Cefiderocol for severe gram-negative infections

NIHR HSRIC ID: 12520

Lay summary

Cefiderocol is a new drug to treat severe infections, which are caused by a particular group of bacteria called gram-negative bacteria, which are increasingly resistant to many antibiotics. Infections such as pneumonia, complicated urinary tract infections and bloodstream infections, are serious infections and a huge problem for the NHS. They prolong patient stay in hospital and increase health costs. Cefiderocol is injected directly into the bloodstream and kills the bacteria in the body that are causing infection.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Severe gram-negative infections: patients with limited treatment options.

TECHNOLOGY

DESCRIPTION

Cefiderocol (GSK-2696266; RSC 649266; S-649266) is an injectable cephem cephalosporin antibiotic, which acts as a cell wall synthesis inhibitor. In the phase III clinical trial, cefiderocol is administered intravenously (IV) at 2g in an infusion lasting 3 hours, and repeated every 8 hours for 7-14 days. Cefiderocol does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, cefiderocol will offer an additional treatment option for patients with severe gram-negative infections who have limited treatment options.

DEVELOPER

Shionogi.

AVAILABILITY, LAUNCH OR MARKETING

Cefiderocol is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Gram-negative bacteria do not retain the crystal violet stain used in bacterial differentiation and are characterised by their cell envelopes which is made of a thin peptidoglycan cell wall. Increasing resistance in gram-negative bacteria is a particular and growing public health concern because of the limited treatment options for infections caused by these organisms, especially those that are resistant to carbapenem antibiotics, which are last-line drugs used to treat those infections. Gram-negative bacterial infections may lead to a number of serious infections that are frequently associated with hospital stay. These include bacteremia, hospital acquired pneumonia (HAP), ventilator associated pneumonia (VAP), and complicated urinary tract infections (cUTI).

HAP occurs after a hospital stay of at least 48 hours. These infections can be very severe and life-threatening due to the patient’s underlying illness and frailty, and the treatment-resistant nature of the pathogens.

VAP is a hospital associated pneumonia that occurs 48 hours or more after tracheal intubation. Early onset VAP occurs within four days of intubation and mechanical ventilation, and is often caused by bacteria that remain sensitive to first line antibiotic therapy, whereas late onset VAP develops after four days and is often caused by multi-drug resistant pathogens.
CUTI are a frequent cause of hospital admissions and healthcare associated complications. The most common pathogen encountered in cUTI are the gram-negative bacteria *Escherichia coli*, other common Enterobacteriaceae (i.e. *Klebsiella* spp. or *Citrobacter* spp.) and *Pseudomonas* spp. Successful treatment remains a challenge due to the majority of pathogens in cUTI showing multi-drug resistance.

**CLINICAL NEED and BURDEN OF DISEASE**

Approximately 99,000 cases of bacteraemia were reported in adults aged over 18 in the UK between April 2011 and March 2012, and just over half of these infections (53%) were caused by gram-negative bacteria. Resistance to antibiotics was common, with resistance to third-generation cephalosporins seen in 9-11% of *E. coli* and *K. spp.* Resistance to carbapenems is also now increasingly being seen, with resistance reported in 9% of *Pseudomonas* and 1% of *Enterobacter* spp. The consequences of antimicrobial resistance include increased treatment failure for common infections and decreased treatment options where antibiotics are vital, such as during certain cancer treatments.

The frequency of cUTI due to resistant gram-negative bacteria is increasing. UTI is the most common hospital-acquired infection and the majority of cases are catheter associated. UTI develops in 25% of patients who require a catheter for over 7 days, with a 5-7% daily risk. The acquisition of a nosocomial UTI adds to the duration and cost of hospitalisation. The gram-negative microbial spectrum of uncomplicated cystitis and pyelonephritis consists mainly of *E. coli* (75%–95%), and other species of Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella pneumoniae*. The frequency of cUTI due to resistant gram-negative bacteria is increasing both in the healthcare and community setting. *E. coli* isolated from patients with community-acquired UTIs are now associated with high rates of resistance to commonly used antimicrobials, and some isolates are multidrug-resistant. The incidence of cUTI increases with age for both sexes. Nosocomial UTI adds to the duration and cost of hospitalisation and nosocomial uropathogens form a reservoir of antibiotic resistant bacteria.

At any one time, 1.5% of hospital inpatients in England have a hospital acquired respiratory infection. Of these people, more than half (at least 7,000 people) have HAP (not including infection associated with intubation). HAP is estimated to increase hospital stay by about 8 days and has a reported mortality rate of between 30 and 70%10,11. These figures include VAP and the clinically distinct HAP in non-intubated patients. VAP is the most common and fatal infection in the intensive care unit. Approximately 10-28% of critical care patients will develop VAP and around 86% of HAP is linked with mechanical ventilation12. VAP occurs in 9-27% of mechanically ventilated patients with approximately 5 cases per 1,000 ventilator days. This results in increasing patient length of stay by 28% and increasing health costs by £6,000 to £22,000 for each occurrence of VAP13. Infection with *Pseudomonas aeruginosa* accounts for 12% of all reported cases of VAP, and is reported to have imipenem resistance rates of around 20%, a drug considered to be first-line therapy for this indication23.

The population likely to be eligible to receive cefiderocol could not easily be estimated from available routine published sources.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


NHS England Policies and Guidance


Other Guidance


CURRENT TREATMENT OPTIONS

It is important to initiate antibiotics as soon as possible after diagnosis, and the choice should be guided by careful consideration of patient specific factors, such as severity of illness and previous antibiotic exposure. In addition, local epidemiology should be considered in line with good antimicrobial surveillance. Infections caused by highly resistant pathogens need treatment with broad-spectrum antibiotics (such as: extended-spectrum penicillins, third-generation cephalosporins, aminoglycosides, carbapenems, or colistin), as recommended by British Society of Antimicrobial Chemotherapy guidance.

Current treatment options for HAP or VAP may include antibiotic therapy, oxygen, and ventilator support. The choice of agent for initial antibiotic therapy will depend on the likelihood of infection with multi-drug resistant pathogens. Late onset pneumonia (>5 days stay in hospital) has a significantly greater risk for being caused by multi-drug resistant pathogens.
bacteria and therefore requires combination antibiotic therapy. This may include an anti-pseudomonal cephalosporin, carbapenem or penicillin administered in combination with an anti-pseudomonal fluoroquinolone, aminoglycoside, or a beta-lactamase inhibitor. In contrast, for early onset pneumonia (<5 days stay in hospital), antibiotic monotherapy may be adequate using an appropriate cephalosporin, quinolone, or extended-spectrum penicillin. Generally, with effective treatment, improvements will be seen within 42 to 72 hours. Antibiotics can be safely discontinued after seven days if signs and symptoms improve (such as a reduction in C-reactive protein, white cell count and temperature, alongside a clinical improvement and an improvement in oxygenation)³.

The major goals of VAP management are early, appropriate antibiotics in adequate doses followed by de-escalation based on microbiological culture results and the clinical response of the patient¹⁸. There is no clear consensus, but many will continue antibiotic treatment for 14-21 days, although seven days of antibiotic therapy may be adequate in many cases⁸.

The management of cUTIs includes the removal of indwelling catheters, if possible, and antibiotic therapy. These infections (including acute pyelonephritis) are frequently caused by gram-negative bacteria and according to European Association of Urology Guidelines, second or third generation cephalosporins, beta-lactam antibiotics (e.g. penicillins) in combination with beta-lactamase inhibitors and quinolones should be used for treatment⁴.

**EFFICACY and SAFETY**

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<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>NCT02714595, CREDIBLE-CR, 1424R2131, 2015-004703-23; cefiderocol vs best available therapy; phase III.</td>
<td>Shionogi</td>
<td>Ongoing</td>
<td>Trial registry¹⁹, manufacturer.</td>
<td>EU (incl UK), USA and other countries.</td>
<td>Randomised, active-controlled.</td>
<td>n=150 (planned); aged ≥18 yrs; clinically documented infection caused by a gram-negative pathogen with evidence of carbapenem resistance; previously treated with an empiric antibiotic other than the study medications, but failed treatment with an identified pathogen which is not susceptible to the empiric treatment and is a carbapenem-resistant gram-negative pathogen; no documented history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam; no co-infection caused by invasive aspergillosis, mucormycosis or other highly lethal mould; no central nervous system infections; no infections requiring &gt;3 wks of antibiotic treatment; no cystic fibrosis or bronchiectasis; no refractory septic shock; no severe neutropenia.</td>
<td>Randomised to cefiderocol 2g IV as a 3 hr infusion every 8 hrs for 7-14 days; or best available therapy with either a polymyxin-based or non-polymyxin-based</td>
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<td>NCT02321800, 1409R2121, 2014-000914-76; cefiderocol vs imipenem/cilastatin; phase II.</td>
<td>Shionogi</td>
<td>Completed</td>
<td>Trial registry¹⁹, manufacturer.</td>
<td>EU (not UK), USA, and other countries.</td>
<td>Randomised, active-controlled.</td>
<td>n=450 (planned); aged ≥18 yrs; hospitalised; complicated urinary tract infections (cUTI) with or without pyelonephritis or acute uncomplicated pyelonephritis; ≥2 of the following: chills, rigors, warmth associated with fever (temperature ≥38°C), flank pain (pyelonephritis), suprapubic/pelvic pain, nausea, vomiting, dysuria, urinary frequency, urinary urgency, costo-vertebral angle tenderness on physical examination; pyuria.</td>
<td>Randomised to cefiderocol 2,000mg IV; or imipenem/cilastatin 1,000mg IV; both every 8 hrs for 7-14 days.</td>
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standard of care, this may include ≤3 antibacterial IV agents for carbapenem resistant gram-negative bacteria continued for 7-14 days.

Follow-up

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<td>Active treatment for 7-14 days, test of cure (TOC) 7 days after end of treatment. Follow up ≥14 days after end of treatment.</td>
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Primary outcomes

| | Clinical outcome in patients with hospital acquired pneumonia/vascular associated pneumonia/health care associated pneumonia or bloodstream infection/sepsis; microbiologic outcome (for gram-negative pathogen) in patients with cUTI. | Clinical and microbiologic response: resolution or improvement of the symptoms present at trial entry and demonstration that bacterial pathogen found at trial entry is reduced to <10⁴ colony-forming unit/mL on urine culture. | |

Secondary outcomes

| | Clinical outcome; microbiologic outcome (for gram-negative pathogen); all-cause mortality; survival time; clinical pulmonary infection score; sequential organ failure assessment score ; adverse events; safety and tolerability profile. | Pharmacokinetics; urine concentrations of cefiderocol; adverse events. | |

Expected reporting date

| | Study completion date reported as May 2018. | Study completion date reported as March 2017. | |

**ESTIMATED COST and IMPACT**

**COST**

The cost of cefiderocol is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: potential for improved outcomes and reduced inpatient stay
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
- None identified

**Other Issues**
Clinical uncertainty or other research question identified

REFERENCES