Can ceftolozane–tazobactam treat nosocomial pneumonia?

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Published Online
September 25, 2019
https://doi.org/10.1016/S1473-3099(19)30523-7

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The emergence of multidrug-resistant Gram-negative bacteria associated with hospital-acquired infections, combined with the scarce development of new antibiotics, has grabbed the attention of scientific and non-scientific communities. However, new antimicrobials have been developed and have expanded the therapeutic options for infections caused by these pathogens. Ceftolozane–tazobactam is a combination treatment comprising a β-lactamase inhibitor (tazobactam), which can inhibit common class A extended-spectrum β-lactamases (ESBLs), and a novel cephalosporin (ceftolozane), which has certain characteristics that make it active against *Pseudomonas aeruginosa*. These characteristics include a high affinity for some penicillin-binding proteins,[1] stability in the presence of chromosomal AmpC-β-lactamases,[2] and robustness against OprD deficiency and efflux systems.[3] These features render the combination an appealing option for some multidrug-resistant Gram-negative bacteria. Ceftolozane–tazobactam has been approved for the treatment of complicated urinary tract and intra-abdominal infections. Use of ceftolozane–tazobactam to treat nosocomial pneumonia caused by multidrug-resistant *P aeruginosa* has been reported in retrospective series, but data from a randomised clinical trial are awaited.

In *The Lancet Infectious Diseases*, Marin Kollef and colleagues report the findings of a randomised, controlled, non-inferiority trial[4] of ceftolozane–tazobactam (2 g ceftolozane plus 1 g tazobactam infused over 1 h every 8 h) versus meropenem (1 g infused over 1 h every 8h) in mechanically ventilated patients with Gram-negative nosocomial pneumonia. The primary outcome was 28-day all-cause mortality in the intention-to-treat population. The non-inferiority margin for the difference in the primary outcome between groups was –10%, and ceftolozane–tazobactam was non-inferior to meropenem (weighted treatment difference 1·1% [95% CI –5·1 to 7·4]). Serious adverse events unrelated to study treatment and serious treatment-related adverse events were more frequent in the ceftolozane–tazobactam group than in the meropenem group (152 [42%] of 361 *vs* 129 [36%] of 359, and eight [2%] *vs* two [1%], respectively). These differences were not significantly different, but this trial, like most randomised trials of efficacy, was not powered to detect safety outcome differences. The frequency of neurotoxic adverse events was low in the study, but such events are difficult to identify in patients who are critically ill and intubated.

Kollef and colleagues' trial has several strengths, including the large sample size (726 patients), the procedures used to ensure proper blinding (eg, use of dummy infusions and drug bags), the stratification of randomisation by diagnosis (ie, ventilator-associated pneumonia *vs* ventilated hospital-acquired pneumonia), and the use of geographical region as a blocking factor to ensure even randomisation across groups within each region.

A 3 g dose of ceftolozane–tazobactam (double the dose approved for other infections) was chosen to ensure the combination would have maximum antibacterial activity, even against bacteria with minimum inhibitory concentrations (MICs) of 8 μg/L—a concentration higher than the breakpoints for *P aeruginosa* and Enterobacteriaceae from the Clinical & Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. In healthy people, doses of 3 g produced concentrations of unbound ceftolozane in epithelial lung fluid of at least 8 mg/L for 40% of the dosing period and 4 mg/L for 50% of the dosing period in nearly 100% of patients.[5] Ceftolozane concentrations in the epithelial lung fluid of mechanically ventilated patients with pneumonia are even higher than those in healthy people. Plasma concentrations above the MIC for 40% to 50% of the dosing interval were associated with a 2-log reduction of *P aeruginosa* in a thigh infection model.[6] In a thigh infection model with Enterobacteriaceae and *P aeruginosa*, a 1-log reduction in colony-forming units was obtained when free plasma concentrations of ceftolozane were higher than the MIC for approximately 30% of the dosing period.[7] In a previous study,[5] nearly 100% of healthy people attained this pharmacokinetic–pharmacodynamic target in epithelial lung fluid with a ceftolozane–tazobactam dose of 1·5 g every 8 h for pathogens with MICs up to 4mg/L, suggesting that the 1·5 g dose would be efficacious against isolates with MICs within the current susceptibility breakpoint.

Previous unsuccessful non-inferiority trials of other antimicrobials in nosocomial pneumonia also drove

the choice of a high dose of ceftolozane–tazobactam in Kollef and colleagues' trial. However, the dose of meropenem used in the trial could have been suboptimal on the basis of studies[8,9] that assessed meropenem penetration into the epithelial lining fluid of patients with nosocomial pneumonia. For equivalent antibacterial activity to high-dose ceftolozane–tazobactam, higher doses of meropenem should have been given—ie, 2 g every 8 h, preferably via extended 3-h infusion.[9,10] The 2016 Infectious Diseases Society of America and American Thoracic Society guideline suggested the optimisation of pharmacokinetic and pharmacodynamic parameters before initiating treatment of nosocomial pneumonias,[10] but Kollef and colleagues' trial was designed before this guideline was published. Despite these pharmacokinetic–pharmacodynamic issues for meropenem, and even though in the microbiological intention-to-treat population the proportion of baseline *P aeruginosa* isolates that was resistant to study treatment was more than four times higher in the meropenem group (13%) than in the ceftolozane–tazobactam group (3%), neither 28-day all-cause mortality nor clinical response at test of cure (the primary and key secondary study outcomes) differed significantly between study arms in the subgroup of patients with ventilator-associated pneumonia, bacteraemia, or *P aeruginosa* infections.

Ceftolozane–tazobactam is a welcome addition to the antibiotic armamentarium for nosocomial pneumonia. Still, in view of the high dose used in this trial and the limited safety data available, close monitoring and surveillance of clinical practice and phase 4 safety registries will be necessary to better define the risk–benefit profile of this new antimicrobial.

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APZ has participated in advisory boards for MSD and Pfizer and has received research grants from Pfizer. ACK declares no competing interests.

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Non-typhoidal salmonella: invasive, lethal, and on the loose

Published **Online** September 24, 2019 https://doi.org/10.1016/S1473-3099(19)30521-3

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In *The Lancet Infectious Diseases*, the GBD 2017 Non-Typhoidal Salmonella Invasive Disease Collaborators[1] estimate the global burden of invasive non-typhoidal salmonella disease using Bayesian meta-regression tools. The results show a high but decreasing number of cases since 2005 with a continuously high case fatality rate, consistent with previous estimates. These findings show that serotypes of *Salmonella enterica* subspecies that cause invasive non-typhoidal salmonella disease are "low-incidence, high-consequence" pathogens.[2] The unique potentiation of mortality from invasive non-typhoidal salmonella disease through HIV infection, malnutrition, and malaria,[3] has further prompted investigation into the burden of this infectious disease in recent times to inform measures for mitigation.