NICE National Institute for Health and Care Excellence

Antimicrobial prescribing: ceftolozane with tazobactam for treating hospital-acquired pneumonia, including ventilator-associated pneumonia

This evidence review sets out the best available evidence on ceftolozane with tazobactam for treating hospital-acquired pneumonia (including ventilator-associated pneumonia). It should be read in conjunction with the evidence summary, which gives the key messages.

Disclaimer

The content of this evidence review was up-to-date in December 2019. See summaries of product characteristics (SPCs), British national formulary (BNF), the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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Background

This evidence review considers ceftolozane with tazobactam for treating hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

HAP is pneumonia that develops 48 hours or more after hospital admission, which was not incubating at hospital admission. VAP is a type of HAP that develops in hospital after intubation and mechanical ventilation. People with severe HAP who require mechanical ventilation during their treatment and after the onset of infection do not meet the definition of VAP (NICE guideline NG139, [pneumonia (hospital-acquired): antimicrobial prescribing](#) and [International ERS/ESICM/ESCMID/ALAT guidelines for the management of HAP and VAP](#)).

Early-onset HAP (2 to 5 days after admission to hospital) is usually caused by *Streptococcus pneumoniae* and other Gram-positive organisms. Late-onset HAP (more than 5 days after admission to hospital) is usually caused by microorganisms that are acquired in hospital, most commonly meticillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and other non-pseudomonal Gram-negative bacteria (NICE guideline NG139, pneumonia (hospital-acquired): antimicrobial prescribing).

At any time, 1.5% of hospital inpatients in England have a hospital-acquired respiratory infection, more than half of which are HAP that is not associated with intubation. HAP is estimated to increase hospital stay by about 8 days and has a reported mortality rate that ranges from 30 to 70% (NICE guideline CG191, [pneumonia in adults](#)). VAP accounts for up to 25% of all infections in intensive care units. The risk is estimated to be 3% per day during the first 5 days of ventilation, 2% per day between days 5 and 10 of ventilation, and 1% per day after that ([Guidelines for the management of HAP in the UK: Report of the Working Party on HAP of the British Society for Antimicrobial Chemotherapy](#)).

NICE has produced the following related guidance on pneumonia:

- [pneumonia (hospital-acquired): antimicrobial prescribing](#)
- [pneumonia in adults](#).

The NICE antimicrobial prescribing guideline on HAP recommends that antibiotic treatment should be started as soon as possible after establishing a diagnosis, and certainly within 4 hours (within 1 hour if the person has suspected sepsis and meets any of the high risk criteria for this). For people with HAP, NICE advises that antibiotic choice should be based on specialist microbiological advice and local resistance data. Intravenous antibiotics are recommended if symptoms or signs are severe (for example, symptoms or signs of sepsis) or the risk of resistance is high. Options for first-line intravenous administration include piperacillin with tazobactam, ceftazidime, ceftriaxone, cefuroxime, meropenem and, taking MHRA safety advice into account, levofloxacin. If MRSA infection is suspected or confirmed, NICE recommends dual therapy with one of the intravenous antibiotics listed above and vancomycin, teicoplanin or, in some circumstances, linezolid.

The NICE antimicrobial prescribing guideline on HAP does not cover VAP. The international guidelines for managing HAP and VAP recommend using a single narrow-spectrum antibiotic for people at a low risk of multidrug-resistant pathogens and low risk of dying. For people at high risk of multidrug-resistant pathogens or high risk of dying who are not in septic shock, the international guidelines on HAP and VAP recommend using a single broad-spectrum antibiotic that is effective against most Gram-negative pathogens, including *Pseudomonas aeruginosa*, (such as meropenem, piperacillin with tazobactam, levofloxacin or ceftazidime). Treatment for MRSA may also be considered with vancomycin or linezolid (International ERS/ESICM/ESCMID/ALAT guidelines for the management of HAP and VAP).

For high risk people who are severely ill or in septic shock, the guidelines advise combination treatment, usually with an antipseudomonal beta-lactam antibiotic (such as meropenem, piperacillin with tazobactam or ceftazidime) plus an aminoglycoside (such as gentamicin) or an antipseudomonal quinolone (such as levofloxacin), with or without a third antibiotic for MRSA. The guidance notes that a third-generation cephalosporin is not reliable for treating infections caused by extended-spectrum beta-lactamase (ESBL) producing Enterobacterales (formerly known as Enterobacteriaceae). Preferred treatment is a carbapenem, although the guidelines suggest there may be a role for other treatments depending on local susceptibilities

(International ERS/ESICM/ESCMID/ALAT guidelines for the management of HAP and VAP).

According to the [English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018 to 2019](#), the proportion of isolates of Gram-negative pathogens resistant to key antibiotics remained broadly stable between 2014 and 2018. However, year-on-year increases in the incidence of bacteraemia meant that the burden of resistance for Gram-negative infections increased over time. The estimated number of bloodstream infections caused by Gram-negative pathogens resistant to 1 or more key antibiotics increased by 32% from 12,972 in 2014 to 17,108 in 2018. The increase was particularly marked for infections caused by Enterobacterales (for example *Escherichia coli*). The burden of resistance remained unchanged for Gram-positive infections over the same period.

The ESPAUR report notes that, between 2017 and 2018, shortages of piperacillin with tazobactam led to increased use of third-generation cephalosporins and fluoroquinolones, and a subsequent 15% increase in antimicrobial-resistant Gram-negative bloodstream infections. Resistance of *E. coli* (and other Enterobacterales such as Klebsiella species) to 3 third-generation cephalosporins (cefpodoxime, cefotaxime and ceftazidime) is used as a broad indicator of the presence of ESBLs (enzymes that make the bacteria resistant to treatment with cephalosporins, which leads to increased morbidity and mortality). Between 2013 and 2018, a statistically significant increase was seen in resistance of *E. Coli* (from 10.7% to 14.1%, $p < 0.001$) and *K. pneumoniae* (from 10.7% to 15.2%, $p < 0.001$) to third-generation cephalosporins too.

The antibiotic considered in this evidence review is a combination of a cephalosporin, ceftolozane, and a beta-lactamase inhibitor, tazobactam.

Product overview

Mode of action

Ceftolozane is a cephalosporin antibacterial, which belongs to the beta-lactam class of antibiotics and predominantly acts against Gram-negative organisms. It binds to penicillin-binding proteins, resulting in inhibition of bacterial cell-wall synthesis and

subsequent cell death. Tazobactam is a beta-lactamase inhibitor, which inhibits many (but not all) class A beta-lactamases (enzymes that cause resistance to beta-lactam antibiotics). By blocking the action of these enzymes, tazobactam allows ceftolozane to act against bacteria that would otherwise be resistant ([Zerbaxa summary of product characteristics](#) and [Zerbaxa European public assessment report](#)).

Regulatory status

Ceftolozane with tazobactam ([Zerbaxa](#), Merck Sharp & Dohme Limited) received a marketing authorisation for treating complicated intra-abdominal infections, acute pyelonephritis and complicated urinary tract infections in adults in September 2015 (see [Complicated urinary tract infections: ceftolozane/tazobactam](#) and [Complicated intra-abdominal infections: ceftolozane/tazobactam](#) for more information).

In August 2019, the indication for ceftolozane with tazobactam was extended to include treating hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adults ([Zerbaxa: Procedural steps taken and scientific information after the authorisation](#)).

Dosing information

Ceftolozane with tazobactam is administered by intravenous infusion. Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam. In adults with creatinine clearance of more than 50 ml/minute, the recommended dosage for HAP and VAP is 2 g/1 g infused over 1 hour, every 8 hours for 8 to 14 days. Lower dosages are recommended in people with renal impairment and creatinine clearance 50 ml/minute or less (summary of product characteristics). No dosage adjustment is needed based on age or hepatic impairment.

Lower dosages are also recommended for people with complicated intra-abdominal infections, acute pyelonephritis and complicated urinary tract infections. See the summary of product characteristics for more information.

Resistance

Mechanisms of bacterial resistance to ceftolozane with tazobactam include production of beta-lactamases that can hydrolyse ceftolozane and which are not inhibited by tazobactam, and modification of penicillin-binding proteins (summary of product characteristics).

The inhibitory spectrum of tazobactam includes many class A beta-lactamases (including CTX-M, SHV, and TEM enzymes), but it does not inhibit all class A enzymes. Also, tazobactam does not inhibit AmpC enzymes (produced by Enterobacterales), serine-based carbapenemases (for example, *Klebsiella pneumoniae* carbapenemases [KPCs]), metallo-beta-lactamases (for example, New Delhi metallo-beta-lactamase [NDM]) or Ambler class D beta-lactamases (OXA-carbapenemases). Therefore, it cannot protect ceftolozane from these.

Ceftolozane with tazobactam is a relatively new antibiotic, which is generally not used first line. Therefore, data on resistance and the impact in clinical practice in the UK are limited. Information on resistance can be found on [Public Health England antimicrobial resistance local indicators](link).

The [ESPAUR report 2018 to 2019](link) states that monitoring the use of new antibiotics and detecting emerging resistance to these medicines is a crucial component of antimicrobial usage surveillance to inform antimicrobial stewardship activities and preserve treatment effectiveness. Although susceptibility testing for newer antibiotics such as ceftolozane with tazobactam is currently uncommon and selective (following resistance to first- and second-line antibiotics), resistance has nonetheless been recorded. The report notes that, in 2018, 298 (0.8%), 67 (1.0%) and 117 (2.8%) of *Escherichia coli*, *Klebsiella pneumoniae* and Pseudomonas species bacteraemia respectively were tested for susceptibility to ceftolozane with tazobactam, and 19 (6.4%), 17 (25.4%) and 10 (8.5%) isolates were resistant.

Effectiveness

This evidence review discusses the best available evidence for ceftolozane with tazobactam for treating hospital-acquired pneumonia (HAP), including ventilator-

associated pneumonia (VAP) in adults, which is the ASPECT-NP phase 3 randomised controlled trial.

ASPECT-NP was a multicentre randomised, controlled, double-blind, non-inferiority trial. It included 726 adults (mean age 60 years) with HAP caused by Gram-negative pathogens who were undergoing mechanical ventilation. Of these, 71% had VAP and 29% had HAP that had worsened and needed mechanical ventilation (ventilated HAP). Ninety two percent of participants were admitted to intensive care. Thirteen percent had previously unsuccessfully used another antibiotic for the current episode of pneumonia. Participants were randomised to receive ceftolozane with tazobactam 2 g/1 g or meropenem 1 g intravenously every 8 hours for 8 to 14 days. The primary outcome reported was 28-day all-cause mortality (the US FDA primary outcome). The key secondary outcome reported was clinical cure at the test-of-cure visit (7 to 14 days after the end of treatment: the EMA primary outcome). Clinical cure was defined as resolution of baseline signs and symptoms of HAP, with no new signs or symptoms and no need for additional antibiotic treatment.

Appendix A summarises details of the included study. Appendix B gives an overview of the results for clinical effectiveness. Appendix E gives details of studies identified in the literature search that were then excluded.

Mortality

At 28 days, 24.0% (87/362) of participants in the ceftolozane with tazobactam group had died compared with 25.3% (92/364) of participants in the meropenem group (intention-to-treat [ITT] population; weighted treatment difference 1.1%, 95% confidence interval [CI] −5.1% to 7.4%). The lower limit of the 95% CI was greater than the prespecified non-inferiority margin of −10%, showing that ceftolozane with tazobactam was statistically non-inferior to meropenem. Sensitivity analyses support this result in the ITT population (Zerbaxa EPAR - Assessment report - variation).

There was no difference in mortality between ceftolozane with tazobactam and meropenem in the microbiological ITT population (participants who received at least 1 dose of study treatment and from whom at least 1 Gram-negative or streptococcal respiratory pathogen susceptible to at least 1 study treatment was cultured from

baseline lower respiratory tract samples [n=511]). However, this secondary outcome was not statistically powered for non-inferiority testing.

In the subgroup of participants with VAP (n=519), there was no difference between the treatments in mortality. In the subgroup of participants with ventilated HAP (n=207), mortality was numerically lower in the ceftolozane with tazobactam group than in the meropenem group. However, these subgroup analyses were not statistically powered for non-inferiority testing.

Clinical cure

At the test-of-cure visit, 54.4% (197/362) of participants in the ceftolozane with tazobactam group experienced clinical cure compared with 53.3% (194/364) of participants in the meropenem group (ITT population; weighted treatment difference 1.1%, 95% CI −6.2% to 8.3%). The lower limit of the 95% CI was greater than the prespecified non-inferiority margin of −12.5%, showing that ceftolozane with tazobactam was statistically non-inferior to meropenem.

There was no difference between ceftolozane with tazobactam and meropenem in clinical cure in the clinically evaluable population (participants who received study treatment, adhered to the study protocol up to the test-of-cure visit and had evaluable clinical outcomes at that timepoint [n=439]). This per-protocol analysis supports the result in the ITT population. However, this secondary outcome was not statistically powered for non-inferiority testing.

Microbiological eradication

Ceftolozane with tazobactam and meropenem also appeared to be similar in terms of microbiological eradication in the microbiological ITT population (n=511), but this was a secondary outcome that was not statistically powered for non-inferiority testing.

Safety

In the ASPECT-NP trial, treatment-related adverse events were reported by 11% (38/361) of participants using ceftolozane with tazobactam and 8% (27/359) of participants using meropenem (no statistical analysis). In the ceftolozane with

tazobactam group, the most commonly reported treatment-related adverse events were abnormal liver function tests, *Clostridioides difficile* (formerly known as *Clostridium difficile*) colitis and diarrhoea.

Serious treatment-related adverse events occurred in 2% (8/361) of participants in the ceftolozane with tazobactam group and 1% (2/359) of participants in the meropenem group (no statistical analysis). No deaths in either group were considered related to study treatment.

Study treatment was discontinued because of treatment-related adverse events in 1% of participants in both groups (4/361 using ceftolozane with tazobactam and 5/359 using meropenem). Study treatment was discontinued because of insufficient therapeutic effects in 6% (23/361) of participants in the ceftolozane with tazobactam group and 4% (15/359) of participants in the meropenem group (no statistical analyses).

The summary of product characteristics states that the most common adverse effects (at least 3 in 100) seen in phase 3 trials assessing ceftolozane with tazobactam for complicated intra-abdominal infections, complicated urinary tract infections (including pyelonephritis) and hospital-acquired pneumonia (including ventilator-associated pneumonia) were nausea, headache, constipation, diarrhoea, pyrexia and raised liver enzymes. These were generally considered mild or moderate in severity.

Appendix B gives details of the results for safety and tolerability from the included studies.

Person-related factors

Ceftolozane with tazobactam is administered by intravenous infusion over 1 hour, every 8 hours (summary of product characteristics). In practice, it is highly likely it will be prescribed and administered in a hospital setting.

Evidence strengths and limitations

ASPECT-NP was a relatively large, well-designed and reported study, which was undertaken in accordance with regulatory requirements. The primary outcome for the

FDA was 28-day all-cause mortality (the key secondary outcome for the EMA) and the primary outcome for the EMA was clinical cure at the test-of-cure visit (7 to 14 days after the end of treatment: the key secondary outcome for the FDA). As is necessary in a non-inferiority study, both intention-to-treat and per-protocol analyses (in the clinically evaluable population) were undertaken for the EMA primary outcome, and their results were consistent. Results for the FDA primary outcome were supported by sensitivity analyses. However, the European public assessment report noted that it was unfortunate that the per-protocol analyses were tested as secondary outcomes rather than co-primary outcomes with the same statistical power (Zerbaxa EPAR - Assessment report - variation).

Although the UK had an active investigational site, no participants were recruited. However, many participants were from Australia, Europe and the USA so the study population is probably applicable to the UK population. The study excluded people with immunosuppression and cystic fibrosis, and people receiving dialysis. Adults only were included and ceftolozane with tazobactam is not currently licensed for treating children and young people.

All study participants were mechanically ventilated and seriously ill; therefore, it is unclear whether the study results are applicable to people with less severe hospital-acquired pneumonia (HAP) or without intubation. Most participants (92%) were admitted to the intensive care unit, 77% had been in hospital for at least 5 days, and about half had been mechanically ventilated for at least 5 days. About 88% of participants had previously used at least 1 other antibiotic in the 14 days before the first dose of study treatment, but few (13%) had previously used another antibiotic unsuccessfully for the current episode of HAP.

The study assessed the efficacy of ceftolozane with tazobactam for treating people with Gram-negative infections, including multidrug-resistant strains of *Pseudomonas aeruginosa* and Enterobacterales. People with infections caused by Gram-positive pathogens only were excluded from the study (these infections are less likely to be resistant to antibiotics and are easier to treat). In the microbiological intention-to-treat population, the most commonly identified lower respiratory tract pathogens were Enterobacterales (usually *Klebsiella pneumoniae* and *Escherichia coli*), which were isolated in 74% (380/511) of participants, and *Pseudomonas aeruginosa*, which was

isolated in 25% (128/511) of participants. Enterobacterales that produce extended-spectrum beta-lactamases (ESBL) were isolated from 31% (157/511) of participants. These pathogens are typical of Gram-negative pathogens that cause HAP and VAP in the UK.

Meropenem is an appropriate comparator because it is often used to treat people with HAP or VAP at high risk of multidrug-resistant Gram-negative pathogens or high risk of dying, such as the population in this study. Only 3% of baseline isolates of *Pseudomonas aeruginosa* were resistant to ceftolozane with tazobactam, whereas 13% were resistant to meropenem. By contrast, around a third of baseline isolates of ESBL-producing Enterobacterales were resistant to ceftolozane with tazobactam but none were resistant to meropenem. Despite the differences in susceptibility profiles, subgroup analyses based on causative pathogens suggested that clinical outcomes were similar between the ceftolozane with tazobactam and meropenem groups. However, these subgroup analyses were not statistically powered for comparison.

To ensure a high concentration in the lungs of the seriously ill people in the study, the dose of ceftolozane with tazobactam used (and subsequently licensed for HAP and VAP) was double that recommended for other indications (2 g/1 g compared with 1 g/0.5 g for complicated urinary tract infections and complicated intra-abdominal infections; summary of product characteristics). According to some reports, higher doses of meropenem may have been preferable as the comparator (2 g 8 hourly over 3 hours for equivalent antibacterial activity to high-dose ceftolozane with tazobactam; Kalil and Zavascki 2019 and Frippiat et al. 2014). This suggests that the study may have underestimated the efficacy of meropenem. However, although specialists advised that high doses of meropenem are sometimes used for HAP and VAP in the UK, standard doses (as used in the study) are generally preferred.

The median length of treatment was about 8 days in both groups in the study. This is consistent with the International ERS/ESICM/ESCMID/ALAT guidelines for the management of HAP and VAP, which suggest using a 7 or 8-day course of antibiotic therapy in most people with VAP.

Appendix C summarises the quality assessment of the included studies.

Estimated impact for the NHS

Other treatments

A wide range of antibiotics, alone or in combination, are used for treating hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) caused by Gram-negative pathogens. Examples include cephalosporins, extended-spectrum penicillins with beta-lactamase inhibitors and carbapenems. Fluoroquinolones and aminoglycosides are also used. Regimens may be changed based on response to treatment or results from microbiological susceptibility testing. Local (or national) antimicrobial prescribing guidelines should be consulted when selecting treatment options for these indications.

NICE has produced an antimicrobial prescribing guideline on HAP, which includes recommendations on choosing an antibiotic. A NICE guideline on pneumonia in adults is also available. The NICE antimicrobial prescribing guideline on HAP does not cover VAP. Treatment options for VAP are available in the International ERS/ESICM/ESCMID/ALAT guidelines for the management of HAP and VAP.

Costs of treatment

The acquisition cost of ceftolozane with tazobactam is £67.03 (excluding VAT) per vial, meaning the cost of 1 day's treatment at the usual dosage for HAP and VAP (2 g/1 g [2 vials] every 8 hours) is £402.18 (BNF, November 2019).

The acquisition costs (excluding VAT) of many other intravenous antibiotics that are used for HAP and VAP (caused or suspected to be caused by Gram-negative pathogens) are lower than that of ceftolozane with tazobactam. For example, the acquisition cost of meropenem alone is £17.78 (excluding VAT) for 1 vial containing 1 g of powder for solution for injection (Drug Tariff, November 2019). The cost of 1 day's treatment with 2 g (2 vials) every 8 hours is £106.68. Piperacillin with tazobactam (4 g/0.5 g every 8 hours) costs from £14.40 per day (BNF, November 2019).

Depending on the proven pathogens contributing to the infection, ceftolozane with tazobactam may need to be given in combination with other antimicrobials for which additional treatment costs would need to be considered.

Current or estimated usage

The manufacturer estimates that usage of ceftolozane with tazobactam will be low, reflecting its anticipated positioning following confirmed susceptibility testing. Usage should be under the guidance of an appropriately experienced infection specialist (such as a clinical microbiologist or infectious diseases consultant), following the principles of good antimicrobial stewardship.

Likely place in therapy

The indication for ceftolozane with tazobactam has been extended to include hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adults. Commissioners and local decision makers need to take safety, efficacy, cost, patient factors and national guidance into account when considering the likely place in therapy of ceftolozane with tazobactam.

The ASPECT-NP study found that a high dose of ceftolozane with tazobactam was non-inferior to meropenem for treating seriously ill people with VAP or ventilated HAP caused by Gram-negative pathogens such as *Pseudomonas aeruginosa* (including multidrug-resistant strains) and Enterobacterales (including producers of extended-spectrum beta-lactamases [ESBL]). Rates of 28-day mortality and clinical cure were similar between the treatment groups.

As the study investigators expected, meropenem had better in vitro activity against Enterobacterales, especially ESBL-producing strains (a third of which were resistant to ceftolozane with tazobactam). Ceftolozane with tazobactam had high (97%) in vitro activity against *Pseudomonas aeruginosa*, whereas 13% of *Pseudomonas aeruginosa* isolates were resistant to meropenem.

Ceftolozane with tazobactam was generally well tolerated. However, limited safety data are available for the high dose used in this study, and subsequently licensed for HAP and VAP. Treatment-related adverse events were more common with ceftolozane with tazobactam than with meropenem (11% [38/361] compared with 8% [27/359 respectively; no statistical analysis). The most commonly reported adverse effects were abnormal liver function tests, *Clostridioides difficile* colitis and diarrhoea.

The manufacturer of ceftolozane with tazobactam (Merck Sharp & Dohme Limited) anticipates that it will be used in line with good antimicrobial stewardship, on the advice of a microbiologist, to treat critically ill ventilated adults with HAP and VAP, who are deteriorating or not responding to initial antibiotic therapy, and who have confirmed or highly suspected *Pseudomonas aeruginosa*.

Specialists involved in producing this evidence summary consider that ceftolozane with tazobactam provides a potentially useful alternative for treating some adults with HAP and VAP who have limited treatment options because they have infections suspected or proven to be caused by Enterobacterales (excluding carbapenem-resistant bacteria) or multidrug-resistant *Pseudomonas aeruginosa.* Local antibiotic resistance patterns will need to be taken into account.

Commissioners and local decision makers will need to consider where ceftolozane with tazobactam fits within local antimicrobial prescribing guidelines for managing the infections covered by the marketing authorisation, taking the principles of antimicrobial stewardship and national guidance into account. As stated in the approved indications, consideration should be given to official guidance on the appropriate use of antibacterial agents. The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use makes recommendations for local decision-making groups on factors to take into account when evaluating a new antimicrobial for local use and for inclusion in the local formulary. This includes: assessing the need for the new antimicrobial; clinical effectiveness; the population in which it will be used; the specific organisms or conditions for which it will be used; local rates and trends of resistance; whether use should be restricted and, if so, how use will be monitored; any urgent clinical need for the new antimicrobial; and any plans for introducing the new antimicrobial.

Other factors to consider are the risks and benefits of treatment, the type of setting to administer intravenous antimicrobials, for example hospital or homecare, antimicrobial monotherapy versus combination therapy, frequency and duration of intravenous administration and monitoring requirements associated with some antimicrobials.

Appropriate use of antimicrobials is important to reduce the serious threat of antimicrobial resistance. Public Health England's 'Start smart − then focus' toolkit outlines best practice in antimicrobial stewardship in the secondary care setting.

Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers and declarations of interest

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Appendices

Appendix A: Summary of included study

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
ASPECT-NP[1] Randomised, controlled, double-blind, phase 3, non-inferiority trial in 263 hospitals in 34 countries[a]	n=726	Adults (≥18 years, mean age 60 years, 71% male) who were intubated and mechanically ventilated, and had ventilator-associated pneumonia (71%) or ventilated hospital-acquired pneumonia (29%)[b] 92% were admitted to intensive care. 13% had previously unsuccessfully used another antibiotic for the current episode of pneumonia Exclusion criteria included a baseline Gram stain with only Gram-positive pathogens and more than 24 hours of treatment within the past 72 hours with antibacterials with Gram-negative activity In the MITT population[c] (n=511), the main pathogens identified in the lower respiratory tract were enterobacteria (74%, usually *Klebsiella pneumoniae* and	Ceftolozane with tazobactam 2 g/1 g IV over 1 hour, every 8 hours for 8 to 14 days (n=362, median duration 7.7 days)[d]	Meropenem 1 g IV over 1 hour, every 8 hours for 8 to 14 days (n=364, median duration 7.7 days)[d]	28-day all-cause mortality in the ITT population	The study enrolled only people who were mechanically ventilated at baseline. People with hospital-acquired pneumonia who did not go on to need mechanical ventilation were not eligible for inclusion. Extended durations of higher doses of meropenem infusion have been recommended for some people with hospital-acquired pneumonia and ventilator-associated pneumonia, which means the study may have underestimated the efficacy of this treatment. However, specialists advised that UK centres generally use standard doses. The study excluded people with immunosuppression and cystic fibrosis, and people receiving dialysis

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
		Escherichia coli) and *Pseudomonas aeruginosa* (25%)				

References:

[1] Kollef, M.H., Novacek, M., Kivistik, U. et al. (2019) [Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial](#). The Lancet Infectious Diseases doi.org/10.1016/S1473-3099(19)30403-7

[a] Participants were enrolled at 119 of the 263 participating hospitals in 29 countries including Australia, Europe and the USA. The UK had an active investigational site but no participants were recruited

[b] Pneumonia was diagnosed if patients had the following clinical and radiographic criteria within 24 hours before the first dose of study treatment: purulent tracheal secretions with at least 1 other clinical criterion (fever $\geq$38°C or hypothermia $\leq$35°C, $\geq$10,000 or $\leq$4,500 white blood cells per microlitre, or $\geq$15% of white blood cells being immature neutrophils) and chest radiographs or scans showing the presence of a new or progressive infiltrate suggestive of bacterial pneumonia. Ventilator-associated pneumonia was diagnosed in people who met the clinical and radiographic criteria for pneumonia and who also had received at least 48 hours of 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 hours (or had been discharged from hospital within the past 7 days), and had at least 1 of the following: new or worsening cough, dyspnoea, tachypnoea, respiratory rate >30 breaths/min, and hypoxaemia, either within 24 hours before intubation or within 48 hours after intubation

[c] Participants who received at least 1 dose of study treatment and from whom at least 1 Gram-negative or streptococcal respiratory pathogen susceptible to at least 1 study treatment was cultured from baseline lower respiratory tract samples

[d] Adjunctive empirical linezolid or an acceptable alternative was given to all participants until lower respiratory tract cultures taken at baseline showed the absence of *Staphylococcus aureus*. Amikacin or an alternative aminoglycoside could also be used in certain circumstances

Abbreviations: ITT, [intention-to-treat](#); IV, intravenously; MITT, microbiological intention-to-treat

Appendix B: Results table

ASPECT-NP

	Ceftolozane with tazobactam	Meropenem	Analysis
Primary outcome			
28-day all-cause mortality in the ITT population[a] (FDA primary outcome)	24.0% (87/362)	25.3% (92/364)	Weighted treatment difference 1.1% (95% CI −5.1% to 7.4%) Ceftolozane with tazobactam was non-inferior to meropenem[b]
Secondary outcomes			
Clinical cure[c] at the test-of-cure visit[d] in the ITT population[a] (EMA primary outcome)	54.4% (197/362)	53.3% (194/364)	Weighted treatment difference 1.1% (95% CI −6.2% to 8.3%) Ceftolozane with tazobactam was non-inferior to meropenem[e]
28-day all-cause mortality in the MITT population[f]	20.1% (53/264)	25.5% (63/247)	Weighted treatment difference 4.4% (95% CI −2.8% to 11.8%)[g]
Clinical cure[c] at the test-of-cure visit[d] in the clinically evaluable population[h]	63.8% (139/218)	64.7% (143/221)	Weighted treatment difference −1.3% (95% CI −10.2% to 7.7%)[g]
Microbiological eradication[i] at the test-of-cure visit[d] in the MITT population[f]	73.1% (193/264)	68.0% (168/247)	Weighted treatment difference 4.5% (95% CI −3.4% to 12.5%)[g]
28-day all-cause mortality in participants with ventilator-associated pneumonia[j] in the ITT population[a]	24.0% (63/263)	20.3% (52/256)	Weighted treatment difference −3.6% (95% CI −10.7% to 3.5%)[k]
28-day all-cause mortality in participants with ventilated hospital-acquired pneumonia[l] in the ITT population[a]	24.2% (24/99)	37.0% (40/108)	Weighted treatment difference 12.8% (95% CI 0.2% to 24.8%)[k]
Safety and tolerability outcomes (safety population[m])			
Percentage of participants with at least 1 treatment-emergent adverse event	86% (310/361)	83% (299/359)	No statistical analysis
Percentage of participants with at least 1 treatment-related adverse event	11% (38/361)	8% (27/359)	No statistical analysis

	Ceftolozane with tazobactam	Meropenem	Analysis
Percentage of participants with least 1 severe treatment-related adverse event	1% (5/361)	1% (3/359)	No statistical analysis
Percentage of participants with least 1 serious treatment-related adverse event	2% (8/361)	1% (2/359)	No statistical analysis
Percentage of participants who died due to a treatment-related adverse event	0% (0/361)	0% (0/359)	No statistical analysis
Percentage of participants who stopped their study treatment because of at least 1 treatment-related adverse event	1% (4/361)	1% (5/359)	No statistical analysis
Percentage of participants who stopped their study treatment because of insufficient therapeutic effect	6% (23/361)	4% (15/359)	No statistical analysis
Percentage of participants experiencing liver function test abnormalities	3% (12/361)	1% (5/359)	No statistical analysis
Percentage of participants experiencing *Clostridioides difficile* colitis	1% (4/361)	<1% (1/359)	No statistical analysis
Percentage of participants experiencing diarrhoea	1% (4/361)	2% (6/359)	No statistical analysis

Reference:

[1] Kollef, M.H., Novacek, M., Kivistik, U. et al. (2019) Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. The Lancet Infectious Diseases doi.org/10.1016/S1473-3099(19)30403-7

[a] All randomised participants (n=726). Participants with missing or indeterminate data were reported as deceased or not meeting the criteria for clinical cure or microbiological eradication (depending on the outcome)

[b] Ceftolozane with tazobactam was found to be non-inferior to meropenem because the 95% CI did not cross −10%

[c] Clinical response at the test-of-cure visit was categorised as cure (resolution of baseline signs and symptoms of hospital-acquired pneumonia, with no new signs or symptoms and no need for additional antibacterial therapies to treat nosocomial pneumonia), treatment failure (progression, relapse, or recurrence of nosocomial pneumonia; insufficient resolution of baseline signs and symptoms; discontinuation of study treatment because of resistant lower respiratory tract pathogens; or death from nosocomial pneumonia), or indeterminate (death from nonattributable causes, discontinuation of study treatment because no Gram-negative or streptococcal isolate could be identified in baseline samples, or missing data)

[d] 7 to 14 days after the end of treatment

[e] Ceftolozane with tazobactam was found to be non-inferior to meropenem because the 95% CI did not cross −12.5%

	Ceftolozane with tazobactam	Meropenem	Analysis

f Participants who received at least 1 dose of study treatment and from whom at least 1 Gram-negative or streptococcal respiratory pathogen susceptible to at least 1 study drug was cultured from baseline lower respiratory tract samples (n=511). Participants with missing or indeterminate data were reported as deceased or not meeting the criteria for clinical cure or microbiological eradication (depending on the outcome)

g This secondary outcome was not statistically powered for non-inferiority testing

h Participants who received study treatment, adhered to the study protocol up to the test-of-cure visit and had evaluable clinical outcomes (cure or failure) at that timepoint (n=439). Participants with missing or indeterminate responses were excluded

i Defined as a ≥1- log reduction in bacterial burden of the original baseline lower respiratory tract pathogen and a per pathogen count of ≤10^4 CFU/mL for endotracheal or sputum specimens, ≤10^3 CFU/mL for a bronchoalveolar lavage specimen, and ≤10^2 CFU/mL for a protected brush specimen specimen) from a follow-up lower respiratory tract culture

j Ventilator-associated pneumonia was diagnosed in people with pneumonia, at least 48 hours of mechanical ventilation and either the presence of hypoxaemia or acute changes in the ventilator support system to enhance oxygenation (n=519)

k This subgroup analysis was not statistically powered for non-inferiority testing

l Ventilated hospital-acquired pneumonia was diagnosed in mechanically ventilated patients with pneumonia who had been in hospital for at least 48 hours (or had been discharged from hospital within the past 7 days), and had at least 1 of the following: new or worsening cough, dyspnoea, tachypnoea, respiratory rate >30 breaths/min, and hypoxaemia, either within 24 hours before intubation or within 48 hours after intubation (n=207)

m all randomly assigned patients who received at least 1 dose of study treatment (n=720)

Abbreviations: CFU, colony-forming units; CI, confidence interval; ITT, intention-to-treat; IV, intravenously; MITT, microbiological intention-to-treat

Appendix C: Quality assessment of included study

Quality assessment question	ASPECT-NP (2019)
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes[a]
Were patients, health workers and study personnel blinded?	Yes[b]
Were the groups similar at the start of the trial?	Yes[c]
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See results table
How precise was the estimate of the treatment effect?	See results table
Can the results be applied in your context? (or to the local population)	Yes[d]
Were all clinically important outcomes considered?	Yes[e]
Are the benefits worth the harms and costs?	See Evidence Summary

[a] Eligible patients were randomised 1:1 using a centralised interactive voice and integrated web-response system. This suggests allocation was concealed

[b] The study sponsor (except for certain treatment 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

[c] Baseline demographic and clinical characteristics were similar between treatment groups in the intention-to-treat population

[d] Although the UK had an active investigational site, no participants were recruited. However, many participants were from Australia, Europe and the USA so the study population is probably applicable to the UK population

[e] The primary outcome was mortality. Secondary outcomes included clinical and microbiological response

Checklist used: CASP RCT checklist

Appendix D: Literature search strategy

Database search strategies

Database: Medline
Platform: Ovid
Version: 1946 to October 03 2019
Search date: 07/10/2019
Number of results retrieved: 17
Search strategy:

Database: Ovid MEDLINE(R) <1946 to October 02, 2019>
Search Strategy:
----
1   healthcare-associated pneumonia/ or pneumonia, ventilator-associated/ (3343)
2   ((hospital or healthcare or nosocomial or ventilator) adj2 pneumonia).tw. (7617)
3   1 or 2 (8375)
4   ((ceftolozane and tazobactam) or zerbaxa).tw. (229)
5   3 and 4 (17)

Database: Medline in-process
Platform: Ovid
Version: 1946 to October 04 2019
Search date: 07/10/2019
Number of results retrieved: 7
Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 02, 2019>
Search Strategy:
----
1   healthcare-associated pneumonia/ or pneumonia, ventilator-associated/ (0)
2   ((hospital or healthcare or nosocomial or ventilator) adj2 pneumonia).tw. (996)
3   1 or 2 (996)
4   ((ceftolozane and tazobactam) or zerbaxa).tw. (98)
5   3 and 4 (7)

Database: Medline epubs ahead of print
Platform: Ovid
Version: October 04 2019
Search date: 07/10/2019
Number of results retrieved: 3
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <October 02, 2019>
Search Strategy:
----
1   healthcare-associated pneumonia/ or pneumonia, ventilator-associated/ (0)
2   ((hospital or healthcare or nosocomial or ventilator) adj2 pneumonia).tw. (137)
3   1 or 2 (137)

4   ((ceftolozane and tazobactam) or zerbaxa).tw. (17)
5   3 and 4 (3)

Database: Medline daily update
Platform: Ovid
Version: October 03 2019
Search date: 07/10/2019
Number of results retrieved: 0
Search strategy
As above

Database: Embase
Platform: Ovid
Version: 1974 to 2019 October 04 2019
Search date: 07/10/2019
Number of results retrieved: 99
Search strategy:

Database: Embase <1974 to 2019 October 04>
Search Strategy:
----
1   hospital acquired pneumonia/ (2570)
2   ventilator associated pneumonia/ (9973)
3   ((hospital or healthcare or nosocomial or ventilator) adj2 pneumonia).tw. (13657)
4   or/1-3 (18153)
5   ceftolozane plus tazobactam/ (609)
6   ((ceftolozane and tazobactam) or zerbaxa).tw. (515)
7   5 or 6 (719)
8   4 and 7 (99)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
        CDSR –Issue 10of 12, Month year October 2019
        CENTRAL – Issue 10 of 12, Month year October 2019
Search date: 03/10/2019
Number of results retrieved: CDSR –0; CENTRAL – 60.

Search Name:
Date Run: 03/10/2019 14:59:51
Comment:

ID   Search   Hits
#1   MeSH descriptor: [Healthcare-Associated Pneumonia] explode all trees   1
#2   MeSH descriptor: [Pneumonia, Ventilator-Associated] explode all trees
        363
#3   ((hospital or healthcare or nosocomial or ventilator) near/2
pneumonia):ti,ab,kw2025
#4   #1 or #2 or #3   2025

#5   (ceftolozane or tazobactam):ti,ab,kw   639
#6   (zerbaxa):ti,ab,kw   5
#7   #5 or #6   639
#8   #4 and #7   60

Database: HTA
Platform: CRD
Version:
Search date: 07/10/2019
Number of results retrieved: 0
Search strategy:
#1   MeSH DESCRIPTOR Pneumonia, Ventilator-Associated EXPLODE ALL
TREES   96
#2   (((hospital or healthcare or nosocomial or ventilator) adj2 pneumonia))
        238
#3   #1 OR #2   259
#4   (((ceftolozane and tazobactam) or zerbaxa))   0
#5   (ceftolozane and tazobactam) OR (zerbaxa)   0

Trials registry search strategies

Clinicaltrials.gov
Search date: 02/10/2019
Number of results retrieved: 3
Search strategy: Pneumonia | zerbaxa OR (ceftolozane and tazobactam) | Phase 3,
4

Clinicaltrialsregister.eu
Search date: 02/10/2019
Number of results retrieved: 2
Search strategy: pneumonia and (zerbaxa OR (ceftolozane and tazobactam)) NB
These are duplicated; found also in clinicaltrials.gov

Appendix E: Excluded studies

A literature search for ceftolozane with tazobactam was conducted which identified 2 references (see search strategy for full details). These references were screened using their titles and abstracts and both references were obtained and assessed for relevance to the ceftolozane with tazobactam (Zerbaxa) product.

One reference identified from the search is included in this evidence review. This is ASPECT-NP, which is the key phase 3 randomised controlled trial. The other paper that was identified (Zhang et al. 2019) is a systematic review and meta-analysis but has not been included because it is not fully published and is available only as an abstract.

A summary of the included phase 3 study is shown in Appendix A.