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Ceftolozane and tazobactam for the treatment of hospital acquired pneumonia

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Abstract

Introduction: Patients admitted to hospitals are at risk of developing nosocomial infections. These types of infections typically occur in immune compromised patients. Furthermore, nosocomial infections are frequently caused by resistant organisms, including nonfermenting gram-negative bacilli such as *Pseudomonas aeruginosa*.

Areas covered: *P. aeruginosa* is a hazardous pathogen. It can resist numerous antibiotics, due to several resistance mechanisms. It is associated with serious illnesses, particularly hospital acquired infections including ventilator associated pneumonia. In the past, only a limited number of anti-pseudomonal drugs were available. However, several therapeutic advancements have been made, in recent years, to target *P. aeruginosa*, including the development of the new cephalosporin: ceftolozane-tazobactam.

Expert opinion: Ceftolozane-tazobactam is a combination of a novel semi-synthetic fifth generation cephalosporin with a well-established beta-lactamase inhibitor. From a structural perspective, ceftolozane-tazobactam has attested increased stability to AmpC β-lactamases. Additionally, ceftolozane-tazobactam is less affected by changes in efflux pumps and porin permeability due to an enhanced affinity to certain penicillin-binding proteins (PBPs). This enables the molecule to overcome the most common anti-drug resistant mechanisms of bacteria. According to previous clinical trials conducted, ceftolozane-tazobactam must be considered when treating patients with confirmed or suspected *P. aeruginosa* respiratory tract infections, either nosocomial pneumonia or ventilator-associated pneumonia.

Keywords: *P. aeruginosa; VAP; Pneumonia; Sepsis; VAT*

Article highlights

- Ceftolozane-tazobactam is a combination of a novel semi-synthetic fifth generation cephalosporin with a well-established beta-lactamase inhibitor.
- Ceftolozane is an oxyimino-aminothiazolyl cephalosporin developed by the addition of amino groups to the 4-position of a 3-amino-2-methylpyrazole cephalosporin, thus improving the minimum inhibitory concentration (MIC) values against AmpC β-lactamases
- Ceftolozane-tazobactam is typically compared to other antimicrobial agents including meropenem, ceftazidime-avibactam, cefepime, piperacillin-tazobactam or colistin.
- Upon inspection of resistant isolates, the susceptibility rate of MDR P. aeruginosa to ceftolozane-tazobactam was 86.6%, whereas in XDR isolates the susceptibility rate was 71.%.
- Ceftolozane-tazobactam must be considered when treating patients with confirmed or suspected P. aeruginosa infection from respiratory tract infections- either nosocomial pneumonia or ventilator-associated pneumonia
- In patients with increased risk of carrying multi-drug resistant strains of P. aeruginosa ceftolozane-tazobactam should also be considered as a treatment option

1. Introduction

Patients admitted to hospitals are at risk of developing nosocomial infections[1]. These types of infections typically occur in immune compromised patients. Furthermore, nosocomial infections are frequently caused by multi-drug resistant organisms (MDRO), including nonfermenting gram-negative bacilli such as *Pseudomonas aeruginosa* [2]. *P. aeruginosa* is a hazardous pathogen. It can resist numerous antibiotics, due to several resistance mechanisms. It is associated with serious illnesses; commonly hospital acquired infections, including ventilator associated lower respiratory tract infections.

In the past, there was only a limited number of anti-pseudomonal drugs available. However, several therapeutic advancements have been made, in recent years, to target *P. aeruginosa*, including the development of the new cephalosporin: ceftolozane-tazobactam.

2. Chemical structure

Ceftolozane-tazobactam is a combination of a novel semi-synthetic fifth generation cephalosporin with a well-established beta-lactamase inhibitor. Ceftolozane is an oxyimino-aminothiazolyl cephalosporin developed by the addition of amino groups to the 4-position of a 3-amino-2-methylpyrazole cephalosporin, thus improving the minimum inhibitory concentration (MIC) values against AmpC β-lactamases [3].

Ceftolozane has attested increased stability to AmpC β-lactamases. Additionally, ceftolozane is less affected by changes in efflux pumps and porin permeability due to an enhanced affinity to certain penicillin-binding proteins (PBPs). This enables the molecule to overcome the most common anti-drug resistant mechanisms of bacteria[4].

Like other cephalosporins, ceftolozane acts on Penicillin-binding proteins (PBPs), inhibiting cell wall synthesis- subsequently inducing cell death. Amongst the PBPs currently known,

ceftolozane has demonstrated a high affinity for PBP1b, PBP1c, PBP2 and PBP3. This has resulted in a strong bactericidal activity against pathogens, particularly *P. Aeruginosa* and *E. coli* [5].

Tazobactam is a penicillanic acid sulfone β-lactamase inhibitor. It has a similar structure to that of sulbactam and is used to protect beta-lactam antibiotics from beta-lactamase catalysis. The addition of tazobactam to ceftolozane, in a 2:1 ratio, expands its spectrum of activity against β-lactamase-producing Enterobacteriaceae, including those producing extended-spectrum β-lactamases (ESBLs)[6,7].

3. Clinical pharmacology

Ceftolozane-tazobactam has been developed to treat multi-drug resistant gram-negative bacterial infections. In preclinical studies, Petraitis et al [8] investigated the pharmacokinetics and efficacy of ceftolozane-tazobactam in persistently neutropenic rabbits. The authors found that ceftolozane-tazobactam was highly active in treatment of experimental P. aeruginosa pneumonia caused by strains [pan-susceptible (PS), outer membrane porin D (OPRD) porin loss (OPRDPL), efflux pump expression (EPE), and AmpC hyperexpression (ACHE)] with the most common resistance mechanisms.

A preclinical study published by Craig et al. conducted in a neutropenic murine thigh infection model found that 2:1 ratio of ceftolozane with tazobactam was the most potent combination studied and the T>MIC required for ceftolozane was less than with other cephalosporins against Pseudomonas aeruginosa and Enterobacteriaceae, including strains with extended-spectrum β-lactamases [9]. In healthy adult participants, ceftolozane-tazobactam was shown to the penetrate plasma and epithelial lining fluid (ELF-) in the lungs. In the study, 1.5 g of ceftolozane-tazobactam was administered every 8 hours [10]. Results from the study indicated an approximate 50% plasma-to-ELF penetration ratio [11]. However, additional studies conducted by Monte Carlo showed that a 3-g dose of ceftolozane-tazobactam in patients with normal renal function would be an adequate concentration for treatment of nosocomial pathogens [11]. A dosing regimen of 3 g every 8 hours

was used during the ASPECT-NP study [12]. Furthermore, the same dosing regimen has also been studied in patients with cystic fibrosis [13].

Ceftolozane-tazobactam has a broad spectrum of activity against gram negative pathogens. However, certain risk factors should be considered when reviewing its role in the treatment of multi-drug resistant bacteria. For instance, Haidar et al. [14] evaluated clinical effectiveness of ceftolozane-tazobactam in 21 adult patients with multi-drug resistant *P. aeruginosa* infections; 86% of these patients had respiratory infections and 43% were transplant recipients. In this study, an overall treatment failure rate of 29% was observed in patients. Additionally, an emergence of resistance against ceftolozane-tazobactam was detected in 14% of patients. Haidar et al. conducted this study using both 1.5 g and 3.0 g dosing regimens every 8 hours [14]. Therefore, the dosing regimen could potentially affect the treatment outcome. Furthermore, a cases series study led by Munita et al. [15] reported 7 treatment failures from a total of 15 patients with pneumonia. A MIC value over 4/4 ug/mL, or a therapy regimen of 1.5 g ceftolozane-tazobactam every 8 hours has been reported as possible explanation for treatment failure. Finally, Fraile-Ribot et al[16], found that the modification of intrinsic (AmpC) and horizontally acquired β-lactamases appears to be the main mechanism leading to ceftolozane-tazobactam resistance in MDR Pseudomonas aeruginosa infections.

In terms of treatment failure, another risk factor to consider is the correct time to initiate an appropriate antibiotic. For instance, in a retrospective study conducted in 20 hospitals, 255 patients with multidrug-resistant *P. aeruginosa* were evaluated [17]. From the 255 cases investigated, a mortality rate of 19% occurred, whilst the clinical success rate was 73.7%. Multivariate analysis highlighted that starting ceftolozane-tazobactam within 4 days of positive culture isolation was associated with better survival rates.

4. Pharmacokinetic

Ceftolozane-tazobactam is currently available in a 2:1 combination ratio, for intravenous use only. The approved dosage for treatment of complicated urinary tract infection (cUTI) or intra-

abdominal infection (cIAI) in patients, with an estimated creatinine clearance (CrCl) > 50 ml/min is 1g of ceftolozane with 500 mg of tazobactam every 8 hours [18] .

Pharmacokinetic values of intravenous ceftolozane-tazobactam in healthy adult subjects are summarized in Table 1 [19][20]. The mean plasma half-life of ceftolozane is approximately 2.3 hours. It is not affected by the dose [21]. Binding of ceftolozane to plasma proteins occurs at quite a low level; approximately 20%. The area under concentration-time curve ceftolozane (AUC) exhibits no significant change over a 10-day treatment period, suggesting no substantial drug accumulation [21][22].

The steady-state volume of distribution of ceftolozane is approximately 13 L. This is close to the average extracellular volume, which indicates that the drug can achieve potential therapeutic concentrations at the extracellular site of infection. Obesity or active infection may increase the apparent volume of distribution, without causing any significant changes in steady-state pharmacokinetic parameters [23].

Ceftolozane does not undergo significant metabolism in the human body, whereas tazobactam is partially metabolized to the inactive M1 metabolite [24]. Both ceftolozane and the M1 metabolite derived from tazobactam are primarily eliminated by renal excretion. Therefore, drug dosage should be adjusted in subjects with renal impairment. In subjects receiving haemodialysis, ceftolozane-tazobactam should be administrated after the haemodialytic treatment, as 90% of the drug is dialyzable [25].

Thus far, clinical trials conducted on the use of ceftolozane-tazobactam in the management of nosocomial pneumonia have yielded promising results, as the drug rapidly distributes in the lungs [26]. Studies on lung pharmacokinetics showed that epithelial lining fluid (ELF) / plasma AUC ratio for ceftolozane and piperacillin were 0.48 and 0.26, respectively. This indicates that ceftolozane penetrates well into the ELF following parenteral administration [10]. Furthermore, ELF concentrations of ceftolozane-tazobactam exceed the minimum inhibitory concentrations (MICs) of most Gram-negative pathogens responsible for nosocomial pneumonias [10] .

A double dose of ceftolozane-tazobactam (which is approved for cUTI and cIAI) should be recommended when treating nosocomial pneumonia, i.e. 3 g, 1.5 g, and 750 mg every 8 hours (rather

than 1.5 g, 750 mg, and 375 mg every 8 hours which is typically recommended for cUTI and cIAI), in patients with normal renal function/mild renal impairment, moderate renal impairment, and severe renal impairment, respectively [11]. The change in drug dosage, when treating nosocomial pneumonia is a consequence of the difference in sites of infection, a 50% plasma-to-ELF penetration ratio is approximately required to achieve similar or improved anti-bacterial effects against microorganisms with a MIC up to 8 mg/L [11]. As with all beta lactam agents ceftolozane-tazobactam can be administered with different schedules. In particular, there is some pharmacology evidence that an in vitro resistance can be overcome by enhancing the drug exposure, by means of increasing the infusion time and doubling the usual dose [27].

The Food and Drug Administration authority have approved dose adjustments for ceftolozane-tazobactam in patients affected by cUTI or cIAI/with renal failure as follows: CrCl 30-50 ml/min: 500/250 mg every 8 hours; CrCl 15-19 ml/min: 250/125 mg every 8 hours; end stage renal disease: loading dose of 500/250 mg followed by 100/50 mg every 8 hours.

5. Clinical microbiology

Ceftolozane-tazobactam has demonstrated potent in vitro activity against a variety of gram-negative pathogens such as *P. aeruginosa* and Enterobacteriaceae. These pathogens produce extended-spectrum β-lactamase, which are commonly involved in the epidemiology of nosocomial pneumonia [28]. At present, ceftolozane-tazobactam is the most active beta lactam agent directed against *P. aeruginosa*, including multi drug resistant (MDR), extensively drug resistant (XDR) and carbapenem resistant strains (do not produce carbapenemase), as the antibiotic is not affected by the most prevalent mechanisms of bacterial resistance [29].

Amongst nosocomial respiratory tract infections, caused by *P. aeruginosa*, ceftolozane-tazobactam susceptibility has previously been reported to be equivalent to 94%-97.5%, despite elevated levels of resistance to conventional parenteral beta-lactams[30][31][29]. Additionally, when comparing cumulative susceptibility rates of antibiotic combinations routinely used against P.

aeruginosa isolates in patients admitted to the intensive care unit, with pneumonia or a bloodstream infection, ceftolozane-tazobactam monotherapy has proven to be more active against isolates than a combination of another β-lactam with a fluoroquinolone or gentamicin. These findings suggest that ceftolozane-tazobactam monotherapy may provide a valid alternative to a combination antimicrobial regimen approach typically used in management of *P. aeruginosa* infections[32].

The activity of ceftolozane-tazobactam against Enterobacteriaceae isolates in the lower respiratory tract has been widely investigated. In two large US studies, ceftolozane–tazobactam was shown to inhibit 90.3-90.6% of Enterobacteriaceae isolates ($MIC_{50/90}$, 0.25/2 mg/L), including non–carbapenem-resistant Enterobacteriaceae isolates with an ESBL phenotype (82.8-85.7% susceptible)[29]. When microorganisms are individually analysed, ceftolozane–tazobactam inhibits 84%-91% of K. *pneumoniae* isolates, 96%-98% of E. *coli* isolates, 78%-96% of S. *marcescens* isolates, and 74%-90% of Enterobacter spp. isolates [33][34].

It is important to note that ceftolozane-tazobactam has limited antimicrobial activity against a number of pathogens, including carbapenemase producing K. *pneumoniae*, metallo-beta-lactamase-producing Enterobacteriaceae and other nonfermenting bacteria such as *Acinetobacter spp* or *Stenotrophomonas spp* [35]. Furthermore, ceftolozane-taezobactam has very limited activity against S. *aureus*, although reports have indicated some in vitro activity against other Streptococcus species. Finally, ceftolozane-tazobactam no activity against enterococci [36].

6. Trials conducted with ceftolozane-Tazobactam

6.1. Phase I trials

An initial phase 1 study [21] was conducted to determine the safety, tolerability, and pharmacokinetic profile of CXA-101 in humans, after single-and multiple-dose intravenous administrations. This study was a single-centre, prospective, randomized, double-blind, placebo-controlled trial of ascending single doses (part 1) and multiple (part 2) doses of CXA-101 intravenously, via a peripheral venous catheter. In part 1, five successive cohorts of eight subjects each (six active, two placebo) were administered a single intravenous dose of the study drug. CXA-

101 was given as a 1-hour intravenous infusion at ascending doses of 250, 500, 1,000, 1,500, and 2,000 mg. In part 2, three successive cohorts of eight subjects each (six active, two placebo) received multiple intravenous doses of the study drug for 10 days. Cohorts 1 and 2 received 500 mg and 1,000 mg CXA-101, respectively. The drug was infused over 1 h every 8 h. Cohort 3 received 1,500 mg of CXA-101infused over 1 h every 12 h.

The 64 subjects enrolled in part 1 and 2 of the study completed the dosing regimen; no participants withdrew from the study. In addition, drug-related systemic adverse events were infrequent and mild. The Cmax and AUC were linear over the dose range. Plasma T1/2 was independent of the dose and dosing duration, averaging 2.3 h (range, 1.86 to 2.64 h). Negligible drug accumulation occurred with the multiple-dose regimens, as evidenced by the minimal change in AUC after 10 days of repeated dosing.

Clearance (CL) of CXA-101 was primarily renal and independent of the dose and dosing duration; averaging a clearance of 102.4 ml/min (15.2%) after a single intravenous dose and 112.2 ml/min (18.7%) after the last of the multiple doses; CL of CXA-101 correlated well with the CL of creatinine. The majority of CXA-101 (92.5% following a single intravenous dose and 95% following multiple intravenous doses) was excreted in the urine as unchanged CXA-101. This observation indicates a need for dosage adjustment in patients with severe degrees of renal impairment.

Another Phase 1, randomized, open-label, comparator-controlled study was designed to compare the ELF penetration of ceftolozane/tazobactam with that of piperacillin/tazobactam)[24]. The primary objective was to compare the ELF-to-plasma AUC ratios of multiple doses of intravenous ceftolozane/tazobactam with piperacillin/tazobactam in healthy adult volunteers. A total of 51 volunteers participated in the trial (25 in ceftolozane/tazobactam group and 26 in the piperacillin/tazobactam group). The mean Cmax values (SD) after administration of ceftolozane/tazobactam for ceftolozane and tazobactam were 67.2 (12.1) and 14.9(2.4) mg/L respectively, and the mean total exposures expressed as AUC0-t (SD) were 158.5(42.1) and 19.3(2.9) mg.h/L respectively. Measurable concentration of ceftolozane/tazobactam were observed in ELF throughout the dosing interval, in all patients. Mean Cmax for ceftolozane in ELF was 21.8 mg/L and the total exposure was 75.1 mg.h/L and for tazobactam 4.5 mg/L and 8.5 mg.h/L

respectively. The total ELF/plasma AUC ratio was 0.48 for ceftolozane (0.26 for piperacillin) and 0.44 for tazobactam. This study highlighted that the ELF concentrations of ceftolozane/tazobactam exceed the MICs for the majority of common Gram- negative pathogens causing nosocomial pneumonia. In addition, the ELF concentration of ceftolozane/tazobactam exceeded 8 mg/L for >60% of the 8 h dosing interval, therefore indicating that a dosing regimen of 1.5 g every 8 h will inhibit the growth of 99% of all *P. aeruginosa.*

Finally, a phase 1 , open-label, multi-centre study (18 USA centres) was performed to evaluate the PK, safety and tolerability of single IV doses of ceftolozane in children from birth (7 days postnatal) to < 18 years with proven/suspected Gram-negative infections, or if the children were receiving perioperative prophylaxis[37]. Thirty-seven patients were enrolled in 6 groups according to age, and given ceftolozane (safety population), 34 patients comprised the PK population. Overall, ceftolozane PK was comparable among children older than 3 months, following administration of single IV doses of ceftolozane (between 20/10 and 30/15 mg/kg according to age). The CL of ceftolozane and tazobactam appeared to be lower and the volume of distribution was slightly higher, in young infants and neonates (7 days postnatal) in comparison to older children. This lower CL observed in young infants and neonates was most likely due to their immature renal function. Therefore, the ceftolozane/tazobactam dose should be adjusted accordingly in this age group (20/10 mg/kg). Although the number of participants was lower in each subgroup, ceftolozane/tazobactam was typically tolerated well; no safety concerns were identified.

6.2. Phase II trials

A phase II, prospective, double-blind, randomized, multi-centre trial was performed to evaluate the safety and efficacy of ceftolozane/tazobactam (1.5 g every 8 h [q8h]) in combination with metronidazole, compared to treatment with meropenem (1 g q8h), for the treatment of cIAIs in hospitalized adults [38]. The primary objective was to determine the clinical response in the microbiological modified intent-to-treat population (mMITT), microbiological evaluable (ME) and clinically evaluable (CE) populations at the test of cure (TOC) visit in the overall population and in

subgroups. A total of 121 were MITT, 82 patients received ceftolozane/tazobactam (for a mean duration of 5.7 days), and 39 patients received meropenem (for a mean duration of 6 days). The most common diagnosis was appendiceal perforation or periappendiceal abscess, followed by cholecystitis and diverticular disease. The most frequent pathogen isolated at participants baseline was *E. coli*; present in 41/61 (67.2%) and 19/25 (76.0%) patients in the ceftolozane/tazobactam and meropenem groups, respectively. The clinical cure rates in the mMITT population was higher in meropenem group (96.0% ;95% CI, 79.6- 99.9) than in the ceftolozane/tazobactam group (83.6%; 95% CI, 71.9-91.8, treatment difference, 12.4%). This difference, was partly, yet not completely, driven by a higher number of patients with a missing or with indeterminate clinical outcome in the ceftolozane/tazobactam group in comparison to the meropenem group. When this factor is taken into consideration, the clinical cure rates at the TOC visit in CE patients were similar (91.4% vs 94.3%) to the v and meropenem groups, respectively. Finally, ceftolozane/tazobactam was shown to be active against other major causative Gram-negative pathogens in cIAIs. ceftolozane/tazobactam demonstrated a 100% microbiological success rate for eradicating *P. aeruginosa and K. pneumoniae.* Therefore, these results suggest that ceftolozane/tazobactam is effective in the treatment of patients with cIAIs.

6.3. Phase III trials

An initial phase III, randomised, double-blind, double-dummy, non-inferiority trial (ASPECT-cUTI) was conducted to evaluate efficacy and safety of ceftolozane/tazobactam (1.5 h q/8h), or intravenous high-dose of levofloxacin (750mg once daily for 7 days) in patients with cUTI or pyelonephritis. The primary endpoint was a composite of microbiological eradication and clinical cure occurring 5–9 days after treatment in the mMITT population [39].

A total of 1028 (94·9%) of randomised patients completed the study, 800 (73·9%) of the patients had a positive urine culture at baseline and were included in mMITT population. The most common microorganism isolated was *E. coli* (78.6%), followed by *K. pnuemoniae* (7.3%) and *P. mirabilis* (3.0%). Baseline susceptibility showed that 2.7% and 26.7% of Gram-negative pathogens

were resistant to ceftolozane/tazobactam and levofloxacin respectively. In the overall cohort, only 2 (0.3%) of *E coli* isolates were resistant to ceftolozane/tazobactam and 24.2% were resistant to levofloxacin. The results indicate that ceftolozane/tazobactam was superior to levofloxacin for composite cure (microbiological eradication and clinical cure) in mMITT (76.9% vs 83.3%), per-protocol population (83·3% vs. 75·4%) and for microbiological eradication in mMITT (80.4% vs 72.1%) and per-protocol populations (86·2% vs 77·6%). The primary and secondary endpoints of the trial supported non-inferiority of ceftolozane/tazobactam to levofloxacin.

This study demonstrates that ceftolozane/tazobactam achieved significantly higher eradication rates than levofloxacin, in patients infected with *Enterobacteriaceae spp*, including ESBL-producing strains. Subsequently, ceftolozane/tazobactam may be an additional therapeutic option for patients with potentially life-threatening infections.

An additional Phase III, multi-centre, prospective, randomized, double-blind, placebo-controlled trial (ASPECT-cIAI) was performed to evaluate efficacy of intravenous v (1.5 g q/8h) plus metronidazole vs meropenem (1g q/8h) plus placebo for the treatment of hospitalized adult patients with cIAI [40]. A total of 806 (81.2%) patients qualified for the MITT population (389 in ceftolozane-tazobactam group and 417 in Meropenem group). *E. coli* (65.1%), *K. pneumoniae* (9.4%), and *P. aeruginosa* (8.9%) were the most frequent gram-negative aerobes isolated; most infections were polymicrobial. Susceptibility rates were similar for ceftolozane-tazobactam and meropenem (97.4% vs. 99.9% for Enterobacteriaceae, and 98.6% vs. 89.9% for *P. aeruginosa* respectively). In all patients, with ESBL-producing Enterobacteriaceae, the clinical cure rate was 95.8% in ceftolozane/tazobactam group and 88.5% in the meropenem group. The clinical cure rate for patients with CTX-M-14/15 ESBL-producing Enterobacteriaceae, was 100% vs 72.7% patients respectively. The clinical cure rate (primary endpoint) in the MITT population was 83.0% in ceftolozane-tazobactam group and 87.3% for meropenem group. Additionally, statistical noninferiority was also observed for clinical cure rate in the ME population (94.2% vs. 94.7% for ceftolozane-tazobactam and Meropenem respectively) at the TOC visit. Failure treatment rates were similar in both subgroups (8.2%). Ultimately, this study highlights that ceftolozane/tazobactam plus

metronidazole is a good treatment option for cIAI, particularly when resistant strains of Enterobacteriaceae or *P. Aeruginosa* are suspected.

Finally a third Phase III, randomised, controlled, double-blind, non-inferiority trial (ASPECT-NP) was performed to assess the efficacy and safety of ceftolozane-tazobactam (3 g q/8h) compared to Meropenem (1g q/8h), in patients with nosocomial pneumonia[12].

The primary efficacy endpoint was 28-day all-cause mortality in the ITT population. A total of 726 patients were included in the ITT population (362 to the ceftolozane-tazobactam group and 364 to the Meropenem group), and 511 in the MITT population (264 and 247 respectively). Enterobacteriaceae, *K. pneumoniae*, *E. coli*, followed by *P. aeruginosa* were the most frequently pathogens isolated, respectively. The 28-day mortality rate in ITT and MITT was similar in the ceftolozane-tazobactam group (24% and 33%) and Meropenem group (25.3% and 29%). Interestingly, in patients with ventilated hospital-acquired pneumonia, and those who had treatment failure prior to study entry, the mortality rate was lower in the ceftolozane-tazobactam group (24.2% and 22.6%) than in Meropenem group (37% and 45%). Overall, no difference was noted in the clinical cure rate per-pathogen in the MITT, when both groups were compared. Finally, the occurrence of adverse events (adverse events) was significantly high in the ceftolozane-tazobactam and Meropenem groups (80% of patients had adverse events). However, these events were a representation of reports generated amongst critically ill patients. Additionally, no deaths were deemed as a study drug related incidence. Ultimately, the results indicate that a high-dose of ceftolozane-tazobactam is a safe and effective treatment option for critically ill patients with nosocomial pneumonia caused by Gram- negative pathogens.

7. Adverse drug reactions

The safety profile of ceftolozane-tazobactam is similar to other betalactams. Thus far, the majority of trials conducted have been designed to administer 1.5 g of ceftolozane-tazobactam, q8h [41]. Yet, the 3 g q8h regimen has not been associated with a higher proportion of adverse events. In the ASPECT-NP study, treatment-related adverse events were reported in 11% of patients treated

with ceftolozane-tazobactam [12]. Severe adverse events were reported in 1% of the cohort, and serious adverse events were reported in an additional 2% of treated patients. The most common adverse events occurrences were liver function test abnormalities (3%), *C. difficile* colitis (1%) and a further 1% were reported as having a *C. difficile* infection. Additionally, diarrhea, atrial fibrillation, erythema and vomiting were also reported at 1% respectively.

8. Expert opinion

In adult patients, ceftolozane-tazobactam has been approved for the treatment of cIAI, in combination with metronidazole [42]. It has additionally been approved for the treatment of cUTI [43]. Furthermore, evidence is successfully accumulating from literature on the use of ceftolozane-tazobactam as first-line, second-line or salvage antimicrobial therapy in the management of serious *P. aeruginosa* infections, including nosocomial pneumonia, acute bacterial skin infections, skin-structure infections, bone infections or primary bacteraemia [44][45][46][47][48] [49], or as first-line therapy in patients with nosocomial pneumonia due to different gram-negative strains [50].

The clinical outcome of nosocomial pneumonia after treatment with ceftolozane-tazobactam has considerably improved over the years, most likely due to a change in the initial dosage of ceftolozane-tazobactam from 1.5 g every 8 hours to 3 g every 8 hours; thereby increasing the probability of reaching a pharmacodynamic target in ELF [51][52][53].

In a retrospective study carried out on 101 patients, who were treated for *P. aeruginosa* infections (ranging in severity) at 22 hospitals in Italy, Bassetti et al. reported an overall clinical success rate of 83.2% [53], in patients treated with ceftolozane-tazobactam. In particular, the overall clinical success for nosocomial pneumonia treated with ceftolozane-tazobactam was 75%. This was consistent with previous findings identified [47]. Notably, patients with sepsis or undergoing continuous renal replacement therapy showed a higher risk for clinical failure with ceftolozane-tazobactam, in this study.

A phase 3 clinical trial for the treatment of hospital-acquired pneumonia, including ventilator-associated pneumonia in intensive care unit patients, comparing ceftolozane-tazobactam at a dosage of 3 g (i.e. 2 g ceftolozane and 1 g tazobactam) every 8 hours with meropenem recently concluded, and highlighted that ceftolozane-tazobactam is an efficacious and well tolerated treatment for Gram-negative nosocomial pneumonia in mechanically ventilated patients, a high-risk, critically ill population[12].

In recent years, the use of colistin to treat healthcare related infections caused by non-fermenting Gram-negative bacilli, particularly *P. aeruginosa* and A. *baumannii,* has led to the emergence of colistin-resistant strains. In a case series, ceftolozane-tazobactam was successfully used to treat patients with kidney failure or those at high risk of kidney failure, who developed ventilator-associated pneumonia from pan-drug-resistant, colistin-resistant *P. aeruginosa* [54].

Clinical failures have been reported with ceftolozane-tazobactam in patients with pneumonia. Therefore, the possibility of ceftolozane-tazobactam resistance should be considered when choosing appropriate therapy for the management of multi-drug resistant Enterobacteriaceae. In the past, studies highlighted that the in vitro selection of ceftolozane-tazobactam resistant *P. aeruginosa* strains is primarily due to mutations or overexpression of the resident AmpC β-lactamase[55][56]. Thus, from a clinical perspective, the possibility of pathogens acquiring resistance to ceftolozane/tazobactam should be always be considered in patients who have had previous exposure to beta-lactams, or in those who have had a poor response to this antibiotic, in the past.

Ceftolozane-tazobactam is a broad-spectrum cephalosporin, approved for the treatment cIAI, cUTI and nosocomial pneumonia including ventilator-associated pneumonia [12,13]. ceftolozane/tazobactam is active against many pathogens including several isolates of multi-drug resistant P. *aeruginosa* [57], Enterobacteriaceae (including strains resistant to cephalosporins) and some ESBL species [58].

Ceftazidime-avibactam, is another novel cephalosporin-betalactamase inhibitor combination [59]. It is also active against some *P. aeruginosa* and Enterobacteriaceae isolates. It has lower antimicrobial activity against *A. baumannii* and some Gram-negative rods.

Ceftolozane-tazobactam is typically compared to other antimicrobial agents including meropenem, ceftazidime-avibactam, cefepime, piperacillin-tazobactam or colistin. Castanheira et al. previously studied the activity of ceftolozane-tazobactam, cefepime, ceftazidime, meropenem, and piperacillin-tazobactam against *P. aeruginosa* and Enterobacteriaceae isolates collected from respiratory tract of inpatients [58]. Overall, the susceptibility rates of *P. aeruginosa* isolates ranged from 96.3% for ceftolozane-tazobactam to 78.6% for piperacillin-tazobactam. Upon inspection of resistant isolates, the susceptibility rate of MDR *P. aeruginosa* to ceftolozane-tazobactam was 86.6%, whereas in XDR isolates the susceptibility rate was 71.%. A recently published paper from Greece showed the synergistic effect of adding amikacin to ceftolozane-tazobactam in treating *P. aeruginosa* highly resistant strains[60]. Whilst examining respiratory samples, Grupper et al. showed that *P. aeruginosa* isolates resistant to meropenem maintained a high susceptibility profile to ceftolozane-tazobactam (92%) and ceftazidime-avibactam (81%) [61]. Furthermore, the susceptibility of Enterobacteriaceae isolates was 95.6% to meropenem, 90.6% to ceftolozane-tazobactam, 88.2% to cefepime, 86.1% to piperacillin-tazobactam and 84% to ceftazidime. When analysing isolates with an ESBL phenotype, Grupper et al. concluded that ceftolozane-tazobactam was active in 82.8% of isolates.

In the ASPECT-NP study, patients with nosocomial pneumonia (ventilator-associated pneumonia or ventilated hospital-acquired pneumonia) were randomized to receive ceftolozane-tazobactam vs meropenem [12]. This study highlighted that nosocomial pneumonia could be as serious as ventilator-associated pneumonia [62]. Patients in the ASPECT-NP study had an APACHE II score above 17, and a mortality rate of 24% in the ceftolozane-tazobactam arm and a mortality rate of 25.3% in the meropenem arm. In patients with ventilated hospital-acquired pneumonia the mortality was 24.2% in the ceftolozane-tazobactam arm vs 37% in the meropenem arm.

According to these results, ceftolozane-tazobactam must be considered when treating patients with confirmed or suspected *P. aeruginosa* infection from respiratory tract infections- either nosocomial pneumonia or ventilator-associated pneumonia (figure 1). Additionally, in patients with increased risk of carrying multi-drug resistant strains of *P. aeruginosa* ceftolozane-tazobactam should also be considered as a treatment option [12,57,63].

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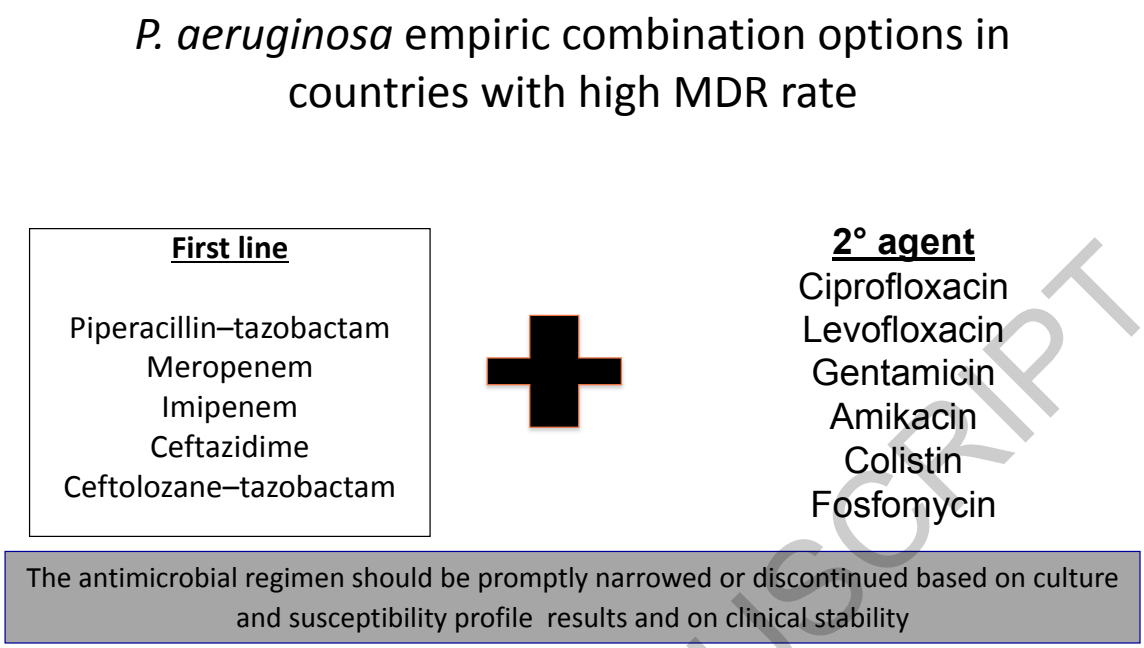
Table 1. Mean Pharmacokinetic values of ceftolozane 1g - tazobactam 0.5g every 8 hours in healthy adult subjects

	CEFTOLOZANE		TAZOBACTAM	
	Day 1	Day 10	Day 1	Day 10
Cmax (mg/dl)	52.8[a] - 69.1[b]	58[a] - 74.4[b]	18.4[b]	18[b]
Tmax (h)	1.02[b] -1.03[a]	1.05[a] - 1.07[b]	1.02[b]	1.01[b]
$AUC_{0\text{-last}}$ (h µg/ml)	148.6[a] - 172[b]	143.3[a] -197[b]	24.4[b]	24.8[b]
$T_{1\backslash 2}$ (h)	2.38[a] - 2.77[b]	2.69[a] - 3.12[b]	0.91[b]	1.03[b]
CL (litres/h)	5.86[b] - 6,73[a]	5.58[b] - 6.98[a]	20.6[b]	20.4[b]
CL_R (litres/h)	5.58[b] - 6.69[a]	6.67[a] - 6.80[b]	12.3[b]	16.3[b]
Volume of distribution (L)	14.6[b] -17.8[a]	14.2[b] - 17.1[a]	18.1[b]	17.9[b]
AI	NA	1.14[b]- 1.155[a]	NA	0.93[b]

C_{max}, maximum plasma concentration, T_{max}, time of plasma concentration, $AUC_{0\text{-last}}$, area under the concentration-time curve from zero hour to infinity, $T_{1\backslash 2}$, half-life in plasma, CL, clearance, CL_R, renal clearance, AI, accumulation index

a. Pharmacokinetics and Safety of CXA-101, a New Antipseudomonal Cephalosporin, in Healthy Adult Male and Female Subjects Receiving Single- and Multiple-Dose Intravenous Infusions[21].
b. Pharmacokinetics and safety of intravenous ceftolozane-tazobactam in healthy adult subjects following single and multiple ascending doses[22].

Figure 1.



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* of interest

** of considerable interest

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