

Widening the net: a literature review of antimicrobial agents with potential suitability for outpatient parenteral antimicrobial therapy services—the importance of storage and stability

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Received 16 June 2021

Accepted 1 November 2021

Published Online First

3 December 2021

EHPH Statement 3:
Production and
Compounding.

ABSTRACT

Objectives Outpatient parenteral antimicrobial therapy (OPAT) services using continuous infusions (CIs) of antimicrobial agents in elastomeric devices require evidence of acceptable stability of the agent over the infusion period. A period of refrigerated storage of filled devices, followed by the CI period, is useful for OPAT services but can present a significant challenge to the stability of drugs. The aims of this study were to review fresh-filled stability data on antimicrobials which would be useful for OPAT services and to identify suitable candidates for further assessment.

Methods Searches identified papers relating to stability assessments of antimicrobials for immediate use tested above 31°C using a stability-indicating method.

Results We identified 18 stability studies published in 12 papers between 2015 and 2020, assessing the stability of 10 agents. Aminopenicillins like ampicillin and amoxicillin appear too unstable for CI, while benzylpenicillin may benefit from buffering to improve its stability. Cephalosporins vary in their stability and CI periods of 24 hours may not be achievable. Of the carbapenems, there are insufficient data for doripenem but meropenem has been extensively studied and is unsuitable for CI longer than 6 hours. Voriconazole may be suitable for CI but needs further investigation.

Conclusions Some drugs identified in our review are unlikely to be suitable for continuous infusion in OPAT services due to instability. Using a ‘fresh-fill’ approach, without refrigerated storage, may make some drugs useful while other agents should be considered for further assessment to Yellow Cover Document standards. The impact of buffering for penicillins should be assessed further.

INTRODUCTION

Outpatient parenteral antimicrobial therapy (OPAT) is an increasingly important treatment modality for patients with infections who require prolonged intravenous antimicrobial treatment, but who can be treated outside the hospital. A recent review of UK National Health Service (NHS) aseptic services estimated that on any given day in England, 3000 patients could be treated with outpatient intravenous therapy (including OPAT) and free up hospital beds.¹ Considerations around the choice of agent and the stability assessment requirements for continuous infusions in elastomeric devices for the UK have been described recently in a systematic review for published data for antimicrobial agents

by Jenkins *et al.*² That review identified a number of publications which described antimicrobial drug stability assessments which were compliant with the NHS Yellow Cover Document (YCD) standards.³

There is no international consensus on standards for stability assessment of antimicrobial agents in elastomeric devices, relevant for OPAT services, and most countries will follow the stipulations of their relevant national pharmacopoeias. A recent review of the use of elastomeric pumps for OPAT by Diamantis *et al* highlighted the importance of assessment of the stability of antibiotics in these devices.⁴ In the UK, the YCD requirements build on, and extend the requirements of the British Pharmacopoeia. One key consideration of the YCD requirements is that stability assessment is conducted at 32°C, to mimic the ‘near body in use’ temperature seen with elastomeric devices.^{3,5} Pragmatic requirements for OPAT services mean that a period of refrigerated storage of the compounded antimicrobial, prior to administration to the patient, is desirable. That said, there are likely to be useful antimicrobial agents where such a period of storage is not feasible from a stability perspective, but which may be amenable to reconstitution in an elastomeric device immediately prior to connecting to a patient (‘fresh-fill’ model).

While the systematic review by Jenkins *et al*² included high-quality information on five key antimicrobial agents, there were a number of papers excluded because they did not include a storage period prior to the in-use stability assessment, or that the ‘in-use’ testing temperature was lower than 32°C. Additionally, Perks *et al* have highlighted the need to have stability data at temperatures up to 34°C to meet the needs of patients in warmer climates.⁶ With the increasing global challenge of antimicrobial resistance, and the need to widen the range of agents available to OPAT services worldwide, it is likely that these excluded papers contain useful information to support further investigation of these agents, either to UK YCD or other relevant standards.

The aim of this review was to extract and summarise the information from these previously excluded papers, to provide useful data to the hospital technical services and OPAT community in order to identify new potential candidates for further stability testing and assessment, to identify those agents which might only be suitable for OPAT services by using a ‘fresh-fill’ approach subject to



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To cite: Jenkins A, Shanu S, Jamieson C, *et al.* *Eur J Hosp Pharm* 2023;**30**:64–69.

appropriate safeguards and risk assessments, and to highlight those agents which are not suitable for any model of continuous infusion. The data identified may also be of use for OPAT services outside the UK which do not have a requirement to test at 32°C or where a greater than 5% loss of the active pharmaceutical ingredient (API) is acceptable.⁶

METHOD

The method for literature search has been previously described in the article by Jenkins *et al.*² This review initially searched the published literature from October 2015 to September 2020 with the search updated in December 2020.

Differences between the protocol and the review

The protocol describes pre-administration storage followed by 'in-use' testing at or above 32°C. Twelve papers were identified in which testing was conducted at 31.1°C or above without pre-administration storage which have been included for discussion in this paper.

RESULTS

Eleven citations were initially identified that adhered to the rigorous stability-testing methodological inclusion criteria of the search protocol but were excluded due to the absence of pre-administration storage testing. One additional citation was found on the search update in December 2020. Ten of these papers were full-text articles and two were conference posters. Authors of the posters were contacted and requested to provide additional information.

A total of 18 stability studies were reported in 12 publications. Of 18 studies, 4 were reports for meropenem, 2 for cefazolin and piperacillin/tazobactam, and 1 report for each of 10 different antimicrobials as follows: amoxicillin, amoxicillin-clavulanic acid, ampicillin, benzylpenicillin, cefepime, cefmetazole, ceftaroline, ceftolozane-tazobactam, doripenem and voriconazole.

Ten of 18 studies used elastomeric devices for storage, seven using the Baxter LV10 (240 mL), two used Baxter Single Day infuser (48 mL), while one did not state the device used. Three studies used infusion bags, two used polypropylene centrifuge tubes, while glass vials or syringes were each reported in one study. Finally, one citation did not state the storage device used.

Sodium chloride 0.9% was the diluent in 17 of the studies, glucose 5% was used in 9 studies, 4 studies from two papers also used what the authors described as 'glucose-electrolyte solutions' and Acetate Ringers solution. One paper used water for injections as the diluent and another study investigated the addition of phosphate or citrate buffers to sodium chloride 0.9% solution to improve stability. Table 1 shows summary of data for included papers.

Under UK standards, the tolerance limit for the API of a manufactured product is between 95% and 105% of the initial concentration at the end of the administration period unless a British Pharmacopoeia monograph exists which states otherwise. Only one study used a range of 95%–105% API to determine shelf life, with the remaining 12 allowing 10% loss. Bearing this in mind, conclusions taken directly from papers permitting up to 10% loss of the active ingredient may result in products which do not comply with UK standards or the British Pharmacopoeia.

Amoxicillin and co-amoxiclav

Binson *et al* studied amoxicillin 6 g in 48 mL water for injections stored in Baxter small volume Single Day infusers at 37°C. The authors found that 16% of the starting concentration of

amoxicillin remained at 24 hours with 5% loss within 2 hours. A further study by Fawaz *et al* of co-amoxiclav 17.1 mg/mL demonstrated 5% loss of the amoxicillin component within 2 hours when stored in glass vials at 37°C, while the clavulanic acid stayed above 90% of initial concentration at 24 hours.⁷ Of note, the presence of visual and subvisual particles was not studied, the stability indicating capability of the high performance liquid chromatography (HPLC) method was not described nor was the reconsideration of the possibility of a co-eluted degradation product.

Ampicillin

Ampicillin 12 g in 240 mL Baxter LV10 elastomeric devices stored at 31.1°C for 24 hours was studied by Nakamura *et al* using one of five diluents described as: sodium chloride 0.9%, glucose 5%, dextrose-electrolyte solution without potassium, dextrose-electrolyte solution with potassium or Acetate Ringers solution.⁸ Shelf life was longest when sodium chloride 0.9% or Acetate Ringers solution was used as diluents, however none of the investigated diluents retained more than 80% of the API at 24 hours.⁸ Data interpolation suggests that 5% loss of ampicillin would be seen within 5 hours in sodium chloride 0.9%.

Benzylpenicillin

Nakamura *et al* also studied benzylpenicillin 14.4 g in 240 mL Baxter LV10 infusers diluted using the same five crystalloids described above at 31.1°C.⁸ Shelf life was longest with Acetate Ringers solution with 92.9%±1.3% of API remaining at 24 hours.⁸

Cefazolin

Cefazolin 6 g in 240 mL sodium chloride 0.9% or glucose 5% in Baxter LV10 infusers and stored at 31.1°C was reported by Akahane *et al*. Only data for the 24-hour time point are presented with 94.4% API remaining for both diluents.⁹ A further study reported cefazolin 1 g in 1000 mL glucose 5% stored in Ecoflac infusion bags at 35°C demonstrated more than 90% of cefazolin remaining at 48 hours.¹⁰ No information was provided on the validity of the HPLC method or its stability indicating capability, and the presence of visual or subvisual particles was not described.

Cefepime

A conference poster describes a stability assessment of cefepime 1 g in 50 mL of sodium chloride 0.9% stored at 33°C for 24 hours in an unspecified container.¹¹ From the available results, cefepime remained at greater than 90% of time zero concentrations for 12 hours when stored at 33°C.¹¹

The authors also described a yellow discolouration of the solution at approximately 12 hours. This is accounted for due to accumulation of a microbiologically inactive, yet toxic, irritant and potentially teratogenic degradant, N-methylpyrrolidine.¹¹

Cefmetazole

Akahane *et al* studied the stability of cefmetazole 8 g diluted in 240 mL of either sodium chloride 0.9% or glucose 5% in Baxter LV10 infusers and stored at 31.1°C. The percentages of API remaining at 24 hours were reported as 92.9±0.8% and 92.4±0.8%, respectively.⁹ Limitations to this paper were previously described above.

Ceftaroline

Al Madfai *et al* report stability of ceftaroline 300 mg diluted in 50 mL sodium chloride 0.9% or glucose 5% in Baxter LV10

Table 1 Summary table

Drug	Paper	Concentration studied	Diluents	Devices	Temperature	API limits	Duration	Additional comments
Amoxicillin ^{7,24}	Binson <i>et al</i>	6 g in 48 mL	Water for injection	Baxter SV infuser	37°C	90%–110%	Within 2 hours	Not suitable for continuous infusion Impact of buffering not investigated
	Fawaz <i>et al</i>	1000 mg in 70 mL (co-amoxiclav 1.2 g in 70 mL)	Glucose 5% Sodium chloride 0.9% Water for injection	Glass vials	37°C	90%–110%	3.5–4.5 hours	
Ampicillin ⁸	Nakamura <i>et al</i>	12 g in 240 mL	Sodium chloride 0.9%	Baxter LV10	31.1°C	90%–110%	Within 5 hours	Not suitable for continuous infusion Impact of buffering not investigated
Benzylpenicillin ⁸	Nakamura <i>et al</i>	14.4 g in 240 mL	Acetate Ringers solution	Baxter LV10	31.1°C	90%–110%	24 hours	Potential for extended stability using buffer Candidate for YCD-compliant stability studies
Cefazolin ^{9,10}	Metsu <i>et al</i>	1 g in 1000 mL	Sodium chloride 0.9%	Ecoflac infusion bags	35°C	90%–110%	48 hours	Potential for extended stability using buffer
	Akahane <i>et al</i>	6 g in 240 mL	Glucose 5% Sodium chloride 0.9%	Baxter LV10	31.1°C	90%–110%	At least 24 hours	Candidate for YCD-compliant stability studies
Cefepime ¹	Ressault <i>et al</i>	1 g in 50 mL	Sodium chloride 0.9%	Unspecified	33°C	90%–110%	Up to 12 hours	Insufficient data to support continuous infusion currently; studies to evaluate stability and degradants required.
Cefmetazole ⁹	Akahane <i>et al</i>	8 g in 240 mL	Glucose 5% Sodium chloride 0.9%	Baxter LV10	31.1°C	90%–110%	At least 24 hours	Insufficient data to support continuous infusion currently; studies to evaluate stability and degradants required
	Al Madfai <i>et al</i>	300 mg in 50 mL	Glucose 5% Sodium chloride 0.9%	Baxter LV10	35°C	95%–105%	Up to 6 hours	Data in elastomeric infusers do not support infusions longer than 6 hours
Ceftolozane-tazobactam ¹³	Raby <i>et al</i>	300–6000 mg in 240 mL	Sodium chloride 0.9%	Baxter LV10	37°C	90%–110%	24 hours	For additional information, also see Jamieson <i>et al</i> ²⁰
Doripenem ⁹	Akahane <i>et al</i>	3 g in 240 mL	Acetate Ringers solution	Baxter LV10	31.1°C	90%–110%	At least 8 hours	Insufficient data to support continuous infusion currently; studies to evaluate stability and degradants required

Continued

Table 1 Continued

Drug	Paper	Concentration studied	Diluents	Devices	Temperature	API limits	Duration	Additional comments
Meropenem ^{9,14-16}	Jamieson <i>et al</i>	1–2 g in 48 mL	Sodium chloride 0.9%	Baxter LV10	32°C	95%–105%	Within 6 hours	Data in elastomeric infusers do not support infusions longer than 6 hours.
	Fawaz <i>et al</i>	2 g in 140 mL	Sodium chloride 0.9%	Infusion bags	33°C	90%–110%	Within 5 hours	Data in elastomeric infusers do not support infusions longer than 6 hours
	Delattre <i>et al</i>	1–2 g in 48 mL	Sodium chloride 0.9%	Syringes	37°C	90%–110%	Within 3 hours	
	Akahane <i>et al</i>	3 g in 240 mL	Sodium chloride 0.9%	Baxter LV10	31.1°C	90%–110%	Within 5–6 hours	
Piperacillin–tazobactam ^{8,10}	Metsu <i>et al</i>	24 and 48 g in 1000 mL	Sodium chloride 0.9%	Ecoflac infusion bags	35°C	90%–110%	48 hours	For additional information, also see Jamieson <i>et al</i> ²⁰
	Akahane <i>et al</i>	18 g in 240 mL	Glucose 5% Sodium chloride 0.9%	Baxter LV10	31.1°C	90%–110%	At least 24 hours	
Voriconazole ¹⁷	Harmanjeet <i>et al</i>	200 mg in 100 mL	Glucose 5% Sodium chloride 0.9%	Baxter SV50	35°C	95%–105%	At least 4 hours	Potential for longer stability however unsure of clinical need

API, active pharmaceutical ingredient; YCD, Yellow Cover Document.

infusers stored at 35°C. The final test point at which more than 95% ceftaroline remained was 6 hours when diluted with sodium chloride 0.9% and 2 hours with glucose 5%.¹²

Ceftolozane–tazobactam

Stability studies of ceftolozane–tazobactam in 240 mL sodium chloride 0.9% stored in Baxter LV10 elastomeric infusers at three concentrations: 1.25, 12.5 and 25 mg/mL were reported by Raby *et al* in studies performed at 37°C.¹³ Tazobactam displayed the greater stability of the two components and demonstrated less than 5% loss after 24 hours, while there was 7% loss across all ceftolozane concentrations.

Doripenem

The stability of doripenem 3 g in 240 mL stored in Baxter LV10 infusers at 31.1°C was investigated using the five diluents used in the Nakamura *et al*⁸ study of ampicillin. Little data were reported other than that stability was optimal in Acetate Ringers solution for which residual percentage of doripenem was 88.7±0.3% at 24 hours.⁹

Meropenem

Fawaz *et al* studied the stability of meropenem 2 g in 140 mL sodium chloride 0.9% stored in polyvinyl chloride infusion bags and reported loss of more than 10% of active ingredient within 5 hours when stored at 33°C.¹⁴ Interpolation of results suggests that 5% loss of meropenem occurred within 3 hours. As described previously, there was incomplete reporting of physical studies and HPLC methodology was absent. Delattre *et al* reported similar instability, with 10% loss within 3 hours when 1 g or 2 g meropenem was diluted with 48 mL sodium chloride 0.9% and stored in syringes at 37°C.¹⁵ Akahane *et al* studied meropenem 3 g in 240 mL Baxter LV10 infusers in one of five diluents previously described by Nakamura *et al* above. Optimal stability was achieved in Acetate Ringers solution with percentage levels of meropenem remaining at 24 hours at 67.7±2.1% following storage at 31.1°C.⁹

Jamieson *et al* investigated the stability of buffered and unbuffered meropenem diluted with sodium chloride 0.9%, stored in an unknown container at 32°C.¹⁶ Citrate and phosphate buffers were used at concentrations between 0.3% and 5% w/v and pH range from 6.0 to 7.0. Meropenem was most stable in a 1% citrate buffer with API percentages at 24 hours of 85.60±(0.08%) and 72.00±(0.11%) at concentrations of 6.25 and 25 mg/mL, respectively. The authors advise that meropenem infusion duration must be limited to 6 hours.¹⁶

Delattre *et al* compared the outcomes of stability tests of branded and three generic versions of meropenem at concentrations of 1 g or 2 g in 48 mL sodium chloride 0.9%.¹⁵ The antimicrobial was prepared in syringes and stored at 37°C. Unusually, the results in this paper present the time, calculated by linear regression, at which 90% of the API remains rather than presenting data on the percentage remaining of API each time point. There was significant interproduct variability, as shown in table 2.

Piperacillin–tazobactam

Metsu *et al* presented data on the stability of piperacillin–tazobactam 24 g and 48 g in 1000 mL sodium chloride 0.9% stored in Ecoflac infusion bags.¹⁰ The authors report greater than 90% of the API remaining after 48 hours when stored at 35°C, irrespective of presence of light or shaking.

Table 2 Range of time taken for four brands of meropenem to degrade by 10% when diluted in sodium chloride 0.9% and stored in syringes at 37°C¹⁵

	1 g in 48 mL		2 g in 48 mL	
	Minimum time/ hour	Maximum time/ hour	Minimum time/ hour	Maximum time/ hour
37°C	4.5±0.2	10.0±0.9	2.9±0.1	3.1±0.2

Akahane *et al*⁹ also reported stability of piperacillin–tazobactam 18 g in 240 mL sodium chloride 0.9% or glucose 5% and stored in Baxter LV10 infusers at 31.1°C. The piperacillin component was the least stable of the two drugs in the combination product. At 24 hours, the tazobactam levels in both diluents remained above the 95% threshold; however, piperacillin levels were 96.3±1.8% in sodium chloride 0.9% and 93.2±1.8% in glucose 5%.

Voriconazole

Harmanjeet *et al* studied voriconazole 200 mg diluted in 100 mL of either glucose 5% or sodium chloride 0.9% in Baxter SV50 infusers (100 mL capacity administered at 50 mL/hour).¹⁷ Infusers were stored at 35°C for 4 hours. Infusers retained greater than 95% of initial voriconazole concentration at the end of the 4-hour infusion.¹⁷

DISCUSSION

Our systematic review identified data on 13 antimicrobial agents which would be of interest to clinicians establishing and developing OPAT services worldwide.

Of the beta-lactam antibiotics identified in our review, amoxicillin and ampicillin appear unsuitable for continuous infusion, but the impact of buffering has not been fully assessed for these products. Benzylpenicillin demonstrated promising stability at 31.1°C using Acetate Ringers solution as the diluent. Beta-lactams, such as benzylpenicillin, flucloxacillin and piperacillin, which lack an amino side chain demonstrate optimal stability in mildly acidic conditions, for example, Acetate Ringers solution.^{10–18} Studies have previously demonstrated the benefit of citrate 0.3% w/v buffer to extend the shelf life of flucloxacillin and piperacillin–tazobactam and therefore benzylpenicillin seems an excellent candidate for further YCD-compliant stability studies using a citrate 0.3% buffer.^{19–20} Smith and McWhinney very recently published stability data for benzylpenicillin 15 and 60 mg/mL buffered benzylpenicillin in LV devices which were stable for 6 days at 2°C–5°C followed by 24 hours at 37°C. For territories where 0.3% citrate buffer is not readily available, consideration could be given to diluting a 4% citrate buffer to the required concentration, as performed by Smith and McWhinney.²¹

Meropenem is not suitable for extended infusion for periods longer than 6 hours; even buffering was unable to improve its stability, as demonstrated by Jamieson *et al* and is unlikely to be useful by continuous infusion for OPAT services due to the frequency at which infuser devices would need to be changed. Evidence presented suggests that doripenem is more stable than meropenem and could be a suitable candidate for further investigations with YCD-compliant studies.⁹

Cephalosporins are attractive agents for OPAT services because of the differences in their spectrum of activity—the ability to choose between different agents would be beneficial, but their stability has been shown to be variable and 12-hour

infusions would appear to be the limit of acceptable stability for some agents. Of those identified in this review, ceftazolin appears most promising and further YCD-compliant studies may be warranted. Cefepime may be suitable for two times per day infusion, but more information is needed on the quantification and clinical relevance of its potentially toxic metabolite, N-methylpyrrolidine. Data from Al Madfai *et al* show that ceftazolin is subject to temperature-driven degradation, with greater losses at 35°C than 25°C or 30°C; when stored at 4°C, there was little degradation.¹² More investigation would be required to determine how this could translate to usefulness for OPAT services. More data are also required for cefmetazole to establish if it could be used in OPAT services as a 12-hour infusion. Investigation of the stability of these agents for ‘fresh-filled’ elastomeric devices could yield benefits and perhaps allow a 24-hour infusion—balancing the inconvenience of fresh filling alongside twice daily changes of elastomeric device with the benefits of patient care away from the inpatient hospital setting.

More extensive data on the stability of ceftazolin, ceftolozane–tazobactam and piperacillin–tazobactam were discussed in a recent review^{2,22} and will not be considered further here.

The stability of voriconazole suggests that it could be a potential OPAT candidate, but longer storage periods need to be studied and given the availability of oral formulations of voriconazole, the role for continuous infusion of voriconazole in OPAT services is not clear.

In the UK, the YCD standards²³ are challenging for many antimicrobial compounds. However, in other territories, different standards are accepted, sometimes allowing up to 10% loss of API, and assessment at lower ‘in-use’ temperatures. It is important to stress that whatever pharmacopoeial limits are applied, these allow for variations in the starting material (API), drug product and reconstitution and dilution process as well as loss through degradation. Hence, allowing for 10% degradation, even when a lower limit of 90% is within the monograph, would require assurance that the starting concentration was at least 100% of stated.

A period of extended refrigerated storage prior to use is a pragmatic consideration for many OPAT services but does pose additional challenges to the stability of some key agents. Where a period of extended refrigerated storage followed by acceptable stability in a 24-hour in-use period is impossible, some OPAT services may be able to use a ‘fresh-fill’ model, where devices are prepared immediately prior to connection to the patient’s vascular access device. There are potential concerns about such an approach, including the ability to aseptically prepare/fill devices in a clinic or home setting, the potential for dilution and reconstitution errors particularly with buffered diluents as well as the logistical challenges of filling devices in a busy OPAT setting. Nonetheless, this may provide a treatment option allowing use of certain antimicrobials with limited stability, or for OPAT services which are unable to access ready-filled devices.

The purpose of this review was to identify potential candidate medicines for comprehensive stability testing and review in elastomeric devices. These would include benzylpenicillin, doripenem, ceftazolin and potentially cefepime if concerns about toxic metabolites are alleviated. The impact of buffering to improve the stability of penicillins should be investigated further. Our findings also highlight other agents which may be of interest to territories where limits broader than the YCD applies, or where a ‘fresh-filled’ elastomeric device, may be the only option.

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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 required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Not applicable.

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