% CI –6·1 to 20·8]).

Ceftolozane–tazobactam was also non-inferior to meropenem in terms of the proportion of patients with clinical cure at the test-of-cure visit (table 2). Study drug was discontinued because of insufficient therapeutic effects in 23 (6%) of 361 patients in the ceftolozane–tazobactam group and 15 (4%) of 359 patients in the meropenem group. The frequency of per-patient clinical cure was generally similar between treatment groups across geographical regions (appendix p 17) and in key predefined patient subgroups (figure 2B), including patients with augmented renal clearance and those in whom previous antibacterial therapy for the current episode of nosocomial pneumonia was unsuccessful before study entry. Results for the other secondary efficacy endpoints were also similar between treatment groups (table 2). Various definitions of augmented renal clearance did not significantly affect results for secondary endpoints (appendix p 21). In the clinically evaluable population, clinical relapse at late follow-up was noted in six (3%) of 218 patients in the ceftolozane–tazobactam group and in ten (5%) of 221 in the meropenem group. Per-pathogen clinical cure in the microbiological intention-to-treat population was similar between treatment groups for patients infected with Enterobacteriaceae and *P aeruginosa* (table 3). Per-pathogen outcomes were also similar between treatment groups in a sensitivity analysis restricted to patients in the microbiological intention-to-treat population infected with pathogens susceptible to both study drugs at baseline (appendix p 20).

The frequency of per-pathogen microbiological eradication (including presumed eradication) in the microbiological intention-to-treat population was similar in both treatment groups for Enterobacteriaceae (145 [74%] of 195 patients in the ceftolozane–tazobactam group *vs* 129 [70%] of 185 in the meropenem group; point difference 4·6% [95% CI –4·4 to 13·6]), ESBL-producing Enterobacteriaceae (56 [67%] of 84 *vs* 52 [71%] of 73; –4·6% [–18·6 to 9·9]), and *P aeruginosa* (47 [75%] of 63 *vs*



(Figure 2 continues on next

B

	Ceftolozane–tazobactam group	Meropenem group	Difference (95% CI*)
Diagnosis			
Ventilator-associated pneumonia	147/263 (55·9%)	146/256 (57·0%)	−1·1 (−9·59 to 7·35)
Ventilated hospital-acquired pneumonia	50/99 (50·5%)	48/108 (44·4%)	6·1 (−7·44 to 19·27)
Age			
<65 years	121/202 (59·9%)	118/204 (44·4%)	2·1 (−7·46 to 11·52)
≥65 years	76/160 (47·5%)	76/160 (47·5%)	0·0 (−10·81 to 10·81)
Renal function			
Normal	132/227 (58·1%)	138/236 (58·5%)	−0·3 (−9·24 to 8·59)
Mild impairment	45/82 (54·9%)	35/77 (45·5%)	9·4 (−6·01 to 24·24)
Moderate impairment	13/35 (37·1%)	11/26 (42·3%)	−5·2 (−28·55 to 18·37)
Severe impairment	7/17 (41·2%)	10/21 (47·6%)	−6·4 (−34·43 to 23·43)
Augmented renal clearance	40/67 (59·7%)	39/64 (60·9%)	−1·2 (−17·49 to 15·16)
APACHE II score			
<20	139/237 (58·6%)	142/247 (57·5%)	1·2 (−7·59 to 9·87)
≥20	58/124 (46·8%)	51/115 (44·3%)	2·4 (−10·07 to 14·80)
CPIS			
≤6	14/25 (56·0%)	14/32 (43·8%)	12·3 (−13·14 to 35·56)
7	15/29 (51·7%)	24/35 (68·6%)	−16·8 (−38·41 to 6·80)
8	21/45 (46·7%)	27/42 (64·3%)	−17·6 (−36·34 to 3·16)
>8	147/263 (55·9%)	129/254 (50·8%)	5·1 (−3·47 to 13·58)
Previous unsuccessful antibacterial therapy for current episode of nosocomial pneumonia†			
Yes	26/53 (49·1%)	15/40 (37·5%)	11·6 (−8·61 to 30·18)
No	171/309 (55·3%)	179/323 (55·4%)	−0·1 (−7·79 to 7·63)
Previous antibacterial use			
Yes	178/318 (56·0%)	171/323 (52·9%)	3·0 (−4·65 to 10·67)
No	19/44 (43·2%)	23/41 (56·1%)	−12·9 (−32·37 to 8·05)
Bacteraemia (Gram-negative respiratory pathogens)			
Yes	9/25 (36·0%)	2/19 (10·5%)	25·5 (−0·67 to 46·38)
No	188/337 (55·8%)	192/345 (55·7%)	0·1 (−7·28 to 7·55)
Adjunctive Gram-negative therapy			
Yes	47/103 (45·6%)	64/112 (57·1%)	−11·5 (−24·29 to 1·82)
No	150/258 (58·1%)	129/246 (52·4%)	5·7 (−2·96 to 14·25)
Duration of hospitalisation‡			
<5 days	48/80 (60·0%)	48/81 (59·3%)	0·7 (−14·12 to 15·55)
≥5 days	148/278 (53·2%)	145/279 (52·0%)	1·3 (−6·98 to 9·49)
Duration of ventilation‡			
<5 days	104/178 (58·4%)	101/184 (54·9%)	3·5 (−6·62 to 13·58)
≥5 days	93/182 (51·1%)	93/176 (52·8%)	−1·7 (−11·96 to 8·53)
Admitted to ICU			
Yes	185/334 (55·4%)	184/334 (55·1%)	0·4 (−7·20 to 7·80)
No	12/28 (42·9%)	10/30 (33·3%)	13·9 (−14·71 to 32·45)
Concurrent vasopressors			
Yes	63/151 (41·7%)	76/168 (45·2%)	−3·4 (−14·20 to 7·32)
No	134/211 (63·5%)	118/196 (60·2%)	2·1 (−6·09 to 12·64)
Causative pathogens			
Monomicrobial	100/164 (61·0%)	94/160 (58·8%)	2·2 (−8·36 to 12·76)
Polymicrobial	60/100 (60·0%)	47/90 (52·2%)	7·8 (−6·23 to 21·42)
Enterobacteriaceae	120/195 (61·5%)	105/186 (56·5%)	5·1 (−4·75 to 14·80)
Pseudomonas aeruginosa	36/63 (57·1%)	39/65 (60·0%)	−2·9 (−19·36 to 13·84)

Figure 2: **Subgroup analysis of 28-day all-cause mortality (A) and clinical response at test of cure (B)**
APACHE II=Acute Physiology and Chronic Health Evaluation II. CPIS=Clinical Pulmonary Infection Score. ICU=intensive care unit. *Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible. †Persistent or worsening signs or symptoms of nosocomial pneumonia after at least 48 h of antibacterial therapy active against Gram-negative pathogens. ‡Before randomisation.

	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
Gram-negative pathogens	157/259 (60·6%)	137/240 (57·1%)	3·5 (–5·1 to 12·1)
Enterobacteriaceae	120/195 (61·5%)	105/185 (56·8%)	4·8 (–5·1 to 14·5)
ESBL-producing Enterobacteriaceae	48/84 (57·1%)	45/73 (61·6%)	–4·5 (–19·3 to 10·7)
Pseudomonas aeruginosa	36/63 (57·1%)	39/65 (60·0%)	–2·9 (–19·4 to 13·8)
Multidrug-resistant *P aeruginosa*	13/24 (54·2%)	6/11 (54·5%)	–0·4 (–31·2 to 31·7)
Extensively drug-resistant *P aeruginosa*	4/10 (40·0%)	2/5 (40·0%)	0·0 (–43·6 to 40·3)

Data are n/N (%). *Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible.

Table 3: **Per-pathogen clinical cure at test-of-cure visit in the microbiological intention-to-treat population**

	Ceftolozane–tazobactam group (n=361)	Meropenem group (n=359)
At least one adverse event		
Overall	310 (86%)	299 (83%)
Severe	143 (40%)	136 (38%)
Serious	152 (42%)	129 (36%)
Leading to study drug discontinuation	37 (10%)	42 (12%)
Resulting in death	105 (29%)	101 (28%)
At least one treatment-related adverse event		
Overall	38 (11%)	27 (8%)
Severe	5 (1%)	3 (1%)
Serious	8 (2%)	2 (1%)
Leading to study drug discontinuation	4 (1%)	5 (1%)
Resulting in death	0	0
Most frequent* treatment-related adverse events		
Clostridioides difficile colitis	4 (1%)	1 (<1%)
Diarrhoea	4 (1%)	6 (2%)
Liver function test abnormalities†	12 (3%)	5 (1%)
Increased aspartate aminotransferase	3 (1%)	3 (1%)
Increased γ-glutamyl-transferase	3 (1%)	0
Increased alanine aminotransferase	2 (1%)	4 (1%)
Unspecified‡	8 (2%)	2 (1%)
Atrial fibrillation	2 (1%)	0
C difficile infection	2 (1%)	1 (<1%)
Erythema	2 (1%)	0
Vomiting	2 (1%)	1 (<1%)

*Treatment-related adverse events that occurred in at least 0·5% of patients in the ceftolozane–tazobactam group. †More than one subcategory of liver function test abnormality was reported in some patients. ‡Reported as either "hepatic enzyme increased" or "abnormal liver function test results".

Table 4: **Adverse events in the safety population**

41 [63%] of 65; 11·5% [–4·5 to 26·7]). A post-hoc analysis in which we excluded presumed eradication also suggested that microbiological eradication was similar between treatment groups (appendix p 22), as was the prospectively assessed occurrence of superinfections and new infections (appendix p 23).

All cause-mortality at 28 days was similar in the ceftolozane–tazobactam group (16 [33%] of 49) and meropenem group (seven [29%] of 24) among patients in the microbiological intention-to-treat population who were infected with pathogens at baseline that were not susceptible to assigned study treatment (weighted proportional difference –5·7% [95% CI –25·9 to 18·1]). The corresponding data were four (25%) of 16 in the ceftolozane–tazobactam group and none of seven in the meropenem group (–25·0% [–49·5 to 13·4]) among patients with ceftazidime non-susceptible *P aeruginosa*, and 18 (22%) of 81 and 20 (28%) of 72 among those with ceftazidime non-susceptible Enterobacteriaceae (5·6% [–8·1 to 19·2]). In a post-hoc sensitivity analysis restricted to patients in the microbiological intention-to-treat group in whom all baseline pathogens were susceptible to both study drugs, mortality with ceftolozane–tazobactam was lower than in the overall microbiological intention-to-treat population, whereas we noted no such difference in mortality among patients given meropenem (appendix p 20).

In the safety population, the proportion of patients with at least one adverse event, the frequencies of specific adverse events and adverse events leading to study drug discontinuation, and the severity of adverse events were similar between groups (table 4; appendix p 29). Serious adverse events were slightly more common in the ceftolozane–tazobactam group than in the meropenem group (table 4; appendix p 27). Most study drug discontinuations related to adverse events were because of fatal adverse events rather than investigator decisions (24 [65%] of 37 discontinuations in the ceftolozane–tazobactam group and 28 [67%] of 42 in the meropenem group). In the study overall, fatal adverse events were distributed across several system organ classes; the most commonly reported fatal adverse events were multiorgan failure, septic shock, brain oedema, and acute cardiac failure (appendix p 28).

Treatment-related adverse events were reported in 38 (11%) patients in the ceftolozane–tazobactam group and 27 (8%) in the meropenem group. The most commonly reported treatment-related adverse events were abnormal liver function tests, *Clostridioides difficile* colitis, and diarrhoea in the ceftolozane–tazobactam group (table 4). Serious treatment-related adverse events occurred in eight (2%) patients in the ceftolozane–tazobactam group and in two (1%) in the meropenem group (appendix p 32). No death was considered to be related to study treatment.

Discussion

In this randomised, controlled trial, we showed that ceftolozane–tazobactam was non-inferior to meropenem in terms of 28-day mortality and clinical response in patients with nosocomial pneumonia, a clinically challenging infection that is associated with a high risk of treatment failure and death.[1,3,8,30] Both study drugs had

similar efficacy across all secondary endpoints, including microbiological endpoints. The baseline pathogen distribution was consistent with previous reports, with most infections due to Enterobacteriaceae and 25% due to *P aeruginosa*.[15,30,31,33] Similar to previously reported surveillance data for hospitalised patients with pneumonia,[15] ceftolozane–tazobactam had high in-vitro activity against *P aeruginosa*, whereas more than 10% of *P aeruginosa* isolates were resistant to meropenem. As expected, meropenem had better in-vitro activity against Enterobacteriaceae, especially ESBL-producing strains (one-third of which were resistant to ceftolozane–tazobactam). Despite these differences in susceptibility profiles, clinical outcomes were similar between treatment groups irrespective of causative pathogen.

All-cause mortality was high (around 25% in each treatment group), but within the previously reported mortality range for this population.[3,34] Most patients had ventilator-associated pneumonia, about two-thirds of whom had late-onset disease. Baseline characteristics were similar between treatment groups in both the ventilator-associated pneumonia and ventilated hospital-acquired pneumonia subgroups, suggesting appropriate stratification by diagnosis. Previous clinical trials in nosocomial pneumonia have generally shown higher 28-day mortality in patients with ventilated hospital-acquired pneumonia than in those with ventilator-associated pneumonia.[34] In our study, a difference in mortality between the two conditions was noted only in the meropenem group, and as a result, 28-day mortality among patients with ventilated hospital-acquired pneumonia was lower in the ceftolozane–tazobactam group than in the meropenem group. However, although the 95% CI for this treatment difference excluded zero, significance cannot be inferred because adjustments for multiple comparisons were not prospectively done for subgroup analyses. Additional post-hoc analyses are planned to explore the reasons for this potential mortality difference.

As expected in this critically ill population, most patients (>80% in both groups) had adverse events, including a substantial proportion of serious, fatal adverse events (>25% in both groups). The types of treatment-emergent adverse events were representative of those typically reported among patients in intensive-care units. In general, adverse events and deaths occurred at similar frequencies in both the ceftolozane–tazobactam and meropenem groups. No deaths were judged to be related to study drugs. The incidence of treatment-related adverse events, including those that were serious or led to study drug discontinuation, was low and similar between treatment groups. The 3 g dose of ceftolozane–tazobactam that we gave seemed to be safe overall, and was not associated with neurotoxic effects (investigator-reported neurological adverse events were similar between treatment groups, and no seizures were recorded)—a concern with high-dose cephalosporins. Compared with the safety profile of the 1·5 g dose that is approved for other indications,[19] no new safety issues were identified with the 3 g dose.

We had two reasons for assessing an increased dose of ceftolozane–tazobactam. First, modelling projected that the 3 g dose would have a high probability of attaining the pharmacokinetic–pharmacodynamic target at the infection site against pathogens with ceftolozane–tazobactam MICs of 8 µg/mL or less.[23] Second, in patients who were critically ill and mechanically ventilated, who are known to have complex antimicrobial pharmacokinetic and pharmacodynamic profiles,[12,13] the 3 g dose had good intrapulmonary penetration and achieved pulmonary pharmacokinetic–pharmacodynamic targets for the entire dosing interval.[21] In other phase 3 trials,[9–11] ceftobiprole, tigecycline, and doripenem did not show non-inferiority to established comparator treatments for nosocomial pneumonia. In those studies, higher doses of the drugs were not used to compensate for the highly variable antimicrobial pharmacokinetics in patients who are critically ill (including those with augmented renal clearance) or for the increased prevalence of nosocomial pathogens with high MICs in that population.[12,13] This oversight could have led to suboptimal dosing in many patients, particularly those with ventilator-associated pneumonia.[12,14]

In another trial[33] in patients with nosocomial pneumonia, ceftazidime–avibactam (another cephalosporin–β-lactamase inhibitor combination) was non-inferior to meropenem.[33] In both treatment groups of that trial, a higher proportion of patients responded to treatment and a lower proportion died than in our study. This difference in outcomes is probably because patients in the ceftazidime–avibactam trial were less critically ill than those in our trial; they had much lower proportions of mechanically ventilated patients (43% *vs* 100% in our study), patients with high Acute Physiology and Chronic Health Evaluation II scores (14% *vs* 33%), and patients with moderate or severe renal impairment (5% *vs* 14%).

A strength of our study was enrolment of critically ill patients who were representative of the target population in terms of baseline clinical and demographic characteristics. Importantly, we enrolled only patients who were mechanically ventilated at baseline—a population at particularly high risk for poor treatment outcomes.[3] The use of quantitative cultures plus clinical diagnostic criteria meant that enrolled patients were likely to have bacterial pneumonia, a diagnosis that was further supported by the fact that almost 75% of patients had Clinical Pulmonary Infection Scores greater than 8 at baseline. US and international clinical practice guidelines recommend 7–8 days of intravenous therapy for nosocomial pneumonia but acknowledge that longer treatment might be required in case of insufficient improvement in clinical, radiographic, and laboratory parameters and in patients with bacteraemia, *P aeruginosa* infection, or certain other underlying conditions (eg, immunodeficiency, cystic

fibrosis).[3,30] In our trial, similar to other phase 3 trials in patients with nosocomial pneumonia over the past 10 years,[9–11,33,34] we permitted longer treatment durations to accommodate the need to tailor treatment duration on the basis of the causative pathogen and patient response. We selected meropenem, an established broad-spectrum first-line antibiotic with potent activity against target pathogens (including many multidrug-resistant strains),[31] as the comparator, rather than a less potent or narrower-spectrum alternative.

We used the meropenem regimen that is generally recommended for pneumonia across clinical guidelines and that is considered effective against respiratory pathogens with meropenem MICs of 2 µg/mL or less.[3,30,35] However, since our study protocol was developed and implemented, clinical practice guidelines for pneumonia have moved towards recommending extended-duration meropenem infusions in patients with pathogens with MICs for meropenem at the high end of the susceptibility or intermediate-susceptibility range (eg, between 2 µg and 4 µg in *P aeruginosa*) and in critically ill patients with augmented renal clearance. Although extended-duration meropenem infusions might benefit some patients, it is unlikely that this approach would have affected outcomes in the meropenem group of our trial, given the low meropenem concentration that inhibited 90% of isolates (1 µg/mL) and that efficacy in patients in the meropenem group with augmented renal clearance was similar to that in the overall study population. Another important limitation of our trial is that we excluded immunosuppressed patients, patients with cystic fibrosis, and patients receiving dialysis. Although exclusion of these patients is standard practice for phase 3 trials in bacterial infections, our data do not permit conclusions about safety and efficacy in these populations, in whom multidrug-resistant Gram-negative pathogens are prevalent. However, some data for immunosuppressed patients are available from three retrospective studies[36–38] in patients who received ceftolozane–tazobactam for various serious infections due to *P aeruginosa*, most of which were multidrug resistant or extensively drug resistant. Each study included a large proportion of patients with pneumonia (32–76%) and a substantial proportion of patients who were immunosuppressed, and showed a promising frequency of treatment success. Further clinical assessment of ceftolozane–tazobactam for the treatment of nosocomial pneumonia in immunosuppressed patients, patients with renal failure, and paediatric patients would be valuable.

In summary, high-dose ceftolozane–tazobactam (3 g every 8 h) is a suitable treatment option for critically ill patients with nosocomial pneumonia caused by *P aeruginosa*, Enterobacteriaceae, and other Gram-negative lower respiratory tract pathogens. Additionally, ceftolozane–tazobactam appeared well tolerated in this high-risk, critically ill patient population.

For more on **Merck Sharp & Dohme's data sharing policy** see http://engagezone.msd.com/ds_documentation.php

Contributors

MHK, CJB, JAH, BY, and EGR conceived, designed, and planned the study. MN, ÜK, ÁR-N, NS, IM-L, J-FT, RGW, BY, and EGR acquired the data, which were analysed by CJB, JAH, GL, BY, and EGR. GL provided statistical reports and input. MHK, MN, ÜK, IM-L, J-FT, RGW, CJB, JAH, GL, BY, JRB, and EGR interpreted the results. CJB, JAH, and EGR wrote the first draft of the Article, which was closely based on a previously presented poster that all authors had been involved in. All authors critically reviewed or revised the Article for important intellectual content.

Declaration of interests

MHK reports advisory board and speaker's bureau fees and institutional research funding from Merck & Co. MN reports investigator fees and institutional research funding from Merck & Co. ÜK and ÁR-N have received institutional research funding from Merck & Co. NS reports lecture fees from Merck Sharp & Dohme (a subsidiary of Merck & Co) and institutional research funding from Merck & Co. IM-L reports personal fees from Merck Sharp & Dohme and Biomerieux, and grants from Grifols, and has received institutional research funding from Merck & Co. J-FT reports grants from Merck Sharp & Dohme, Biomerieux, and Brahms; personal fees from Merck Sharp & Dohme, Pfizer, and Nabriva; and has received institutional research funding from Merck. RGW reports grants and personal fees from Merck & Co, Shionogi, Polyphor, Melinta, the Medicines Company, and Arsanis; personal fees from Microbiotix, KBP Biosciences, and Meiji-Seiko; and has received institutional research funding from Merck & Co. CJB, JAH, GL, BY, JRB, and EGR are employees of Merck Sharp & Dohme, and hold stock and stock options in Merck & Co.

Data sharing

Merck Sharp & Dohme's data sharing policy, including restrictions, is available online. Requests for access to the clinical study data can be submitted online or via email (dataaccess@merck.com).

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