

Complicated intra-abdominal infections: ceftolozane/tazobactam

Evidence summary

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www.nice.org.uk/guidance/esnm75

Key points from the evidence

The content of this evidence summary was up-to-date in June 2016. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

In a randomised controlled trial (RCT) in adults with complicated intra-abdominal infections, intravenous ceftolozane/tazobactam plus metronidazole was found to be non-inferior to intravenous meropenem plus saline (placebo) in terms of clinical cure rates 24–32 days after starting treatment. However, it is unclear whether the results apply to some populations; for example, people aged over 65 years, or those with renal impairment or who are at a higher risk of dying. Appendiceal perforation or abscess was the most common diagnosis in the study and less information is available on using ceftolozane/

tazobactam in people with other diagnoses.

In 2 RCTs in people receiving ceftolozane/tazobactam for complicated intra-abdominal or urinary tract infections, the most commonly reported adverse effects were nausea, headache, constipation, diarrhoea and pyrexia, which were generally mild or moderate in severity.

Ceftolozane/tazobactam may be an option for treating complicated intra-abdominal infections in some adults, when the pathogen is resistant to first-line empirical treatment options but susceptible to ceftolozane/tazobactam, or when first-line options are contraindicated. The acquisition cost of ceftolozane/tazobactam is more than that of many other intravenous antibiotics that are commonly used for complicated intra-abdominal infections.

Regulatory status: Ceftolozane/tazobactam received a marketing authorisation in September 2015 and was launched in the UK in November 2015.

<p>Effectiveness</p> <p>In the ASPECT-cIAI RCT (n=993):</p> <ul style="list-style-type: none"> • Ceftolozane/tazobactam plus metronidazole was found to be non-inferior to meropenem plus saline (placebo) in terms of clinical cure rates for complicated intra-abdominal infection, 24–32 days after starting treatment. • Treatment failure was similar between the groups. The most common reasons for treatment failure were persisting or recurrent abdominal infection requiring an additional intervention and the requirement for additional antibiotics for ongoing complicated intra-abdominal infection. 	<p>Safety</p> <p>According to the European public assessment report:</p> <ul style="list-style-type: none"> • The safety profiles of ceftolozane/tazobactam and meropenem were broadly similar. • Most treatment-emergent adverse events seen with ceftolozane/tazobactam were mild-to-moderate in severity and typical of beta-lactam agents. • Reporting rates for nausea, constipation, abdominal pain, pyrexia, headache, hypotension, hypokalaemia and raised liver function test results were consistently higher with ceftolozane/tazobactam (n=1,015) compared with comparators (n=1,032) in 2 RCTs in complicated intra-abdominal infections and complicated urinary tract infections.
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Patient factors	Resource implications
<ul style="list-style-type: none"> Discontinuation rates due to treatment-emergent adverse events were similar between the treatment arms in the 2 RCTs (about 2% according to the European public assessment report). The majority of participants in ASPECT-clAI were aged 18–64 years (77%), with normal renal function (70%) and an APACHE II score of 0–10 (87%), suggesting a low risk of mortality. Therefore, the results may not apply to higher risk populations. In the study, 43% of people had appendiceal perforation or peri-appendiceal abscess (summary of product characteristics). The study results are less applicable to people with other diagnoses. 	<ul style="list-style-type: none"> A vial of ceftolozane/tazobactam costs £67.03 excluding VAT (MIMS, April 2016). A 7-day course of treatment costs £1,407.63 excluding VAT and any procurement discounts and administration costs. This is higher than the costs of other intravenous antibiotics that may be used for complicated intra-abdominal infection.

Introduction and current guidance

Intra-abdominal infections include a wide spectrum of conditions from uncomplicated appendicitis to faecal peritonitis. In complicated intra-abdominal infections, the infection progresses from a single organ and affects the peritoneum, causing intra-abdominal abscesses or diffuse peritonitis. Peritoneal contamination may result from surgery-associated infection, trauma or spontaneous perforation (for example, appendicitis, perforated ulcer or diverticulitis) ([European public assessment report](#)).

Complicated intra-abdominal infections are frequently caused by gram-negative bacteria (such as *Escherichia coli*), with or without anaerobic pathogens. Second or third

generation cephalosporins in combination with metronidazole, beta-lactam antibiotics (such as penicillins) in combination with beta-lactamase inhibitors and carbapenems are commonly used for treating complicated intra-abdominal infections. However, increasing resistance to commonly prescribed antimicrobial agents is a recognised serious global problem ([European public assessment report](#)). Ceftolozane/tazobactam was developed to address antimicrobial resistance in serious infections caused by gram-negative pathogens.

[Full text of introduction and current guidance.](#)

Product overview

[Zerbaxa powder for concentrate for solution for infusion](#) contains ceftolozane, a new cephalosporin antibiotic, and tazobactam, an established beta-lactamase inhibitor, which can protect ceftolozane from hydrolysis by some beta-lactamases, broadening its spectrum of activity ([European public assessment report](#)).

Ceftolozane/tazobactam is indicated for treating complicated intra-abdominal infections in adults. The dosage is 1 g/0.5 g administered intravenously over 1 hour every 8 hours for 4–14 days. Lower doses should be used in people with moderate to severe renal impairment. Metronidazole should be co-administered with ceftolozane/tazobactam if anaerobic pathogens are suspected of causing the intraabdominal infection because ceftolozane/tazobactam is not reliably active against anaerobes. See the [summary of product characteristics](#) and [European public assessment report](#) for more information.

Ceftolozane/tazobactam is also indicated for complicated urinary tract infections (including acute pyelonephritis), which are discussed in another [evidence summary](#).

[Full text of product overview.](#)

Evidence review

- This evidence summary is based on the key phase III licensing study for ceftolozane/tazobactam, ASPECT-clAI. This study was a prospective, randomised, double-blind, non-inferiority trial, which included adults with complicated intra-abdominal infections (43% with appendiceal perforation or abscess) who received intravenous ceftolozane/tazobactam 1 g/0.5 g plus metronidazole 500 mg (n=487) every 8 hours or intravenous meropenem 1 g plus saline (placebo, n=506) every 8 hours for 4–10 days. Treatments could be continued for up to 14 days in people who had multiple abscesses, non-appendix-related diffuse peritonitis, failure of prior antimicrobial therapy or hospital-acquired infection. Outcomes were tested in the following populations:
 - intention-to-treat (ITT): all randomised participants regardless of receipt of study drug
 - microbiological ITT (MITT): all randomised participants with at least 1 baseline pathogen identified in the abscess or peritoneal fluid, regardless of susceptibility to the study drug
 - clinically evaluable per-protocol (CE): all randomised participants who received the protocol specified amount of study drug, met the protocol specific disease definition of complicated intra-abdominal infection, adhered to trial procedures, and had a test-of-cure visit within the specified window (24–32 days after starting treatment)
 - microbiologically evaluable (ME) per-protocol: the subset of CE participants who had at least 1 baseline infecting pathogen identified that was susceptible to the study drug.

The primary objective of the study was to demonstrate non-inferiority of ceftolozane/tazobactam plus metronidazole compared with meropenem in terms of clinical cure rates at the test-of-cure visit in the MITT population. Clinical cure was defined as complete resolution or significant improvement in signs and symptoms of the index infection, with no additional antimicrobials or interventions required.

- In the MITT population, ceftolozane/tazobactam plus metronidazole was found to be non-inferior to meropenem plus saline in terms of clinical cure rates at the test-of-cure visit. The clinical cure rate was 83.0% in the ceftolozane/tazobactam group compared with 87.3% in the meropenem group (weighted difference –4.2%, 95% confidence interval [CI] –8.91% to 0.54%). The lower limit of the 95% CI for the difference between the study treatments was more than –10% and, therefore, met the statistical requirement for non-inferiority. This result was confirmed in the ME per-protocol population, as is required to prove non-inferiority. In the ME population, the clinical cure rates were 94.2% and 94.7% respectively (weighted difference –1.0%, 95% CI –4.52 to 2.59). The results were also consistent in the ITT and CE populations, and in analyses at other time points.
- Clinical failure was defined as death due to complicated intra-abdominal infection before the test-of-cure visit, persistent or recurrent infection requiring additional intervention, and treatment with additional antimicrobials for ongoing symptoms of intra-abdominal or surgical site infection. In both treatment groups, in the MITT population, 8.2% of patients failed treatment at the test-of-cure visit. The most common reasons for treatment failure were persisting or recurrent abdominal infection requiring an additional intervention (2.8% of failures in the ceftolozane/tazobactam plus metronidazole group and 3.6% of failures in the meropenem plus saline group: statistical analysis not reported) and the requirement for additional antibiotics for ongoing complicated intra-abdominal infection (3.3% and 2.6% respectively: statistical analysis not reported).
- The frequency of treatment-emergent adverse events was similar in both treatment groups (44.0% with ceftolozane/tazobactam plus metronidazole compared with 42.7% with meropenem plus saline). The most common adverse events in either group were nausea (7.9% and 5.8% respectively) and diarrhoea (6.2% and 5.0% respectively). Statistical analyses were not reported.

- According to the [summary of product characteristics](#), in 2 phase III studies (total n=2,047: 1,015 taking ceftolozane/tazobactam and 1,032 taking meropenem or levofloxacin), the most common adverse effects reported in 3 in 100 people or more receiving ceftolozane/tazobactam for complicated intra-abdominal infections ([ASPECT-cIAI](#)) and complicated urinary tract infections ([ASPECT-cUTI](#)) were nausea, headache, constipation, diarrhoea and pyrexia. These were generally mild or moderate in severity. A decline in renal function has been seen in patients receiving ceftolozane/tazobactam. As with many other antibiotics, ceftolozane/tazobactam carries a risk of *Clostridium difficile* infection. (See the NICE evidence summary medicines and prescribing briefing on the [risk of Clostridium difficile infection with broad-spectrum antibiotics](#).)
- The [ASPECT-cIAI](#) study has various limitations that should be taken into account when considering its application to practice. For example, the majority of participants were aged 18–64 years (77%), with no renal impairment (70%) and an Acute Physiology and Chronic Health Evaluation ([APACHE](#)) II score (used to predict mortality in intensive care units on a scale of 0–71) of 0–10 (87%), suggesting a low risk of mortality. Therefore, the results may not be generalisable to older people, particularly those with severe renal impairment or a high risk of mortality. People who were immunocompromised or had severe neutropenia were excluded from the study, as were those with severe or rapidly progressing disease such as septic shock, and those not expected to survive for 4–5 weeks. Therefore, the results may not apply to these patients. Ceftolozane/tazobactam has not been studied in children and is only indicated for use in adults.
- The [Committee for Medicinal Products for Human Use](#) (CHMP) concluded that, although [ASPECT-cIAI](#) met its pre-defined primary end point, with supportive sensitivity analyses, the broad indication of complicated intra-abdominal infection is poorly supported based on this single pivotal study. The CHMP noted that about half of people had a primary focus of infection in the appendix compared with a maximum of 30% recommended in [CHMP guidance](#). Also, cure rates were very high for infections of appendiceal origin (for example, 89% with ceftolozane/tazobactam and 92% with meropenem in the ITT population) and much lower for infections originating from the colon (for example, 66% and 71% respectively in the ITT population) ([European public assessment report](#)).

[Full text of evidence review.](#)

Context

Guidelines by the [Surgical Infection Society](#) and the [Infectious Diseases Society of America](#) and the [World Society of Emergency Surgery](#) recommend empirical antibiotic treatment with single or combination antimicrobial regimens depending on the severity of infection, the pathogens presumed to be involved (taking into account whether the infection is community- or healthcare-associated) and local antibiotic resistance patterns. Treatment regimens commonly include beta-lactam/beta-lactamase inhibitor combinations, carbapenems, cephalosporins, metronidazole, fluoroquinolones and aminoglycosides.

A vial of ceftolozane/tazobactam costs £67.03 excluding VAT ([MIMS](#) April 2016). Therefore, the cost of a course of treatment ranges from £804.36 for 4 days to £2,815.26 for 14 days, excluding VAT and any procurement discounts and administration costs. The acquisition cost of ceftolozane/tazobactam is more than that of many other intravenous antibiotics that are commonly used for complicated intra-abdominal infections.

[Full text of context.](#)

Estimated impact for the NHS

Appropriate use of antibiotics is important to reduce the serious threat of antibiotic resistance and the risk of healthcare-associated infections such as *C. difficile*. Commissioners and local decision makers will need to determine where ceftolozane/tazobactam fits within local hospital antibiotic policies and guidelines for managing complicated intra-abdominal infections, taking the principles of antimicrobial stewardship into account.

The manufacturer of ceftolozane/tazobactam, Merck Sharp & Dohme Limited, anticipates that the antibiotic will be used in line with good antimicrobial stewardship, on the advice of a microbiologist, to treat gram-negative infections, when the pathogen is resistant to first-line empirical treatment options but susceptible to ceftolozane/tazobactam.

Public Health England's [Start smart – then focus](#) toolkit outlines best practice in antimicrobial stewardship in the secondary care setting. NICE has issued guidance on [antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#).

[Full text of estimated impact for the NHS.](#)

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

Intra-abdominal infections include a wide spectrum of conditions, from uncomplicated appendicitis to faecal peritonitis. In complicated intra-abdominal infections, the infection progresses from a single organ and affects the peritoneum, causing intra-abdominal abscesses or diffuse peritonitis. Peritoneal contamination may result from surgery-associated infection, trauma or spontaneous perforation (for example, appendicitis, perforated ulcer or diverticulitis) ([European public assessment report](#)).

Complicated intra-abdominal infections are commonly encountered in general surgery and have been estimated to be responsible for 20% of all severe sepsis episodes in the intensive care unit. Overall mortality rates are reported to be as high as 25%. Effective management of complicated intra-abdominal infection requires early diagnosis, appropriate surgical intervention and empiric, broad-spectrum antimicrobial treatment ([European public assessment report](#)).

The pathogens most frequently encountered in complicated intra-abdominal infections are the gram-negative bacteria *Escherichia coli*, other common Enterobacteriaceae (for example, *Proteus* spp. or *Klebsiella* spp.), *Pseudomonas aeruginosa* and *Bacteroides fragilis*. Second or third generation cephalosporins in combination with metronidazole, beta-lactam antibiotics (such as penicillins) in combination with beta-lactamase inhibitors and carbapenems are commonly used for treating complicated intra-abdominal infections. However, increasing resistance to commonly prescribed antimicrobial agents is a recognised serious global problem ([European public assessment report](#)). The [English surveillance programme for antimicrobial utilisation and resistance \(ESPAUR\) report \(2015\)](#) found that, overall, antibiotic resistant infections continue to increase. Notably, the rate of

E. coli and *Klebsiella pneumoniae* bloodstream infections increased by 15.6% and 20.8% respectively from 2010 to 2014. No data were reported for intra-abdominal infections.

NICE has not published a clinical guideline on managing complicated intra-abdominal infections. Information can be found in guidelines by the [Surgical Infection Society](#) and the [Infectious Diseases Society of America](#) and the [World Society of Emergency Surgery](#). These recommend empirical antibiotic treatment with single or combination antimicrobial regimens depending on the severity of infection, the pathogens presumed to be involved (taking into account whether the infection is community- or healthcare-associated) and local antibiotic resistance patterns. The guidelines state that bacteriological cultures often have little impact on the course of treatment and are not necessary for all patients. However, results of microbiological analysis of intra-abdominal samples can be used to customise antibiotic treatment and ensure adequate antimicrobial activity in high-risk patients who may harbour resistant pathogens and in patients in whom the causative pathogens and related resistance patterns are not predictable.

This evidence summary outlines the best available evidence for a new antimicrobial that is licensed for complicated intra-abdominal infections, ceftolozane/tazobactam. Ceftolozane/tazobactam was developed to address antimicrobial resistance in serious infections caused by gram-negative pathogens ([Solomkin et al. 2015](#)).

Product overview

Drug action

[Zerbaxa powder for concentrate for solution for infusion](#) contains ceftolozane and tazobactam. Ceftolozane is a new cephalosporin antibiotic. Like other cephalosporins, it binds to penicillin-binding proteins, resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death. Tazobactam is an established beta-lactamase inhibitor, which can protect ceftolozane from hydrolysis by some beta-lactamases, broadening its spectrum to include most beta-lactamase-producing *E. coli*, *K. pneumoniae* and other Enterobacteriaceae ([European public assessment report](#)).

Licensed therapeutic indication

Ceftolozane/tazobactam (Zerbaxa) received a marketing authorisation in September 2015 and was launched in the UK in November 2015. It is indicated for treating complicated

intra-abdominal infections, acute pyelonephritis and complicated urinary tract infections in adults. The [summary of product characteristics](#) states that consideration should be given to official guidance on the appropriate use of antibacterial agents.

Evidence for using this product for complicated urinary tract infections (including acute pyelonephritis) is outlined in another [evidence summary](#).

Course and cost

For people with complicated intra-abdominal infections and creatinine clearance of more than 50 ml/minute, the recommended dosage is ceftolozane/tazobactam 1 g/0.5 g administered intravenously over 1 hour every 8 hours for 4–14 days. Lower doses should be used for people with moderate or severe renal disease or end stage renal failure. Metronidazole should be co-administered with ceftolozane/tazobactam if anaerobic pathogens are suspected of causing the intra-abdominal infection because ceftolozane/tazobactam is not reliably active against anaerobes. See the [summary of product characteristics](#) and [European public assessment report](#) for more information.

A vial of ceftolozane/tazobactam 1 g/0.5 g costs £67.03 excluding VAT ([MIMS](#), April 2016). Therefore, the cost of a course of treatment ranges from £804.36 to £2,815.26, excluding VAT and any procurement discounts and administration costs.

Evidence review

This evidence summary is based on the key phase III licensing study for ceftolozane/tazobactam for complicated intra-abdominal infections ([ASPECT-cIAI](#)). Information from the published paper is supplemented with information from the [European public assessment report](#) (EPAR) for ceftolozane/tazobactam where necessary.

ASPECT-cIAI ([Solomkin et al. 2015](#))

- Design: The study was a prospective, [randomised](#), double-[blind](#), controlled non-inferiority trial, which was undertaken in 128 centres worldwide (approximately 80% Europe, [EPAR](#)).

- **Population:** It included 993 hospitalised adults (mean age 51 years, 94% white) with clinical evidence of complicated intra-abdominal infections. The origin of infection was the appendix in around half of participants, and the most common diagnosis was appendiceal perforation or abscess. Over 80% of participants had peritonitis. Exclusions were management of infection using abdominal repair in which the fascia was not closed, severe renal impairment (creatinine clearance less than 30 ml/minute), and use of systemic antibiotic therapy for intra-abdominal infection for more than 24 hours before the first dose of study drug, unless this treatment failed. Treatment failure was defined by the need for additional intervention and persistent signs of ongoing infection with a positive culture of intra-abdominal abscess or peritoneal fluid, despite over 48 hours of prior antimicrobial therapy. In participants, the mean baseline Acute Physiology and Chronic Health Evaluation (APACHE) II score (which is used to predict mortality in intensive care units on a scale of 0–71) was 6, suggesting an estimated mortality risk of about 8%. About a third of participants had mild or moderate renal impairment. The most common gram-negative bacteria isolated at baseline were *E. coli* (about 65%) *K. pneumoniae* (about 9%), and *P. aeruginosa* (about 9%). About two-thirds of infections were polymicrobial and the rate of beta-lactamase-producing Enterobacteriaceae was about 7%.
- **Intervention and comparator:** Participants were randomised 1:1 to receive intravenous ceftolozane/tazobactam 1 g/0.5 g plus metronidazole 500 mg (n=487) every 8 hours or intravenous meropenem 1 g plus saline (placebo, n=506) every 8 hours for 4–10 days. Treatments could be continued for up to 14 days in people who had multiple abscesses, non-appendix-related diffuse peritonitis, failure of prior antimicrobial therapy or hospital-acquired infection. Approximately 50% of participants received treatment for up to 7 days, and an additional 37% received treatment for up to 10 days. The doses of ceftolozane/tazobactam and meropenem were reduced in people with moderate renal failure (creatinine clearance 30–50 ml/min). The methods suggest that allocation was concealed. Baseline demographic characteristics were similar between the treatment groups.

- Outcomes: Clinical outcomes were assessed at the end of therapy (within 24 hours of the last dose of study drug), the test-of-cure visit (24–32 days after starting treatment) and the late follow-up visit (38–45 days after starting treatment). Clinical cure was defined as complete resolution or significant improvement in signs and symptoms of the index infection, with no additional antimicrobials or interventions required. Clinical failure was defined as death due to complicated intra-abdominal infection before the test-of-cure visit, persistent or recurrent infection requiring additional intervention, and treatment with additional antimicrobials for ongoing symptoms of intra-abdominal or surgical site infection. An indeterminate response was recorded when trial data were not available for evaluation of efficacy for any reason, including death unrelated to the index infection, or in extenuating circumstances that precluded classification as cure or failure. Patients with missing clinical outcome data or indeterminate responses were considered to have failed treatment in the intention-to-treat analysis (ITT: all randomised patients regardless of receipt of study drug) and the microbiological ITT analysis (MITT: all randomised patients with at least 1 baseline pathogen identified in the abscess or peritonitis fluid, regardless of susceptibility to the study drug). However, they were excluded from the per-protocol analyses, which included clinically evaluable (CE) and microbiologically evaluable (ME) populations. The CE population included all randomised patients who received the protocol specified amount of study drug, met the protocol specific disease definition of complicated intra-abdominal infection, adhered to trial procedures, and had a test-of-cure visit within the specified window. The ME population included the subset of CE patients who had at least 1 baseline infecting pathogen identified that was susceptible to the study drug. The primary objective of the study was to demonstrate non-inferiority of ceftolozane/tazobactam plus metronidazole compared with meropenem in terms of clinical cure rates at the test-of-cure visit in the MITT population. Non-inferiority was considered proven if the lower limit of the 95% confidence interval (CI) for the difference between the study treatments was more than –10%. Secondary outcomes included clinical cure in the ME, ITT and CE populations, and various ME population subgroups. Microbiological outcomes and safety and tolerability were also assessed.

Table 1 Summary of ASPECT-cIAI

	Ceftolozane/ tazobactam plus metronidazole	Meropenem plus saline	Analysis

Randomised	n=487	n=506	
Efficacy (MITT population)^a	n=389	n=417	
Primary outcome: clinical cure at test-of-cure visit ^b	83.0% (323/389)	87.3% (364/417)	Weighted difference –4.2% 95% CI –8.91% to 0.54% Ceftolozane/tazobactam plus metronidazole is statistically non-inferior to meropenem plus saline ^c
Selected secondary outcomes:			
Clinical cure at test-of-cure visit ^b in the MEPP population ^d	94.2% (259/275)	94.7% (304/321)	Weighted difference –1.0% 95% CI –4.52% to 2.59% Statistical non-inferiority shown ^c
Clinical cure at test-of-cure visit ^b in the ITT population ^e	83.6% (407/487) ^f	86.2% (436/506) ^f	Difference –2.6% 95% CI –7.08% to 1.87% ^g
Clinical cure at test-of-cure visit ^b in the CE PP population ^h	94.1% (353/375) ^f	94.0% (375/399) ^f	Difference 0.1% 95% CI –3.30% to 3.55% ^g
Clinical cure at end of therapy visit ⁱ in the MITT population ^a	89.2% (347/389) ^f	92.3% (385/417) ^f	Difference –3.1% 95% CI –7.23% to 0.89% ^g
Treatment failure at the test-of-cure visit ^b in the MITT population ^a	8.2% (32/389)	8.2% (34/417)	Difference 0% Statistical analysis not reported
Treatment failure at the test-of-cure visit ^b in the ME PP population ^d	5.8% (16/275)	5.3% (17/321)	Difference 0.5% Statistical analysis not reported
Safety^j	n=482	n=497	

Patients reporting serious treatment-emergent adverse events	8.1% (39/482)	7.2% (36/497)	Statistical analysis not reported
Patients reporting serious treatment-related adverse events	0.2% (1/482) ^k	0.2% (1/497) ^k	Statistical analysis not reported
Patients discontinuing treatment due to treatment-related adverse events	0.6% (3/482)	0.8% (4/497)	Statistical analysis not reported
Patients reporting treatment-emergent adverse events	44.0% (212/482)	42.7%(212/497)	Statistical analysis not reported
Deaths reported ^l	2.3% (11/482)	1.6% (8/497)	Statistical analysis not reported

Abbreviations: CE, clinically evaluable; CI, confidence interval; ITT, intention-to-treat; ME, microbiologically evaluable; MITT, microbiological intention-to-treat; PP per-protocol.

^a The MITT population includes all randomised patients with at least 1 baseline pathogen identified in abscess or peritonitis fluid, regardless of susceptibility to study drug.

^b 24–32 days after starting treatment (median 27 days in the MITT population).

^c The lower limit of the 95% CI is –8.91%, which is within the pre-specified non-inferiority margin of –10%.

^d The ME population is the subset of the clinically evaluable population (see footnote h) with at least 1 baseline infecting pathogen identified that was susceptible to study drug.

^e The ITT population includes all randomised patients regardless of receipt of study drug.

^f Number of patients not reported and calculated from the available data.

^g It is unclear whether these differences are weighted and whether the results were assessed for non-inferiority.

^h The CE population includes all randomised patients who received the protocol specified amount of study drug, met the protocol specific disease definition of complicated intra-abdominal infection, adhered to trial procedures, and had a test-of-cure visit within the specified window.

ⁱ Within 24 hours of the last dose of study drug.

^j The safety population includes all treated patients (EPAR).

^k *Clostridium difficile* infection.

^l All were considered unrelated to study treatment.

Clinical effectiveness

In ASPECT-clAI, in the microbiological intention-to-treat (MITT) and per-protocol (ME) populations, ceftolozane/tazobactam plus metronidazole was found to be non-inferior to meropenem plus saline (placebo) in terms of clinical cure rates at the test-of-cure visit, 24–32 days (median 27 days) after starting treatment. In the MITT population, the clinical cure rate was 83.0% (323/389) in the ceftolozane/tazobactam group compared with 87.3% (364/417) in the meropenem group (weighted difference –4.2%, 95% CI –8.91% to 0.54%: the primary outcome). In the ME population, the clinical cure rates were 94.2% (259/275)

and 94.7% (304/321) respectively (weighted difference –1.0%, 95% CI –4.52 to 2.59). The results were consistent in the clinical intention-to-treat (ITT) and per-protocol (CE) populations, and in analyses at other time points. See table 1 for more details.

In both treatment groups, in the MITT population, 8.2% of patients failed treatment at the test-of-cure visit. The most common reasons for treatment failure were reported to be persisting or recurrent abdominal infection requiring an additional intervention (2.8% of failures in the ceftolozane/tazobactam plus metronidazole group and 3.6% of failures in the meropenem plus saline group: statistical analysis not reported) and the requirement for additional antibiotics for ongoing complicated intra-abdominal infection (3.3% and 2.6% respectively: statistical analysis not reported). Other reasons for failure were postsurgical wound infection and death due to complicated intra-abdominal infection.

In subgroup analyses, compared with the overall ME population, clinical cure rates with both treatments were generally found to be lower in high-risk patients (for example, people aged 65 years or more, or with APACHE II scores of 10 or more, moderate renal impairment, or small bowel or colon infections). However, the number of patients in these subgroups is small, limiting the statistical power to detect differences between subgroups.

According to the European public assessment report, in the ITT population, treatment failure was more likely to occur in the ceftolozane/tazobactam group compared with the meropenem group in elderly patients (44.2% compared with 27.1% respectively) and patients with peritonitis (76.6% compared with 64.3% respectively) or who had undergone laparotomy (64.9% compared with 48.6% respectively). Statistical analyses were not reported.

When individual baseline pathogens were assessed, clinical cure rates were generally high and broadly similar between the groups. In the ME population, the most commonly isolated pathogen was *E. coli* and the rate of clinical cure was 94.7% with ceftolozane/tazobactam plus metronidazole and 93.5% with meropenem (statistical analysis not reported).

According to the European public assessment report, a high cure rate (over 95%) was seen in both treatment arms at the end of therapy visit (within 24 hours of the last dose of study drug), indicating that ceftolozane/tazobactam has a rapid initial effect. Also, approximately 75% of patients were clinically evaluable at the late follow-up visit (38-45 days after starting treatment) and none had a relapse.

Safety and tolerability

ASPECT-cIAI

In this phase III study in people with complicated intra-abdominal infections, the frequency of treatment-emergent adverse events was similar in both treatment groups (44.0% [212/482] with ceftolozane/tazobactam plus metronidazole compared with 42.7% [212/497] with meropenem plus saline). The most common adverse events in either group were nausea (7.9% [38/482] and 5.8% [29/497] respectively) and diarrhoea (6.2% [30/482] and 5.0% [25/497] respectively). Serious adverse events occurred in 8.1% (39/482) and 7.2% (36/497) of people in the ceftolozane/tazobactam plus metronidazole and meropenem groups respectively. Treatment-related serious adverse events occurred in 1 person in each treatment group (both *Clostridium difficile* infection). Statistical analyses were not reported. See table 1 for more information.

Summary of product characteristics

According to the summary of product characteristics, in 2 phase III studies, the most common adverse effects reported in 3 in 100 people or more receiving ceftolozane/tazobactam (n=1,015) for complicated intra-abdominal infections (ASPECT-cIAI) and complicated urinary tract infections (ASPECT-cUTI) were nausea, headache, constipation, diarrhoea and pyrexia. These were generally mild or moderate in severity. Other common adverse events (occurring in between 1 in 10 and 1 in 100 people) were thrombocytosis, hypokalaemia, anxiety, insomnia, dizziness, hypotension, abdominal pain, vomiting, rash, and increases in the liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Antibiotic-associated colitis and pseudomembranous colitis have been reported with ceftolozane/tazobactam. These types of infection may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftolozane/tazobactam. In such circumstances, the discontinuation of therapy with ceftolozane/tazobactam and the use of supportive measures together with the administration of specific treatment for *C. difficile* should be considered.

A decline in renal function has been seen in patients receiving ceftolozane/tazobactam. Lower doses should be used for people with pre-existing moderate or severe renal disease or end stage renal failure. See the summary of product characteristics for more information

on contraindications and adverse effects of ceftolozane/tazobactam.

European public assessment report

The EPAR noted that the safety profile in the 2 phase III studies ([ASPECT-cIAI](#) and [ASPECT-cUTI](#), total n=2,047: 1,015 taking ceftolozane/tazobactam and 1,032 taking meropenem or levofloxacin) was broadly similar between treatments within each indication (complicated intra-abdominal and urinary tract infection). Overall rates of adverse events did not increase with duration of therapy and most treatment-emergent adverse events seen with ceftolozane/tazobactam were mild-to-moderate in severity and typical of beta-lactam agents.

There were some differences in rates of adverse events. In particular, reporting rates were consistently higher with ceftolozane/tazobactam in the phase III studies for nausea, constipation, abdominal pain, pyrexia, headache, hypotension, hypokalaemia and raised ALT and AST.

The report noted that there were no major concerns raised by the small difference in numbers of deaths or by the distribution of numbers and types of serious adverse events. Discontinuation rates due to treatment-emergent adverse events were similar between the treatment arms in the studies (2% [20/1015] with ceftolozane/tazobactam with or without metronidazole compared with 1.9% [20/1032] with meropenem or levofloxacin: statistical analysis not reported).

Evidence strengths and limitations

The [ASPECT-cIAI](#) study has various limitations that should be taken into account when considering its application to practice. For example, the majority of participants were white (94%) and aged 18–64 years (77%), with normal renal function (70%) and an [APACHE II](#) score of 0–10 (87%), suggesting a low risk of mortality. Therefore, the results may not be generalisable to non-white and older people, particularly those with severe renal impairment or who are at a higher risk of dying. Ceftolozane/tazobactam has not been studied in children and is only indicated for use in adults.

The most common diagnosis in the study was appendiceal perforation or peri-appendiceal abscess (43% [420/970]), with 33% (137/420) of these people having diffuse peritonitis at baseline ([summary of product characteristics](#)). Less information is available on using ceftolozane/tazobactam in people with other diagnoses. The [European public assessment](#)

report notes that people who were immunocompromised or had severe neutropenia were excluded from the study, as were those with severe or rapidly progressing disease such as septic shock, and those not expected to survive for 4–5 weeks. Therefore, the results may not apply to these patients.

As is necessary in a non-inferiority study, both ITT and per-protocol analyses were undertaken, and their results were consistent, as is required to demonstrate non-inferiority of one intervention to another (see European Medicines Agency guidance on Points to consider on switching between superiority and non-inferiority). In the paper by Solomkin et al. 2015, the stated primary objective of ASPECT-clAI was to demonstrate non-inferiority of ceftolozane/tazobactam plus metronidazole compared with meropenem in terms of clinical cure rates at the test-of-cure visit in the MITT population. However, to meet the requirements of the European Medicines Agency, the primary analysis considered the CE population, which is reported in the European public assessment report. Nevertheless, the results were consistent across both populations.

According to the European public assessment report, subgroup analyses mostly favoured meropenem, particularly in the ITT population. The report advises that the manufacturer of ceftolozane/tazobactam considered that these differences were caused by higher rates of indeterminate outcomes in the ceftolozane/tazobactam group. Also, the difference was mainly driven by premature discontinuations of study drug caused by adverse effects and patient withdrawals.

In its assessment of ceftolozane/tazobactam, the Committee for Medicinal Products for Human Use (CHMP) states that, although ASPECT-clAI met its pre-defined primary end point, with supportive sensitivity analyses, the broad indication of complicated intra-abdominal infection is poorly supported based on this single pivotal study. The CHMP notes that about half of people in the ITT and CE populations had a primary focus of infection in the appendix compared with a maximum of 30% recommended in CHMP guidance. On this basis, it is not unexpected that half of the total patients received 4–7 days therapy. In the ITT and ME populations, the cure rates were very high for infections of appendiceal origin (for example, 89% with ceftolozane/tazobactam and 92% with meropenem in the ITT population) and much lower for infections originating from the colon (for example, 66% and 71% respectively in the ITT population) (European public assessment report).

Because there is only one 'not very satisfactory' study, the CHMP accepted the indication on condition that the major limitations of the study were reflected in the summary of

product characteristics, including the percentage of people with appendiceal infections, the low APACHE II scores and the few cases of accompanying bacteraemia (European public assessment report).

In the European public assessment report, the CHMP notes that ceftolozane/tazobactam combines a new beta-lactam antibiotic with an established inhibitor that has known limitations in its range of beta-lactamase inhibition. However, it considers that tazobactam may protect ceftolozane from some beta-lactamase-producing bacteria that could otherwise hydrolyse the beta-lactam. The CHMP also notes that ceftolozane itself may have some utility in treating *P. aeruginosa* that are resistant to several other agents via specific mechanisms, but tazobactam does not influence the activity of ceftolozane against such strains. The specific infection types that have been studied are listed in the summary of product characteristics.

The CHMP considered the addition of metronidazole to ceftolozane/tazobactam to be appropriate because most intra-abdominal infections are polymicrobial, involving both aerobic and anaerobic organisms. The summary of product characteristics states that metronidazole should be co-administered with ceftolozane/tazobactam if anaerobic pathogens are suspected of causing the intra-abdominal infection.

Context

Alternative treatments

Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America and the World Society of Emergency Surgery recommend empirical antibiotic treatment with single or combination antimicrobial regimens depending on the severity of the intra-abdominal infection, the pathogens presumed to be involved (taking into account whether the infection is community- or healthcare-associated) and local antibiotic resistance patterns.

According to the guidelines, antibiotics that are used alone or in combination for treating complicated intra-abdominal infections in adults include:

- beta-lactam/beta-lactamase inhibitor combinations, such as piperacillin/tazobactam
- carbapenems, such as meropenem

- cephalosporins, such as cefuroxime or ceftriaxone, plus metronidazole
- fluoroquinolones, such as ciprofloxacin, plus metronidazole
- aminoglycosides, such as gentamicin, plus metronidazole.

Costs of alternative treatments

Costs are not included for all antibiotic regimens that may be considered for treating complicated intra-abdominal infections because of the wide range of options, variability in formulations, dosages and durations, and use of a variety of combinations of antibiotics. Also, antibiotic regimens may be changed based on response to treatment or results of microbiological susceptibility testing.

Table 2 lists acquisition costs of the antibiotics used in the study together with some other commonly used options to give a broad indication of the range of costs of intravenous antibiotics for intra-abdominal infections. Oral preparations may also be used and are generally less expensive. Note that the continued need for parenteral antibiotics should be reviewed after 48–72 hours and, if appropriate, treatment should be switched to oral therapy (see Public Health England's [Start smart – then focus](#) toolkit for more details).

Table 2 Costs of some intravenous antibiotics used for intra-abdominal infections

Antibiotic(s) and dosage(s) ^a	Cost per vial or bottle	Cost per 7-day course ^b
Ceftolozane/tazobactam 1 g/0.5 g 8 hourly plus metronidazole 500 mg 8 hourly	£67.03 ^c plus £3.10 ^d	£1,407.63 plus £65.10 Total £1,472.73
Meropenem 1 g 8 hourly	£16.00 ^c	£336.00
Piperacillin/tazobactam 4 g/0.5 g 8 hourly	£15.17 ^c	£318.57
Cefuroxime 750 mg 8 hourly plus metronidazole 500 mg 8 hourly	£2.34 ^c plus £3.10 ^d	£49.14 plus £65.10 Total £114.24

Ciprofloxacin 400 mg 2 or 3 times daily plus metronidazole 500 mg 8 hourly	£22.85 ^c plus £3.10 ^d	£319.90 or £479.85 plus £65.10 Total £385.00 or £544.95
Gentamicin 3–6 mg/kg daily (240–480 mg daily for a 80 kg adult) plus metronidazole 500 mg 8 hourly	£1 per 80 mg ^c plus £3.10 ^d	£21 to £42 plus £65.10 Total £86.10 to £107.10
<p>^a Dosages are for intravenous administration as used in ASPECT-clAI and/or as indicated in the individual summaries of product characteristics.</p> <p>^b The median duration of treatment in ASPECT-clAI was 7 days. The treatment duration may vary depending on factors such as the type of infection and severity of illness. Also, the continued need for parenteral antibiotics should be reviewed after 48–72 hours. Costs do not take into account any procurement discounts or administration costs.</p> <p>^c Cost (excluding VAT) obtained from MIMS, April 2016.</p> <p>^d Cost (excluding VAT) obtained from the BNF, April 2016.</p>		

Estimated impact for the NHS

Likely place in therapy

In [ASPECT-clAI](#), ceftolozane/tazobactam plus metronidazole was found to be non-inferior to meropenem plus saline in terms of clinical cure rates 24–32 days after starting treatment in adults with complicated intra-abdominal infections. However, it is unclear whether the results apply to some populations; for example, people aged over 65 years or who are immunocompromised, or those with severe neutropenia, renal impairment or a higher risk of dying. The most common diagnosis in the study was appendiceal perforation or peri-appendiceal abscess (43% according to the [summary of product characteristics](#)) and less information is available on using ceftolozane/tazobactam in people with other diagnoses.

There was no marked difference in the safety profile between ceftolozane/tazobactam and comparators (meropenem and levofloxacin) in 2 pivotal RCTs for complicated

intra-abdominal infections and complicated urinary tract infections. However, nausea, constipation, abdominal pain, pyrexia, headache, hypotension, hypokalaemia and raised ALT and AST were reported more commonly in people taking ceftolozane/tazobactam.

The acquisition cost of ceftolozane/tazobactam is more than that of other intravenous antibiotics that are commonly used for complicated intra-abdominal infections.

Appropriate use of antibiotics is important to reduce the serious threat of antibiotic resistance and the risk of healthcare-associated infections such as *C. difficile* infection. (See the NICE evidence summary medicines and prescribing briefing for more information on the [risk of Clostridium difficile infection with broad-spectrum antibiotics](#).) Public Health England's [Start smart – then focus](#) toolkit outlines best practice in antimicrobial stewardship in the secondary care setting. 'Start smart' indicates that antibiotics should be started within 1 hour of diagnosis (or as soon as possible) in people with severe and life-threatening infections (particularly where the cause of infection is uncertain) and in line with local antibiotic prescribing guidance. In people with less severe infection, local prescribing guidance should recommend narrow-spectrum antibiotics that cover the expected pathogens.

'Focus' indicates that the clinical diagnosis and continuing need for antibiotics should be reviewed within 48–72 hours, with 5 options to consider:

- stop antibiotics if there is no evidence of infection
- switch antibiotic formulation from intravenous to oral
- change antibiotic – ideally to a narrower spectrum, but broader if required
- continue antibiotics and document next review date
- start outpatient parenteral antibiotic therapy.

Commissioners and local decision makers will need to consider where ceftolozane/tazobactam fits within local hospital antibiotic policies and guidelines for managing complicated intra-abdominal infections, taking the principles of antimicrobial stewardship into account. (See the [relevance to NICE guidance programmes](#) section below for links to NICE guidance on antimicrobial stewardship.) Local hospital antibiotic policies generally limit the options that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the

microbiologist or physician responsible for the control of infectious diseases. (See the BNF section on [principles of antibiotic therapy](#).)

The manufacturer of ceftolozane/tazobactam, Merck Sharp & Dohme Limited, anticipates that the antibiotic will be used in line with good antimicrobial stewardship, on the advice of a microbiologist, to treat gram-negative infections, when the pathogen is resistant to first-line empirical treatment options but susceptible to ceftolozane/tazobactam.

Estimated usage

Merck Sharp & Dohme Limited estimate that usage of ceftolozane/tazobactam will be low, reflecting its anticipated positioning following confirmed susceptibility testing.

Relevance to NICE guidance programmes

The use of ceftolozane/tazobactam was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

NICE has issued guidance on [antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#) (NICE guideline NG15). A related [NICE pathway](#) and [quality standard](#) on antimicrobial stewardship are also available.

A NICE key therapeutic topic on [antibiotic prescribing – especially broad spectrum antibiotics](#) (NICE advice KTT9) supports medicines optimisation in this area. A NICE evidence summary medicines and prescribing briefing summarises the [risk of Clostridium difficile infection with broad-spectrum antibiotics](#) (NICE advice ESMPB1). These publications are not NICE guidance.

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

David Ladenheim, Antimicrobial Pharmacist, East and North Hertfordshire NHS Trust

Professor Mark H. Wilcox, Professor of Medical Microbiology, Leeds Teaching Hospitals and University of Leeds

Declarations of interest

David Ladenheim declared no relevant interests.

Professor Mark Wilcox has received consulting fees from Abbott Laboratories, Actelion, Astellas, AstraZeneca, Bayer, Biomérieux, Cerexa, Cubist, Durata, The European Tissue Symposium, The Medicines Company, MedImmune, Merck, Motif Biosciences, Nabriva,

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About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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