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 Andrew Seaton |
| 2. Name of organisation | NHS Greater Glasgow an Clyde and Scottish Antimicrobial Prescribing Group |
| 3. Job title or position | Consultant in infectious diseases and Chair |
| 4. Please specify your role from the examples given: | An employee or representative of a healthcare professional organisation that represents cliniciansA specialist in the treatment of people with this conditionA specialist in the clinical evidence base for this condition or ceftazidime with avibactamCommissioning services for a CCG or NHS England in generalCommissioning services for a CCG or NHS England for the condition for which NICE is considering ceftazidime with avibactamResponsible 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)** |
| 6. Did your nominating organisation make a submission? | Yes |
| 7. Did you write your nominating organisation’s submission? | No |
| 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. | Yes |
| **Current treatment of severe gram-negative infections, where resistance is suspected/confirmed** |  |
| 9. What is the main aim of treatment? | Cure of infection and survival of patientTo support the limitation of carbapenem antibiotics as part of an antimicrobial stewardship (AMS) strategy |
| 10. What do you consider a clinically significant treatment response? | Dependent on site of infection. Broadly: clinical improvement such that antibiotic therapy is discontinued with no clinical or microbiological relapse within 28-30 days |
| 11. How are severe gram-negative infections, where resistance is suspected/confirmed, currently treated in the NHS?  | Depending on the clinical situation and nature of the resistance mechanism treatment will vary: Colistin + Meropenem, Tigecycline + Meropenem, Colistin + Amikacin + Meropenem. Ceftaz/Avibactam in this context may be co-prescribed with anther agent such as meropenem.In addition Ceftaz/Avibactam may be used as a carbapenem sparing agent as part of an AMS initiative. In this case it would be used as an alternative to meropenem e.g. in ESBL infections |
| a) Are any clinical guidelines used, and if so, which?  | [Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party† | Journal of Antimicrobial Chemotherapy | Oxford Academic (oup.com)](https://academic.oup.com/jac/article/73/suppl_3/iii2/4915406?login=true) |
| 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.)
 | Well defined in that treatment is very much led by clinical microbiologists based on the resistance profile of the organism isolated and the tolerability of the regimen (including renal and hepatic function).Treatment choices poorly defined as very much individualised.Laboratory diagnostics are crucial to guide tailored treatmentExperience is from Scotland |
| 1. What impact would ceftazidime with avibactam have on the current pathway of care?
 | It would be a welcome addition to the available antimicrobial options. It would likely be used as a carbapenem sparing antibiotic to limit carbapenem resistance. Particularly useful in antimicrobial stewardship initiatives in critical care and haemato-oncology units where such MDR Gram negative infections are more prevalent. Its use would be limited to specialist initiation under microbiology/infection specialist direction |
| 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? | Use is limited to clinical microbiology initiation in Critical care, Haemato-oncology, Cystic fibrosis and Renal units. In Scotland at least use is very low volume currently |
| 13. Will ceftazidime with avibactam be used (or is it already used) in the same way as current care in NHS clinical practice?  | Use would be more widespread as AMR increases |
| 14. What rules will be used to start treatment? Do these include any additional testing that is not currently routinely available on the NHS?  | Use will be led/initiated by infection specialists - including as part of a specific AMS initiative to spare carbapenemsTesting for sensitivity within the microbiological laboratory |
| 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? | Expert microbiology advice with understanding of local epidemiologyOrAs part of local AMS strategy to limit empirical carbapenem use |
| 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) | No difference and no additional requirements |
| Benefits of ceftazidime with avibactam |  |
| 17. Do you expect ceftazidime with avibactam to provide clinically meaningful benefits compared with current care?  | Major benefit might be in some circumstances to limit carbapenem use |
| 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.  | By limiting use of empirical carbapenems in higher risk patients development of carbapenem resistance may be reduced |
| 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?  | Reduction in AMR will enable other treatments and reduce associated healthcare associated infection risks This could be particularly relevant in the context of rise in MDR Gram negative infections observed in some large COVID-19 critical care units where empirical escalation to meropenem is frequent |
| 1. Spectrum value (benefits of replacing broad spectrum antimicrobials with narrow spectrum antimicrobials).
 | Yes – through minimisation of use of carbapenem agents |
| 1. Insurance value (having antimicrobials available for sudden increase of infections with pathogens resistant to existing antimicrobials).
 | Value particularly in resistant Pseudomonal infections e.g. Cystic fibrosisAlso provides an option for those patients who experience intolerance to other anti-Gam negative agents  |
| 1. Diversity value (having a range of treatment options available)
 | Yes – gives other treatment options as well as another AMS tool to curb over use of carbapenems |
| 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? | Transmission – reduction in empirical carbapenem use |
| 20. Are there any groups of people for whom ceftazidime with avibactam would be more or less effective (or appropriate) than the general population?  | It would likely be used as a carbapenem sparing antibiotic to limit carbapenem resistance. Particularly useful in antimicrobial stewardship initiatives in critical care and haemato-oncology units where such MDR Gram negative infections are more prevalent. Its use would be limited to specialist initiation under microbiology/infection specialist directionAlso drug interactions or other patient factors (e.g. allergy, intolerability, renal failure) may sometimes limit use of alternative antibiotics |
| 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? | Generally well tolerated compared to comparator regimens |
| **Sources of evidence** |  |
| 22. Do the clinical trials on ceftazidime with avibactam reflect current UK clinical practice? | No. The drug is used infrequently and the reality is it would be used for:1. Specific patients (with MDR infection) rather than clinical conditions (intra-abdominal infection/ complex UTI)
2. Specific AMS initiatives – a means to target reduction in carbapenems
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| 1. If not, how could the results be extrapolated to the UK setting?
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| 1. What, in your view, are the most important outcomes, and were they measured in the trials?
 | Non-inferiority in intra-abdominal and complex urinary tract infections including bacteraemia. Non-inferiority implies an alternative treatment (to carbapenems) can be utilised in some situations as determined by infection specialists |
| 1. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?
 | Clinical trials examine cure vs failure of treatment usually at 28-30 days post treatment |
| 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 although there would be concern for C. difficile if use of this agent were to become uncontrolled – this should be prevented by infection specialist control of the agent. |
| 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? | There is not widespread use of this agent as yet due to its non-formulary status. Most data therefore comes from either clinical trials or compassionate use. |
| **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 that I am aware of |
| 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. | * **Antimicrobial stewardship**: Urgent need for antimicrobials to (when required) **substitute** carbapenems to minimise carbapenem resistance and preserve their future use
* **Direct patient care:** Urgent need for antimicrobials to **augment the available agents** in treatment of multidrug resistant Gram negative infections
* Evidence of non-inferiority to carbapenems in some key clinical situations which allows this agent to be considered for targeted use as above
* Potential benefits over other agents where toxicity / treatment failure may be higher (e.g. Colistin, Tigecycline)
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Thank you for your time.

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