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

Aims

To:

- To identify the publicly accessible stability data for betalactam antimicrobials relevant to the intensive/ critical care setting.
- To document stability data compliant with the 'Standard Protocol for Deriving and Assessment of Stability, Part 1 Aseptic Preparations (Small Molecules) for betalactam antimicrobials under clinical environmental conditions e.g. 25 +/- 2°C.
- Identify studies that highlight instability as well as those that confer extended stability.

OPAT Stability Search Protocol

Databases: Medline, PubMed, EMBASE, CINAHL, BMJ Journals, Cochrane Database for citations in English published before December 2021.

Process Step	**Keywords**
#1	Title or abstract: [Betalactam OR penicillin OR cephalosporin OR carbapenem OR monobactam OR amoxicillin OR ampicillin OR aztreonam OR benzylpenicillin OR cefazolin OR cefepime OR cefotaxime OR cefoxitin OR ceftaroline OR ceftazidime OR ceftriaxone OR ceftolozane OR cefiderocol OR clavulanic acid OR co-amoxiclav OR doripenem OR ertapenem OR flucloxacillin OR imipenem OR meropenem OR piperacillin OR temocillin OR ticarcillin]
#2	Title or abstract: [Drug stability OR drug storage OR stability OR shelf life]
#3	Title or abstract: [Syringes OR elastomeric OR drug delivery device* OR drug delivery system OR infusion OR continuous infusion]
#4	#1 AND #2 AND #3

Inclusion Criteria

- Articles accessible in full and in English.
- Investigation of formulation for intravenous administration
- Testing under relevant storage conditions e.g. room temperature or 25 +/- 2°C
- At least 90%–110% of active pharmaceutical ingredient (API) and in compliance with BP standards if monograph suggest tighter limits to remain to confer stability.
- Use of a validated stability indicating assay, e.g. HPLC.
- Complete physical stability testing, e.g. physical appearance, pH, colorimetry, sub-visible particulate assessment.
- Identification and quantification of degradation products if limits on such are stated in the BP monograph

- At least three samples tested at each time point.
- Testing of low and high 'clinically significant' concentrations.
- All samples tested in duplicate.

Exclusion Criteria

- Studies that do not comply with the minimum data set of the 'Standard Protocol for Deriving and Assessment of Stability, Part 1 (Small Molecules).
- Solutions to which buffers e.g citrate or phosphate, are added
- Data beyond 24 hours. The maximum shelf-life that will be assigned is 24 hours.
- Antimicrobials with no role in the critical/intensive care setting.

Two reviewers will independently screen articles for inclusion, discuss and resolve discrepancies, and undertake data abstraction. A third reviewer will arbitrate, if necessary.

Data abstraction and synthesis

Data of selected articles will be abstracted onto a customised data extraction sheet focusing on inclusion criteria and building on the categories included in the first review. Variables in the previous review included: author and year; title of the study; country of origin; temperature range; API range; design; number of samples and duplication. Additional variables we will seek to extract include: identification and quantification of degradation products and whether there are BP limits for these and any COVID-19 related findings.

Key findings from each study will be summarised and presented in tables. Reviewers will code the variables and resolve any disputes through mutual discussion and arbitration by a third reviewer if necessary.

References:

1 NHS PQAC Committee. Standard Protocol for Deriving and Assessment of Stability, Part 1 Aseptic Preparations (Small Molecules). Fifth Edition, 2019.

Table 1S: Summary of Studies from Which Data Could Not Be Extracted with Reasons

Citation	Antibiotic Studied	Reason for Data Exclusion
Viaene E.; Chanteux H.; Servais H. *et al* Comparative stability studies of antipseudomonal beta-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). Antimicrobial Agents and Chemotherapy; 2002; 46 (8); 2327-2332	Aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam	Water for injection used as diluent which is not used in clinical practice so data cannot be used for shelf life assignment.
Stiles ML, Tu YH, Allen LV. Stability of cefazolin sodium, cefoxitin sodium, ceftazidime, and penicillin G sodium in portable pump reservoirs. Am J Hosp Pharm 1989;46:1408–12.	Benzylpenicillin, cefazolin, cefoxitin and ceftazidime	Water for injection used as diluent which is not used in clinical practice so data cannot be used for shelf life assignment.
Behin S, Punitha I, Krishnan S. Physical and chemical stability studies on cefotaxime and its dosage forms by stability indicating HPTLC method. International Journal of Pharmaceutical, Chemical and Biological Sciences 2012;2:517–23.	Cefotaxime	Water for injection used as diluent which is not used in clinical practice so data cannot be used for shelf life assignment.
Borst DL, Sesin GP, Cersosimo RJ. Stability of selected beta-lactam antibiotics stored in plastic syringes. NITA: Journal of the National Intravenous Therapy Association 1987;10:368–72.	Cefoxitin	Water for injection used as diluent which is not used in clinical practice so data cannot be used for shelf life assignment.
Plumridge R.J.; Rieck A.M.; Annus T.P *et al.* Stability of ceftriaxone sodium in polypropylene syringes at -20, 4, and 20 degrees C. American Journal of Health-System Pharmacy. 1996; 53(19); 2320-2323	Ceftriaxone	Water for injection used as diluent which is not used in clinical practice so data cannot be used for shelf life assignment.
Berthoin K, Le Duff CS, Marchand-Brynaert J, et al. Stability of meropenem and doripenem solutions for administration by continuous infusion. J Antimicrob Chemother 2010;65:1073–5.	Doripenem and meropenem	Water for injection used as diluent which is not used in clinical practice so data cannot be used for shelf life assignment.
Carroll JA. Stability of flucloxacillin in elastomeric infusion devices. Journal of Pharmacy Practice and Research 2005;35:90–3	Flucloxacillin	No samples taken from stored infusers at time zero therefore percentage remaining of active pharmaceutical ingredient cannot be calculated.
Voumard R, Van Neyghem N, Cochet C, et al. Antibiotic stability related to temperature variations in elastomeric pumps used for outpatient parenteral antimicrobial therapy (OPAT). J Antimicrob Chemother 2017;72:1462–5.	Meropenem and others	Temperature conditions described as 'real life' without clarity on temperatures at which pumps were stored.

Table 2S: Countries in Which Stability Research Took Place

Country	Number of Papers (Reference)
USA	23 (32,34-6, 40-1, 43, 45, 48-51, 53-4,57, 60, 63, 65-7, 69, 78, 80)
Australia	7 (26-7, 29, 39, 62, 73, 77)
France	7 (16-7, 19, 46-7, 55, 58)
Belgium	6 (37-8, 52, 56, 68, 71)
UK	4 (20, 61, 72, 74)
Canada	3 (31, 42, 44)
Japan	2 (24, 30)
Brazil	1 (70)
Germany	1 (76)
India	1 (21)
Indonesia	1 (22)
New Zealand	1 (28)
Norway	1 (58)
South Korea	1 (25)
Spain	1 (79)
Thailand	1 (75)