Systematic review of room temperature stability of key beta-lactam antibiotics for extended infusions in inpatient settings

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ejhpharm-2023-003855).

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Received 24 May 2023
Accepted 26 September 2023
Published Online First 17 October 2023

EAHP Statement 3: Production and Compounding.

ABSTRACT

Background Extended infusion (EI) of beta-lactam antibiotics may offer clinical benefits aligned with improved probability of target attainment for critical pharmacokinetic/pharmacodynamic parameters that correlate with efficacy. There is much research interest in prolonged and continuous infusions (collectively, extended infusions) of beta-lactams to improve patient outcomes, particularly in critically ill patients in intensive care. While definitive clinical trial data demonstrating beneficial outcomes is awaited, there has been limited focus on the stability of the agents given by EI, which may be an equally critical parameter. EI may allow for savings in nursing time due to reduced need for drug reconstitution. We set out to examine the data for stability for EI at room temperature, consistent with the requirements of 'A Standard Protocol for Deriving and Assessment of Stability- Part 1 Aseptic Preparation (Small Molecules)', which allows a 5% loss of active pharmaceutical ingredient (API) applicable for those territories that use the British Pharmacopoeia also for a 10% loss applicable in much of rest of the world.

Methods Searches using preferred reporting items for systematic reviews and meta-analyses (PRISMA) principles for stability data on freshly prepared beta-lactam antimicrobials for extended administration at room temperature (at or above 23°C) were conducted in November 2021 and updated in December 2022.

Results We found data to support the extension of the shelf life of 12 key beta-lactam antibiotics once reconstituted (aztreonam, amoxicillin, benzylpenicillin, flucloxacillin, piperacillin/tazobactam, cefazolin, cefmetazole, ceftaroline, ceftazidime, ceftriaxone, imipenem and meropenem) compliant with the NHS protocol, and data for five other agents (ticarcillin, cefepime, cefiderocol, cefoxitin and doripenem) which would be acceptable in regions outside the UK beyond that listed in the Summary of Product Characteristics. This review has not been registered under PROSPERO.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Extended infusions of beta-lactam antibiotics may support achievement of desired pharmacokinetic and pharmacodynamic targets in critically ill patients, but the evidence for clinical benefit is debated. Extended infusions require assurance that the drug is stable and meets pharmacopeial specifications or stability standards over the infusion period, however many summaries of manufacturers product characteristics for key antibiotics lack this information. This might limit the benefits that could be gained by extended infusion of these agents.

WHAT THIS STUDY ADDS

⇒ This study adds to the evidence base for extended infusion of 12 key beta-lactam antibiotics for territories using 95–105% limits for active pharmaceutical ingredient (API), and a further five agents for territories using 90–110% API to confirm stability, by systematically assessing data that supports the extension of their shelf life once reconstituted. No shelf life extension could be determined for a further six agents.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This systematic review provides data to support the wider use of extended infusions in clinical practice for key beta-lactam antibiotics, which may deliver clinical benefit to patients and release nursing time spent preparing intermittent infusions.

INTRODUCTION

There is considerable interest in approaches to optimise the clinical use of antibiotics for critically ill patients, given the increasing challenge of antimicrobial resistance, the relative dearth of new antibiotics coming to market and the morbidity and mortality associated with infection caused by multi-resistant pathogens.[1 2]

Beta-lactam antibiotics remain the most widely used classes of antibiotics, both in the UK and world-wide.[1 3] These agents demonstrate time dependent killing,[4] with effectiveness related to proportion of time that the free drug concentration is above the minimum inhibitory concentration (MIC) for the organism (%fT>MIC), with a minimum of 20–40% required for bacteriostatic effects, depending on the agent, and higher for bactericidal effect; concentrations that are more than four times the MIC of the pathogen further increase effectiveness.[5 6] Achieving these targets can be challenging for critically unwell patients due to altered physiology (increased volumes of distribution or augmented renal clearance, for example), deep-seated infections or patients infected with pathogens with high MICs.[5] For example, recent French guidelines for critically ill patients advocate achievement of a $\%fT>_{4\text{-}8}$xMIC for 100% of the dose interval.[7]

To cite: Jenkins A, Jamieson C, Santillo M. *Eur J Hosp Pharm* 2024;**31**:2–9.

Administering beta-lactam antibiotics by extended infusion (EI) (collectively, either a continuous infusion (CI) over 24 or more hours, or prolonged infusion (PI) over less than 24 hours), rather than intermittent or short infusion would increase the probability of target attainment for these parameters, maximising efficacy and limiting the emergence of resistance.[8] Numerous clinical trials and meta-analyses have been carried out over the last two decades to investigate whether continuous infusion of these agents improves outcomes such as mortality or clinical cure rates, but a definitive answer is still unknown.

A meta-analysis of trials of extended or continuous infusion vs short-term infusion of cephalosporins found no difference in clinical cure rates or mortality.[9] Roberts *et al* conducted a meta-analysis of three randomised clinical trials of patients with severe sepsis treated with continuous or intermittent infusions of beta-lactam antibiotics. They found that CI was associated with decreased hospital mortality at 30 days and higher clinical cure rates, but this was not statistically significant.[10] The meta-analysis of trials looking at extended or continuous infusions of a carbapenem or piperacillin-tazobactam conducted by Falagas *et al* found CI resulted in lower mortality than short-term infusions.[11] Vardakas *et al* conducted a meta-analysis on the effect of CI of anti-pseudomonal beta-lactams (cephalosporins, carbapenems and penicillins) on mortality of patients with sepsis, compared with short-term administration. They found that it was associated with lower all-cause mortality (risk ratio 0.7, 95% CI 0.56 to 0.87) for carbapenems and penicillins but not cephalosporins.[12] The BLING III trial is a prospective, multicentre, open phase 3 trial currently underway. BLING III is comparing continuous infusion with standard intermittent infusion of beta-lactam antibiotics in critically ill patients with sepsis and may address the confounding seen in other studies and meta-analyses.[13]

In addition to the potential clinical benefits of EI for beta-lactams, there is also a potential workforce benefit. A recent time and motion study found it can take up to 22 minutes to prepare and administer an intravenous dose of medication.[14] Given that many beta-lactam antibiotics require frequent dosing, administration via extended infusion could release time for other patient care duties.

Many studies have looked at the clinical impact of extended or continuous infusions of antimicrobial agents, however the physicochemical stability of the agents involved in these studies has been less focused on. Recent guidelines from France, while advocating the use of CI for critically ill patients, also note that consideration must be given to the chemical stability of these antibiotics over the intended infusion period.[7] Ensuring that stability is maintained over the time course of the infusion is an important consideration, to ensure the agent can deliver the clinical benefit intended while providing assurance that there are no degradants that may cause toxicity.

We aimed to review the evidence for room temperature (25±2°C) stability of key beta-lactam antibiotics to provide data on which agents would be suitable for an extended infusion at room temperature. A Standard Protocol for Deriving and Assessment of Stability- Part 1 Aseptic Preparation (Small Molecules)[15] was used as the framework to assess the quality of the evidence. In addition to setting out the required methodology for deriving stability, the protocol sets limits on the amount of active pharmaceutical ingredient (API). This limit is 95–105% of the starting concentration at the end of the assigned shelf life. Exceptions to this limit are if there is a British Pharmacopoeia (BP) monograph specifying a different acceptable range, for example flucloxacillin and benzylpenicillin infusions. In contrast in territories where the BP is not used API ranges of 90–110% are used to assign stability and therefore shelf-life. We extracted data for both allowable API ranges since the data would be relevant for an international audience. We also aimed to specify the longest appropriate time period for an extended infusion for each agent, where this would be longer than that listed in the Summary of Manufacturer Product Characteristics (SmPC). We set the maximum duration of stability at 24 hours. This is the generally accepted limit assigned to a product prepared outside the pharmacy for example, in the ward environment. In this way, clinicians can be confident that the agents chosen for extended infusions are suitable for this administration method and meet pharmacopoeial requirements.

METHOD

This systematic review searched MEDLINE, EMBASE, CINAHL and PubMed for articles published in full-text for stability data on freshly prepared beta-lactam antimicrobials for extended administration at room temperature. The initial search was completed in November 2021 and updated in December 2022. For the full search strategy see online supplemental information.

The titles and abstracts of all citations were reviewed for inclusion by two of the three authors. Any discrepancies were considered and resolved by the third author. Citations were considered appropriate for inclusion if a beta-lactam antimicrobial shelf-life was assessed using a stability-indicating method at temperatures at or above 23°C.

Following title and abstract review, citations included were similarly reviewed in full text for final inclusion by the authors. Additionally, the references of all included texts were searched for additional papers not identified by the previously described process. Data from the final list of included papers were extracted to a spreadsheet to assess for compliance with methodological standards outlined in A Standard Protocol for Deriving and Assessment of Stability Part 1- Small Molecules.[15] Data extraction fields included:

1. Author(s), date and place of publication
2. Beta-lactam studied
3. Concentration(s) tested
4. Storage conditions including temperature, humidity, and presence of light
5. Range of active pharmaceutical ingredient required by the citation to confer stability
6. Presence of a stability indicating assay
7. Physical stability assessments reported
8. Time points
9. Number of samples and replicated studies

Finally, the extracted information was compared with the United Kingdom (UK) and European Union (EU) SmPC and in their absence we compared the information with the US monograph. The aim throughout was to evaluate if the data from included papers supported extension of shelf-life beyond that stated in the licensed product information. Data will be presented for two limits, 95–105% API for those territories using the BP and 90–110% for the rest of the world.

RESULTS

Search outputs from databases yielded the following outputs: MEDLINE (129), EMBASE (139), CINAHL (48) and PubMed (196). Database outputs were combined and deduplicated resulting in 214 citations. Seventy references were excluded following title and abstract review, nine reports were unable to

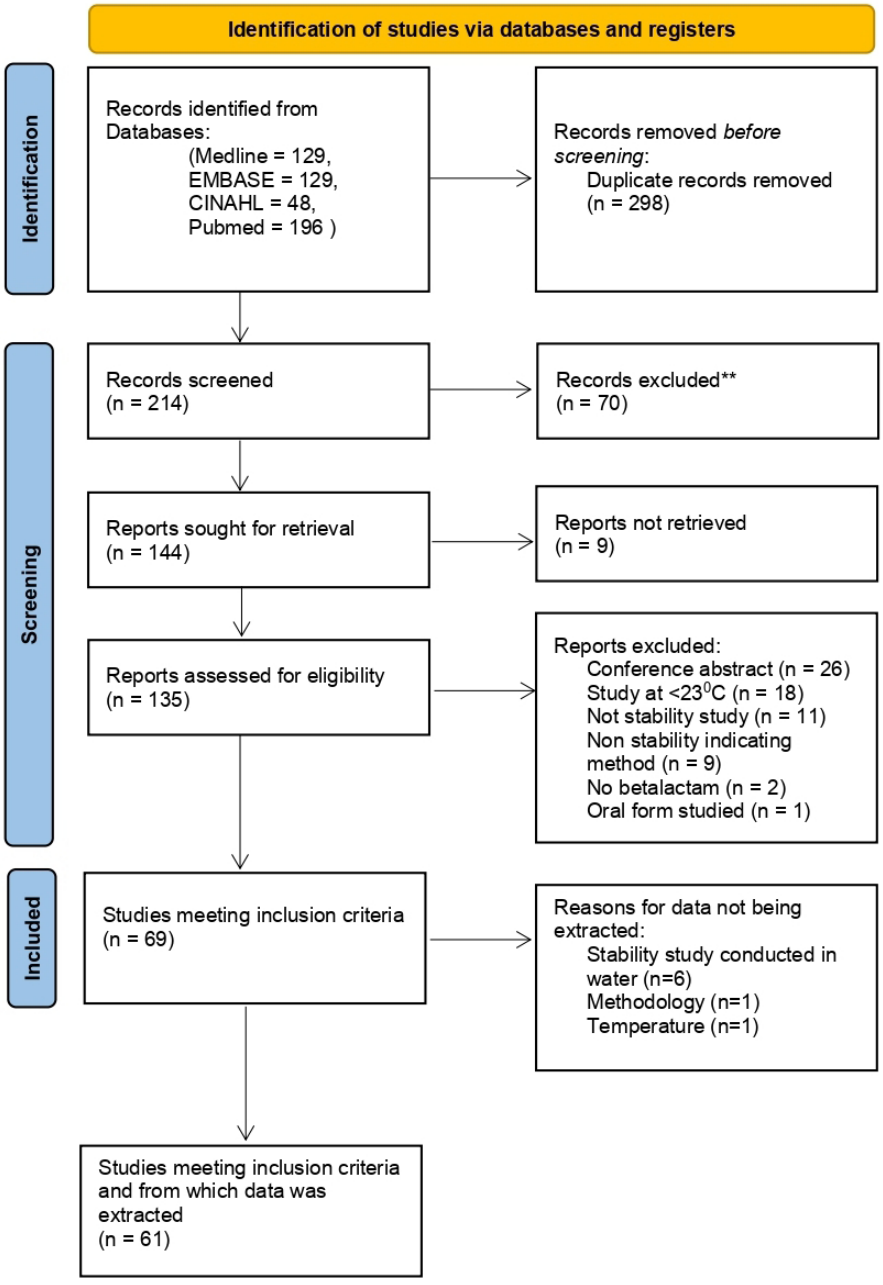

Figure 1 PRISMA Diagram.[87]

be accessed in full-text and a further 66 were excluded following review of the full-text (figure 1).[16]

A total of 69 papers reporting stability data on 23 beta-lactam antibiotics met the criteria described in the review protocol (see online supplemental information) and were included in the review. Data from eight papers were not extracted, the reasons for this are shown in the table 1S in the online supplemental information. Of the 61 included papers from which data were extracted, 10 were published before 2000, 13 were published between 2000–2009 and 38 were published between 2010–2022.

Stability research was conducted in 16 countries with USA the dominant contributor with 23 papers published. Seven papers published research from each of Australia and France and six from Belgium. The full country list can be found in online supplemental table 2S.

Of 23 beta-lactams included in the stability reports there were sufficient data to extend the shelf life of the reconstituted product beyond that stated in the SmPC or the SmPC stated a shelf life of 24 hours. This was the case for 12 medicines using 95–105% limits of API and five medicines using the 90–110% limits of API (table 1).

Monobactams

Data from two studies support shelf life extension of aztreonam 10–120 mg/mL in sodium chloride 0.9% to 24 hours, an increase over the 60 minute shelf life listed in the SmPC.[17–19]

Penicillins

Penicillins are known to have limited stability in aqueous solution. Amoxicillin stability is concentration dependent, with higher concentrations being less stable – we found data to support a 6 hour infusion at a concentration of 25 mg/mL in sodium chloride 0.9%.[19–23]

Table 1 Summary of beta-lactam stability when stored at 25±2°C.

Agent	Summary of Product Characteristics: Room temperature stability data (Drug manufacturer)	Statement on stability permitting up to 5% loss of API unless alternative standard in BP monograph (UK standard)*	Statement on stability permitting up to 10% loss of API	Additional comments	References
Ampicillin	Immediate use	Insufficient evidence to extend beyond SPC			19 25 35 36 37
Amoxicillin	30 min	Amoxicillin 25 mg/mL in NaCl 0.9% for 6 hours.			19 20 21 22 23
Aztreonam	24 hours at 2–8°C followed by 60 min at room temp	Aztreonam 10–120 mg/mL in NaCl 0.9% stable for 24 hours at room temp			17 18 19
Benzylpenicillin*	Immediate use	Benzylpenicillin 60 mg/mL (unbuffered) in Acetate Ringers Solution stable for 24 hours at room temp		Consideration of pH variation with acetate Ringers. International variation.	19 25 26 27–29
Cefazolin	12 hours	Cefazolin 5–40 mg/mL in NaCl 0.9% or glucose 5% stable for 24 hours at room temperature.			19 31 41–46
Cefepime	18 hours	Insufficient evidence to extend beyond SPC	Cefepime 8 mg/mL in sodium chloride 0.9% or glucose 5% at room temperature for 24 hours		17–19 46–49
Cefiderocol	24 hours at 2–8°C followed by 6 hours at 25°C	Insufficient evidence to extend beyond SPC	Cefiderocol 62.5 mg/mL in NaCl 0.9% or glucose 5% for 12 hours at room temperature		19 50 51
Cefmetazole	N/a	Cefmetazole 33 mg/mL in NaCl 0.9% or glucose 5% stable for 8 hours at room temperature	Cefmetazole 33 mg/mL in NaCl 0.9% or glucose 5% stable for 24 hours at room temperature		19 31
Cefotaxime	24 hours	Insufficient evidence to extend beyond SPC			19 60 61
Cefoxitin	4 hours at 25°C	Insufficient evidence to extend beyond SPC	2–200 mg/mL in sodium chloride 0.9% or glucose 5% stable for 24 hours at room temperature	Some evidence for extension however fresh studies would be required	19 44 52
Ceftaroline	12 hours at 2–8°C and 6 hours at 25°C	Ceftaroline 6 mg/mL in NaCl 0.9% stable for 12 hours at room temp	Ceftaroline 6 mg/mL in NaCl 0.9% stable for 24 hours at room temperature		19 53 54
Ceftazidime	2 hours at 25°C	Ceftazidime 5–120 mg/mL in NaCl 0.9% for 16 hours at room temperature			18 19 24 44–46 49 55–59
tolazone-tazobactam	24 hours at room temperature	Insufficient evidence to extend beyond SPC			19 62–64
Ceftriaxone	Immediate use	Ceftriaxone 5–40 mg/mL in NaCl 0.9% for 24 hours at room temperature			19 46
Cefuroxime	Immediate use	Insufficient evidence to extend beyond SPC			19 44
Doripenem	12 hours at 25°C	Insufficient evidence to extend beyond US monograph	Doripenem 5.3–11.1 mg/mL in sodium chloride 0.9% for 24 hours at room temperature	US data sheet only	19 31 65–67
Ertapenem	6 hours at 25°C	Insufficient evidence to extend beyond SPC		Shelf-life should not be extended until the nature of solution discolouration is investigated	19 81
Flucloxacillin†	Immediate use	Flucloxacillin 50 mg/mL in sodium chloride 0.9% for 24 hours			19 27 30
Imipenem-cilastatin	Immediate use	2.5–5.0 mg/mL 3 hours at 25°C in NaCl 0.9%	2.5–5.0 mg/mL in sodium chloride 0.9% for 9 hours at room temperature		18 19 68
Meropenem	From immediate use up to 4 hours depending on manufacturer	Meropenem 6.25–25 mg/mL in NaCl 0.9% Stable for 4 hours at 25°C	Meropenem 10–12 mg/mL in sodium chloride 0.9% or glucose 5% stable for 8 hours at room temperature. Meropenem 40 mg/mL in sodium chloride 0.9% or glucose 5% stable for 6 hours at room temperature		18 19 31 69–80
Piperacillin-tazobactam	From immediate use to 24 hours depending on manufacturer	Piperacillin-tazobactam 22.5–90 mg/mL in NaCl 0.9% or glucose 5% at least 24 hours at room temp			17 19 31–33
Temocillin	24 hours at 25°C	Insufficient evidence to extend beyond SPC			19 38–40
Ticarcillin-clavulanate	N/a	No UK or EU SPC No statement on stability at room temperature due to limited data available	Ticarcillin-clavulanate 12/0.8-150/10 mg/mL in sodium chloride 0.9% stable for 24 hours at room temperature.		17 34

*British Pharmacopeial standard for benzylpenicillin infusion permits API range of 90–110%.
†British Pharmacopeial standard for flucloxacillin infusion permits API range of 90–105%.
API, active pharmaceutical ingredient ; BP, British Pharmacopoeia; EU, European Union; min, minutes; N/a, not applicable; NaCl, Sodium chloride 0.9%; SPC, Summary of Product Characteristics; temp, temperature; UK, United Kingdom; US, United States.

Benzylpenicillin infusion is one product for which the BP standard permits an API range of 90–110%.[24] Benzylpenicillin 60 mg/mL retained 90% of the API for 24 hours when reconstituted with acetate Ringer's solution.[19 25–29] Acetate Ringers' solution is rarely used in the UK or the EU as a diluent for pharmaceuticals and the pH of commercially available solutions can differ between countries; care should be taken before extrapolating to local practice.

In the BP 2024,[24] flucloxacillin infusion limits will be permitted to be 90–105%, consequently a shelf life of flucloxacillin 50 mg/mL in sodium chloride 0.9% can be extended to 24 hours at room temperature based on the 2024 monograph.[19 27 30]

We found several papers investigating the stability of piperacillin-tazobactam, with some conflicting results and we have accordingly assigned a shelf life of 24 hours within the concentration range 22.5–90.0 mg/mL when diluted in either sodium chloride 0.9% or glucose 5%.[17–19 31–33]

Ticarcillin with clavulanic acid has no European or UK SmPC, however the US monograph supports stability as follows with the concentration as expressed in ticarcillin: 10–100 mg/mL in sodium chloride 0.9% or glucose 5% for 24 hours.[34] Arlicot et al., studied ticarcillin-clavulanic acid diluted in sodium chloride 0.9% at concentrations between 12/0.8 – 150/10 mg/mL at 35°C.[17] At 24 hours all pumps retained more than 90% of the active pharmaceutical ingredients.

Data from included papers for ampicillin[25 35–37] and temocillin[38–40] was insufficient to extend the shelf life beyond that stated in the SmPC.

Cephalosporins

Cefazolin in a defined concentration range of 5–40 mg/mL and diluted in sodium chloride 0.9% or glucose 5% can be assigned a shelf life of 24 hours, an increase from the 12 hours specified in the SmPC.[19 31 41–46]

While there is insufficient evidence to extend the shelf life of cefepime or cefiderocol using 95–105% limits, for those using 90–110% limits cefepime 8 mg/mL in either glucose 5% or sodium chloride 0.9%, stability can be extended to 24 hours.[17–19 47–49] Similarly, cefiderocol 62.5 mg/mL in glucose 5% or sodium chloride 0.9% can be extended to 12 hours at room temperature.[50 51]

Cefmetazole, although not licensed in the UK or the EU, can be assigned an 8 hour shelf life at a concentration of 33 mg/mL and diluted in sodium chloride 0.9% or glucose 5% for those using 95–105% limits and 24 hours in areas using 90–110%.[31]

There is insufficient evidence to support shelf life extension for cefoxitin when using 95–105% limits on API; however for those using 90–110% limits cefoxitin 2–200 mg/mL in sodium chloride 0.9% or glucose 5% can be given a shelf-life of 24 hours.[44 52]

At room temperature, the shelf life of ceftaroline 6 mg/mL in sodium chloride 0.9% can be extended to 12 hours when using 95–105% API limits. It can be extended to 24 hours when using 90–110% limits, an increase over that specified in the SmPC.[53 54] Assignment of stability of ceftazidime is more complex with an additional requirement for the pyridine content to remain less than 0.5% of ceftazidime starting concentration as well as retaining the active pharmaceutical ingredient.[24] Data from the studies enabled a shelf life of 16 hours to be assigned when ceftazidime 5–120 mg/mL is reconstituted in sodium chloride 0.9%.[18 44–46 49 55–59]

A 24 hour shelf life can be assigned to solutions of ceftriaxone of 5–40 mg/mL in sodium chloride 0.9% at 25°C.[46]

Data from included papers for cefepime,[48 49] cefiderocol,[50 51] cefotaxime[60 61] or ceftolozane-tazobactam[62–64] was insufficient to extend the shelf-life beyond that stated in the SmPC.

Carbapenems

Carbapenems are known to have limited stability in aqueous solutions. The doripenem SmPC supports a shelf life of 12 hours in sodium chloride 0.9% when stored at room temperature.[65] We found data to support shelf life extension for those areas using API tolerated limits of 90–110% for doripenem 5.3–11.1 mg/mL in sodium chloride 0.9% for 24 hours.[31 66 67]

The shelf life of imipenem-cilastatin at a concentration of 2.5–5.0 mg/mL in sodium chloride 0.9% could be extended to 3 hours for those using 95–105% API limits; and up to 9 hours for areas using 90–110%.[18 68]

Evidence to support an increase in shelf-life to 4 hours for meropenem 6.25–25.0 mg/mL in sodium chloride 0.9% was identified for those using 95–105% API limits.[18 19 31 69–80] In areas using 90–110% API limits, the shelf life of meropenem 10–12 mg/mL in 0.9% sodium chloride or glucose 5% could be extended to 8 hours or 6 hours at a concentration of 40 mg/mL.[18 19 31 69–80]

Data from included papers for ertapenem[81] was insufficient to extend the shelf life beyond that stated in the SmPC.

DISCUSSION

We compared the stability data described in the SmPC for a range of beta-lactam antibiotics with published stability data identified through systematic review in order to determine if an extended shelf life could be assigned to each agent, utilising the NHS protocol for deriving and assigning stability[15] as a framework. We found data to support an extension of the shelf life for 12 beta-lactam antibiotics for API limits of 95–105% and 17 when using 90–110% API limits which will allow clinicians to administer these agents by extended infusion, should clinical situations require this. Our data was from studies published in 16 countries and has broad applicability to clinical practice in the UK, EU and further afield.

In the UK, the requirement for stability assessment of small molecules such as beta-lactam antibiotics is set out in the document titled A Standard Protocol for Deriving and Assessment of Stability- Part 1 Aseptic Preparation (Small Molecules).[15] This sets out a gold standard framework for deriving stability, one requirement of which is that the assay for the active pharmaceutical ingredient is stability indicating, usually by high performance liquid chromatography, an assessment which is not uniformly carried out in published data. For example, the recent publication by Longuet *et al* assessed stability and assigned shelf lives of longer durations than we did for several antibiotics, but some of the papers included in their review did not use stability indicating methodology and were excluded from our review.[82]

While the results of meta-analyses point towards a mortality benefit with extended infusions for critically ill patients, definitive evidence is required and further clinical trials are underway including the BLING III trial.[10–13] While it was outside the scope of our systematic review, it would be useful to know if delivering suitable beta-lactams by extended infusion could provide other benefits that might outweigh the practical challenges involved. EI of penicillins such as piperacillin-tazobactam and flucloxacillin is common in outpatient parenteral antimicrobial therapy (OPAT) services in the UK.[83] While this supports operational and capacity issues in a clinically stable patient group by facilitating once daily administration, there is a question as to whether EI

of antibiotics could be used more routinely for inpatients as suggested by Vardakas *et al*.[12] There is data to support a financial argument, as EI could deliver equivalent treatment using less drug, equating to financial savings.[84–86] Using less drug may also help achieve reductions in total drug exposure for patients, which could be important for the gut microbiome, although this would need to be balanced with the concern of resistance development. However, if EI is the optimal way to deliver beta-lactam therapy by improving the probability of target attainment and resistance suppression, then this argument becomes less powerful. Further research in this area is warranted.[8]

Many beta-lactam antibiotics have relatively short half-lives and require frequent dosing. This can be a burden for nursing staff who traditionally prepare and administer drugs, and for critically ill patients with low nurse to patient ratios. It could impact patient care and while there may be an upfront time cost associated with preparation of an extended infusion, there would undoubtedly be downstream time savings as shown in several studies.[84 85] In addition, the use of extended infusions in clinical settings such as intensive care units is common, as is the infrastructure required to deliver them (eg, infusion pumps).

Our systematic review has some limitations. We only looked at the evidence for beta-lactam antibiotics with a maximum duration for 24 hours, as these are widely used in clinical practice in the EU and UK and are the main focus for clinical trials studying the clinical benefits of extended infusions. There is data for extended infusions of antibiotics such as vancomycin and the quality of the stability data for these should be reviewed.[87] EI may not be feasible in non-ICU settings such as general medical or surgical wards where patients are generally less unwell, there may be less access to infusion pumps to administer extended infusions and it may be inconvenient for patients who are mobile. Using elastomeric devices to deliver extended infusions could alleviate this problem but would require access to compounded devices which could place a burden on pharmacy aseptic services. Extended infusions may also be challenging to deliver in resource limited settings. In the UK, the document 'A Standard Protocol for Deriving and Assessment of Stability-Part 1 Aseptic Preparation (Small Molecules)' specifies a limit of acceptable active pharmaceutical ingredient loss of 5%, unless a greater loss is allowed in the British Pharmacopoeia monograph for the agent, and this is a higher threshold than is required by other countries; as such, options for EI of many beta-lactams in UK clinical practice are more limited.

There are important quality aspects to risk based stability assessment which frontline clinicians may not be aware of, so it is important that any associated guidance for extending the infusion period of antibiotics is supported by robust evidence. We recommend that pharmaceutically trained staff who are familiar and experienced in stability assessments, local standards and pharmacopoeial monographs should be consulted when proposals to extend the infusion period of drugs are made, and that there is a careful evaluation of the quality of the literature supporting any extension.

Conclusion

Our systematic review has found data to support the extension of shelf life of many beta-lactams, antibiotics (12 using API limits of 95–105% and 17 while using 90–110% limits) that will support their administration by extended infusion. While the clinical benefit of extended infusions remains to be definitively determined, there are operational benefits that can be achieved now with these data. Indeed, intensive care units in the UK, EU and further afield already have the infrastructure in place and staff with experience of using extended infusions to do this.

Correction notice This article has been corrected since it was first published. The concentration of cefiderocol should be 62.5 mg/mL rather than 7.5 mg/mL.

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Contributors All authors contributed equally to the protocol development, review of literature and authorship of the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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