NICE Guidance – Complicated urinary tract infections: ceftolozane/tazobactam

Full Evidence Summary

Introduction and Current Guidance

Urinary tract infection is a non-specific term that refers to infection anywhere in the urinary tract, from the urethra to the bladder and the ureters to the kidneys (Frassetto 2015). According to the European Association of Urology Guidelines on urological infections (http://uroweb.org/guideline/urological-infections/?type=archive), complicated urinary tract infections 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
- urinary obstruction (such as stones or tumour)
- anatomical abnormalities
- peri- and post-operative urinary tract infection, including renal transplantation.

Pyelonephritis is 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 in an immunocompetent person with a normal urinary tract anatomy and kidney function. As for urinary tract infections generally, acute pyelonephritis is considered to be complicated in people with increased susceptibility, for example: children or older people; people with functional or structural abnormalities of the genitourinary tract or people who are immunocompromised, such that the infection is more likely to be severe. However, most episodes are uncomplicated and are cured with no residual renal damage (Frassetto 2015). Complicated urinary tract infections are a frequent cause of hospital admissions and a common healthcare associated complication. The pathogens most commonly encountered in complicated urinary tract infections are the gram-negative bacteria *Escherichia coli*, other common Enterobacteriaceae (for example, *Proteus* spp., *Klebsiella* spp. or *Citrobacter* spp.) and *Pseudomonas* spp. Successful treatment has become increasingly more challenging because the majority of pathogens responsible for healthcare associated complicated urinary tract infections, including catheter-related infections, are now commonly resistant to multiple antimicrobial agents (European public assessment report [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003772/human_med_001917.jsp&mid=WC0b01ac058001d124]).

The English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2015) (https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report) found that, overall, antibiotic resistant infections continue to increase. Notably, the rate of *E. coli* and *Klebsiella pneumoniae* bloodstream infections increased by 15.6% and 20.8% respectively from 2010 to 2014. Urinary tract infections are most commonly caused by *E. coli* (recorded in more than half of all the mandatory surveillance reports for *E. coli* bacteraemia when foci of infection are reported). The data indicate that 97% of *E. coli* isolates for urinary tract infection from GP practices, other community sources (such as care homes and outpatient clinics) and acute trusts were susceptible to nitrofurantoin. Resistance to trimethoprim was seen in over a third (35–37%) of isolates and resistance to amoxicillin was seen in over 50% of isolates, in all 3 settings. It is unclear if these data include cases of complicated urinary tract infections. Also, specialists involved in the production of this evidence summary noted that the results could be prone to bias because samples may have been be submitted from a population with a higher likelihood of antimicrobial resistance caused by, for example, failed treatments, recurrent infection or repeated courses of antibiotics.

Risk factors for resistance should be taken into consideration before prescribing antibiotics for urinary tract infection according to Public Health England guidance for primary

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care on managing common infections (https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care).

As well as some other groups, Public Health England advises performing culture and sensitivity testing in people with a higher risk of recurrent urinary tract infection (such as those aged over 65 years or with urinary catheters), and people with abnormalities of the genitourinary tract or suspected pyelonephritis.

The management of suspected community-acquired bacterial urinary tract infection in adults aged 16 years and over is covered in the NICE quality standard on urinary tract infection in adults (https://www.nice.org.uk/guidance/qs90). This includes women who are pregnant, people with indwelling catheters and people with other diseases or medical conditions such as diabetes. The guidance was developed to contribute to a reduction in emergency admissions for acute conditions that should not usually require hospital admission, and improvements in health-related quality of life. It does not make any recommendations around antibiotic treatment of complicated urinary tract infection, but includes 7 statements that describe high-quality care for adults with urinary tract infection.

This evidence summary outlines the best available evidence for a new antimicrobial that is licensed for complicated urinary tract infections and acute pyelonephritis, ceftolozane/tazobactam. Ceftolozane/tazobactam was developed to address antimicrobial resistance in serious infections caused by gram-negative pathogens (Wagenlehner et al. 2015).

Product Overview

Drug Action

Zerbaxa powder for concentrate for solution for infusion (http://www.medicines.org.uk/emc/medicine/31132) contains ceftolozane and tazobactam. Ceftolozane is a new cephalosporin antibiotic. Like other cephalosporins, it binds to penicillin-binding proteins, resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death. Tazobactam is an established beta-lactamase inhibitor, which can protect ceftolozane from hydrolysis by some beta-lactamases, broadening its spectrum to include most beta-lactamase producing *E. coli*, *K. pneumoniae,* and other Enterobacteriaceae (European public assessment report).

Licensed Therapeutic Indication

Ceftolozane/tazobactam (Zerbaxa) received a marketing authorisation in September 2015 and was launched in the UK in November 2015. It is indicated for the treatment of complicated intra-abdominal infections, acute pyelonephritis and complicated urinary tract infections in adults. The summary of product characteristics (http://www.medicines.org.uk/emc/medicine/31132) states that consideration should be given to official guidance on the appropriate use of antibacterial agents.

Evidence for using this product for complicated intra-abdominal infections is outlined in another evidence summary (https://www.nice.org.uk/guidance/esnm75).

Course and Cost

Each vial of Zerbaxa contains ceftolozane 1 g and tazobactam 0.5 g. For people with acute pyelonephritis and complicated urinary tract infections and creatinine clearance of more than 50 ml/min, the recommended dose is 1 g ceftolozane/0.5 g tazobactam administered intravenously over 1 hour every 8 hours for 7 days. Lower doses should be used for people with moderate or severe renal disease or end stage renal failure. See the summary of product characteristics for more information.

Each vial of 1.0 g ceftolozane/0.5 g tazobactam costs £67.03 (MIMS, April 2016). Therefore, the cost of a course of treatment is £1,407.63, excluding VAT, any procurement discounts and administration costs.

Evidence Review

This evidence summary is based on the key phase III licensing study for ceftolozane/tazobactam for complicated urinary tract infections, including acute pyelonephritis (ASPECT-cUTI). Information from the European public assessment report (EPAR) for ceftolozane/tazobactam has been used to clarify and supplement data from the published study included in this evidence summary.

ASPECT-cUTI (Wagenlehner et al. 2015)

- Design: The study was a prospective, randomised, double-blind, double-dummy, controlled non-inferiority trial, which was undertaken in 135 centres worldwide (EPAR: 75% Europe).
- Population: It included 1,083 hospitalised adults (mean age 49 years, 85.8% white) with clinical evidence of acute pyelonephritis (82.0%) or complicated lower urinary tract infections (18.0%), who had been admitted to hospital for IV antibiotic therapy and had a pre-treatment baseline urine culture specimen obtained within 36 hours before the first dose of the study drug. Pyelonephritis was defined by the presence of 2 or more of the following symptoms: fever accompanied by rigors, chills or warmth; flank pain; costovertebral angle or suprapubic tenderness on physical examination; or nausea or vomiting. Complicated lower urinary tract infections included all these symptoms plus

suprapubic pain, dysuria, urinary frequency or urgency, and at least 1 of the following: male with urinary retention, indwelling urinary catheter, current obstructive uropathy, or any functional or anatomical urogenital tract abnormality. Exclusions included participants with concomitant infections that required treatment with non-study antibacterial agents that had gram-negative activity, or an infection at baseline that the investigator determined would require more than a 7-day course of treatment. Participants with underlying immune-compromising illnesses or those on immunosuppressant therapies were also excluded, as were participants with severe or rapidly progressing disease such as septic shock, and those not expected to survive the 4 to 5 week study period. People with severe renal impairment (creatinine clearance less than 30 ml/min) and significant laboratory abnormalities were also excluded (EPAR). At baseline, 34.3% of participants had mild or moderate renal impairment and 24.9% were 65 years or older. Most of the 7.8% cases of bacteraemia were caused by *E. coli* and were identified in participants with pyelonephritis. The most common gram-negative bacteria isolated at baseline were *E. coli* (about 79%) *K. pneumoniae* (about 7%), and *P. mirabilis* and *P. aeruginosa* (both about 3%). About 97% of infections were monomicrobial and the rate of beta-lactamase producing Enterobacteriaceae was about 15%.

- Intervention and comparator: Participants were randomised 1:1 to receive IV ceftolozane/tazobactam 1 g/0.5 g (n=543) every 8 hours or IV levofloxacin 750 mg (n=540) once daily and IV saline (placebo) twice daily (as a double-dummy) for 7 days. The doses of ceftolozane/tazobactam and levofloxacin were reduced in people with renal impairment (creatinine clearance of 50 ml/min or less). All participants received study drugs before the urine culture results were known because they were not typically available until day 3. If the results showed resistance to 1 or both study drugs, investigators could modify treatment by stopping the study drug or by adding or replacing it with a non-study antibiotic, decided on the basis of the patient's clinical response. Although not explicitly stated by the author, the methods suggest that allocation was concealed. Baseline demographic characteristics were similar between the treatment groups.
- Outcomes: Clinical outcomes were assessed at the test-of-cure visit (5 to 9 days after the last dose of study drug) and the late follow-up visit (21 to 42 days after the end of study treatment). Clinical cure was defined as complete resolution, substantial improvement or return to pre-infection signs and symptoms of the index infection, without the need for additional antibiotics. Clinical failure was defined as the presence of 1 or more signs or symptoms of complicated lower urinary tract infection or pyelonephritis requiring additional antibiotics, or an adverse event leading to premature discontinuation of the study drug and the starting of additional antibiotic therapy. Microbiological eradication was defined as a test-of-cure urine culture with fewer than 10^4 colony-forming units per ml of the baseline pathogen. The primary outcome was composite cure, defined as achieving clinical cure and microbiological eradication of all baseline uropathogens. The modified intention-to-treat (MITT) population was defined as all randomised participants who received at least 1 dose of study drug. The microbiological MITT (mMITT) population was defined as all randomised participants in the MITT with growth of 1 or 2 baseline pathogens (of at least 10^5 colony-forming units per ml in the urine culture) analyses. The per-protocol (PP) population included all randomised participants in the mMITT population who adhered to the treatment protocol and had a clinical assessment and interpretable urine culture at the test-of-cure visit 5 to 9 days after the last dose of study drug. Participants with missing clinical outcome data or indeterminate responses were considered to have failed treatment in the mMITT analyses. However, they were excluded from the PP analyses. The primary objective of the study was to demonstrate non-inferiority of ceftolozane/tazobactam compared with levofloxacin in terms of the difference in composite cure rates (defined as clinical cure and microbiological eradication of all baseline uropathogens) at the test-of-cure visit in the mMITT population. Non-inferiority was considered proven if the lower limit of the 95% confidence interval (CI) for the difference between the study treatments was more than −10%. This was also tested in the PP population as a secondary outcome. Although superiority was not pre-specified as a secondary outcome, it was considered proven if the lower limit of the 95% CI for the difference between the study treatments was more than 0%. Microbiological outcomes and safety and tolerability were also assessed (Wagenlehner et al. 2015).

Clinical Effectiveness

In the ASPECT-cUTI study, in the microbiological intention-to-treat (mMITT) and per-protocol (PP) populations, ceftolozane/tazobactam was non-inferior to levofloxacin in terms of composite cure at the test-of cure visit, 5 to 9 days after the last dose of study drug. In the mMITT population the composite cure rate was 76.9% in the ceftolozane/tazobactam group compared with 68.4% in the levofloxacin group (treatment difference 8.5% 95% CI 2.3% to 14.6%: the primary outcome) and this was comparable in the PP population (83.3% compared with 75.4% for ceftolozane/tazobactam and levofloxacin respectively, treatment difference 8.0% 95% CI 2.0% to 14.0%: secondary outcome). Ceftolozane/tazobactam was also found to be statistically significantly superior to levofloxacin for composite cure in

Table 1 Summary of ASPECT-cUTI

	Ceftolozane/tazobactam	Levofloxacin	Analysis
Randomised	n=543	n=540	
Efficacy (mMITT)[a]	n=398	n=402	
Primary outcome: composite cure at test-of-cure visit[b]	76.9% (306/398)	68.4% (275/402)	Treatment difference 8.5% 95% CI 2.3% to 14.6% Ceftolozane/tazobactam was statistically non-inferior to levofloxacin[c]
Selected secondary outcomes:			
Composite cure at test-of-cure visit[b] in the PP[d] population	83.3% (284/341)	75.4% (266/353)	Treatment difference 8.0% 95% CI 2.0 to 14.0 Statistical non-inferiority[c] and superiority[e] shown
Microbiological eradication at test-of-cure visit[b] in the mMITT[a] population	80.4% (320/398)	72.1% (290/402)	Treatment difference 8.3% 95% CI 2.4% to 14.1%
Microbiological eradication at test-of-cure visit[b] in the PP[d] population	86.2% (294/341)	77.6% (274/353)	Treatment difference 8.6% 95% CI 2.9% to 14.3%
Clinical cure at test-of-cure visit[b] in the mMITT[a] population	92.0% (366/398)	88.6% (356/402)	Treatment difference 3.4% 95% CI −0.7% to 7.6% Not statistically significant
Clinical cure at test-of-cure visit[b] in the PP[d] population	95.9% (327/341)	93.2% (329/353)	Treatment difference 2.7% 95% CI −0.8% to 6.2% Not statistically significant
Safety[f]	n=533	n=535	
Patients reporting treatment-emergent adverse events	34.7% (185/533)	34.4% (184/535)	Descriptive data reported. Statistical analysis not undertaken
Patients reporting serious adverse events	2.8% (15/533)[g]	3.4% (18/535)	Descriptive data reported. Statistical analysis not undertaken
Deaths reported[h]	<0.2% (1/533)	none reported	Descriptive data reported. Statistical analysis not undertaken

CI, confidence interval; mMITT, microbiological modified intention-to-treat; PP, per-protocol population. [a]The mMITT population includes all randomised participants in the modified intention-to-treat population with growth of 1 or 2 baseline pathogens of at least 10^5 colony-forming units per ml in the urine culture. [b]5 to 9 days after the last dose of study drug. [c]The lower limit of the 95% CI is within the pre-specified non-inferiority margin of −10%. [d]The PP population includes all randomised participants who received at least 1 dose of study treatment, adhered to the treatment protocol and had a clinical assessment and interpretable urine culture at the test-of-cure. [e]The lower limit of the 95% CI was more than 0% in both the primary and key secondary analysis populations, and the treatment difference was positive, indicating superiority of ceftolozane/tazobactam over levofloxacin. [f]The safety population includes all participants who received at least 1 dose of the study drug. One patient randomised to ceftolozane/tazobactam actually received levofloxacin and was included in the levofloxacin group for all safety analyses. [g]Including 2 patients with C. difficile infection which was deemed to be related to study treatment. [h]Bladder cancer which was considered unrelated to study treatment.

both populations, although the clinical relevance of this difference between the groups is unclear. See Table 1 for more details.

In the mMITT population, the clinical cure rates were 92.0% and 88.6% with ceftolozane/tazobactam and levofloxacin respectively (treatment difference 3.4%, 95% CI −0.7% to 7.6%), with no statistically significantly difference between the groups. The results were consistent in the PP population and in analyses at the late follow up visit (21 to 42 days after the last dose of study treatment).

Ceftolozane/tazobactam was found to be statistically significantly better than levofloxacin for microbiological eradication (see Table 1 for more details). However, baseline susceptibility testing to study drugs showed that in the mMITT population, 2.7% of gram-negative pathogens at baseline were resistant to ceftolozane/tazobactam, whereas 26.7% were resistant to levofloxacin (of which 0.3% and 24.2% respectively were *E. coli* isolates). When individual baseline pathogens were assessed at the test-of-cure visit, microbiological eradication rates for gram-negative bacteria were statistically significantly higher in the ceftolozane/tazobactam group than the levofloxacin group, reflecting the level of baseline resistance to levofloxacin. In the PP population, the most commonly isolated pathogen was *E. coli* and the rate of microbiological eradication was 90.5% (237/262) with ceftolozane/tazobactam and 79.6% (226/284) with levofloxacin (treatment difference 10.9%, 95% CI 4.9% to 16.8%). Similarly, the rate of microbiological eradication for *P. aeruginosa* was higher with ceftolozane/tazobactam (85.7% [6/7]) compared with levofloxacin (58.3% [7/12], treatment difference 27.4%; 95% CI −15.9 to 56.3) but not statistically significant. The EPAR states that, generally, most of the people who were recorded as not having microbiological eradication after treatment were still found to be clinically cured, and these people were considered to have asymptomatic bacteriuria.

The EPAR reports that, in the mMITT population, 14.3% of patients in the ceftolozane/tazobactam group and 23.4% of patients in the levofloxacin group experienced treatment failure at the test-of-cure visit and people with complicated lower urinary tract infection, rather than pyelonephritis, predominated. Superinfections occurred in 3.8% of ceftolozane/tazobactam patients and 5.7% of levofloxacin patients and new infections were observed in 8.8% and 6.5% of patients respectively, predominantly due to *Enterococcus* spp.

In subgroup analyses of the mMITT population (Wagenlehner et al. 2015), composite cure rates at the test-of-cure visit were statistically significantly higher for ceftolozane/tazobactam than for levofloxacin in high-risk patients (for example, people aged 65 years or more [70.0% compared with 53.5%, treatment difference 16.5%, 95% CI 3.0% to 29.2%] or with complicated lower urinary tract infections [67.1% compared with 47.3%, treatment difference 19.8%, 95% CI 3.7% to 34.6%]) and those with levofloxacin-resistant uropathogens (60.0% compared with 39.3%, treatment difference 20.7%, 95% CI 7.2% to 33.2%) or beta-lactamase producing uropathogens (62.3% compared with 35.1%, treatment difference 27.2%, 95% CI 9.2% to 42.9%). However, the numbers of patients in these subgroups are small, limiting the statistical power to detect differences between treatment groups.

Safety and Tolerability

ASPECT-cUTI In this phase III study in people with complicated urinary tract infections or acute pyelonephritis, the frequency of adverse events was similar in both treatment groups (34.7% [185/533] with ceftolozane/tazobactam compared with 34.4% [184/535] with levofloxacin). The most common adverse events in either group were:

- headache (5.8% [31/533] and 4.9% [26/535] respectively),
- constipation (3.9% [21/533] and 3.2% [17/535] respectively),
- nausea (2.8% [15/533] and 1.7% [9/535] respectively) and
- diarrhoea (1.9% [10/533] and 4.3% [23/535] respectively).

Serious adverse events occurred in 2.8% (15/533) and 3.4% (18/535) of people in the ceftolozane/tazobactam and levofloxacin groups respectively. Treatment-related serious adverse events occurred in 2 people in the ceftolozane/tazobactam group (*Clostridium difficile* infection in each person) both of whom recovered by the time of late follow-up. The investigators report that most adverse events were mild to moderate and the incidence of treatment-limiting adverse events was less than 2% in each treatment group. Statistical analyses were not reported. See Table 1 for more information.

Summary of Product Characteristics

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

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

A decline in renal function has been seen in people receiving ceftolozane/tazobactam. Lower doses should be used for people with pre-existing moderate or severe renal disease or end stage renal failure.

European Public Assessment Report

A total of 2,076 subjects were randomised into the phase III studies, including 1,083 in the complicated urinary tract infection trial (ASPECT-cUTI) and 993 in the complicated intra-abdominal infection trial (ASPECT-cIAI), the majority of whom were included in the safety population. The EPAR noted that the safety profile in the 2 phase III studies was broadly similar between treatments within each indication (ASPECT-cUTI and ASPECT-cIAI, total n=2,047: 1,015 taking ceftolozane/tazobactam and 1,032 taking levofloxacin or meropenem). Overall rates of adverse events did not increase with duration of therapy and most treatment-emergent adverse events seen with ceftolozane/tazobactam were mild-to-moderate in severity and typical of beta-lactam agents.

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

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

Evidence Strengths and Limitations

The licensing application for ceftolozane/ tazobactam was based on 2 double-blind RCTs (ASPECT-cUTI and ASPECT-cIAI) for different indications and the EPAR states that the design of the studies including the participant selection criteria, analyses population and non-inferiority margins comply with Committee for Medicinal Products for Human Use (CHMP) guidance on the evaluation of medicinal products indicated for treatment of bacterial infections (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000401.jsp&mid=WC0b01ac0580034cf2). However, the EPAR reports that the proportions of specific types of infections supporting the indications of complicated urinary tract and intra-abdominal infections did not comply with CHMP recommendations. For example, for studies evaluating the efficacy of investigative antibiotics in people with complicated urinary tract infection, CHMP guidance recommends that participants with a diagnosis of acute pyelonephritis are studied separately because they do not always require parenteral treatment. The CHMP also recommends that, in such studies, conducted in people who are unable to take oral antibiotics, the proportion of participants enrolled with pyelonephritis should be limited. ASPECT-cUTI mainly enrolled people with acute pyelonephritis (82%) and it is unclear from the data if these participants were unable to take oral antibiotic therapy or required parenteral therapy for another reason.

In the ASPECT-cUTI study in adults with complicated urinary tract infection and acute pyelonephritis, ceftolozane/tazobactam was non-inferior to levofloxacin for the primary composite outcome of microbiological eradication and clinical cure in the mMITT population at the test-of-cure visit. As is necessary in a non-inferiority study, this analysis was repeated in the PP population (a secondary outcome), and the results of the analyses were consistent across both populations, as is required to demonstrate non-inferiority of one intervention to another (see European Medicines Agency guidance on Points to consider on switching between superiority and non-inferiority [http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500003658&mid=WC0b01ac058009a3dc]).

The prevalence of complicated urinary tract infections due to beta-lactamase producing *E. coli* is increasing. In ASPECT-cUTI, Wagenlehner et al. conclude that, because the study results show that ceftolozane/tazobactam has a spectrum of activity against beta-lactamase producing *E. coli*, it provides another treatment option for people with infections due to these pathogens. Similarly, Wagenlehner et al. report that the results of ASPECT-cUTI confirm previous in vitro study outcomes showing that ceftolozane/tazobactam has activity against *P. aeruginosa*, of which there are multidrug resistant strains. However, because of the low incidence of *P. aeruginosa* in people in ASPECT-cUTI, statistical analyses (which were found to be non-significant) are likely to be underpowered.

The ASPECT-cUTI study has various limitations that should be taken into account when considering its application to practice. The EPAR reports that there was a study inclusion criterion specifying that participants required IV antibiotics,

suggesting that their complicated urinary tract infection was severe. However, evaluation of infection severity and symptoms (such as systemic laboratory diagnostic biomarkers or the presence of urosepsis) are not reported, although 7.3% and 8.2% of patients had bacteraemia at baseline for ceftolozane/tazobactam and levofloxacin respectively (Wagenlehner et al. 2015).

The study population primarily included younger women of white ethnic origin (74.0% were females, mean age 48 years, 85.8% white). People over 65 years were in the minority (24.9%), as were people with moderate renal impairment (7.3%). This may limit the generalisability of the results to other populations such as men, postmenopausal women and people with renal impairment. The summary of product characteristics advises that people with severe neutropenia or who were immunocompromised were excluded from the phase III trials, as were people with severe renal impairment and pregnant or breastfeeding women. Ceftolozane/tazobactam has not been studied in children and is only indicated for use in adults. Additionally, more than 80% of participants had a diagnosis of acute pyelonephritis and the EPAR reports that the pivotal study provides poor support for use of ceftolozane/tazobactam in complicated lower urinary tract infections because there were only 60 people in the PP population with this diagnosis who received this study treatment (and 66 people in the PP population treated with levofloxacin).

The dosage of levofloxacin (750 mg daily) used in the study was higher than the daily dose recommended in the summary of product characteristics (500 mg daily) because the study protocol specified the US licensed dosage (750 mg). However, the European Association of Urology Guidelines on urological infections recommends levofloxacin 750 mg once daily for the initial parenteral treatment of severe uncomplicated pyelonephritis. The baseline susceptibility testing to study drugs showed that approximately 30% of gram-negative and 57% of gram-positive pathogens were resistant to levofloxacin and according to the EPAR this biased the results in favour of ceftolozane/tazobactam and suggests that levofloxacin was not a good choice of comparator.

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

The CHMP acknowledged the limitations of the single study data but accepted that ceftolozane/tazobactam may be of use in people with complicated urinary tract infection due to certain beta-lactamase producing pathogens. Consequently, the summary of product characteristics reflects the limitations of the evidence including the exclusion from clinical trials of people who were immunocompromised or those with severe neutropenia and the small percentage of people included with complicated lower urinary tract infections (18% in total, 60 people in the PP population taking ceftolozane/tazobactam, 1 of whom had accompanying bacteraemia at baseline).

Context

Alternative Treatments

According to the European Association of Urology Guidelines on urological infections, the successful treatment of complicated urinary tract infections includes effective antimicrobial therapy and optimal management of the underlying urological abnormalities or other diseases. Empirical antibiotic treatment of symptomatic infections should take into account:

- possible pathogens causing the infection
- local antibiotic resistance patterns
- the severity of the underlying urological problem (including evaluation of renal function)
- the severity of the illness
- suspicion of bacteraemia.

To date, it has not been shown that any agent or class of agents is superior in cases in which the infective organism is susceptible to the drug administered (European Association of Urology Guidelines on urological infections).

For complicated urinary tract infections, the European guideline suggests options for empirical treatment when local resistance is sufficiently low, are fluoroquinolones, aminopenicillins combined with a beta-lactamase inhibitor, third generation cephalosporins (for example, cefotaxime or ceftriaxone), aminoglycosides and co-trimoxazole. In the case of initial failure (less than 3 days' treatment) or clinically severe infection, a broader-spectrum antibiotic 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. Similar antibiotic regimens are suggested for severe and complicated acute pyelonephritis. After a few days of parenteral therapy and clinical improvement, patients may be switched to oral treatment.

Intense use of any antimicrobial, especially when used empirically in people with a high likelihood of recurrent

infection, will lead to the emergence of resistant microorganisms in subsequent infections. To limit this problem the choice of therapy should be guided by urine culture whenever possible and the initial empirical selection of an antimicrobial agent should be re-evaluated once culture results are available (European Association of Urology Guidelines on urological infections). The clinical diagnosis and continuing need for antibiotics should be reviewed within 48−72 hours (Public Health England 'Start smart – then focus' [https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus]).

Public Health England makes similar recommendations for the treatment of acute pyelonephritis in their guidance for primary care on managing common infections (https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care). Urine should be sent for culture and susceptibility testing, and empirical antibiotic treatment with ciprofloxacin or co-amoxiclav should be started. Trimethoprim may be used if susceptibility testing shows that the infection is sensitive to this antibiotic. Some people may require hospital admission if they do not respond to treatment. Outpatient parenteral antibiotic treatment may be an option on the advice of a microbiologist.

Costs of Alternative Treatments

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

Table 2 lists acquisition costs of the antibiotics used in the study together with some other commonly used options to give an indication of the range of costs of antibiotics for complicated urinary tract infections that might be considered alongside ceftolozane/tazobactam. Procurement discounts and administration costs vary and are not taken into account. Note that the continued need for parenteral antibiotics should be reviewed after 48–72 hours and, if appropriate, treatment should be switched to oral therapy (see Public Health England's 'Start smart – then focus' toolkit for more details).

Estimated Impact for the NHS

Likely Place in Therapy

In ASPECT-cUTI, ceftolozane/tazobactam was non-inferior to levofloxacin for the composite primary outcome of microbiological eradication and clinical cure rates, 5 to 9 days after the last dose of treatment in adults with complicated urinary tract infections. However, there was no statistically significant difference in clinical cure rates and it is unclear whether the results apply to some populations; for example, men, people aged over 65 years or who are immunocompromised, or those with severe neutropenia, severe renal impairment, or infections other than acute pyelonephritis. Ceftolozane/tazobactam has not been studied in pregnant or breastfeeding women and is not licensed for use in children.

There was no marked difference in the safety profile between ceftolozane/tazobactam and comparators (levofloxacin and meropenem) in 2 pivotal RCTs for complicated urinary tract infections and complicated intra-abdominal infections (ASPECT-cUTI and ASPECT-cIAI respectively). However, nausea, constipation, abdominal pain, pyrexia, headache, hypotension, hypokalaemia and raised ALT and AST were reported more commonly in people taking ceftolozane/tazobactam.

Table 2 Costs of some antibiotics used for complicated urinary tract infections

Antibiotic and dosage[a]	Unit Cost	Cost per 7-day course[b]
Ceftolozane/tazobactam 1 g/0.5 g IV 8 hourly	£67.03[c] per 1 g/0.5 g vial	£1,407.63
Levofloxacin 500 mg (750 mg used in ASPECT-cUTI) IV daily	£25.10[c] per 500 mg infusion	£175.70 (£263.55)
Piperacillin/tazobactam 4 g/0.5 g IV 8 hourly	£15.17[c] per 4 g/0.5 g vial	£318.57
Cefotaxime 2 g–12 g IV daily in divided doses	£8.57[c] per 2 g vial	£59.99–£359.94
Cefuroxime 1.5 g IV 8 hourly	£4.70[c] per 1.5 g vial	£98.70
Ceftazidime 1–2 g IV 8 or 12 hourly	£7.92 [c] per 1 g vial	£110.88–£332.64
Ceftriaxone 1–2 g IV daily	£9.58[d] per 1 g £19.18[d] per 2 g vial	£67.06–£134.26
Ciprofloxacin IV 400 mg 8 or 12 hourly or oral 500 mg 12 hourly	£22.85[c] per 400 mg vial £1.02[d] for 10 x 500 mg tablets	£319.90–£479.85 £1.43
Meropenem 0.5–1 g IV 8 hourly	£8.00[c] per 0.5 g vial	£168.00–£336.00
Gentamicin IV 3–6 mg/kg in divided doses or 160 mg once daily may be used	£1.00[c] per 80 mg vial	£21.00–£42.00[e] or £14.00[e]

IV, intravenous. [a]Dosages are as used in ASPECT-cUTI or as indicated in the individual summaries of product characteristics. They do not represent the full range that can be used (dependent on patient characteristics) nor do they imply therapeutic equivalence. [b]The duration of treatment in ASPECT-cUTI was 7 days. The treatment duration may vary depending on factors such as the type of infection and severity of illness. In practice, the continued need for parenteral antibiotics should be reviewed after 48-72 hours and with clinical improvement, switched to oral therapy as soon as appropriate. Costs do not take into account any procurement discounts or administration costs. [c]Cost (excluding VAT) obtained from MIMS, May 2016. [d]Cost (excluding VAT) obtained from Drug Tariff, May 2016. [e]Cost shown for dose range for average 80 kg person.

The acquisition cost of ceftolozane/tazobactam is more than that of other IV antibiotics that are commonly used for complicated urinary tract infections and acute pyelonephritis (see cost Table 2).

Appropriate use of antibiotics is important to reduce the serious threat of antibiotic resistance and the risk of healthcare-associated infections such as *C. difficile* infection. (See the NICE evidence summary medicines and prescribing briefing for more information on the risk of *Clostridium difficile* infection with broad-spectrum antibiotics [http://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence].) Public Health England's 'Start smart – then focus' toolkit outlines best practice in antimicrobial stewardship in the secondary care setting. 'Start smart' indicates that antibiotics should be started within 1 hour of diagnosis (or as soon as possible) in people with severe and life-threatening infections (particularly where the cause of infection is uncertain), in line with local antibiotic prescribing guidance. In people with less severe infection, local prescribing guidance should recommend narrow-spectrum antibiotics that cover the expected pathogens.

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

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

As well as efficacy, safety, individual user factors and cost, commissioners and local decision makers will need to take into account the principles of antimicrobial stewardship when considering the likely place in therapy of ceftolozane/tazobactam within hospital antibiotic policies for managing complicated urinary tract infections and acute pyelonephritis. (See the relevance to NICE guidance programmes section in next column for links to NICE guidance on antimicrobial stewardship.) Local hospital antibiotic policies generally limit the options that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases. (See the BNF section on principles of antibiotic therapy [https://www.medicinescomplete.com/mc/bnf/current/PHP78148-antibacterials-principles-of-therapy.htm]).

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

Estimated Usage

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

Relevance to NICE Guidance Programmes

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

NICE has issued guidance on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NICE guideline NG15 [http://www.nice.org.uk/guidance/ng15]). A related NICE pathway (http://pathways.nice.org.uk/pathways/antimicrobial-stewardship) and quality standard (https://www.nice.org.uk/guidance/qs121) on antimicrobial stewardship are also available.

A NICE key therapeutic topic on antibiotic prescribing – especially broad spectrum antibiotics (NICE advice KTT9 [http://www.nice.org.uk/advice/ktt9]) supports medicines optimisation in this area. A NICE evidence summary medicines and prescribing briefing summarises the risk of *Clostridium difficile* infection with broad-spectrum antibiotics (NICE advice ESMPB1 [http://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence]). These publications are not NICE guidance.

Development of this Evidence Summary

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

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Declarations of Interest

Matthew Dryden has been involved in research projects on new antibiotics funded by Pharmacia, Pfizer, Bayer, Astra Zeneca and Merck and has been on advisory boards or received honoraria fees for presentations from Pfizer, AZ, Bayer, Merck, Motif Bio, Eumedica. None of the fees and grants were specifically for ceftolozane/tazobactam.

Ian Pearce has no declaration of interest to declare.

Mark Wilcox has received consulting fees from Abbott Laboratories, Actelion, Astellas, AstraZeneca, Bayer, Biomèrieux, Cerexa, Cubist, Durata, The European Tissue Symposium, The Medicines Company, MedImmune, Merck, Motif Biosciences, Nabriva, Optimer, Paratek, Pfizer, Roche, Sanofi-Pasteur, Seres, Summit, and Synthetic Biologics. He has also received lecture fees from Abbott, Alere, Astellas, AstraZeneca, Merck, Pfizer and Roche; and grant support from Abbott, Actelion, Astellas, Biomèrieux, Cubist, Da Volterra, The European Tissue Symposium, Merck and Summit. None of the fees and grants were specifically for ceftolozane/tazobactam.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.
The document reproduced here is the full evidence summary; the complete document is available from https://www.nice.org.uk/advice/esnm74

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

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