Clinical and NHS commissioning expert statement

Ceftazidime with avibactam for treating severe aerobic Gram-negative bacterial infections

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

You can provide a unique perspective on ceftazidime with avibactam 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
* We are committed to meeting the requirements of copyright legislation. If you intend to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
* Your response should not be longer than 13 pages.

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| **About you** |  |
| 1. Your name | Dr Nick Brown |
| 2. Name of organisation | British Society for Antimicrobial Chemotherapy (BSAC)Royal College of Pathologists |
| 3. Job title or position | Consultant Medical Microbiologist, Cambridge University Hospitals NHS Foundation Trust, Cambridge |
| 4. Please specify your role from the examples given: | [x]  An employee or representative of a healthcare professional organisation that represents clinicians[x]  A specialist in the treatment of people with this condition[ ]  A specialist in the clinical evidence base for this condition or ceftazidime with avibactam[ ]  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 ceftazidime with avibactam[ ]  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 Society for Antimicrobial Chemotherapy (BSAC) &****Royal College of Pathologists** |
| 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. |  |
| **Current treatment of severe gram-negative infections, where resistance is suspected/confirmed** |  |
| 9. What is the main aim of treatment? |  |
| 10. What do you consider a clinically significant treatment response? |  |
| 11. How are severe gram-negative infections, where resistance is suspected/confirmed, currently treated in the NHS?  |  |
| a) Are any clinical guidelines used, and if so, which?  |  |
| 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.)
 |  |
| 1. What impact would ceftazidime with avibactam have on the current pathway of care?
 |  |
| Using ceftazidime with avibactam in clinical practice |  |
| 12. To what extent and in which population(s) is ceftazidime with avibactam currently being used in your local health economy? |  |
| 13. Will ceftazidime with avibactam be used (or is it already used) in the same way as current care in NHS clinical practice?  |  |
| 14. What rules will be used to start treatment? Do these include any additional testing that is not currently routinely available on the NHS?  | Infection due to an organism that is resistant to more commonly used narrow spectrum antibiotics. Antimicrobial susceptibility testing will be required (but this is performed as routine already). |
| 15. If information about the pathogen is very limited (ie susceptibility data and gene testing results are not yet available) – what specific rules/criteria determine that it’s appropriate to use ceftazidime with avibactam in the risk-based empiric treatment setting? | I propose that it would be inappropriate to use ceftazidime-avibactam in the absence of specific susceptibility data indicating that it is required to treat a multiply resistant organism where there are no other treatment options. That is, in general, empiric treatment with this agent would be inappropriate. On occasion, a patient may be known to have been previously colonised or infected with a resistant organism and then deteriorate. In this circumstance, it is possible to envisage a scenario where a clinician might want to ‘cover’ the known resistant organism using ceftazidime-avibactam. However, this is not a situation where knowledge about the pathogen is limited. |
| 16. Will ceftazidime with avibactam 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) | There are no issues relating to its use. It is similar to other commonly used beta-lactam antibiotics. |
| Benefits of ceftazidime with avibactam |  |
| 17. Do you expect ceftazidime with avibactam to provide clinically meaningful benefits compared with current care?  |  |
| 18. Please comment on the potential benefits of ceftazidime with avibactam 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/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam). |  |
| 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 any published evidence relating to ceftazidime-avibactam use and outcome measures that might relate to transmission value. However, I think that this is an important category to consider because the antibiotic-resistant infections likely to be treated with ceftazidime-avibactam are currently relatively uncommon in the UK and therefore prevention of onward spread is seen as an infection control high priority (akin to a ‘search and destroy’ approach). It would be of theoretical benefit to ensure that infections are treated with an effective antibiotic to ensure more rapid cure. A further consideration is that patients often have long term colonisation with the resistant organism as part of the gut flora and this means that they are a potential risk to others even when an infection has been treated satisfactorily. Of the proposed outcome measures, length of stay is likely to be the most relevant with regards to transmission, as patients who have been discharged to home are unlikely to be a source of transmission to others.  |
| 1. Enablement value (enabling other treatments and procedures to take place eg 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?  | Colonisation with a multiply-resistant microorganism may be considered a relative contraindication for some procedures (for example, bone marrow transplantation, solid organ transplantation) although this is not absolute and many Units are now prepared to proceed regardless (with appropriate infection control precautions to prevent transmission in hospital). This is a pragmatic approach in a patient with a life-threatening condition, where it is known that eradication of the resistant organism from the gut is probably impossible. Ceftazidime-avibactam will have no influence on this situation. However, ceftazidime-avibactam might have value in treating a septic patient with an infection due to a resistant organism where the presence of the infection would delay the planned intervention. Treatment in this situation could be considered enablement.I cannot think of a situation in current UK practice where ceftazidime-avibactam would have enablement value wider than the immediate patient.Any study on a critical care unit would need to be performed in an area where the prevalence of resistant organisms is high (specifically carbapenemase-producing organisms such as KPC that would be susceptible to ceftazidime-avibactam).  |
| 1. Spectrum value (benefits of replacing broad spectrum antimicrobials with narrow spectrum antimicrobials).
 | Ceftazidime-avibactam is a very broad spectrum agent in its own right and would not have spectrum value. |
| 1. Insurance value (having antimicrobials available for sudden increase of infections with pathogens resistant to existing antimicrobials).
 | Ceftazidime-avibactam does have value in increasing the number of therapeutic options for the treatment of resistant organisms. Currently used antimicrobial regimens currently include a combination of different agents that are potentially toxic (e.g. colistin), or of limited efficacy.  |
| 1. Diversity value (having a range of treatment options available)
 | As above, ceftazidime-avibactam increases the range of available options and therefore may reduce the reliance on currently used agents. |
| 19. Which of these elements of value (transmission, enablement, spectrum, insurance, diversity) does ceftazidime with avibactam have the greatest potential to impact? That is, the greatest potential to improve population health outcomes? | My own view is that ceftazidime-avibactam has insurance value and diversity value  |
| 20. Are there any groups of people for whom ceftazidime with avibactam would be more or less effective (or appropriate) than the general population?  | No |
| 21. How do any side effects or adverse effects of ceftazidime with avibactam affect the management of infection and the patient’s quality of life? | No significant issues. Patients who are allergic to penicillins may also be allergic to ceftazidime-avibactam. |
| **Sources of evidence** |  |
| 22. Do the clinical trials on ceftazidime with avibactam reflect current UK clinical practice? | Clinical trials in patients with Gram negative blood stream infection or patients with hospital acquired pneumonia may not reflect the likely restricted use of cetazidime-avibactam in the UK, where only patients with an infective organism resistant to all other options are treated. However, they do provide reassurance of efficacy in the general type of infection.Other use of cetazidime-avibactam is likely to be off-label. For example, there is an increasing practice of using cetazidime-avibactam in combination with aztreonam in the treatment of metalo-beta-lactamase-producing organisms (eg. NDM carbapenemases). There is no strong evidence to support this practice, but its benefit is plausible. |
| 1. If not, how could the results be extrapolated to the UK setting?
 | Ideally, performing trials using only patients with infections due to resistant organisms (for example, those producing carbapenemases). This is problematic as the number of these infections is small. |
| 1. What, in your view, are the most important outcomes, and were they measured in the trials?
 |  |
| 1. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?
 |  |
| 1. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?
 |  |
| 23. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?  | No. |
| 24. How do data on real-world experience compare with the trial data? | As above. Our own local use of cetazidime-avibactam has been driven by the type of carbapenemase-producing organisms that we encounter. We see few KPC producing organisms (where cetazidime-avibactam might be commonly used) and more NDM producing organisms (where we are using cetazidime-avibactam in combination with aztreonam). |
| **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 ceftazidime with avibactam? | Not in UK practice |
| 25b. Consider whether these issues are different from issues with current care and why. |  |
| **Key messages** |  |
| 26. In up to 5 bullet points, please summarise the key messages of your statement. | * My response is written to add to the professional response from BSAC and RCPath and does not repeat all of the points raised.
* Cetazidime-avibactam may have insurance value and diversity value, but I feel that it will be difficult to measure transmission, enablement and spectrum value.
* In part, this is because patients with infections due to multiply-resistant organisms also have gut colonisation with the organism. This is not impacted by treatment with cetazidime-avibactam and the risks of transmission or later infection remain.
* Studies using length of stay in hospital are likely to have most relevance to transmission value.
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