

Antimicrobial prescribing: Ceftazidime/avibactam

Evidence review on ceftazidime/avibactam

NICE evidence summary 16

Evidence review

November 2017

Final

*Developed by the National Institute for
Health and Care Excellence*

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the [Welsh Government](#), [Scottish Government](#), and [Northern Ireland Executive](#). All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

© NICE 2017. All rights reserved. Subject to [Notice of rights](#).

ISBN: 978-1-4731-2471-4

Final

Antimicrobial prescribing: Ceftazidime/avibactam

Introduction and current guidance

Gram-negative pathogens for example *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* are frequently associated with complicated intra-abdominal infections, complicated urinary tract infections and hospital acquired pneumonia. Managing these infections requires oral or intravenous antimicrobials. The choice and route of the antimicrobial(s) depends on the site and severity of infection, the pathogens presumed or known (after cultures) to be involved and local antimicrobial resistance patterns.

Complicated intra-abdominal infections

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. The EPAR for ceftazidime/avibactam does not give information about intra-abdominal infections so the EPAR for a related combination of antimicrobials has been used ([EPAR: ceftolozane/tazobactam](#)). Peritoneal contamination may result from surgery-associated infection, trauma or spontaneous perforation (for example, appendicitis, perforated ulcer or diverticulitis) (EPAR: ceftolozane/tazobactam). The pathogens most frequently seen in complicated intra-abdominal infections are gram-negative bacteria *E coli*, other common *Enterobacteriaceae* (for example, *Proteus* or *Klebsiella*), *P aeruginosa* and *Bacteroides fragilis*. Effective management of complicated intra-abdominal infection requires early diagnosis, appropriate surgical intervention and empiric, broad-spectrum antimicrobial treatment (EPAR: ceftolozane/tazobactam).

Complicated urinary tract infections

According to the European Association of Urology [Guidelines on urological infections](#) (2015), complicated urinary tract infections (including pyelonephritis) are associated with certain conditions, such as structural or functional

abnormalities of the genitourinary tract, or the presence of underlying disease in the lower or upper urinary tract, which increases the risk of persistent or relapsing infection. Factors associated with complicated urinary tract infections include indwelling urinary catheters, anatomical abnormalities, urinary obstruction and peri- and post-operative urinary tract infection.

Pyelonephritis is an infection of the upper urinary tract and can occur in 1 or both kidneys. Acute pyelonephritis may be caused by bacteria ascending from the lower urinary tract or spreading via the bloodstream to the kidney. It is considered to be uncomplicated if it is caused by a typical pathogen and occurs in an immunocompetent person with a normal urinary tract anatomy and kidney function. However, in people with increased susceptibility, for example: children or older people or people who are immunocompromised, acute pyelonephritis is considered to be complicated as the infection is more likely to be severe. The pathogens most commonly encountered in complicated urinary tract infections are the gram-negative bacteria *E coli*, other common *Enterobacteriaceae* (for example, *Proteus.*, *Klebsiella.* or *Citrobacter.*) and *Pseudomonas spp.*

Hospital acquired pneumonia

Hospital-acquired pneumonia is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission ([Pneumonia in adults: diagnosis and management \[2014\] NICE clinical guideline 191](#)). Early-onset (occurring within 4 days of admission)

hospital-acquired pneumonia is usually caused by the same pathogens as community-acquired pneumonia and has a good prognosis. Late-onset (starting 5 days or more after admission) hospital-acquired pneumonia has a worse prognosis and is usually caused by microorganisms that are acquired from the hospital environment. As well as, methicillin-resistant *Staphylococcus aureus* (MRSA), *P aeruginosa* and other non-pseudomonal gram-negative bacteria are the most common causes ([Pneumonia in adults: diagnosis and management \[2014\] NICE clinical guideline 191 \[final scope\]](#)).

Hospital-acquired pneumonia is estimated to increase hospital stays by 7 to 9 days and has a mortality of between 30 and 70%. These figures include hospital-acquired pneumonia that develops in people who are intubated on an

intensive care unit. This is known as ventilator-associated pneumonia and is clinically different from hospital-acquired pneumonia in non-intubated people (NICE clinical guideline in development on pneumonia: final scope).

See '[other treatments](#)' for the treatment of complicated intra-abdominal infections, complicated urinary tract infections and hospital-acquired pneumonia.

The prevalence of multidrug-resistant gram-negative pathogens, including extended-spectrum beta-lactamase producing (ESBL) and carbapenemase-producing *Enterobacteriaceae* (CPE) and *P aeruginosa* is increasing worldwide ([Carmeli et al. 2016](#)). Certain pathogens are predisposed to acquire and spread resistance. *Enterobacteriaceae* (particularly *Escherichia coli* and *Klebsiella pneumoniae*) and *P aeruginosa* are commonly associated with beta-lactamase-mediated resistance irrespective of the site of infection ([EPAR: ceftazidime/avibactam](#)).

Hospitals continue to increase their use of antimicrobials of last resort currently available: piperacillin/tazobactam, carbapenems and colistin ([English surveillance programme for antimicrobial utilisation and resistance \(ESPAUR\) report 2016](#)). There is evidence of increasing bacterial resistance to last resort antimicrobials, limiting the treatment options for people with serious infections. (Carmeli et al. 2016). Beta-lactamases are a major cause of resistance to beta-lactam antibacterial agents in infections caused by gram-negative pathogens ([EPAR: ceftazidime/avibactam](#)). The use of carbapenems is threatened by the growing prevalence of carbapenemase-producing pathogens (Carmeli et al. 2016). Therefore, alternative treatment options and carbapenem-sparing regimens for people with serious infections caused by multidrug-resistant gram-negative pathogens are urgently needed (Carmeli et al. 2016).

This evidence summary – antimicrobial prescribing outlines the best available evidence for a new antimicrobial, ceftazidime/avibactam ([Zavicefta](#)) that could be an option for treating serious infections caused by gram-negative pathogens.

Product overview

Mode of action

Ceftazidime/avibactam ([Zavicefta](#)) is a combination antimicrobial that consists of ceftazidime and avibactam. Ceftazidime is an established third generation cephalosporin that inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin binding proteins, leading to bacterial cell lysis and death ([summary of product characteristics \[SPC\]: ceftazidime/avibactam](#)).

Avibactam is a non-beta-lactam beta-lactamase inhibitor that protects ceftazidime from hydrolysis by a wide range of serine beta-lactamases. Importantly, the range of inhibition of avibactam includes class A extended spectrum-beta-lactamases and carbapenemases (for example *Klebsiella pneumoniae* carbapenemase), class C beta-lactamases and some class D oxacillinases and carbapenemases ([European Public Assessment Report \[EPAR\]: ceftazidime/avibactam](#)).

In a series of *in vitro* and *in vivo* studies, ceftazidime/avibactam was shown to be active against ceftazidime-resistant, and many carbapenem-resistant clinical isolates of *Enterobacteriaceae* and *P aeruginosa* (EPAR: ceftazidime/avibactam).

Regulatory status

Ceftazidime/avibactam (Zavicefta, Pfizer Limited) received a marketing authorisation in June 2016 and was launched in the UK in March 2017. It is indicated for treating the following infections in adults:

- complicated intra-abdominal infection,
- complicated urinary tract infection, including pyelonephritis,
- hospital-acquired pneumonia including ventilator associated pneumonia, and
- infections due to aerobic gram-negative organisms in adults with limited treatment options.

The SPC recommends that ceftazidime/avibactam should be used to treat infections due to aerobic gram-negative organisms in adults with limited treatment options only after consultation with a physician with appropriate experience in managing infectious diseases and consideration should be given to official guidance on the appropriate use of antimicrobial agents ([SPC: ceftazidime/avibactam](#)).

Dosing information

Ceftazidime/avibactam is available as a powder for concentrate to reconstitute and administer by infusion. For all its licensed indications, in adults with creatinine clearance of 51 ml/min or more, the dose is 2 g/0.5 g every 8 hours given by intravenous infusion administered over 2 hours. The recommended durations of treatment vary and are given in the SPC depending on the indication:

- complicated intra-abdominal infection is 5 to 14 days,
- complicated urinary tract infection, including pyelonephritis is 5 to 10 days (total duration may include intravenous followed by appropriate oral treatment),
- hospital-acquired pneumonia, including ventilator-associated pneumonia is 7 to 14 days, and

- infections due to aerobic gram-negative organisms in adults with limited treatment options, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the person's clinical and bacteriological progress.

Ceftazidime/avibactam should be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process, or used in combination with an antibacterial agent active against gram-positive pathogens when these are known or suspected to be contributing to the infectious process. The SPC states that there is very limited experience with the use of ceftazidime/avibactam for more than 14 days. See the SPC for further dosing advice and information.

Dose adjustments are recommended in the SPC for people with an estimated creatinine clearance of 50 ml/min or less. No dose adjustments are needed for older people and in people with hepatic impairment.

Ceftazidime/avibactam is not licensed for use in children and young people under 18.

Cost

A vial of ceftazidime/avibactam 2 g/0.5 g costs £85.70 excluding VAT ([BNF](#), October 2017). For a treatment course of 5 to 14 days depending on the indication, the cost therefore ranges from £1,285.50 to £3,599.40, excluding VAT, any procurement discounts and administration costs.

Evidence review

A literature search was conducted which identified 12 references (see [search strategy](#) for full details). These references were screened using their titles and abstracts and 10 references were obtained and assessed for relevance.

Three references were identified from the search (REPRISE [[Carmeli Y et al. 2016](#)], RECLAIM 1 and 2 [[Mazuski JE et al. 2016](#)] and RECAPTURE 1 and 2 [[Wagenlehner FM et al. 2016](#)]) as meeting the inclusion criteria for this evidence summary. The included studies examined the efficacy and safety of ceftazidime/avibactam in adults with complicated intra-abdominal infections and complicated urinary tract infections.

The [European Public Assessment Report \(EPAR\)](#) for ceftazidime/avibactam included data from 5 phase 3 studies in people with complicated intra-abdominal infection, complicated urinary tract infection and hospital acquired pneumonia. Three of the phase 3 [randomised controlled trials](#) (RCTs) were published and have been included in this evidence summary (REPRISE, RECLAIM 1 and 2 and RECAPTURE 1 and 2). The EPAR reported the results of the single studies, RECLAIM and RECAPTURE, whereas the published papers reported pooled results of RECLAIM 1 and 2 and RECAPTURE 1 and 2. The fourth phase 3 RCT (in people with complicated intra-abdominal infection, RECLAIM 3) was not prioritised as the paper by Mazuski et al. 2016 also included people with complicated intra-abdominal infection and was a larger study. The fifth RCT ([REPROVE study](#)) that assessed the safety and efficacy of ceftazidime/avibactam in people with nosocomial pneumonia, including ventilator-associated pneumonia, was not published at the time the literature search was conducted and was not included. The EPAR only reported the pharmacokinetic data from the REPROVE study.

A summary of the included studies is shown in table 1 (see [evidence tables](#) for full details).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
REPRISE (Carmeli et al. 2016) Open-label RCT	Adults aged 18 to 90 years with cUTI or cIAI caused by ceftazidime resistant gram-negative pathogens (n= 333)	For cUTI (n=306): IV ceftazidime/avibactam 2 g/0.5 g 3 times a day or best available treatment ^a for 5 to 21 days For cIAI (n=27): ceftazidime/avibactam 2 g/0.5 g plus IV metronidazole 500 mg 3 times a day or best available treatment ^a for 5 to 21 days	Clinical response (cure, failure or indeterminate) at test-of-cure visit (7 to 10 days after last infusion of the study medicine)
RECLAIM 1 & 2 RCTs ^b (Mazuski et al. 2016)	Adults aged 18 to 90 years (18 to 65 years in India) with cIAI ^c (n=1,066)	IV ceftazidime/avibactam 2 g/0.5 g 3 times a day plus IV metronidazole 500 mg 3 times a day or meropenem 1 g 3 times a day for 5 to 14 days	Clinical cure at test-of-cure visit (28 to 35 days from randomisation) to assess non-inferiority of ceftazidime/avibactam plus metronidazole to meropenem
RECAPTURE 1 & 2 RCTs ^b (Wagenlehner et al. 2016)	Adults aged 18 to 90 years who had cUTI or acute pyelonephritis considered to be serious and requiring hospitalisation for IV antimicrobial treatment ^c (n=1033)	IV ceftazidime/avibactam 2 g/0.5 g 3 times a day or IV doripenem (not available in the UK) 500 mg 3 times a day with a possible switch to oral antimicrobials after 5 or more days treatment (total treatment duration 10 days or up to 14 days for bacteraemia)	To assess non-inferiority of ceftazidime/avibactam with doripenem the following outcomes were used: Per-patient favourable microbiological response at test-of-cure (21 to 25 days after randomisation) Combined symptom resolution/microbiological eradication at test-of-cure Patient reported symptom resolution at day 5 of treatment
<p>^a Preferred best available treatment options for cIAIs and cUTIs were 5 to 21 days treatment with IV meropenem, imipenem, doripenem, colistin and for cIAI only tigecycline, administered intravenously, but any treatment, including combination treatment was allowed. BAT mainly included imipenem or meropenem.</p> <p>^b Studies reported as pooled analysis in the paper</p> <p>^c Populations included participants with ceftazidime-resistant and –susceptible pathogens</p>			
Abbreviations: BAT, best available treatment; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; RCT, randomised controlled trial			

The remaining 7 references were excluded. These are listed in [excluded studies](#) with reasons for their exclusion.

Clinical effectiveness

Published RCT data were only available for 2 of out of the 4 licensed indications for ceftazidime/avibactam: complicated intra-abdominal infections and complicated urinary tract infections.

Ceftazidime/avibactam is also licensed for treating hospital-acquired pneumonia including ventilator-associated pneumonia, and infections due to aerobic gram-negative organisms in adults with limited treatment options.

[NCT01808092](#) is a RCT (REPROVE study) that assessed the efficacy and safety of ceftazidime/avibactam compared with meropenem in adults with hospital-acquired pneumonia including ventilator-associated pneumonia. This study has been completed but it is not published. The EPAR states that the approval of license for the indication of ceftazidime/avibactam to treat people with nosocomial pneumonia is primarily based on a pharmacokinetic-pharmacodynamic analysis, complemented by clinical data on ceftazidime alone and on ceftazidime/avibactam in other infections, as well as pharmacokinetic data from patients with hospital-acquired pneumonia.

The use of ceftazidime/avibactam to treat people with infections due to gram-negative aerobic pathogens who have limited treatment options is based on microbiological data, pharmacokinetic-pharmacodynamic analyses and clinical efficacy data in complicated intra-abdominal infections and complicated urinary tract infections, including efficacy against ceftazidime-resistant pathogens that express a range of beta-lactamases (EPAR: ceftazidime/avibactam). The EPAR states that there is a lack of clinical experience with ceftazidime/avibactam for treating infections at other body sites.

Of the 3 included studies, [REPRISE](#) (n=333 randomised) was the only study that investigated the effect of ceftazidime/avibactam in adults with ceftazidime-resistant pathogens with complicated intra-abdominal infections

(n=27) and complicated urinary tract infections (n=306).

Ceftazidime/avibactam was compared with best available treatment (mainly imipenem [48%] and meropenem [39%]). Participants with complicated intra-abdominal infection were given intravenous metronidazole in addition to ceftazidime/avibactam. The median duration of treatment was between 10 and 12 days. The primary outcome was clinical response (cure, failure or indeterminate) at test of cure visit (7 to 10 days after last infusion of the study drug) in all participants who had at least 1 ceftazidime-resistant pathogen and received at least 1 dose of study medicine (microbiologically modified intention to treat [mMITT] population). All participants with complicated intra-abdominal infections (100%) reported previous antimicrobial use prior to study enrolment, compared with 48% of participants with complicated urinary tract infections reporting previous antimicrobial use.

Clinical cure was defined as complete resolution or substantial improvement of signs and symptoms of the index infection, such that no further antimicrobial therapy (other than those allowed per protocol) was necessary. Additionally for participants with complicated intra-abdominal infections, cure also required that no drainage or surgical intervention was needed after 96 hours from randomisation. The overall proportion of participants with complicated intra-abdominal infection and complicated urinary tract infection with ceftazidime-resistant pathogens with a clinical cure at the test of cure visit were similar with ceftazidime/avibactam (91% [140/154], 95% [confidence interval](#) [CI] 85.6% to 94.7%) and best available treatment (91% [135/148], 95% CI 85.9% to 95%). No statistical comparison was made between the 2 groups. The results for clinical failure and indeterminate along with their definitions can be found in [results](#) table 6. The clinical response results of subgroups (secondary outcome) with complicated intra-abdominal infection and complicated urinary tract infection are briefly discussed under each indication.

REPRISE also reported the number of participants with 28-day all-cause mortality in the mMITT analysis set (secondary outcome). Three participants in the ceftazidime/avibactam plus metronidazole group (all with complicated

urinary tract infections) and 4 participants in the best available treatment (n=3 with complicated urinary tract infections and n=1 with complicated intra-abdominal infection) group died on or before day 28. No between group statistical analysis was conducted in the study.

Complicated intra-abdominal infections

An overview of the results for clinical effectiveness can be found in [results tables](#).

Clinical response (cure, failure or indeterminate)

The efficacy results for [RECLAIM 1 and RECLAIM 2](#) were presented as pooled results by Mazuski et al. 2016. RECLAIM 1 and 2 (n=1,066) examined the efficacy of ceftazidime/avibactam plus metronidazole compared with meropenem in people with complicated intra-abdominal infection with both ceftazidime-resistant and -susceptible pathogens present. The primary outcome of clinical cure was defined as complete resolution or significant improvement of signs and symptoms of index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary. Clinical cure at the test-of-cure (28 to 35 days after randomisation) was assessed by non-inferiority of ceftazidime/avibactam plus metronidazole to meropenem (assessed by using the lower limit of the 95% CI for between group differences being above at least -12.5%, European Medicines Agency [EMA] limit). Ceftazidime/avibactam plus metronidazole (median of 7 days treatment) was found to be non-inferior to meropenem (median of 8 days treatment) at the test-of-cure visit. Eighty-three percent (429/520) of participants had a clinical cure in the ceftazidime/avibactam plus metronidazole group compared with 85% (444/523) in the meropenem group (difference -2.4%, 95% CI -6.90% to 2.10%) in the modified intention to treat (MITT) population. Non-inferiority was also shown in the clinically evaluable (CE) population (which included participants in the MITT population with no treatment deviations from protocol), see [results table 7](#). The most common primary diagnosis in the study was appendiceal perforation or periappendiceal abscess (approximately 40%).

The EPAR states that ceftazidime/avibactam showed almost consistent numerical inferiority to meropenem in each pre-defined analysis population and participant subgroup. Lower cure rates were seen with ceftazidime/avibactam plus metronidazole compared with meropenem in participants with moderate renal impairment at baseline (creatinine clearance between 30 ml/min and 50 ml/min) and those with an [acute physiology and chronic health evaluation](#) (APACHE) II score of more than 10. The EPAR suggests that participants on ceftazidime/avibactam with rapid recovery in creatinine clearance were more likely to have been temporarily under-dosed than similar participants on meropenem based on the greater percentage reduction in recommended dose for the ceftazidime/avibactam (dose reduced by 66%) compared with meropenem (dose reduced by 33%). To reduce the risk of potential under-dosing, the manufacturer has since revised the dose adjustment for people with creatinine clearance of 50 ml/min or less (see [summary of product characteristics \[SPC\]: ceftazidime/avibactam](#)). As for the lower cure rate seen in people with an APACHE II score of more than 10, the EPAR states that further analysis of the clinical cure rates in this subgroup indicated that there was no significant difference between the treatment arms (statistical analysis not reported).

RECLAIM 1 and 2 also reported clinical cure rate in a subgroup population that included participants with ceftazidime-resistant pathogens (secondary outcome). Clinical cure rate was 83% (39/47) for participants with ceftazidime-resistant pathogens in the ceftazidime/avibactam plus metronidazole group compared with 86% (55/64) of participants with ceftazidime-resistant pathogens in the meropenem group at the test-of-cure visit (difference -3.0%, 95% CI -17.89% to 10.60%).

Although not reported as a primary or secondary outcome, clinical failure occurred in 9% (47/520) in the ceftazidime/avibactam plus metronidazole group and 7.5% (39/523) in meropenem group. The most common reasons for failure were reported to be the participant previously meeting criteria for failure, ongoing symptoms requiring additional antimicrobials and post-surgical wound infections.

In [REPRISE](#), the proportion of participants with complicated intra-abdominal infections (n=27, randomised) with clinical cure at the test-of-cure visit was 80% (8/10; 95% CI 47.9% to 95.6%) in the ceftazidime/avibactam plus metronidazole group compared with 55% (6/11; 95% CI 27.0% to 80.0%) in the best available treatment group.

Complicated urinary tract infections including pyelonephritis

An overview of the results for clinical effectiveness can be found in [results tables](#).

The efficacy results for [RECAPTURE 1 and 2](#) were presented as pooled results by Wagenlehner et al. 2016. RECAPTURE 1 and 2 (n=1,033) examined the efficacy of ceftazidime/avibactam compared with doripenem (not available in the UK) in people with complicated urinary tract infection, including pyelonephritis with both ceftazidime-resistant and -susceptible pathogens. Seventy-two percent of participants in the study had pyelonephritis. The 3 primary outcomes (2 Food and Drugs Administration [FDA] outcomes and 1 EMA outcome) were: patient-reported symptom resolution from baseline at day 5, combined microbiological eradication and symptom resolution at the test-of-cure (21 to 25 days after randomisation) and per-patient favourable microbiological response (microbiological eradication) at the test-of-cure (refer to results, table 6 for outcome definitions).

In the mMITT population, non-inferiority (lower limit of the 95% CI within the FDA pre-specified margin of -10% and within the EMA pre specified margin of -12.5%) of ceftazidime/avibactam compared with doripenem was found for all 3 primary outcomes. Patient-reported symptomatic resolution from baseline at day 5 was found in 70% (276/393) of participants in the ceftazidime/avibactam group compared with 66% (276/417) participants in the doripenem group (difference 4%, 95% CI -2.39% to 10.42%). Combined symptomatic resolution and microbiological eradication at test-of-cure was found in 71% (280/393) participants in the ceftazidime/avibactam group compared with 65% (269/417) participants in the doripenem group (difference 6.7%, 95% CI 0.30% to 13.12%). For the EMA primary endpoint, per patient favourable microbiological response at test-of-cure was found in 77% (304/393) of

participants in the ceftazidime/avibactam group compared with 71% (296/417) of participants in the doripenem group (difference 6.4%, 95% CI 0.33% to 12.36%). The median durations of intravenous treatment were 7 and 8 days for ceftazidime/avibactam and doripenem respectively. No data was available in the study to verify the results of the primary outcomes in the microbiologically evaluable (ME) and CE populations (see Wagenlehner et al. 2016 for population details).

The EPAR states that subgroup analysis of the microbiological eradication at test-of-cure favoured ceftazidime/avibactam except in the subgroups aged 75 years or more and in those with moderate renal impairment at baseline. In terms of the participants with moderate renal impairment, they may have been under-dosed similarly to the participants in RECLAIM 1 and 2.

Per-patient favourable microbiological response (microbiological eradication) at test-of-cure in participants with ceftazidime-resistant pathogens (secondary outcome) was lower than that seen for the primary outcome in the overall population with ceftazidime-resistant or –susceptible pathogens. For ceftazidime/avibactam the microbiological eradication rate was 63% (47/75) compared with 61% (51/84) in the doripenem group (difference 2%, 95% CI –13.18% to 16.89%).

Investigator-determined clinical cure at the test-of-cure (secondary outcome) was similar between ceftazidime/avibactam and doripenem (90.3% and 90.4%, difference –0.1%, 95% CI –4.23% to 4.03%).

In [REPRISE](#), the proportion of participants with complicated urinary tract infections (n=306, randomised) with clinical cure at the test-of-cure visit were similar between the 2 groups (92% [132/144], 95% CI 86.3% to 95.4% in the ceftazidime/avibactam group and 94% [129/137], 95% CI 89.3% to 97.2% in the best available treatment group).

Safety and tolerability

An overview of the results for safety and tolerability can be found in the [results tables](#).

The [EPAR](#) for ceftazidime/avibactam states that the safety profile of ceftazidime/avibactam generally reflects that already known for ceftazidime alone. However, it is not possible to draw any definitive conclusions regarding the possible effects of avibactam on the adverse event profile of ceftazidime. The EPAR suggests that it is not appropriate to compare adverse events frequencies between ceftazidime/avibactam and those of ceftazidime alone due to the different ranges of doses used and the different indications they both cover. The safety of ceftazidime/avibactam was compared with only carbapenems and safety data was limited to participants with complicated intraabdominal infections and complicated urinary tract infections. The participants with complicated intra-abdominal infection received metronidazole in addition to ceftazidime/avibactam which confounds the comparisons made.

The [SPC](#) states that ceftazidime/avibactam is contraindicated in people with hypersensitivity to the active substances, excipients or to any cephalosporin antibiotic or severe hypersensitivity to any other type of beta lactam antibacterial agent (for example penicillins, monobactams or carbapenems). The SPC includes a number of special warnings and precautions for use including hypersensitivity reactions, *Clostridium difficile*-associated diarrhoea (can range in severity from mild to life threatening) renal impairment, nephrotoxicity and direct Coombs test and potential risk of haemolytic anaemia (see SPC for further details).

The SPC for ceftazidime/avibactam reports that the most common adverse events occurring in 1 in 20 people or more receiving ceftazidime/avibactam were positive, direct Coombs test, nausea, and diarrhoea. Other adverse events listed as common (1 in 100 people or more) include candidiasis, headache, dizziness, maculopapular rash, eosinophilia, thrombocytosis, thrombocytopenia, vomiting, abdominal pain, raised liver function tests, urticaria, pruritus, pyrexia and infusion site reactions.

Ceftazidime and avibactam are eliminated by the kidneys and the SPC states that the dose should be reduced in people with renal impairment according to the degree of renal impairment. Additionally, in these people, close monitoring of the estimated creatinine clearance is recommended in the SPC as it can

change quickly, especially in the early treatment of the infection (SPC: ceftazidime/avibactam). The SPC has updated the dose and frequency recommendations for ceftazidime/avibactam in people with a creatinine clearance of 50 ml/min or less to ensure optimal dosing as a result of the findings from the studies. See the SPC for further information.

In the 3 studies, the proportion of participants reporting adverse events (studies reported usually of mild to moderate intensity) were similar between the 2 groups across the studies (see results tables). In [REPRiSE](#) and [RECLAIM 1 and 2](#), the most common adverse event reported was gastrointestinal-related (13% [21/164] in the ceftazidime/avibactam group and 18% [30/168] in the best available treatment group [which commonly used imipenem or meropenem] and 22% [118/529] in ceftazidime/avibactam and 16% [82/529] in meropenem group respectively). Diarrhoea, nausea and vomiting were most frequently reported. *Clostridium difficile* colitis was also reported in each treatment group in RECLAIM 1 and 2 (n=1 in each group), and occurred in 2 of the participants in the ceftazidime/avibactam group in [RECAPTURE 1 and 2](#). In RECAPTURE 1 and 2, the most common adverse event was headache which developed in 7.4% (38/511) of ceftazidime/avibactam participants and 7.9% (40/509) of doripenem treated participants. Gastrointestinal-related adverse events (nausea, diarrhoea and constipation) were the second most common adverse events reported (8% [40/511] in the ceftazidime/avibactam group and 5% [23/509] in the doripenem group).

For the overall rate of serious adverse events and discontinuation of study medicine see results tables. The nature of these serious adverse events were not specified in the studies. The [EPAR](#) states that most common serious adverse events found from a pooled analysis of 2 studies (including RECLAIM) in people with complicated intra-abdominal infection in the ceftazidime/avibactam group were acute renal failure, pulmonary embolism and respiratory failure. Two serious adverse events in each treatment group were assessed as medicine-related, including hypersensitivity and hepatic enzymes increased in the ceftazidime/avibactam group and drug eruption

(drug-related skin reaction) and transaminases increased in the meropenem group (EPAR: ceftazidime/avibactam). In REPRISE, RECLAIM 1 and 2 and RECAPTURE 1 and 2, adverse events leading to discontinuation of the study medicine were reported to be, 0.6% (1/164), 2.6% (14/529) and 1.4% (7/511) in the ceftazidime/avibactam with or without metronidazole groups compared with 1.2% (2/168) in best available treatment group, 1.3% (7/529) in the meropenem group and 1.2% (6/509) in doripenem group respectively.

In RECLAIM 1 and 2, 2.5% (13/529) of the participants died in the ceftazidime/avibactam plus metronidazole group compared with 1.5% (8/529) in the meropenem group. Of these reported deaths, 5 of the participants (4 in the ceftazidime/avibactam plus metronidazole group and 1 in the meropenem group) had moderate renal impairment at baseline and 9 of the participants (6 and 3 participants, respectively) were reported to have died from progression of their complicated intra-abdominal infection. REPRISE reported a total of 7 deaths in the study, 3 deaths in the ceftazidime/avibactam plus metronidazole group compared with 4 in the best available treatment group (see also 28-day mortality in [clinical effectiveness](#)). In REPRISE, deaths reported in the ceftazidime/avibactam group were caused by cardiorespiratory arrest, cardiac arrest, and renal failure. Both REPRISE and RECLAIM 1 and 2 state that deaths were not considered to be related to the study medicine. There were no deaths reported in the treatment groups in RECAPTURE 1 and 2.

For full information see [SPC for ceftazidime/avibactam](#).

Evidence strengths and limitations

The populations included in the RCTs reviewed in this evidence summary all had complicated intra-abdominal infection or complicated urinary tract infections. There were no published clinical efficacy studies that examined ceftazidime/avibactam for use in people with hospital-acquired pneumonia or for use in people with limited treatment options due to aerobic gram-negative pathogens. In addition, the studies were carried out in a non-UK population in which case the microbiological resistance profiles may differ to that in the UK.

Of the included studies, [REPRISE](#) was the only study that examined the efficacy of ceftazidime/avibactam in people specifically with ceftazidime-resistant gram-negative pathogens. REPRISE was conducted in a population with either complicated intra-abdominal infection or complicated urinary tract infection. In REPRISE the number of participants with complicated intra-abdominal infection were low (n=27) compared with participants with complicated urinary tract infection (n=306) limiting the applicability of the efficacy results to people with complicated intra-abdominal infection with ceftazidime-resistant pathogens. The number of participants in the mMITT population with ceftazidime-resistant pathogens identified in [RECLAIM 1 and 2](#) and [RECAPTURE 1 and 2](#) were very small (13.5% [111/823] and 19.6% [159/810]).

In RECLAIM 1 and 2, more than 80% of the participants with complicated intra-abdominal infection had an [APACHE II](#) score of 10 or less and approximately 40% had appendix related complicated intra-abdominal infection. This limits the applicability of the results to people with APACHE II scores of more than 10 and with other associated complications of intra-abdominal infection. In RECAPTURE 1 and 2, approximately 70% of the participants with complicated urinary tract infection had a diagnosis of pyelonephritis. This limits the applicability of the results to people with other types of complicated urinary tract infections. In REPRISE, most of the participants with complicated intra-abdominal infections had an APACHE II score of 10 or less (67%). Similar to RECLAIM 1 and 2, this limits the applicability of the results to people with an APACHE II score of 10 or more. In RECLAIM 1 and 2 and RECAPTURE 1 and 2, there were only a small number of participants with bacteraemia at baseline (3.4% and 8.8% respectively) and participants with a creatinine clearance of 30 ml/min or less were excluded from the studies. This limits the applicability of the results to people who have bacteraemia or a creatinine clearance of 30 ml/min or more.

Although all included studies were carried out in an international and multicentre setting, none of the studies included the UK population which may limit the applicability of the results to UK practice. Drop-out rates were similar

between the 2 treatment groups in each study (approximately 10% or less in each treatment group).

The active comparator used in the studies was mainly the carbapenem antimicrobials doripenem, imipenem and meropenem. Specialists who reviewed this evidence summary suggested that meropenem is a reasonable comparator. Although, the study protocols in RECLAIM 1 and 2 were designed to minimise use of other antimicrobials, at the investigators discretion, open-label vancomycin, linezolid, or daptomycin could be added to each treatment group if *Enterococcus* species or MRSA was suspected or isolated. This may have confounded the results as it was not clear how many participants received additional antimicrobials. Specialists who commented on this evidence review advised that in practice, additional further antimicrobials are added to standard care when treating complicated intra-abdominal infections where resistant enterococci is suspected and gram-positive cover is required (see [dosing information](#)).

In RECAPTURE 1 and 2, the active comparator was doripenem, a carbapenem which is not available in the UK. According to the study, it was chosen as the comparator based on its efficacy in complicated urinary tract infection and because other carbapenems were not approved for this indication in the selected study regions. In REPRISE, the most common antimicrobials used in participants with complicated urinary tract infection were imipenem and meropenem. Although carbapenems are not used as first-line treatment for complicated urinary tract infection in the UK, specialists involved in producing this evidence summary have advised that carbapenems, as a class may be considered as a treatment option when multi-drug resistant bacteria are suspected or if there has been treatment failure.

RECLAIM 1 and 2 (n=1066) and RECAPTURE 1 and 2 (n=1033) were multi-centre, double-blind, active-comparator RCTs with low risk of bias (see evidence tables). REPRISE (n=333) was a relatively small open-label RCT. In REPRISE, both participants and investigators knew whether ceftazidime/avibactam or best available treatment was being used. In addition, investigators analysing the data and assessing outcomes were aware of the

group assignment. This could have introduced bias and affected both participant and investigator perceptions of efficacy and safety. A limitation of REPRISE was that it did not carry out any statistical analysis for the results, however the study may provide valuable information for clinicians in terms of the effectiveness of ceftazidime/avibactam in people with ceftazidime-resistant pathogens.

RECLAIM 1 and 2 and RECAPTURE 1 and 2 were non-inferiority studies. For non-inferiority studies, analysis should be conducted for the ITT population and per protocol population; non-inferiority can only be confirmed if both populations support this. The European Medicines Agency guidance on [Points to consider on switching between superiority and non-inferiority](#) states that in a non-inferiority trial, the full analysis set (ITT population) and the per protocol analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation of the study results. However, no data was available in the RECAPTURE 1 and 2 study to verify the results of the primary outcomes in the microbiologically evaluable (ME) and CE populations.

In RECAPTURE 1 and 2, to assess one of the FDA co-primary outcomes, a non-validated questionnaire was used to assess symptoms in people with complicated urinary tract infections. The study states that the questionnaire used was based on a validated patient-reported symptom assessment questionnaire used in people with uncomplicated urinary tract infection to detect symptoms over time. This may limit the validity and reliability of the results of the primary outcome that was used to assess non-inferiority of ceftazidime/avibactam to doripenem. REPRISE included clinical response as the primary outcome which took into account clinical cure, failure and indeterminate. RECLAIM 1 and 2 also looked at clinical cure as the primary outcome. Specialists who commented on this evidence summary suggested that the primary outcomes selected to assess the efficacy of ceftazidime/avibactam were reasonable given the complexity of the infections involved.

An overview of the quality assessment of each included study can be found in [evidence tables](#).

Resistance

The [SPC](#) states that bacterial resistance mechanisms that could potentially affect ceftazidime/avibactam include mutant or acquired penicillin binding proteins (PBPs), decreased outer membrane permeability to either compound, active efflux of either compound and beta-lactamase enzymes refractory to inhibition by avibactam and able to hydrolyse ceftazidime.

Ceftazidime/avibactam is a new antimicrobial and 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 local antimicrobial resistance indicators](#). Specialists who commented on this evidence summary identified 2 papers ([Humphries et al. 2015](#) and [Shields et al. 2016](#)) that reported cases of resistance to ceftazidime/avibactam in the US.

Data analysis is still ongoing to assess the proportion of participants with clinical cure at the test-of-cure visit by resistance mechanisms in the mMITT and extended ME analysis set in the REPRISE study.

Estimated impact for the NHS

Other treatments

There are no UK-based guidelines for the management of complicated intra-abdominal infections or complicated urinary tract infections in adults. NICE is developing an [antimicrobial prescribing guideline](#) on managing complicated urinary tract infections. Specialists who commented on this evidence summary highlighted that in addition to local guidelines based on local epidemiology, US-based guidelines by the [Surgical Infection Society and the Infectious Diseases Society of America](#) and the [World Society of Emergency Surgery](#) are referred to for complicated intra-abdominal infections and the European Association of Urology [Guidelines on urological infections](#) (2015) is referred to for complicated urinary tract infection.

Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America and the World Society of Emergency Surgery recommend empirical antimicrobial 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-acquired or healthcare-associated) and local (and national) antimicrobial resistance patterns. According to these guidelines, antimicrobials 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.

For complicated urinary tract infections, the European [guideline](#) suggests options for empirical treatment when local resistance is sufficiently low (less than 20%), are fluoroquinolones, aminopenicillins combined with a beta-

lactamase inhibitor, third generation cephalosporins (for example, cefotaxime or ceftriaxone) and aminoglycosides. In the case of initial failure (less than 3 days' treatment) or clinically severe infection, a broader-spectrum antimicrobial should be chosen that is also active against *Pseudomonas*. Options include fluoroquinolones (if not used for initial therapy), piperacillin plus a beta-lactamase inhibitor, further third generation cephalosporins (ceftazidime) and carbapenems with or without an aminoglycoside. After a few days of parenteral therapy and clinical improvement, patients may be switched to oral treatment.

The NICE guideline on [pneumonia](#) recommends to offer antimicrobial therapy as soon as possible after diagnosis, and certainly within 4 hours to people with hospital-acquired pneumonia. The antimicrobial choice should be based on local antimicrobial prescribing guidelines and clinical circumstances and a treatment duration of 5 to 10 days should be considered.

Costs of other treatments

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

Table 2 gives a broad indication of the range of costs of the intravenous antimicrobials commonly used in the UK for the indications reviewed in this evidence summary. Local (or national) antimicrobial prescribing guidelines should be referred to when selecting treatment options for the indications covered in the evidence summary. Depending on the pathogens contributing to the infection, ceftazidime/avibactam may need to be given in combination with other antimicrobials for which additional treatment costs would need to be considered, for example, intravenous metronidazole used in combination with ceftazidime/avibactam for anaerobic cover for the treatment of complicated

intra-abdominal infections. Oral antimicrobial preparations may also be used and are generally less expensive.

Table 2 Costs of other treatments

Medicine ^a	Intravenous dose ^b	Cost
Ceftazidime/ avibactam	2 g/0.5 g 8 hourly	£85.70 per 2 g/0.5 g vial ^c
Ceftazidime	1-2 g 8 hourly	£1.39 to £8.79 per 1 g vial £2.77 to 17.59 per 2 g vial ^c
Ceftolozane/ tazobactam	1 g/0.5 g 8 hourly	£67.03 per vial ^c
Ceftriaxone	1 g to 4 g daily	£9.58 per 1 g vial £19.18 per 2 g vial ^d
Ciprofloxacin	400 mg 2 to 3 times daily	£2.08 to 19.79 per 400 mg vial ^c
Co-amoxiclav	1 g/0.2 g 8 hourly	£1.08 to £2.97 per 1 g/0.2 g vial ^c
Gentamicin	3-5 mg/kg daily (240-400 mg for a 80 kg adult)	£1.00 to £4.00 per 80 mg vial ^c
Meropenem	0.5-1 g 8 hourly	£8.07 per 0.5 g vial £16.12 per 1 g vial ^d
Piperacillin/ Tazobactam	4 g/0.5 g 8 hourly or 6 hourly	£8.70 per 2 g/0.25 g vial ^d
^a Examples in this table are not all licensed for the indications covered in the evidence summary, see individual SPCs for further information ^b Doses have been presented for cost comparison purposes and do not represent the full range that can be used and do not imply therapeutic equivalence. Taken from the relevant SPC for intravenous treatment. For further information on dosing for particular indications refer to the SPC. ^c Costs based on British National Formulary October 2017; excluding VAT. ^d Costs based on Drug Tariff October 2017; excluding VAT		
Abbreviations: SPC, summary of product characteristics		

Current or estimated usage

The manufacturer of ceftazidime/avibactam (Pfizer Limited) anticipates that usage will be low, following the principles of good antimicrobial stewardship and under the guidance of a microbiologist. Pfizer Limited expects that ceftazidime/avibactam will be used to treat people with infections suspected to be caused by multi-drug resistant aerobic gram-negative bacteria according to its licensed indications.

Likely place in therapy

Ceftazidime/avibactam is licensed for treating complicated intra-abdominal infections, complicated urinary tract infections, including pyelonephritis, hospital acquired pneumonia, including ventilator-associated pneumonia, and infections due to aerobic gram negative organisms in adults with limited treatment options. Published RCT data were only available for 2 of out of the 4 licensed indications for ceftazidime/avibactam: complicated intra-abdominal infections and complicated urinary tract infections.

In [REPRISE](#), although there were no statistical comparison's made between the 2 groups for any outcomes, ceftazidime/avibactam had similar clinical cure rates compared with best available treatment (mainly with imipenem and meropenem) in adults with ceftazidime-resistant pathogens with complicated intra-abdominal infection and complicated urinary tract infection at the test-of-cure visit. Approximately 90% of the participants in REPRISE had complicated urinary tract infection. [RECLAIM 1 and 2](#) and [RECAPTURE 1 and 2](#) included participants who had ceftazidime-resistant and -susceptible pathogens. RECLAIM 1 and 2 found that ceftazidime/avibactam plus metronidazole was non-inferior to meropenem in terms of clinical cure rates at the test-of-cure visit for the treatment of complicated intra-abdominal infection. [RECAPTURE 1 and 2](#) found that ceftazidime/avibactam was non-inferior to doripenem (not available in the UK) for the primary outcomes of per-patient favourable microbiological response, patient-reported symptom resolution at day 5 of treatment and combined microbiological eradication and symptom resolution at the test-of-cure visit for the treatment of complicated urinary tract infection including pyelonephritis.

It is unclear whether the results apply to some populations for example people with severe renal impairment or on dialysis, with infections other than those included in the studies, with bacteraemia or with a higher risk of dying. The most common diagnosis in RECLAIM 1 and 2 was appendiceal perforation or periappendiceal abscess (approximately 40%) and in RECAPTURE 1 and 2, approximately 70% of the participants with complicated urinary tract infection had a diagnosis of pyelonephritis.

REPRISE was the only study that assessed the efficacy of ceftazidime/avibactam in a population that had ceftazidime-resistant pathogens. Although it found similar clinical cure rates between ceftazidime/avibactam and best available treatment, there was no statistical analyses to assess the significance these findings. Therefore there is limited efficacy data for the use of ceftazidime/avibactam in people with ceftazidime-resistant pathogens, particularly those with complicated intra-abdominal infection (8% included in REPRISE compared with 92% with complicated urinary tract infections). The [EPAR](#) states that although the efficacy results support the use of ceftazidime/avibactam for the treatment of ceftazidime-resistant pathogens in complicated urinary tract infection, due to high drug concentrations predicted in the urinary tract, it cannot necessarily be assumed that the same level of efficacy will be exerted at the other sites in the body.

There were no published RCT data for using ceftazidime/avibactam to treat hospital-acquired pneumonia or to treat aerobic gram-negative infections with limited treatment options and so the likely place of therapy for these 2 indications is unclear.

The safety profile of ceftazidime/avibactam generally reflects that already known for ceftazidime alone, however, it is not possible to draw any definitive conclusions regarding the possible effects of avibactam on the adverse event profile of ceftazidime (EPAR: ceftazidime/avibactam). In addition, it is not appropriate to compare adverse events frequencies between ceftazidime/avibactam and those of ceftazidime due to different ranges of doses used and the different indications they both cover. Safety data was limited to only people with complicated intra-abdominal and complicated urinary tract infections.

The acquisition cost of ceftazidime/avibactam is higher than other intravenous antimicrobials that are commonly used for complicated intra-abdominal infections, complicated urinary tract infections and hospital-acquired pneumonia.

Local decision makers need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of ceftazidime/avibactam for its licensed indications. The EPAR states that in a series of *in vitro* and *in vivo* studies, ceftazidime/avibactam was shown to be active against ceftazidime-resistant, and many carbapenem-resistant clinical isolates of *Enterobacteriaceae* and *P aeruginosa*. However, there is limited evidence that ceftazidime/avibactam is effective in treating people with ceftazidime-resistant pathogens. The EPAR also states that very few pathogens expressing serine carbapenemases have been treated with ceftazidime/avibactam.

Specialists involved in reviewing this evidence summary have suggested that ceftazidime/avibactam is likely to be a treatment option for complicated intra-abdominal infections and complicated urinary tract infections if a person's infection does not respond to commonly used antimicrobials and when there is known resistance to other antimicrobials. Use of ceftazidime/avibactam will need to be informed by understanding the mechanisms by which pathogens evolve to develop resistance.

Commissioners and local decision makers will need to consider where ceftazidime/avibactam fits within local (and national) antimicrobial prescribing guidelines for managing complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired pneumonia and treating infections due to aerobic gram-negative organisms in adults with limited treatment options, taking the principles of antimicrobial stewardship into account. As stated in the approved indications, consideration should be given to official guidance on the appropriate use of antibacterial agents. (See the [Relevance to other NICE programmes](#) section for links to NICE guidance on [antimicrobial stewardship](#)). 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, frequency 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.

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on [NHS Choices](#).

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's [good practice guidelines](#). These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to

decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other NICE programmes

The use of ceftazidime/avibactam 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 managing [pneumonia in adults](#) and has produced guidelines relating to antimicrobial stewardship:

- [Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#) (2015) NICE guideline (NG15)
- [Antimicrobial stewardship: changing risk-related behaviours in the general population](#) (2017) NICE guideline (NG63)
- NICE pathways on [pneumonia](#) and [antimicrobial stewardship](#) are also available. See also the NICE quality standards on [pneumonia in adults](#), [urinary tract infections in adults](#) and [antimicrobial stewardship](#). NICE guidance on [managing common infections](#) is being developed.

As well as guidance, NICE produces advice publications which do not constitute formal NICE guidance but critically appraise the evidence to help decision-making. A NICE key therapeutic topic [considers antimicrobial prescribing](#). Four NICE evidence summaries consider the use of other antimicrobials for the conditions included in this summary:

[ceftolozane/tazobactam for complicated intra-abdominal infections](#), [ceftolozane/tazobactam for complicated urinary tract infections](#), [fosfomycin trometamol for multidrug resistant urinary tract infections](#) and [telavancin for hospital-acquired pneumonia caused by methicillin-resistant *Staphylococcus aureus*](#).

References

Carmeli Y, Armstrong J, Laud PJ et al. (2016) [Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections \(REPRISE\): a randomised, pathogen-directed, phase 3 study](#). *The Lancet* 16 (6), 661–673

Mazuski JE, Gasink LB, Armstrong J et al. (2016) Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. *Clinical infectious disease* 62, 1380–1389

Wagenlehner FM, Sobel JD, Newell P et al. (2016) Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract Infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomised trial program. *Clinical infectious disease* 63 (6), 754–62

Evidence tables

Table 3 REPRISE

Study reference	Carmeli Y, Armstrong J, Laud PJ et al. (2016) Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant <i>Enterobacteriaceae</i> and <i>Pseudomonas aeruginosa</i> complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study . The Lancet 16 (6), 661–673
Unique identifier	NCT01644643 ,
Study type	Multicentre open-label randomised phase 3 trial.
Aim of the study	To assess the efficacy, safety and tolerability of ceftazidime/avibactam compared with BAT in adults with complicated urinary tract infection or complicated intra-abdominal infection due to ceftazidime-resistant gram-negative pathogens.
Study dates	January 2013 to September 2014
Setting	Hospital setting in 16 countries (excluding UK) ^a .
Number of participants	333 randomised, n=306 with cUTI and n=27 with cIAI.
Population	<p>Adults (45% female/55% male) aged 18 to 90 years with cUTI (92%) or cIAI (8%) caused by ceftazidime-resistant^b gram-negative pathogens.</p> <p>Approximately 80% had CrCl greater than 50 ml/min.</p> <p>Of the participants with diagnosed cUTI, 45% were acute pyelonephritis and 55% were without pyelonephritis.</p> <p>Of the participants with cIAI, 67% had an APACHE II score of 10 or less and 19% had an APACHE II score of 10 or more.</p> <p>Over half (52%) of the participants in the study had previous antimicrobial treatment (48% with cUTI and 100% with cIAI).</p> <p>The most common pathogens identified in cUTI and cIAI were <i>Enterobacteriaceae</i> pathogens, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i> and <i>Enterobacter cloacae</i>. <i>Pseudomonas aeruginosa</i> was also reported.</p>
Inclusion criteria	<p>Adults with cUTI had to have a positive urine culture in the 5 days prior to screening, containing 10⁵ CFU/mL or greater of at least 1 gram-negative uropathogen known to be ceftazidime-resistant^b (the isolate from the study-qualifying culture). Also, with either confirmed acute pyelonephritis or complicated lower urinary tract infection without pyelonephritis with predefined signs and symptoms and at least 1 complicating factor.</p> <p>Adults with cIAI had to have a ceftazidime-resistant^b gram-negative pathogen isolated from an abdominal source during a surgical intervention and specified signs and symptoms of cIAI. In addition to at least 1 of 8 specified diagnoses made during surgical intervention: cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gall bladder wall; diverticular disease with perforation or</p>

	<p>abscess; appendiceal perforation or peri-appendiceal abscess; acute gastric and duodenal perforations, only if operated on greater than 24 hours after perforation occurred; traumatic perforation of the intestines, only if operated on greater than 12 hours after perforation occurred; secondary or tertiary peritonitis; or intra-abdominal abscess.</p> <p>Adults with ongoing symptoms of either cUTI, pyelonephritis or cIAI at the time of screening and an isolated causative ceftazidime-resistant gram-negative pathogen could be included regardless of previous antimicrobial therapy if they had worsening of objective symptoms or signs of infection after 48 hours or longer of therapy, or absence of improvement after 72 hours or longer of therapy.</p>
Exclusion criteria	<p>For cUTI and cIAI, exclusion criteria included:</p> <ul style="list-style-type: none"> • estimated CrCl of less than 6 ml/min (Cockcroft-Gault formula) • evidence of abnormal liver function as defined by the study protocol • infection due to a gram-negative bacterial species that was unlikely to respond to ceftazidime/avibactam treatment • infection considered unlikely to respond to 5 to 21 days of study treatment. <p>Adults with cUTI were also excluded if they had: more than 2 pathogens isolated from the participant's study-qualifying urine culture, renal transplant, suspected or known complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, or prostatitis, or history of any illness that, could confound the results of the study or pose additional risk to the participant, or permanent urinary diversion or vesicoureteral reflux.</p> <p>Adults with cIAI were also excluded if they had an APACHE II score of greater than 30, or had: previously undergone a liver, pancreas, or small-bowel transplant, infections limited to the hollow viscus, acute suppurative cholangitis, infected necrotising pancreatitis, or pancreatic disease, abdominal wall abscess or small bowel obstruction without perforation, or ischaemic bowel without perforation, surgery requiring staged abdominal repair, or 'open abdomen' technique, or marsupialisation or history of serious allergy, hypersensitivity or any serious reaction to metronidazole.</p>
Intervention(s)	<p>For cUTI: ceftazidime/avibactam 2 g/0.5 g^c infusion administered over 2 hours, every 8 hours for 5 to 21 days.</p> <p>For cIAI: ceftazidime/avibactam 2 g/0.5 g^c infusion administered over 2 hours followed by metronidazole 500 mg infusion administered over 1 hour, both antimicrobials were given every 8 hours for 5 to 21 days.</p>
Comparator(s)	<p>Preferred BAT^d options for cUTI^e and cIAI^e were 5 to 21 days treatment with meropenem^f, imipenem^f, doripenem^g, colistin and for cIAI only tigecycline, administered intravenously, but any therapy including combination treatment was allowed.</p>

	<p>Other options used as monotherapy for cUTI included amikacin, ertapenem, ertapenem sodium, gentamicin and piperacillin/tazobactam.</p> <p>Any BAT regimens may have been with or without metronidazole</p>	
Length of follow-up	<p>Test-of-cure visit was 7 to 10 days after last infusion of study therapy.</p> <p>cUTI: 2 follow-up visits at 21 to 25 days (follow-up visit 1^h) and at 28 to 32 days (follow-up visit 2) from randomisation.</p> <p>clAI: 1 follow-up visit at 28 to 35 days from randomisation.</p>	
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> Clinical response (cureⁱ, failure^j or indeterminate^k) at test-of-cure^{l,m}. 	
	<p>Secondary outcomes^m:</p> <ul style="list-style-type: none"> Reasons for treatment change or discontinuation. 28-day all-cause mortality. 	
	<p>Safety outcomes:</p> <ul style="list-style-type: none"> Adverse events including severity, discontinuation of study drug and death. Laboratory parameters, including liver function tests, ECG, and vital signs checks and physical examinations. 	
Source of funding	AstraZeneca	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes ⁿ
	Were patients, health workers and study personnel blinded?	No ^o
	Were the groups similar at the start of the trial?	Yes
	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 table 6
	How precise was the estimate of the treatment effect?	See table 6
	Can the results be applied in your context? (or to the local population)	Unclear ^a
	Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See advice	
Study limitations	<ul style="list-style-type: none"> Open-label study. Majority of participants recruited from eastern Europe. Small numbers of participants with clAI in this study. No formal statistical comparisons between the intervention and comparator groups were made. 	

	<ul style="list-style-type: none"> The ceftazidime/avibactam renal dose adjustment protocol differed from the dose adjustments specified in the SPC for ceftazidime/avibactam.
Comments	<p>^a The study was mainly carried out in Eastern European adults (80% of randomised population).</p> <p>^b Ceftazidime-resistant isolates were defined as <i>Enterobacteriaceae</i> and <i>P aeruginosa</i> with susceptibility results that were intermediate or resistant using CLSI testing criteria or resistant using ECAS testing criteria. For <i>Enterobacteriaceae</i> and <i>P aeruginosa</i>, ceftazidime-resistance MIC were 8 mg/L or greater and 16 mg/L or greater, respectively.</p> <p>^c The dose of ceftazidime/avibactam was reduced in participants with moderate to severe renal impairment. The study used the following doses for participants with a: CrCl of 31 to 50 ml/min 1 g/0.25 g every 12 hours, CrCl of 16 to 30 ml/min 1 g/0.25 g every 24 hours and CrCl of 6 to 15 ml/min 0.5 g/0.125 g every 24 hours. The dose adjustments used in the study differ from that stated in the SPC for ceftazidime/avibactam.</p> <p>^d BAT was determined by the investigator on the basis of standard of care and local label recommendations.</p> <p>^e The most commonly prescribed antimicrobials used as BAT in participants with cUTI and cIAI were imipenem (50% and 33% respectively) and meropenem (37% and 60% respectively).</p> <p>^f For participants with cUTI, the most common total daily dose of imipenem was 1.5–4.0 g (84%), the most common total daily dose of meropenem was 1.5–3.0 g (95%), The common total daily dose of imipenem and meropenem used in participants with cIAI were not reported in the study.</p> <p>^g Doripenem is not available in the UK.</p> <p>^h Depending on the duration of the study drug therapy, follow-up 1 visit may have occurred prior to (or overlapped with) the test-of-cure visit.</p> <p>ⁱ Clinical cure was defined as complete resolution or substantial improvement of signs and symptoms of the index infection, such that no further antimicrobial therapy (other than those allowed per protocol) was necessary. Additionally for participants with cIAI, cure also required that no drainage or surgical intervention was needed after 96 hours from randomisation.</p> <p>^j Clinical failure was defined as: death related to the index infection, the requirement of treatment with additional antimicrobials (not included in the protocol or those discontinuing antimicrobials due to an adverse event) for ongoing symptoms of the index infection or when participants had previously met the criteria for failure following the end of treatment visit. Additionally for participants with cIAI, clinical failure was defined when there was persistent or recurrent infection within the abdomen documented by the findings of reintervention after 96 hours from randomisation or there were post-surgical wound infections defined as an open wound with signs of local infection, that required additional antimicrobial or non-routine wound care.</p> <p>^k Indeterminate findings were defined as study data not available for evaluation of efficacy for any reason.</p>

	<p>^l Analysed in the mMITT analysis set that included all the participants with cUTI or cIAI with at least 1 ceftazidime-resistant gram-negative pathogen and who received at least 1 dose of study medicine.</p> <p>^m The study did not conduct statistical analyses for any of the outcomes.</p> <p>ⁿ Randomisation codes were computer-generated using AstraZeneca global randomisation scheme.</p> <p>^o Participants and people administering treatment, assessing outcomes and analysing the data were not masked to group assignment.</p>
<p>Abbreviations: APACHE, Acute physiology and chronic health evaluation; BAT, best available therapy; CFU/mL, colony-forming units; cIAI, complicated intra-abdominal infection; CLSI, Clinical and laboratory standards institute; cUTI, complicated urinary tract infection; CrCl, creatinine clearance; ECAS, European committee on antimicrobial susceptibility; MIC, minimum inhibitory concentration; mMITT, microbiological modified intent-to-treat; SPC, summary product characteristics.</p>	

Table 4 RECLAIM 1 & 2

Study reference	Mazuski JE, Gasink LB, Armstrong J et al. (2016) Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program . Clinical infectious disease 62, 1380–1389
Unique identifier	NCT01499290
Study type	Two identical, prospective, randomised, multicentre, double-dummy, double-blind, comparative non-inferiority studies with pooled results.
Aim of the study	To evaluate the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in hospitalised adults with cIAI.
Study dates	March 2012 to April 2014
Setting	Hospital setting at 136 centres across 30 countries (excluding UK)a.
Number of participants	1066 randomised
Population	<p>Adults (37% female/63% male) aged 18 to 90 years (18 to 65 years in India) with cIAI diagnosed (with ceftazidime susceptible and –resistant pathogens) requiring surgical intervention or percutaneous drainage within 24 hours before or after randomisation. Approximately 90% of the participants had normal renal function or mild renal impairment (CrCl of 50 ml/min). Less than 10% of the participants had moderate renal impairment (CrCl between 30 to 50 ml/min).</p> <p>The majority of the participants included were of white origin (76%). Approximately 80% of the participants had an APACHE II score of 10 or less and the most common primary diagnosis was</p>

	<p>appendiceal perforation or periappendiceal abscess (approximately 40%).</p> <p>The most common pathogens isolated included Enterobacteriaceae pathogens (83%) and <i>Pseudomonas aeruginosa</i> was the most common frequently reported gram-negative pathogen (9%).</p> <p>Approximately 62% of the participants had received prior systemic antimicrobial therapy in the 72 hours before randomisation.</p>
Inclusion criteria	<p>Intra-operative/post-operative enrolment with visual confirmation of an intra-abdominal infection associated with peritonitis including at least 1 listed diagnosis during the surgical intervention as specified in the study protocol.</p> <p>Or</p> <p>Pre-operative enrolment with confirmation of infection by surgical intervention within 24 hours of study entry meeting the pre-specified clinical criteria as per study protocol.</p> <p>Participants who had previously received systemic antimicrobial therapy during the 72-hour period before study entry were included only if they had a new infection or were considered to have failed previous antimicrobial treatment.</p>
Exclusion criteria	<p>Key exclusion criteria included diagnosis of traumatic bowel perforation managed operatively within 12 hours; perforation of gastroduodenal ulcers managed operatively within 24 hours; intra-abdominal processes in which the primary cause was unlikely to be infectious; abdominal wall abscess, bowel obstruction, or ischemic bowel without perforation; simple cholecystitis or gangrenous cholecystitis without rupture; simple appendicitis; acute suppurative cholangitis; and infected necrotising pancreatitis or pancreatic abscess.</p> <p>Participants were also excluded if they had the following:</p> <ul style="list-style-type: none"> • estimated CrCl of 30 ml/min or less calculated by Cockcroft-Gault method. • abnormal liver function test and haematology results as defined by the study protocol • body mass index greater than 45 kg/m² • APACHE II score greater than 30.
Intervention(s)	Ceftazidime/avibactam 2 g/0.5 g infusion administered over 2 hours, every 8 hours followed by metronidazole 500 mg infusion administered over 1 hour every 8 hours for 5 to 14 days ^{b,c} .
Comparator(s)	Meropenem 1 g infusion administered over 30 minutes, every 8 hours for 5 to 14 days ^{c,d} .
Length of follow-up	Test-of-cure visit was between 28 to 35 days after randomisation and late follow-up visit was between 42 to 49 days after randomisation.
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Clinical cure^f at test-of-cure visit (assessed by non-inferiority of ceftazidime/avibactam plus metronidazole to meropenem).

	Other selected outcomes: <ul style="list-style-type: none"> • Clinical failure at test-of-cure visit. • Evaluation of the efficacy of ceftazidime/avibactam plus metronidazole or meropenem against ceftazidime-resistant pathogens. 	
	Safety outcomes: <ul style="list-style-type: none"> • Number of adverse events including severity, discontinuation and death. 	
Source of funding	AstraZeneca	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes
	Were patients, health workers and study personnel blinded?	Yes
	Were the groups similar at the start of the trial?	Yes
	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 table 7
	How precise was the estimate of the treatment effect?	See table 7
	Can the results be applied in your context? (or to the local population)	Unclear
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See advice
Study limitations	<ul style="list-style-type: none"> • Some participants were found to have sub-therapeutic doses of ceftazidime/avibactam administered to them based on their renal function after enrolment. The ceftazidime/avibactam renal dose adjustment protocol differed from the dose adjustments specified in the SPC for ceftazidime/avibactam. • More than 80% of participants had an APACHE II score of 10 or less. • Approximately 40% of the participants had cIAI with a primary diagnosis related to the appendix. 	
Comments	<p>a Study centres were based in the US, Asia, Canada, Europe, India, Middle East, South America and South Africa. The number of participants from each area was not reported in the study.</p> <p>b The dose of ceftazidime/avibactam was reduced to 1 g/0.25 g every 12 hours in participants with a CrCl of 31 to 50 ml/min. The SPC for ceftazidime/avibactam recommends a dose of 1 g/0.25 g, every 8 hours for participants with a CrCl of 31 to 50 ml/min.</p> <p>c After 5 or more full days of intravenous treatment, it could be discontinued if clinical improvement was shown.</p>	

	<p>d The dose of meropenem was reduced to 1 g every 12 hours in participants with a CrCl of 31 to 50 ml/min (in line with the SPC for meropenem).</p> <p>e Non inferiority of ceftazidime/avibactam plus metronidazole to meropenem was considered demonstrated if the lower limit of the 2 sided 95% CI around the treatment difference was greater than -12.5% (EMA) or greater than -10.0% (FDA). Assessed in the mMITT population (participants who met clinical disease criteria and had 1 or more pathogens identified at baseline) and the MITT population (participants who received study drug and met the clinical disease criteria) and verified in the CE population (the MITT population but with no deviation from the protocol).</p> <p>g Clinical failure was defined as any of the following: death related to cIAI, persisting or recurring abdominal infection, postsurgical wound infection requiring additional antimicrobials, ongoing cIAI symptoms requiring additional antimicrobials, or any previously met criteria for failure.</p> <p>f Defined as complete resolution or significant improvement of signs and symptoms of index infection such that no further antimicrobial therapy, drainage, or surgical intervention was necessary.</p> <p>h Based on CLSI break point-defined resistant and intermediate categories for ceftazidime, MIC 8 mg/L or more against Enterobacteriaceae and 16 mg/ or more against P aeruginosa.</p> <p>i Participants were randomised according to a central randomisation schedule, using a block size of 4. This method of randomisation suggests allocation was concealed.</p> <p>j Studies used non-UK settings and participants.</p>
<p>Abbreviations: APACHE, Acute physiology and chronic health evaluation; CE, clinically evaluable; EMA, European Medicines Agency; cIAI, complicated intra-abdominal infection; CLSI, Clinical and Laboratory Standards Institute; CrCl, creatinine clearance; FDA, Food and Drugs Administration; mMITT, microbiological modified intent-to-treat; MITT, modified intention-to-treat; SPC, summary of product characteristics.</p>	

Table 5 RECAPTURE 1 & 2

Study reference	Wagenlehner FM, Sobel JD, Newell P et al. (2016) Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract Infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomised trial program . Clinical infectious disease 63(6), 754–62
Unique identifier	NCT01599806 , NCT01595438
Study type	Two identical phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group non-inferiority studies with pooled results.
Aim of the study	To compare the efficacy and safety of ceftazidime/avibactam and doripenem ^a in people with cUTI including acute pyelonephritis.

Study dates	October 2012 to August 2014
Setting	Hospital setting at 160 centres across 25 countries ^b (non-UK).
Number of participants	1033 randomised
Population	<p>Adults (69% female/31% male) aged 18 to 90 years who had cUTI or acute pyelonephritis (with ceftazidime-susceptible and -resistant pathogens) considered by the investigator to be serious and requiring hospitalisation for intravenous antimicrobial therapy.</p> <p>Approximately 80% of the participants were of white origin. The most common diagnosis was pyelonephritis (72% of participants). Approximately 90% of the participants had a CrCl of 50 ml/min or more.</p> <p>Main pathogens present in the urine at baseline were <i>Enterobacteriaceae</i> pathogens (95%) of which approximately 74% were <i>Escherichia coli</i>. Nineteen percent were extended-spectrum beta-lactamase positive <i>Enterobacteriaceae</i>. Approximately 5% of the pathogens were <i>Pseudomonas aeruginosa</i>.</p> <p>Approximately 7% of the participants had received antimicrobial treatment before study entry.</p>
Inclusion criteria	<p>Participants with clinically suspected and/or bacteriologically documented cUTI^c or acute pyelonephritis^d considered by the investigator to be serious and requiring hospitalisation for IV antimicrobials. Diagnosis was based on positive urine cultures obtained within 48 hours of enrolment showing 1 to 2 gram-negative uropathogens at 10⁵ CFU/ml or more, and pyuria. Participants could be enrolled before cultures were available, providing that positive results were expected, the study medicines were considered appropriate empiric therapy, and a urine gram stain showed gram-negative bacilli and no gram-positive bacteria.</p> <p>Indwelling bladder catheters in place for more than 24 hours had to be removed or replaced (unless considered unsafe or contraindicated) before the baseline urine collection.</p>
Exclusion criteria	Key exclusion criteria included: participants with complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, or prostatitis; UTI symptoms potentially attributable to another process; urinary diversion or vesicoureteral reflux; CrCl of 30 ml/min or less (including people on dialysis).
Intervention(s)	<p>Ceftazidime/avibactam 2 g/0.5 g infusion administered as 2 concurrent 1 hour infusions every 8 hours^e.</p> <p>Participants meeting prespecified clinical improvement criteria (as specified in the study protocol) after 5 days or more of intravenous therapy could be switched to oral ciprofloxacin (500 mg every 12 hours) or sulfamethoxazole-trimethoprim (800 mg/160 mg every 12 hours) for those with a fluoroquinolone-resistant pathogen, administered approximately 8 hours after the last dose of intravenous treatment.</p>

	Total study treatment duration (intravenous plus optional oral therapy) was 10 days, or up to 14 days for participants with bacteraemia.	
Comparator(s)	<p>Doripenem^a 500 mg infusion administered over 1 hour (followed by a 1-hour matching placebo infusion to maintain blinding) every 8 hours^f.</p> <p>The same intravenous to oral antimicrobial switch protocol that applied to the intervention group was also allowed in the comparator group. The total study treatment duration was the same as in the intervention group.</p>	
Length of follow-up	Test-of-cure visit was 21 to 25 days after randomisation and late follow-up visit was 45 to 52 days after randomisation.	
Outcomes	<p>Primary outcomes (assessed by non-inferiority of ceftazidime/avibactam to doripenem^a)^g:</p> <ul style="list-style-type: none"> • FDA co-primary outcomes: patient-reported symptomatic resolution^h at day 5 and combined symptomatic resolution/microbiological eradicationⁱ at test-of-cure. • EMA outcome: per-patient favourable^j microbiological response at test-of-cure. 	
	<p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Per-patient favourable^j microbiological response in participants with ceftazidime-resistant^k pathogens at test-of-cure. • Clinical cure^l determined by the investigator at all test-of-cure. 	
	<p>Safety outcomes:</p> <ul style="list-style-type: none"> • Any adverse event, serious adverse events, adverse events leading to discontinuation of study drug or death. 	
Source of funding	AstraZeneca and Actavis plc.	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes ^m
	Were patients, health workers and study personnel blinded?	Yes ^m
	Were the groups similar at the start of the trial?	Yes
	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 table 8
	How precise was the estimate of the treatment effect?	See table 8
	Can the results be applied in your context? (or to the local population)	Unclear ^{a,b}
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See advice

Study limitations	<ul style="list-style-type: none"> • A validated questionnaire was not used to assess symptoms in cUTI. The PSAQ was based on a validated questionnaire for uncomplicated UTI. • Doripenem is not available in the UK, and was chosen as the comparator based on its efficacy in cUTI and the fact that other carbapenems were not approved for cUTI in all study regions. Doripenem was withdrawn in the European Economic Area in July 2014 for reasons related to its efficacy and safety in nosocomial pneumonia, but it remains available for the treatment of cUTI (including acute pyelonephritis) in the US and in various other countries. • The ceftazidime/avibactam renal dose adjustment in the study protocol differed from the dose adjustments specified in the SPC for ceftazidime/avibactam.
Comments	<p>^a Doripenem is not available in the UK.</p> <p>^b The study was mainly carried out in Eastern European adults (75% of randomised population).</p> <p>^c cUTI without pyelonephritis was defined as presence of 2 or more symptoms, including 1 or more urinary tract infection-specific symptom (dysuria, urgency, frequency, and suprapubic pain with onset/worsening within the previous 7 days) as well as 1 or more complicating factor.</p> <p>^d Acute pyelonephritis was indicated by flank pain with onset/worsening within the previous 7 days, and/or costovertebral angle tenderness, with fever and/or nausea/vomiting.</p> <p>^e The dose of ceftazidime/avibactam was reduced to 1 g/0.25 g every 12 hours in participants with a CrCl of 31 to 50 ml/min. The SPC for ceftazidime/avibactam recommends a dose of 1 g/0.25 g every 8 hours for people with a CrCl of 31 to 50 ml/min.</p> <p>^f The dose of doripenem^a was reduced to 250 mg every 8 hours in participants with a CrCl of 31 to 50 ml/min.</p> <p>^g Non inferiority of ceftazidime/avibactam to doripenem was considered demonstrated if the lower limit of the 2 sided 95% CI around the treatment difference was greater than –12.5% (EMA) or greater than –10.0% (FDA). Assessed in the mMITT population (all randomised participants with minimum disease criteria and eligible baseline pathogens) and results were verified in the ME and CE populations (both populations were similar in that the participants were those that were included in the mMITT population and had received 48 hours or more of the study treatment or received treatment for less than 48 hours if certain criteria listed in the protocol were met).</p> <p>^h Symptomatic resolution (or return to pre-morbid state) of UTI specific symptoms except flank pain with resolution or improvement in flank pain (based on PSAQ).</p> <p>ⁱ Microbiological eradication was defined when the urine culture taken within 48 hours prior to randomisation and compared with the culture from the test-of-cure visit (or other visits) showed less than 10⁴ CFU/ml of the original uropathogen, and the participant was not bacteraemic.</p>

	<p>^j Per-patient favourable microbiological response was defined as 'favourable' if there was eradication of the pathogen(s).</p> <p>^k Based on CLSI break points (range not provided by the study).</p> <p>^l Clinical cure was defined as improvement or resolution of all or most pre-therapy signs and symptoms of the index infection such that no additional antimicrobials (other than those specified in the study protocol) were required.</p> <p>^m Participants were randomised 1:1 using a computer-generated central randomisation code and an interactive voice/web response system. This method of randomisation suggests allocation was concealed.</p>
<p>Abbreviations: CE, clinically evaluable; CFU, colony forming unit; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; FDA, Food and Drugs Administration; IV, intravenous; PSAQ, patient-reported symptom assessment questionnaire; ME, microbiologically evaluable; mMITT, microbiological modified intent-to-treat; MIC, minimum inhibitory concentration</p>	

Results tables

Table 6 REPRISE ([Carmeli Y et al. 2016](#))

	Ceftazidime/ Avibactam (plus metronidazole for cIAI only)	Best available treatment^a	Analysis
N^b	154^c	148^d	
Primary outcome			
Overall number of participants with a clinical cure ^e at test-of-cure visit ^{f,g}	140/154 (91%, 95% CI 85.6% to 94.7%)	135/148 (91%, 95% CI 85.9% to 95.0%)	No formal statistical comparisons between treatment groups were conducted
Overall number of participants with treatment failure ^h at test-of-cure visit ^{f,i,j}	2/154 (1.3%)	2/148 (1.4%)	
Overall number of participants with an indeterminate response ^k at test-of-cure visit ^{f,i}	12/154 (7.8%)	11/148 (7.4%)	
Selected secondary outcomes			
Number of participants requiring a treatment change/discontinuation of the study drug ^l	11/154 (7.1%)	9/148 (6.1%)	No statistical analysis conducted
Number of participants with 28-day all-cause mortality	3/154 (1.9%)	4/148 (2.7%)	
Safety and tolerability outcomes			
n^m	164	168	
Number of participants with any adverse event	51/164 (31.1%)	66/168 (39.2%)	No statistical analysis conducted
Number of participants with a serious adverse event	9/164 (5.8%)	10/168 (5.9%)	
Number of participants discontinuing study drug due to adverse event	1/164 (0.6%)	2/168 (1.2%)	
	^a The most commonly prescribed antimicrobials used as BAT in participants with cUTI and cIAI were imipenem (50% and 33% respectively) and meropenem (37% and 60% respectively). ^b Out of the 333 participants randomised, 302 were eligible for inclusion in the mMITT population for efficacy analysis. The mMITT analysis set included all the participants with cUTI or		

	<p>cIAI with at least 1 ceftazidime-resistant gram negative pathogen and who received at least 1 dose of study drug</p> <p>^c Of the 154 participants in the treatment group, 94% (n=144) had cUTI and 6% (n=10) had cIAI.</p> <p>^d Of the 148 participants in the BAT group, 93% (n=137) had cUTI and 7% (n=11) had cIAI.</p> <p>^e Defined as complete resolution or substantial improvement of signs and symptoms of the index infection, such that no further antimicrobial therapy (other than those allowed per protocol) was necessary. Additionally for participants with cIAI, cure also required that no drainage or surgical intervention was needed after 96 hours from randomisation.</p> <p>^f Visit for the test-of-cure was 7 to 10 days after last infusion of study treatment.</p> <p>^g For participants with cUTI in the ceftazidime/avibactam group, 92% (95% CI 86.3% to 95.4%) had clinical cure at the test-of-cure compared with 94% (95% CI 89.3% to 97.2%) in the BAT group. For participants with cIAI 80% (95% CI 47.9% to 95.6%) of participants in the ceftazidime/avibactam group had clinical cure at the test-of-cure compared with 55% (95% CI 27.0% to 80.0%) in the BAT group.</p> <p>^h Clinical failure was defined as: death related to the index infection, the requirement of treatment with additional antimicrobials (not included in the protocol or those discontinuing antimicrobial treatments due to an adverse event) for ongoing symptoms of the index infection or when participants had previously met the criteria for failure following the end of treatment visit. Additionally for participants with cIAI, clinical failure was defined when there was persistent or recurrent infection within the abdomen documented by the findings of reintervention after 96 hours from randomisation or there were post-surgical wound infections defined as an open wound with signs of local infection, that required additional antimicrobials or non-routine wound care.</p> <p>ⁱ Results from EPAR for ceftazidime/avibactam</p> <p>^j For participants with cUTI in the ceftazidime/avibactam group, 1.4% had clinical failure at the test of cure compared with 1.5% in the BAT group. For participants with cIAI no clinical failure was reported.</p> <p>^k Indeterminate finding defined as study data not available for evaluation of efficacy for any reason.</p> <p>^l Nineteen participants with cUTI required a treatment change during the study period: 11 participants (7.6%) in the ceftazidime/avibactam group and 8 participants (5.8%) in the BAT group. Only 1 cIAI participant in the BAT group required a treatment change during the study period. The most common reason for a treatment change was a change in CrCl during the study.</p> <p>^m Safety analysis set (n=332) included all participants who received at least 1 dose of study medicine.</p>
	<p>Abbreviations: BAT, best available treatment; CI, confidence interval; cIAI, complicated intra-abdominal infection; cUTI,</p>

	complicated urinary tract infection; CrCl creatinine clearance; mMITT, microbiological modified intent-to-treat
--	---

Table 7 RECLAIM 1 & 2 (Mazuski JE et al. 2016)

	Ceftazidime/ avibactam plus metronidazole	Meropenem	Analysis
N^a	520	523	
Primary outcome			
Number of participants with clinical cure ^b at test-of-cure visit ^c	429/520 (82.5)	444/523 (84.9%)	Difference in clinical cure rate -2.4% (95% CI -6.90% to 2.10%) Ceftazidime/avibactam plus metronidazole was statistically non-inferior to meropenem ^{d,e}
Selected secondary outcomes			
Number of participants with clinical failure ^f at the test-of-cure visit ^c	47/520 (9%)	39/523 (7.4%)	Not reported
N^g	413	410	
Number of participants with ceftazidime-resistant pathogens with clinical cure at test-of-cure visit ^c	39/47 (83%)	55/64 (85.9%)	Difference in clinical cure rate -3.0% (95% CI -17.89% to 10.60%)
Safety and tolerability outcomes			
N^{h,i}	529	529	
Number of participants with any adverse event ^j	243/529 (45.9%)	227/529 (42.9%)	Not reported
Number of participants with any serious adverse event	42/529 (7.9%)	40/529 (7.6%)	
Number of participants with any adverse event leading to discontinuation	14/529 (2.7%)	7/529 (1.3%)	
Number of participants with any adverse event leading to death	13/529 (2.5%)	8/529 (1.5%)	
^a Of the 1066 randomised, 1043 participants were included in the MITT population which included participants who received the study treatment and met the clinical disease criteria.			

^b Defined as complete resolution or significant improvement of signs and symptoms of index infection such that no further antimicrobial therapy, drainage, or surgical intervention was necessary.

^c The test-of-cure visit was 28 to 35 days after randomisation.

^d The lower limit of the 95% CI is within the prespecified EMA non inferiority margin of -12.5%.

^e Non-inferiority was also shown for the CE population (MITT population with no protocol deviations), clinical cure rates at test of cure visit for ceftazidime/avibactam and meropenem were 92% (376/410) and 93% (385/416) respectively (difference -0.8%, 95% CI -4.61% to 2.89%).

^f Defined as death related to CIAI, persisting or recurring abdominal infection, postsurgical wound infection requiring additional antimicrobials, ongoing CIAI symptoms requiring additional antimicrobials, or any previously met criteria for failure.

^g Analysis carried out in the mMITT population which included participants with 1 or more ceftazidime-resistant gram-negative pathogen (n=823).

^h Analysed in the safety population (n=1058) that included participants who had received 1 or more dose of the study drug. Safety data were assessed from time of consent up to and including the late follow-up visit (42 to 49 days after randomisation).

ⁱ Participants with multiple adverse events were counted once for each system organ class or preferred term.

^j Each participant is counted only once within a treatment group in the overall summary.

Abbreviations: CIAI, complicated intra-abdominal infection; mMITT, microbiologically modified intention to treat; MITT, modified intention-to-treat; CE, clinically evaluable; EMA, European Medicines Agency; CI, confidence interval

Table 8 RECAPTURE 1 & 2 ([Wagenlehner FM et al. 2016](#))

	Ceftazidime/ Avibactam	Doripenem	Analysis
N^a	393	417	
Primary outcomes			
Number of participants with per-patient favourable microbiological response ^b at test-of-cure ^c	304/393 (77.4%)	296/417 (70.9%)	Difference 6.4% (95% CI 0.33% to 12.36%) Ceftazidime/avibactam was statistically non-inferior to doripenem ^{d,e}
Number of participants with patient-assessed symptom resolution ^f from baseline (or return to	276/393 (70.2%)	276/417 (66.2%)	Difference 4% (95% CI -2.39% to 10.42%) Statistical non-inferiority shown ^{d,e}

premorbid state) at day 5			
Combined patient-assessed symptomatic resolution (or return to premorbid state) and microbiological eradication ^b at test of cure ^c	280/393 (71.2%)	269/417 (64.5%)	Difference 6.7% (95% CI 0.30% to 13.12%) Statistical non inferiority shown ^{d,e}
Selected secondary outcomes			
Per-patient favourable microbiological response ^b at test-of-cure ^c in participants with a ceftazidime-resistant pathogen	47/75 (62.7%)	51/84 ^g (60.7%)	Difference 2.0% (95% CI -13.18% to 16.89%)
Investigator-determined clinical cure ^h at test-of-cure ^c	355/393 (90.3%)	377/417 (90.4%)	Difference -0.1% (95% CI -4.23% to 4.03%)
Safety and tolerability outcomes			
Nⁱ	511	509	
Any adverse event	185/511 (36.2%)	158/509 (31%)	Not reported
Adverse event with an outcome of death	0	0	
Serious adverse event	21/511 (4.1%)	12/509 (2.4%)	
Adverse event leading to discontinuation of study drug	7/511 (1.4%)	6/509 (1.2%)	
<p>^a Of the 1033 randomised, 810 participants were included in the mMITT population that included all participants with a confirmed cUTI diagnosis and a positive study entry urine culture defined as 10⁵ CFU/ml or more of a gram-negative pathogen and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count.</p> <p>^b Defined as eradication of the pathogen(s) with urine culture showing less than 10⁴ CFU/ml of the original uropathogen when the urine culture taken within 48 hours prior to randomisation was compared with the culture from the test-of-cure visit and the participant was not bacteraemic.</p> <p>^c Test of cure visit was 21 to 25 days after randomisation.</p>			

^d The lower limit of the 95% CI is within the prespecified EMA non-inferiority margin of -12.5% and FDA non-inferiority margin of -10.0%.

^e Data was not available to include results of the primary outcomes from the ME and CE populations to verify the non-inferiority of ceftazidime/avibactam to doripenem.

^f Symptomatic resolution of UTI-specific symptoms except flank pain with resolution or improvement in flank pain from baseline at day 5 visit (based on the PSAQ).

^g One participant in the doripenem group had 2 ceftazidime-resistant pathogens isolated at baseline.

^h Clinical cure was defined as improvement or resolution of all or most pre-therapy signs and symptoms of the index infection such that no additional antimicrobials (other than those specified in the study protocol) were required.

ⁱ Analysed in the safety analysis population set (n=1020) that included participants who received any amount of study medicine.

Abbreviations: CE, clinically evaluable; CFU, colony forming units; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; FDA, Food and Drugs Administration; ME, microbiologically evaluable; mMITT, microbiological modified intent-to-treat; PSAQ, patient-reported symptom assessment questionnaire.

Excluded studies

Study reference	Reason for exclusion
Buckman SA et al. (2016) Ceftazidime-avibactam for the treatment of complicated intra-abdominal infections Expert Opinion Pharmacotherapy. Dec17 (17), 2341–2349	Not a relevant study
Lucasti C et al. (2013) Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial. The journal of antimicrobial chemotherapy 68, 1183–92	Study not prioritised (not the best available evidence: phase II dose-finding study).
Qin X et al. (2017) A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. International Journal of Antimicrobial Agents 49, 579–588	Study not prioritised (not the best available evidence: based on population origin and number of participants in study).
Sader HS et al. (2015) Ceftazidime/avibactam tested against gram-negative bacteria from intensive care unit (ICU) and non-ICU patients, including those with ventilator-associated pneumonia. International Journal of Antimicrobial Agents 46, 53–59	Poor relevance against search terms
Sharma et al. Ceftazidime-Avibactam: A Novel Cephalosporin/ β -Lactamase Inhibitor Combination for the Treatment of Resistant Gram-negative Organisms. Clinical Therapeutics. 2016 Mar 38(3), 431–44	Not a relevant study
Temkin E et al. (2017) Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrobial Agents and Chemotherapy 61(2)	Study not prioritised (not the best available evidence: phase II dose-finding study).
Vazquez J A et al. (2012) Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: Results of a prospective, investigator-blinded, randomized study. Current Medical Research and Opinion 28, 1921–1931	Study not prioritised (not the best available evidence: case series study).

Terms used in this evidence summary

Acute Physiology and Chronic Health Evaluation (APACHE) II score

This is a scoring system (scale of 0 to 71) that uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. Lower scores are better ([Knaus et al. 1985](#)).

Search strategy

Database: Medline

Platform: Ovid

Version: 1946 to May Week 1 2017

Search date: 12/05/17

Number of results retrieved: 43

Search strategy:

-
- 1 ceftazidime.tw. (7162)
 - 2 Ceftazidime/ (3529)
 - 3 1 or 2 (7788)
 - 4 avibactam.tw. (168)
 - 5 3 and 4 (123)
 - 6 ceftazidime-avibactam.tw. (101)
 - 7 zavicefta.tw. (0)
 - 8 avycaz.tw. (3)
 - 9 (ctz-avi or caz-avi).tw. (2)
 - 10 or/5-9 (123)
 - 11 Randomized Controlled Trial.pt. (461944)
 - 12 Controlled Clinical Trial.pt. (94024)
 - 13 Clinical Trial.pt. (520955)
 - 14 exp Clinical Trials as Topic/ (312693)
 - 15 Placebos/ (34925)
 - 16 Random Allocation/ (92524)
 - 17 Double-Blind Method/ (146986)
 - 18 Single-Blind Method/ (24505)
 - 19 Cross-Over Studies/ (42069)
 - 20 ((random\$ or control\$ or clinical\$) adj3 (trial\$ or stud\$)).tw. (912214)
 - 21 (random\$ adj3 allocat\$).tw. (25676)
 - 22 placebo\$.tw. (178301)
 - 23 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw. (144088)
 - 24 (crossover\$ or (cross adj over\$)).tw. (66058)
 - 25 or/11-24 (1633940)
 - 26 animals/ not humans/ (4363829)
 - 27 25 not 26 (1522910)
 - 28 Observational Studies as Topic/ (2192)
 - 29 Observational Study/ (35803)
 - 30 Epidemiologic Studies/ (7573)
 - 31 exp Case-Control Studies/ (869940)
 - 32 exp Cohort Studies/ (1680942)
 - 33 Cross-Sectional Studies/ (245173)
 - 34 Controlled Before-After Studies/ (238)
 - 35 Historically Controlled Study/ (114)
 - 36 Interrupted Time Series Analysis/ (268)
 - 37 Comparative Study.pt. (1809371)
 - 38 case control\$.tw. (94094)
 - 39 case series.tw. (44604)
 - 40 (cohort adj (study or studies)).tw. (116094)
 - 41 cohort analy\$.tw. (4782)
 - 42 (follow up adj (study or studies)).tw. (41062)
 - 43 (observational adj (study or studies)).tw. (60099)
 - 44 longitudinal.tw. (163437)
 - 45 prospective.tw. (414348)

- 46 retrospective.tw. (338628)
- 47 cross sectional.tw. (209980)
- 48 or/28-47 (3844156)
- 49 ("phase 3" or "phase three").tw. (8825)
- 50 25 or 48 or 49 (4825341)
- 51 10 and 50 (43)
- 52 limit 51 to english language (43)

Database: Medline in-process

Platform: Ovid

Version: May 11, 2017

Search date: 12/05/17

Number of results retrieved: 16

Search strategy:

-
- 1 ceftazidime.tw. (575)
 - 2 Ceftazidime/ (0)
 - 3 1 or 2 (575)
 - 4 avibactam.tw. (85)
 - 5 3 and 4 (71)
 - 6 ceftazidime-avibactam.tw. (63)
 - 7 zavicefta.tw. (1)
 - 8 avycaz.tw. (1)
 - 9 (ctz-avi or caz-avi).tw. (4)
 - 10 or/5-9 (72)

Database: Medline epubs ahead of print

Platform: Ovid

Version: May 11, 2017

Search date: 12/05/17

Number of results retrieved: 6

Search strategy:

-
- 1 ceftazidime.tw. (99)
 - 2 Ceftazidime/ (0)
 - 3 1 or 2 (99)
 - 4 avibactam.tw. (22)
 - 5 3 and 4 (20)
 - 6 ceftazidime-avibactam.tw. (19)
 - 7 zavicefta.tw. (0)
 - 8 avycaz.tw. (0)
 - 9 (ctz-avi or caz-avi).tw. (2)
 - 10 or/5-9 (20)

Database: Embase

Platform: Ovid

Version: 1974 to 2017 Week 19

Search date: 12/05/17

Number of results retrieved: 89

Search strategy:

-
- 1 ceftazidime.tw. (10355)
 - 2 ceftazidime/ (34747)
 - 3 1 or 2 (35823)

- 4 avibactam.tw. (277)
- 5 avibactam/ (290)
- 6 4 or 5 (409)
- 7 3 and 6 (275)
- 8 ceftazidime-avibactam.tw. (179)
- 9 zavicefta.tw. (2)
- 10 avycaz.tw. (27)
- 11 (ctz-avi or caz-avi).tw. (17)
- 12 or/7-11 (289)
- 13 exp Clinical Trials/ (227995)
- 14 Randomization/ (73182)
- 15 Placebo/ (303875)
- 16 Double Blind Procedure/ (137212)
- 17 Single Blind Procedure/ (26443)
- 18 Crossover Procedure/ (50734)
- 19 ((random\$ or control\$ or clinical\$) adj3 (trial\$ or stud\$)).tw. (1321927)
- 20 (random\$ adj3 allocat\$).tw. (34370)
- 21 placebo\$.tw. (252215)
- 22 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw. (198633)
- 23 (crossover\$ or (cross adj over\$)).tw. (86988)
- 24 or/13-23 (1772523)
- 25 nonhuman/ not human/ (3903193)
- 26 24 not 25 (1704126)
- 27 Clinical study/ (148433)
- 28 Case control study/ (110682)
- 29 Family study/ (21388)
- 30 Longitudinal study/ (97176)
- 31 Retrospective study/ (522626)
- 32 comparative study/ (737349)
- 33 Prospective study/ (368958)
- 34 Randomized controlled trials/ (120082)
- 35 33 not 34 (365490)
- 36 Cohort analysis/ (284866)
- 37 cohort analy\$.tw. (8132)
- 38 (Cohort adj (study or studies)).tw. (186209)
- 39 (Case control\$ adj (study or studies)).tw. (104923)
- 40 (follow up adj (study or studies)).tw. (54351)
- 41 (observational adj (study or studies)).tw. (105453)
- 42 (epidemiologic\$ adj (study or studies)).tw. (90231)
- 43 (cross sectional adj (study or studies)).tw. (137181)
- 44 case series.tw. (69040)
- 45 prospective.tw. (641112)
- 46 retrospective.tw. (592822)
- 47 or/27-32,35-46 (2932973)
- 48 ("phase 3" or "phase three").tw. (22024)
- 49 26 or 47 or 48 (4149473)
- 50 12 and 49 (91)
- 51 limit 50 to english language (89)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley

Version:

CDSR – 4 of 12, April 2017

DARE – 2 of 4, April 2015 (legacy database)

CENTRAL – 4 of 12, April 2017

HTA – 4 of 4, October 2016

NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 12/05/17

Number of results retrieved: CDSR 0 ; DARE 0 ; CENTRAL 23 ; HTA 0 ; NHS EED 0.

Search strategy:

#1	ceftazidime:ti,ab	761
#2	[mh ceftazidime]	414
#3	{or #1-#2}	787
#4	avibactam:ti,ab	24
#5	#3 and #4	23
#6	ceftazidime-avibactam:ti,ab	23
#7	zavicefta:ti,ab	0
#8	avycaz:ti,ab	0
#9	(ctz-avi or caz-avi):ti,ab	0
#10	{or #5-#9}	23

Development of this evidence summary – antimicrobial prescribing

The [evidence summary: process guide](#) (2017) 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

Professor Mark H. Wilcox, Professor of Medical Microbiology & Consultant Microbiologist, Leeds Teaching Hospitals & University of Leeds

David Ladenheim, Pharmaceutical Adviser, East and Northern Hertfordshire Clinical Commissioning Group

Dr Matthew Dryden, Consultant Microbiologist and Infection Specialist, Hampshire Hospitals NHS Foundation Trust

Declarations of interest

Professor Mark H. Wilcox has received consulting fees from Abbott Laboratories, Actelion, Aicuris, Astellas, Astra-Zeneca, Bayer, Biomérieux, Cambimune, Cerexa, Da Volterra, The European Tissue Symposium, The Medicines Company, MedImmune, Merck, Meridian, Motif Biosciences, Nabriva, Paratek, Pfizer, Qiagen, Roche, Sanofi-Pasteur, Seres, Summit, Synthetic Biologics and Valneva; lecture fees from Abbott, Alere, Allergan, Astellas, Astra-Zeneca, Merck, Pfizer & Roche; and grant support from Abbott, Actelion, Astellas, Biomérieux, Cubist, Da Volterra, MicroPharm, Morphochem AG, Sanofi-Pasteur, Seres, Summit and The European Tissue Symposium, Merck.

David Ladenheim attended a free Eumedita sponsored event, East of England Antimicrobial Pharmacists Network

Dr Matthew Dryden: consulting or lecture honoraria from Bayer, Wyeth, Janssen-Cilag, Pfizer, AstraZeneca, Cubist, Merck and Motif Bio; investigator

on antibiotic trials for Bayer, Pfizer, Basilea, Wyeth, AstraZeneca and Merck.

No advisory board or trials were related to ceftazidime/avibactam

About this evidence summary – antimicrobial prescribing

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.