NICE advice

Antimicrobial prescribing: cefiderocol

Evidence summary
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Product overview

The content of this evidence summary was up to date in November 2020. See summaries of product characteristics, British national formulary, the Medicines and Healthcare products Regulatory Agency or NICE websites for up-to-date information.

Cefiderocol (Fetcroja, Shionogi) is a siderophore cephalosporin antibiotic that is given intravenously. It has a marketing authorisation for the treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options.

Advisory statement on likely place in therapy

Cefiderocol may be an option for treating infections due to gram-negative aerobic organisms in adults who have limited treatment options, particularly when other antimicrobials have failed. Take account of local antimicrobial resistance and seek specialist microbiological advice. Follow recommendations on new antimicrobials in the NICE guideline on antimicrobial stewardship.

The summary of product characteristics for cefiderocol (SPC for cefiderocol) includes a warning

about the higher mortality rate seen in people with pneumonia, bacteraemia or sepsis due to carbapenem-resistant gram-negative organisms. The cause of the increase in mortality has not been established; however, there was an association between mortality and infection due to *Acinetobacter species*.

Rationale

The European Public Assessment Report (EPAR) for cefiderocol states that there is still an unmet need for antimicrobial agents with an acceptable safety profile that are active against carbapenem-resistant gram-negative organisms. The EPAR states that few new antimicrobial agents addressing carbapenem-resistance have been launched in recent years. Of those that have been launched none are active against class B beta-lactamases and they have no or limited activity against class D beta-lactamases.

Only 1 randomised controlled trial (RCT; Bassetti et al. 2020) was conducted in the target population identified by the EPAR (that is adults with infections due to carbapenem-resistant gram-negative organisms). Carbapenem resistance can be a good indicator of multidrug resistance and infections with limited treatment options. Data from this RCT (n=152) suggested that the efficacy of cefiderocol was similar to best available treatment. The study included people with hospital-acquired pneumonia, ventilator-associated and healthcare-associated pneumonia, bloodstream infection or sepsis, or complicated urinary tract infections. The EPAR concluded that, because of its limited size, this study can only be regarded as supportive of efficacy.

Two additional RCTs are included in this evidence review, Portsmouth et al. (2018) and Wunderink et al. (2020). However, neither of these studies were conducted in a population with infections due to carbapenem-resistant gram-negative organisms.

The EPAR states that the possible ability of cefiderocol to meet an unmet need (treatment of carbapenem-resistant organisms expressing beta-lactamases, particularly Ambler Class B or D enzymes) is based mainly on in vitro data, and on non-clinical efficacy data.

An increase in mortality was seen in Bassetti et al. (2020) with cefiderocol compared with best available treatment. Statistical significance was not reported because this was a descriptive study. This mortality difference was primarily seen in the subsets of people who were infected with *Acinetobacter species*, with or without co-infection with another pathogen. The EPAR concluded that it could not rule out a potential problem with effectiveness of cefiderocol against carbapenem-resistant *Acinetobacter*.

The NICE guideline on antimicrobial stewardship makes recommendations on the effective use of new antimicrobials. Cefiderocol should be targeted to those most likely to benefit from its use, following specialist microbiological advice to help monitor use and limit antimicrobial resistance.

Factors for decision making

Effectiveness and safety

Evidence was from 3 randomised controlled trials (RCTs). Bassetti et al. (2020) was the only randomised controlled trial (RCT) that was conducted in a population with carbapenem-resistant gram-negative organisms (which can be a good indicator of multidrug resistance). The other 2 RCTs (Portsmouth et al. 2018 and Wunderink et al. 2020) included in this evidence review were not conducted in populations with infections caused by carbapenem-resistant gram-negative organisms.

Bassetti et al. (2020) was a small open-label RCT in adults with hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP), bloodstream infection or sepsis, or complicated urinary tract infections (UTI) caused by carbapenem-resistant gram-negative organisms. Overall, this study showed that the clinical cure rates at the test of cure assessment for people with HAP, VAP or HCAP (n=59 in the microbiological intention to treat [mITT] population) and bloodstream infection or sepsis (n=37 in mITT population) were numerically similar between the cefiderocol and best available treatment groups (primary outcomes). For people in the small subgroup with complicated UTI (n=22 in mITT population), there was a numerically higher clinical cure rate in the cefiderocol group compared with the best available treatment group at the test of cure assessment (secondary outcome). The statistical significance of all outcomes was not assessed in this study. However, the European Public Assessment Report (EPAR) concluded that, generally, clinical cure rates at this time point (7 days, plus or minus 2 days after the end of treatment) were similar for both treatment arms.

Portsmouth et al. (2018) showed that cefiderocol was non-inferior to imipenem with cilastatin on the composite primary outcome of clinical response and microbiological response in adults with complicated UTI caused by gram-negative uropathogens. In Wunderink et al. (2020), cefiderocol plus linezolid was non-inferior to meropenem plus linezolid for the primary outcome of all-cause mortality at day 14 in adults with HAP, VAP or HCAP caused by a gram-negative pathogen. There was also no statistically significant difference between the 2 groups for the secondary outcome of clinical cure rates at test of cure assessment.

The EPAR concluded that, with the exception of the unexplained imbalance in mortality rate (an

increase in mortality with cefiderocol compared with best available treatment) seen in Bassetti et al. (2020), the safety profile of cefiderocol is typical of cephalosporins.

The summary of product characteristics (SPC) for cefiderocol gives the most frequent adverse reactions as diarrhoea (8.2%), vomiting (3.6%), nausea (3.3%) and cough (2%). *Clostridioides difficile*-associated diarrhoea has been reported with cefiderocol and should be considered in people using this medicine who present with diarrhoea. Cephalosporins have also been implicated in triggering seizures.

The British National Formulary information on cephalosporins states that the principal adverse effect is hypersensitivity. About 0.5% to 6.5% of people sensitive to penicillin will also be allergic to cephalosporins.

Limitations of the evidence

Cefiderocol has a marketing authorisation for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options. Carbapenem resistance to infections caused by gram-negative organisms can be a good indicator of multidrug resistance and those infections that have limited treatment options. Only 1 study (Bassetti et al. 2020) was conducted in people with infections caused by carbapenem-resistant gram-negative organisms.

Bassetti et al. (2020) was a small open-label RCT with a heterogenous population. It was also only a descriptive study without hypothesis testing and full statistical analysis. The EPAR concluded that, because of its limited size, this study can only be regarded as supportive of efficacy. The EPAR states that the evidence from Portsmouth et al. (2018) and Wunderink et al. (2020) cannot be used to establish the efficacy of cefiderocol for the treatment of carbapenem-resistant gram-negative organisms.

The SPC states that the use of cefiderocol to treat infections due to gram-negative aerobic organisms when there are limited treatment options is based on pharmacokinetic-pharmacodynamic analyses for cefiderocol and the limited clinical data from Bassetti et al. (2020).

The SPC includes a warning on the increase in mortality seen in Bassetti et al. (2020) with cefiderocol compared with best available treatment, when used to treat infections due to carbapenem-resistant gram-negative organisms and an association with infections due to *Acinetobacter species*. In Wunderink et al. (2020), there was no statistically significant difference between the cefiderocol plus linezolid and meropenem plus linezolid groups for all-cause mortality at 14 days and 28 days. However, this was a different pneumonia study population from that in

Bassetti et al. (2020). In Wunderink et al. (2020) participants with pneumonia caused by a known carbapenem-resistant pathogen at the time of randomisation were excluded. The EPAR stated that, although there was no difference noted in mortality between the treatment groups in the Wunderink et al. (2020) study with regards to participants infected with *Acinetobacter baumannii*, the data from this study population and from Portsmouth et al. (2018) could not be used to rule out a potential problem with effectiveness of cefiderocol against carbapenem-resistant *Acinetobacter*.

The SPC also includes a warning on the limitations of the clinical data, and states that in clinical trials cefiderocol has been used to treat the following types of infection: complicated UTIs; HAP, VAP, HCAP; sepsis and bacteraemia (some people with no identified primary focus of infection), but not other infections such as complicated intra-abdominal infections.

Person-centred factors

Cefiderocol is administered over 3 hours by intravenous (IV) infusion at a frequency of every 8 hours (SPC for cefiderocol). Specialists who commented on this evidence review highlighted that in practice this means that people receiving cefiderocol will need to have good IV access, because they may need more than one cannula or a central venous access to allow for other IV infusions that they might need to receive.

Cefiderocol is most likely to be prescribed and administered in a hospital setting.

Antimicrobial resistance

Cefiderocol is a new antimicrobial, so data on resistance and the impact in clinical practice in the UK are limited. Information on resistance can be found on Public Health England's antimicrobial resistance local indicators.

The SPC for cefiderocol includes details on mechanisms that may lead to resistance. The in vitro antibacterial activity of cefiderocol against normally susceptible species is not affected by most beta-lactamases, including metallo-enzymes. Cefiderocol has little or no activity against most gram-positive organisms and anaerobes.

Resource implications

Cefiderocol 1 g powder for concentrate for infusion costs £1,319 for a pack of 10 vials (personal communication with the manufacturer).

The recommended dosage for adults with normal renal function is 2 g every 8 hours (SPC for cefiderocol). The duration of treatment will depend on the site of infection; the cost of a 10-day treatment course would be £7,914. The cost of 1 day's treatment at the usual dose (2 g [2 vials] every 8 hours) is £791.40.

See the full evidence review for more information.

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