Clinical and NHS commissioning expert statement

Cefiderocol for treating severe aerobic Gram-negative bacterial infections

Thank you for agreeing to give us your views on cefiderocol and its possible use in the NHS.

You can provide a unique perspective on cefiderocol in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. **You do not have to answer every question** – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

* Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable.
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* Your response should not be longer than 13 pages.

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| **About you** |  |
| 1. Your name | Anna Goodman |
| 2. Name of organisation | British Infection Association |
| 3. Job title or position | Consultant in Infectious Diseases |
| 4. Please specify your role from the examples given: | **An employee or representative of a healthcare professional organisation that represents clinicians**  **A specialist in the treatment of people with this condition**  A specialist in the clinical evidence base for this condition or cefiderocol  Commissioning services for a CCG or NHS England in general  Commissioning services for a CCG or NHS England for the condition for which NICE is considering cefiderocol  Responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)  Other (please specify) |
| 5. Name of your nominating organisation | British Infection Association |
| 6. Did your nominating organisation make a submission? | Yes |
| 7. Did you write your nominating organisation’s submission? | Yes |
| 8. If you did not write your nominating organisation’s submission, do you agree with its content? We would encourage you to complete this form even if you agree with your nominating organisation’s submission, but this is not compulsory. | **N/A** |
| **Current treatment of severe gram-negative infections, where resistance is suspected/confirmed** |  |
| 9. What is the main aim of treatment? | The main aim of treatment with cefiderocol is to reduce mortality in specifically cases of severe highly-resistant gram-negative infections such as carbapenem-resistant Enterobacterales (carbapenemase-producing Enterobacterales= CPE) and resistant ‘non-fermenters’ such as *Acinetobacter* sp. Fortunately, although severe gram negative infection is common, the rates of resistant organisms remains very low in the UK such that the main aim of treatment would be to provide a treatment option for exceptional highly resistant organisms causing severe infection.  As reported in the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (<https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report>) . There were ~43 641 bloodstream infections due to *E. coli* reported in the UK to PHE in 2019 with 99.8% susceptible to carbapenem antibiotics (0.01% were resistant and 0.01% were intermediate). More resistance is seen in Klebsiella species, though they themselves are less common as a cause of disease, but susceptibility of *Klebsiella pneumonia* remained as high as98.6% (1.1% resistance) and *Klebsiella oxytoca* 99.8%.  Gram negative bacteraemia is common with bacteraemia rates of 77.3 (*E.coli*) 19.7 cases (*Klebsiella* spp.) and 7.7 (*P. aeruginosa)* per 100,000 population reported to PHE in 2019/2020 (<https://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-annual-epidemiological-commentary>) but fortunately in the UK in the most part remains sensitive to alternate antibiotic treatments, such as carbapenems. The mortality associated with severe gram negative infection is considerable and in 2017/2018 5865 people died within 30 days of *E.coli* bacteraemia with overall 41,125 cases representing 30 day mortality of 14%. Mortality is higher than this with resistant organisms of the kind for which we would use cefiderocol. For example, in the CREDIBLE-CR trial which recruited the type of patients one might expect to use this agent in the all-cause mortality at day 28 was 34 of 150 participants (22.6%). |
| 10. What do you consider a clinically significant treatment response? | A clinically significant treatment response at a population level could be a reduction in mortality or microbiological recurrence. There could be clinical cure in the form of resolution of signs or symptoms such that no further antibiotics are required. Microbiological eradication may be clinically important in some cases. A reduction in clinical recurrence or clinical failure, hospital bed days or reduced time to recovery would also be applicable. In an individual patient it may be clinical improvement or prevention of recurrence in a situation where other agents have failed due to resistance or intolerance.  Listed in the PICO are:  - All-cause mortality  - Clinical cure (complete resolution of signs/symptoms of the index infection such that no further antimicrobial therapy is needed)  - Microbiologic eradication  - Emergence of resistance  - Hospital days  - Intensive care unit (ICU) days  - Readmission rate within 90 days of treatment  - Number of treatment days  - Health-related quality of life  - Adverse events (including those associated with Clostridium Difficile infection and renal toxicity)  These seem appropriate outcomes to review though need review within the specific population expected to benefit from the treatment which is limited in number. |
| 11. How are severe gram-negative infections, where resistance is suspected/confirmed, currently treated in the NHS? | There is a wide range of treatments for severe gram-negative infections which will depend on the organism identified and the likely organisms found at the treating centre. Initially we do not presume there to be high levels of resistance though resistance is always ‘suspected’ at some level. For example, at my hospital the first-line (usual) treatment would be a combination of antibiotics so that if there were resistance to one agent then other agents may be effective. For example we may choose to prescribe cefuroxime with metronidazole plus gentamicin in combination for someone admitted from home with sepsis. If they acquired the sepsis in hospital we would instead use co-amoxiclav + gentamicin. If we were aware they had known gentamicin-resistant organisms previously we would use amikacin instead of gentamicin. If we knew they had a highly-resistant organism previously we might use a range of antibiotics including but not limited to the following only if susceptible on laboratory testing- all may be combined with other agents and some of these agents may be used alone in certain clinical situations: amikacin, ceftazidime (which possible), meropenem/ertapenem, ciprofloxacin/levofloxacin, co-trimoxazole, temocillin if appropriate to the scenario, piptazobactam, gentamicin (if susceptible), ceftolozone-tazobactam, cetazidime-avibactam, colistin, fosfomycin, tigecycline. |
| a) Are any clinical guidelines used, and if so, which? | We would use the guidelines appropriate to the specific clinical scenario (e.g. we might use a guideline for ventilator associated pneumonia if that is where the infection was) combined with more general guidance if applicable such as this UK review (doi:10.1093/jacamr/dlaa075).  There is an IDSA guideline for difficult to treat organisms (<https://www.idsociety.org/practice-guideline/amr-guidance/>) which may be referred to but this is less relevant for UK practice. |
| 1. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | There are differences of opinion between professionals as the cases are rare with a range of pathogens and the treatment needs to be targeted to both the pathogen and the site of infection. This is why all guidelines on the topic advise specialist discussions rather than direct choices of management. |
| 1. What impact would cefiderocol have on the current pathway of care? | If offered widely to all clinicians it is likely that the introduction of cefiderocol to routine care would lead to subsequent resistance to cefiderocol through antibiotic exposure pressure. It is likely it would be used in cases in which there was no resistance for example. If available solely to infection specialists in combination with specialist pharmacists with restrictions to use where other agents have failed or resistance to this agent is known it could provide salvage therapy in challenging cases and provide an additional option in an arena with very limited treatment options. |
| Using cefiderocol in clinical practice |  |
| 12. To what extent and in which population(s) is cefiderocol currently being used in your local health economy? | We do not often see the type of cases that would require this agent locally. Local clinicians have used the treatment on compassionate grounds for a single patient who had a clinical salvage benefit in a private sector setting (<https://academic.oup.com/cid/article/68/11/1932/5174241#135661804>) – this case was imported. The agent has been considered for use in 2 patients this year locally. If it were available to us we would expect to consider its use for <5 patients per year based on current resistance patterns. This could increase if our local epidemiology of infections changed. |
| 13. Will cefiderocol be used (or is it already used) in the same way as current care in NHS clinical practice? | It would be used in a very specific population of difficult to treat patients with multi-resistant organisms without other treatment options or who were unable to tolerate other treatment options. |
| 14. What rules will be used to start treatment? Do these include any additional testing that is not currently routinely available on the NHS? | If we were to use it it would only be in the scenario where there was proven resistance or intolerance to all alternative agents. We would need cefedirocol *in vitro* testing to be available in the laboratory but this is not complicated to set up- though would have a cost associated as special plates are used in microbiology for resistance testing. |
| 15. If information about the pathogen is very limited (i.e susceptibility data and gene testing results are not yet available) – what specific rules/criteria determine that it’s appropriate to use cefiderocol in the risk-based empiric treatment setting? | We would not be likely to use this agent empirically. |
| 16. Will cefiderocol be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments, additional clinical requirements or additional monitoring needed) | Cefiderocol would be likely to be easier for patients and health professionals to use than some alternative agents as the toxicity is low and therapeutic drug level monitoring is not required. |
| Benefits of cefiderocol |  |
| 17. Do you expect cefiderocol to provide clinically meaningful benefits compared with current care? | We would not expect measurable benefits at a population level but for individual patients the availability of this treatment we would expect could give clinically meaningful benefits. We would expect this to be of the order currently of <5 patients per year across a large hospital of ~1000 beds. This may be comparable with our current use of e.g. ceftolozone/tazobactam which has been prescribed 5-10 times this year locally. |
| 18. Please comment on the potential benefits of cefiderocol in relation to the 5 following elements of value, and how these elements of value could be quantified and captured in an economic analysis.  Please be aware that more detailed definitions of these elements of value are provided in chapter 7 of the [protocol for this evaluation.](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/models-for-the-evaluation-and-purchase-of-antimicrobials/Cefiderocol-protocol.docx) |  |
| 1. Transmission value (avoiding onwards spread of pathogens in the population).   Please include suggestions for surrogate outcomes to measure transmission benefit, for example length of hospital stay/length of stay in an intensive care unit, and provide any available evidence that supports the link between these outcomes. | I am not aware of evidence that this agent would be expected to have a significant role in avoiding transmission of highly-resistant pathogens. We would be using it for treatment and not colonisation and resistant organisms are therefore likely to remain present e.g. in the stool. There is a theoretical risk that it may have a negative impact on this value as there may be an increase in cefiderocol-resistant organisms over time if a population is exposed to this agent. Given the small numbers of patients likely to receive this agent and the difficulties of testing resistance to it *in vitro* (it would not be routinely tested- only tested in cases in which you considered using the agent) it would be likely to be difficult to detect and measure this negative impact if present until the impact had occurred. So it is a risk of using the agent and the use of the agent should be restricted if we are to protect its activity in the cases for which we need it. |
| 1. Enablement value (enabling other treatments and procedures to take place e.g. chemotherapy, organ transplant, surgical procedures).   Please comment on the potential for enablement value **beyond** the person being treated for the infection, considering the impact of the infection on other hospital patients and members of staff.  Can you suggest a specific intensive care unit which would make a good case study for modelling enablement value? | There would not be expected to be a positive impact on infection in the other hospital patients or members of staff. There could be a negative impact e.g. staff could become colonised with a highly resistant organism which was resistant to cefiderocol but this is a theoretical risk currently rather than measured risk.  For individual patients the treatment could theoretically lead to a possible transplant in a salvage situation though I am not aware of many situations where realistically that is currently likely. I am not aware for example of anyone who has been declined an operation or transplant due to an organism that there is evidence it could be treated (and cleared) by cefiderocol. As such it is unclear how this very rare event could be modelled in an ICU, even one where transplants were performed. In lung transplants there are cases where resistance of colonising bacteria can prevent transplantation but a lack of evidence that this treatment would alter the situation (and some evidence of recurrence of resistant bacteria following treatment- e.g. <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1847/6032716>). |
| 1. Spectrum value (benefits of replacing broad spectrum antimicrobials with narrow spectrum antimicrobials). | This is unlikely to be a key benefit of the introduction of this agent. The spectrum value is likely to be negative rather than positive if considering this agent as an alternative to e.g. amikacin. |
| 1. Insurance value (having antimicrobials available for sudden increase of infections with pathogens resistant to existing antimicrobials). | This is a theoretical potential benefit for this agent. To determine the size of the likely benefit you would need to scope units to determine their resistance rates and the number of clinical cases they may see which would be resistant to all other options. I expect these would be very low numbers currently in the UK but if there were an outbreak of a particular resistant organism there would be a likely benefit. A better approach to this aspect which is likely to be more cost effective is however infection control and funding would be more appropriately allocated to such an approach. |
| 1. Diversity value (having a range of treatment options available) | This is the key potential benefit of this agent. There is a clear role for the treatment in rare cases (perhaps 100/year across the UK) for whom other agents are ineffective or the patient cannot tolerate. There may also be even smaller numbers of cases whose chronic infections could finally be treated with this agent if it became available (e.g. a highly-resistant prosthetic joint infection). |
| 19. Which of these elements of value (transmission, enablement, spectrum, insurance, diversity) does cefiderocol have the greatest potential to impact? That is, the greatest potential to improve population health outcomes? | Cefiderocol has the greatest potential to impact for diversity value. |
| 20. Are there any groups of people for whom cefiderocol would be more or less effective (or appropriate) than the general population? | There are groups for whom cefiderocol may be more effective due to their chronic infection with a resistant pathogen without alternative treatments. These very small numbers of cases might include a patient with an infected prosthetic joint or vascular graft for example. The case report of salvage therapy in endocarditis referred to above is an example of this. Also another example is here (<https://www.sciencedirect.com/science/article/pii/S1201971221005245>). Such cases are rare. One might expect a potential benefit in chronic colonisation such as cystic fibrosis but the available evidence available does not appear to support that (<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1847/6032716>). As such cases are colonisation rather than active infection the bacteria recurred after treatment. |
| 21. How do any side effects or adverse effects of cefiderocol affect the management of infection and the patient’s quality of life? | The expected side effects or adverse events are similar to cephalosporins and doctors are therefore familiar with their management. They are relatively low compared to other agents used to treat such resistant bacteria. They may include renal dysfunction (e.g. interstitial nephritis) or seizures for example but such events usually resolve prior to discharge from hospital. In the case of penicillin/beta-lactam allergy a life-threatening allergy could occur with long-term impacts and this is true of all beta-lactam antibiotics. |
| **Sources of evidence** |  |
| 22. Do the clinical trials on cefiderocol reflect current UK clinical practice? | No- although the UK offered to join the trials a lack of patients in the UK meant that our practice e.g. for empiric therapy, was quite different and we lacked eligible patients. |
| 1. If not, how could the results be extrapolated to the UK setting? | The empiric results cannot be extrapolated to a UK setting due to our low rates of resistance. The comparisons in those with confirmed infection can be extrapolated. |
| 1. What, in your view, are the most important outcomes, and were they measured in the trials? | Mortality is a key outcome which was measured as a secondary outcome in trials without evidence of benefit and some evidence of harm.  APEKS-cUTI- the primary outcome was a composite of clinical and microbiological outcomes at test of cure (7 days after treatment cessation). Cefiderocol was found to be non-inferior to imipenem-cilastatin in patients with complicated UTI caused by carbapenem-susceptible gram-negative bacteria. This was used for FDA licensing. Although in the UK we would not routinely use the comparator imipenem-cilastatin the trial did establish that the treatment is safe to use and has efficacy in **carbapenem-sensitive** complicated UTI.  CREDIBLE-CR found increased mortality in the cefedirocol arm but the trial design and high mortality meant this was a risk inherent in the trial design and may have occurred due to chance.  The primary outcome of CREDIBLE-CR was   * For nosocomial pneumonia/bloodstream infection/sepsis- clinical cure at test of cure (7 days +/- 2) in the carbapenem-resistant microbiological ITT population. * For cUTI –microbiological eradication at test of cure (7 days +/- 2) In the carbapenem-resistant microbiological ITT population   In this trial it took 2.5 years to recruit 150 patients across the world- highlighting that the clinical presentation and microbiological profile is fortunately infrequent. 34% of those receiving cefiderocol and 18% of those in the control arm (best available therapy) died by the end of study. Although end-point rates were similar in the primary outcome the design of the trial the trial was not non-inferiority but a descriptive study.  APEKS-NP  In this trial adults with hospital-acquired, ventilator-acquired or health-care associated gram negative pneumonia were treated with either cefiderocol or meropenem 2g tds in combination with linezolid. The primary end-point was all cause mortality at D14 in the intention to treat population and this was a non-inferiority trial with a 12.5% margin. All cause mortality was 18/145 patients treated with linezolid and cefiderocol and 17/146 patients treated with linezolid and meropenem. This is applicable to UK patients (though we may use meropenem 1g tds and not via infusion as in this trial) so can be considered in evidence. |
| 1. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | Primary outcome measures used were not surrogates. |
| 1. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | Not that I am aware of |
| 23. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | A systematic review of the evidence might be limited by consideration of use in an empiric setting in which it might not be reasonably used in UK practice. |
| 24. How do data on real-world experience compare with the trial data? | The trials were in specific subpopulations so may not always be applicable. |
| **Equality** |  |
| 25a. Are there any potential [equality issues](https://www.nice.org.uk/about/who-we-are/policies-and-procedures/nice-equality-scheme) that should be taken into account when considering cefiderocol? | Racial variation, gender, and ethnic and deprivation factors have been associated with rates of severe sepsis in some settings. This should be considered in the analysis. |
| 25b. Consider whether these issues are different from issues with current care and why. | If the treatment is of more benefit for a particular population when introduced this may be relevant. |
| **Key messages** |  |
| 26. In up to 5 bullet points, please summarise the key messages of your statement. | * Cefiderocol is unlikely to be appropriate for empiric use in a current UK setting * Cefiderocol may provide a benefit in those with highly-resistant infections or with intolerance to other agents * Cefiderocol does not require therapeutic drug monitoring and may have lower rates of side effects than alternative agents for an individual patient * Cefiderocol may provide effective salvage treatment in rare situations * The number of patients likely to currently benefit from cefiderocol is very small but the clinical impact may be very high for those patients |

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