Guidance on the appropriate use of cefiderocol from HSE Antimicrobial Resistance Infection Control Team (version 1, June 2024)

For: Consultant Microbiologists, Infectious Disease Physicians, and Antimicrobial Pharmacists

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Indication

Cefiderocol is a novel cephalosporin antibiotic. It may be considered for use in treatment of patients with severe infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Cefiderocol should only be prescribed if there are no suitable alternative treatment options. Cefiderocol is not expected to have a role in general empiric therapy of Gram-negative infection.

Recommendations [1]

Cefiderocol should be used only on the recommendation of a Consultant Microbiologist or Infectious Disease Physician.

The decision to use cefiderocol should be guided by results from tests for microbiological susceptibility and mechanisms of resistance that confirm that the infection is susceptible to cefiderocol, and not susceptible to other suitable antibiotics.

If these results are not yet available, cefiderocol may be offered, but only if the infection:

- needs urgent treatment, and
- is expected to be susceptible to cefiderocol and not to other suitable antibiotics.

As well as considering susceptibility, judgements about whether an alternative treatment is suitable may take account of concerns about its toxicity, availability or interactions with other drugs, and its spectrum of activity.

Antimicrobial stewardship considerations

Cefiderocol is a WHO AWaRe reserve group antibiotic and should be treated as a “last resort” treatment option.

- Its use should be targeted to highly specific patients and settings
- It should be subject to monitoring and utilisation reporting in order to preserve its effectiveness (e.g. named - patient based dispensing)
- Consideration should be given to ensuring appropriate supply processes and procedures are in place in the hospital to restrict the use of cefiderocol, including addition of cefiderocol to the hospital’s restricted antimicrobial list following local agreement. See HSE AMRIC antimicrobial stewardship guidance for all healthcare settings

Method of administration[2]
Cefiderocol is administered by intravenous infusion over 3 hours. The dosage schedule and further details are available on the Summary of Product Characteristics. Dosage adjustment is needed for people with renal impairment.

Special populations
There are no or limited data on the use of cefiderocol in pregnancy, during breastfeeding or in children below 18 years of age.

Re-imbursement
Fetcroja® (Cefiderocol) 1g x 10 vials is licensed in Ireland and has been approved for reimbursement by the HSE.
Reimbursement is quarterly through HSE, Acute Operations.

Limitations of the clinical data[2, 3]
There is limited clinical data to support the efficacy and adequacy of the dose of cefiderocol for the treatment of the target carbapenem-resistant organisms. The evidence for use of cefiderocol to treat patients with infections due to carbapenem-resistant organisms expressing β-lactamases, particularly Ambler Class B or D enzymes, relies on pharmacokinetic-pharmacodynamic analyses for cefiderocol and on limited clinical data from a small randomised clinical trial.

APEKS-cUTI was a phase 2 study, involving 452 adults with complicated UTI. Results for the composite endpoint of microbiological eradication and clinical cure per subject at TOC in the Micro-ITT population were 72.6% (n/N; 183/252) in the cefiderocol group and 54.6% (n/N; 65/119) in the imipenem-cilastatin group. This study did not specifically study infections caused by carbapenem-resistant organisms. This study was not designed to support an indication for treatment of cUTI.

CREDIBLE CR was a small descriptive phase 3 study involving 152 adults with various serious infections caused by bacteria that were resistant to carbapenems including HAP/ VAP/ HCAP, cUTI and BSI/ sepsis. This study compared cefiderocol 2g infused IV over 3 hours q8h to best available therapy (BAT) defined locally by study site. The clinical cure rate for subjects with HAP/ VAP/ HCAP were 50.0% (n/N', 20/40; 95% CI, 33.8, 66.2) in the cefiderocol group and 52.6% (n/N', 10/19; 95% CI, 28.9, 75.6) in the BAT group. The clinical cure rate for subjects with BSI/ sepsis were 43.5% (n/N', 10/23; 95% CI, 23.2, 65.5) in the cefiderocol group and 42.9% ((n/N', 6/14; 95% CI, 17.7, 71.1) in the BAT group. The microbiological eradication rate for subjects with cUTI were 52.9% (n/N', 9/17; 95% CI, 27.8,77.0) in the cefiderocol group and 20.0% (n/N', 1/5; 95% CI, 0.5, 71.6) in the BAT group. This study can only be regarded as supportive of efficacy for the intended indication because of its limited size.

It should also be noted that a higher all-cause mortality rate was observed in patients treated with cefiderocol as compared to BAT in CREDIBLE CR study. The higher day 28 all-cause mortality rate with cefiderocol occurred in patients treated for nosocomial pneumonia, bacteraemia and/ or sepsis [25/101 (24.8%) vs. 9/49 (18.4%) with BAT; treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with cefiderocol through end-of-study [34/101 (33.7%) vs. 9/49 (18.4%) with BAT; treatment difference 15.3%, 95% CI (-0.2, 28.6)]. The cause of the increase in mortality has not been established. In the cefiderocol group there was an association between mortality and infection with Acinetobacter spp., which accounted for the majority of infections due to non-fermenters. In contrast, mortality was not higher in cefiderocol vs. BAT patients with infections due to other

non-fermenters. The data indicate a potential problem for cefiderocol in the treatment of Acinetobacter spp., with or without shock.

APEKS-NP was a phase 3 study of 148 participants that compared all-cause mortality, clinical and microbiological outcomes of treatment with cefiderocol or meropenem in adult subjects with documented HAP/VAP/HCAP caused by Gram negative pathogens. In summary, the APEKS-NP study showed that cefiderocol was noninferior to meropenem for all-cause mortality at Day 14. The microbiological eradication rates and clinical cure rates were generally similar for cefiderocol and meropenem at TOC, with activity against the major causative pathogens.

Efficacy data from the APEKS-NP study and from patients with pneumonia in the CREDIBLE-CR study support the use of cefiderocol for the treatment of lung infections.

Even though non-inferiority of cefiderocol was met in the APEKS-cUTI and APEKS-NP studies, the efficacy of cefiderocol for the intended indication was not established in these studies because the target organisms of the indication was not specifically studied

Guideline note:
In the National CPE Expert Group Guideline, A Guide to Treatment of Infection with Carbapenem Resistant Organism 2019, cefiderocol is mentioned only as a pipeline agent. This guideline will be updated in due course in line with the updated data referred to here.

References

1. Adapted from NICE Cefiderocol for treating severe drug-resistant gram-negative bacterial infections 2022. https://www.nice.org.uk/guidance/hte2/chapter/1-Recommendations
2. Fetcroja 1g powder for concentrate for solution for infusion Summary of Product Characteristics. Accessed May 2024: https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf
3. European Medicines Agency Assessment Report Fetcroja 2020. https://www.ema.europa.eu/en/documents/assessment-report/fetcroja-epar-public-assessment-report_en.pdf