



International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the American College of Clinical Pharmacy, British Society for Antimicrobial Chemotherapy, Cystic Fibrosis Foundation, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists

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Endorsed by the American College of Clinical Pharmacy (ACCP), the British Society for Antimicrobial Chemotherapy (BSAC), the Cystic Fibrosis Foundation (CFF), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Diseases Society of America (IDSA), the Society of Critical Care Medicine (SCCM), and the Society of Infectious Diseases Pharmacists (SIDP).

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Abstract

Intravenous β -lactam antibiotics remain a cornerstone in the management of bacterial infections due to their broad spectrum of activity and excellent tolerability. β -lactams are well established to display time-dependent bactericidal activity, where reductions in bacterial burden are directly associated with the time that free drug concentrations remain above the minimum inhibitory concentration (MIC) of the pathogen during the dosing interval. In an effort to take advantage of these bactericidal characteristics, prolonged (extended and continuous) infusions (PIs) can be applied during the administration of intravenous β -lactams to increase time above the MIC. PI dosing regimens have been implemented worldwide, but implementation is inconsistent. We report consensus therapeutic recommendations for the use of PI β -lactams developed by an expert international panel with representation from clinical pharmacy and medicine. This consensus guideline provides recommendations regarding pharmacokinetic and pharmacodynamic targets, therapeutic drug-monitoring considerations, and the use of PI β -lactam therapy in the following patient populations: severely ill and nonseverely ill adult patients, pediatric patients, and obese patients. These recommendations provide the first consensus guidance for the use of β -lactam therapy administered as PIs and have been reviewed and endorsed by the American College of Clinical Pharmacy (ACCP), the British Society for Antimicrobial Chemotherapy (BSAC), the Cystic Fibrosis Foundation (CFF), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Diseases Society of America (IDSA), the Society of Critical Care Medicine (SCCM), and the Society of Infectious Diseases Pharmacists (SIDP).

KEYWORDS

beta-lactams, consensus, infectious diseases, prolonged infusion

1 | INTRODUCTION

Beta-lactam (β -lactam) antibiotics are among the most commonly prescribed antibiotics in the hospital setting due to their high efficacy and relatively safe profile.¹ Nonetheless, an increase in β -lactam minimum inhibitory concentrations (MICs) due to emerging resistance and large intra- and interpatient variability in drug exposures have demonstrated the necessity of optimizing pharmacokinetic (PK) and pharmacodynamic (PD) dosing parameters to promote positive patient outcomes.²⁻⁴ With β -lactams, reductions in bacterial burden are best predicted by the time the free concentration of the drug remains above the MIC during the dosing interval ($fT_{>MIC}$).^{2,3} Consequently, many studies have shown β -lactam $fT_{>MIC}$ to be suboptimal across a myriad of disease states and clinical settings.⁵⁻⁷ Routine administration of most intravenous β -lactams is a 30–60 min short infusion (SI). However, extending the infusion duration over 3–4 h or administering continuously over the dosing interval can substantially increase $fT_{>MIC}$. Dosing regimens where the infusion durations are equal to or longer than 1 h, including continuous infusion, are generally referred to as prolonged infusion (PI) β -lactam dosing. PI β -lactam dosing regimens have been implemented into clinical practice in hospitals globally and evaluated as a strategy to improve outcomes across diverse patient

populations⁸⁻¹⁰; however, these dosing regimens are not yet standard clinical practice. Inconsistent use underscores a collective lack of clarity about the efficacy of PI strategies and practical barriers such as how to optimally deliver and monitor β -lactam antibiotics through PI mechanisms.

Herein, we provide an expert-based consensus on the use of β -lactam agents as PIs. This international guideline sought to summarize literature comparing PI versus SI in the following populations: severely ill and nonseverely ill adult patients, pediatric patients, and obese patients. Additionally, we address therapeutic drug monitoring (TDM) and stability questions as they relate to PI. Systematic reviews, grading summaries, where applicable, and expert advice are provided.

2 | METHODS

2.1 | Endorsing organizations and consensus recommendation panel

Endorsing organizations were identified and contacted prior to the commencement of any work. A total of seven endorsing societies, represented by the 17 study authors, agreed to the methods for review and summary of evidence of PI β -lactams as described

below. Endorsing societies included: the American College of Clinical Pharmacy (ACCP), the British Society for Antimicrobial Chemotherapy (BSAC), the Cystic Fibrosis Foundation (CFF), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Diseases Society of America (IDSA), the Society of Critical Care Medicine (SCCM), and the Society of Infectious Diseases Pharmacists (SIDP).

Conflict of interest was handled according to International Committee of Medical Journal Editors standards. The authors declared all potentially relevant conflicts to ACCP for review of significance and potential conflict resolution (Appendix 1). Members with relevant conflicts were recused from voting on guideline statements and recommendations.

Authors were divided into five working subgroups to address (1) PK/PD, (2) clinical outcomes, (3) TDM, (4) stability and special populations including pediatric patients and obesity, and (5) special populations with altered renal function including augmented renal clearance (critically ill and cystic fibrosis [CF]) as well as advanced renal impairment (renal replacement therapies). Subgroup membership intentionally represented distributions of professional degree (i.e., PharmD, MD, PhD), clinical specialty, and geographic representation.

2.2 | Definitions

For this document, we defined infusions over at least 3 h as PI where PI included both extended infusion (EI) and continuous infusion (CI). The term PI will be used when referring to both EI and CI. However, the description of data in evidence summaries and recommendations still distinguish between EI and CI, as appropriate. Infusions up to 60 min were defined as SI, except when given as an intravenous push or bolus where it is expressly noted. Infusions between 60 min and 3 h were not classified.

2.3 | Development of PICO questions and recommendations

Draft questions of clinical importance were developed by each work group using the PICO (Population, Intervention, Comparator, and Outcome) format. Each group identified between three to five questions for further review. Proposed PICO questions and important background topics (i.e., non-PICO questions that were determined to be necessary for the understanding of PK/PD targets and to inform clinical recommendations) were proposed to the entire guideline committee; agreement among greater than 70% of the voting quorum members was required for the establishment of PICO questions. Non-PICO questions were titled "Background Consensus Statements." Each group was tasked with assessing all identified literature from the systematic search as described below in order to assess quality, summarize, and format recommendations or statements for each topic. Recommendations and statements were assessed by the full panel of guideline authors at virtual monthly meetings that were held from June 2021 to September 2022. A first circulated

draft document was provided to guideline authors in September 2021, with all PICO and recommendation statements made available to all authors. Each author had the opportunity to review, suggest revisions, and respond to comments from panel members. The draft document was sent to supporting societies for review and comment (February 2022). Supporting societies had the option to make the document available for public comment. Guideline authors, within their subgroups, were formally tasked with responding to comments and revision. The penultimate draft was compiled and sent to all guideline authors for final review and comment in July 2022. The panel voted on each recommendation statement and voting results may be found in the summary of recommendations provided in Table 1. A final document was sent to organizing groups for final review, with the option to support the harmonized final document.

2.4 | Literature search and screening process

Medline (Ovid), Embase (Ovid), and Cochrane (Wiley) databases were searched by a contracted senior medical librarian using search terms such as *extended infusion, continuous infusion, prolonged infusion, beta-lactams, penicillins, cephalosporins, carbapenems, monobactams, beta-lactamase inhibitors, pharmacokinetics, pharmacodynamics, critically ill, renal impairment, renal replacement therapy, augmented renal clearance, therapeutic drug monitoring, stability, cystic fibrosis, pediatrics, and obesity*. The search strategy used variations in text words found in the title, abstract, or keyword fields, and relevant subject headings to retrieve articles pertaining to β -lactams combined with PI. Only English language articles were retrieved in search of studies comparing PI versus SI. Conference abstracts, commentaries, editorials, and letters were excluded. Systematic reviews and meta-analyses were also excluded, though their references were scanned for additional pertinent citations. The original search of literature through October 18, 2020 (Appendix 2) generated 6351 articles to be screened. The search was updated in October 2021 to capture any articles published during the preparation of these consensus recommendations.

Article screening was assigned to each work group and completed using Rayyan,¹¹ an online screening tool. As a function of the background or PICO questions addressed, certain literature types were excluded. Clinical data were separated from preclinical data (i.e. in vitro and animal data). Groups 1, 2, and 3 (questions I to V and VII to X) excluded case reports, and groups 2, 4, and 5 (questions VI to XII) excluded in vitro and animal studies. Titles and abstracts of each article were manually screened by two reviewers in each group for relevance to the PICOs with study inclusion requiring agreement by two authors. Disagreements required adjudication by a third author.

2.5 | Review and grading of evidence

The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was utilized, where appropriate, to evaluate the quality of evidence and determine the strength of recommendations.¹² Data from selected articles were independently

TABLE 1 Summary of questions and consensus statements/recommendations for the use of prolonged infusion (PI) beta-lactam antibiotics.

Background (non-PICO) questions and consensus statements/recommendations

I. Are there microbiologic targets for bacterial killing and resistance suppression for β -lactams in preclinical PK/PD models of infections?

1. Preclinical targets for reductions in CFU are 40%–70% $fT_{>MIC}$ for SI and up to 4-h EI, and 100% $fT_{>MIC}$ with concentrations that exceed up to four to eight times free drug over the steady-state concentration (fC_{ss}) for CI. No absolute target guarantees suppression of resistance but exceeding the MIC by four to six times may minimize resistance (Panel vote 17-0 in favor of this consensus statement)

II. Does PI of β -lactams result in enhanced bacterial killing relative to SI in preclinical PK/PD models of infections?

2. In vitro and animal data, predominately with gram-negative bacteria, demonstrated equivalent or better killing for PI compared with SI; this is likely attributable to greater $fT_{>MIC}$ with PI compared with SI (Panel vote 17-0 in favor of this consensus statement)

III. Do PI β -lactams minimize resistance emergence relative to SI in preclinical PK/PD models of infections?

3. β -lactams given by PI may reduce the emergence of resistance. β -lactam agent, the bacterial species, MIC, and initial inoculum are important factors affecting the emergence of resistance (Panel vote 17-0 in favor of this consensus statement)

IV. Is there a role for therapeutic drug monitoring (TDM) of PI β -lactams?

4. We suggest that β -lactam TDM and personalized dosing may be considered on a patient-by-patient, indication-by-indication, and drug-by-drug basis until further evidence is available. We cannot recommend for or against routine TDM for PI β -lactams at this time. *Consensus recommendation* (Panel vote 17-0 in favor of this recommendation)

V. What β -lactam concentration or exposure should be targeted when performing TDM?

5. There is insufficient evidence to recommend a single concentration or exposure to target when performing β -lactam TDM; however, evidence does exist for a minimum exposure. When TDM is performed, we suggest minimum plasma exposures of at least 50%–70% $fT_{>MIC}$ be targeted for β -lactams when administered as SI and EI. For β -lactams administered as CI, we suggest 100% $fT_{>MIC}$ with concentrations at least four times the MIC (Panel vote 17-0 in favor of this consensus statement)

VI. Are there stability concerns when delivering PI β -lactam infusions?

6. There are general stability concerns that should be considered on a drug-by-drug basis when delivering β -lactams by PI (Panel vote 17-0 in favor of this consensus statement)

PICO Questions and Recommendations

VII. Should PI β -lactam antibiotics be preferred over SI dosing in severely ill adult patients to improve mortality or clinical cure?

7. We suggest PI β -lactam antibiotics over SI to reduce mortality or increase clinical cure among severely ill adult patients, particularly those with gram-negative infections. *Conditional recommendation; very low certainty of evidence* (Panel vote 17-0 in favor of this recommendation)

TABLE 1 (Continued)

VIII. Should PI β -lactam antibiotics be preferred over SI in nonseverely ill adult patients to improve mortality and clinical cure?

8. We cannot recommend for or against PI β -lactam antibiotics over SI to reduce mortality and increase clinical cure among nonseverely ill adult patients. *Conditional recommendation; very low certainty of evidence* (Panel vote 17-0 in favor of this recommendation)

IX. Is the use of PI β -lactam antibiotics safer than SI among adult and pediatric patients?

9. We cannot recommend for or against the use of PI over SI to provide a safety advantage and reduce adverse effects of β -lactam antibiotics. *Conditional recommendation; very low certainty of evidence* (Panel vote 17-0 in favor of this recommendation)

X. Should a loading dose be administered over no loading dose when using PI β -lactam antibiotics in adults to improve mortality or clinical cure?

10. We suggest use of a loading dose over no loading dose when initiating CI β -lactam antibiotics to improve clinical success and we cannot recommend for or against a loading dose with EI. *Conditional recommendation; very low certainty of evidence* (Panel vote 17-0 in favor of this recommendation)

XI. Should PI β -lactam antibiotics be used in children versus SI to improve efficacy?

11. We cannot recommend for or against routine use of PI for any specific clinical situations or in any specific patient populations (e.g., severely ill, obese, neonates) to improve efficacy of β -lactam agents in the pediatric population. *Conditional recommendation, very low certainty of evidence* (Panel vote 16-0 in favor of this recommendation; 1 author abstained from voting)

XII. Should PI β -lactam antibiotics be used in obese patients versus SI to improve efficacy?

12. We cannot recommend for or against routine use of PI to improve efficacy of β -lactam agents in obese patients. *Consensus recommendation* (Panel vote 17-0 in favor of this recommendation)

Abbreviations: β -lactam, beta-lactam; CFU, colony-forming unit; CI, continuous infusion; EI, extended infusion; fC_{ss} , free drug over the steady-state concentration; $fT_{>MIC}$, free concentration of drug that remains above MIC during the dosing interval; MIC, minimum inhibitory concentration; PI, prolonged infusion; PICO, population, intervention, comparison, outcome; PK, pharmacokinetic; PD, pharmacodynamic; SI, short infusion; TDM, therapeutic drug monitoring.

extracted and agreement by two authors was required for each article graded. In vitro or animal studies and simulation studies were not amenable to GRADE criteria and thus were not evaluated using these criteria. Recommendations stemming from ungraded data or areas of insufficient evidence were labeled as “Consensus Recommendations.” GRADE evidence summary tables are available in the supplementary material (Tables S1–S3).

2.6 | Meta-analyses

Meta-analyses were performed when that methodology informed the PICO and sufficient randomized controlled trials (RCTs) were

(Continues)

available to be instructive with the results. Observational studies were not meta-analyzed. All meta-analyzed outcomes were binary. Risk ratio (RR) and 95% confidence interval were calculated for individual studies as well as pooled treatment effects. Statistical heterogeneity was measured by Higgins' I^2 and τ^2 , and tested using Cochran's Q statistic. τ^2 was calculated using a DerSimonian-Laird estimator. Significant heterogeneity was defined as $I^2 \geq 50\%$ or p -value < 0.05 . A fixed-effect model (i.e., Mantel-Haenszel method) was utilized for meta-analysis when there was no significant heterogeneity between the studies. Otherwise, a random-effect model (i.e., inverse variance method) was used. Continuity correction was applied when studies with zero events were included. Publication bias was assessed by examining funnel plots for asymmetry and calculating Egger's test, where a p -value < 0.05 would indicate significant publication bias. All analyses were performed in R (Version 4.0.4) using the "meta" package.

3 | CONSENSUS STATEMENTS AND RECOMMENDATIONS

3.1 | Background question I

Are there microbiologic targets for bacterial killing and resistance suppression for β -lactams in preclinical PK/PD models of infections?

3.1.1 | Background consensus statement 1

Preclinical targets for reductions in colony-forming units (CFU) are 40%–70% $fT_{>MIC}$ for SI and up to 4-h EI, and 100% $fT_{>MIC}$ with concentrations that exceed up to four to eight times free drug over the steady-state concentration (fC_{ss}) for CI. No absolute target guarantees suppression of resistance but exceeding the MIC by four to six times may minimize resistance.

3.1.2 | Evidence summary

The below summary of evidence applies to β -lactams alone and not in combination with β -lactamase inhibitors that have various exposure-response relationships based on the individual β -lactamase inhibitor and thus are out of scope for the question. Representative preclinical models included the one-compartment chemostat model,^{13,14} hollow fiber infection model (HFIM),^{15–18} and animal models (including mice,¹⁹ rabbits,²⁰ and swine²¹). Animals were immunosuppressed¹⁹ and immunocompetent.²² Animal models typically covered invasive tissue infections (e.g., infected thigh), pneumonia, and bacteremia. β -lactams studied included penicillins, cephalosporins, and carbapenems. Both gram-positive and gram-negative pathogens were represented. Broadly, targets differ based on (1) model (e.g., chemostat vs animal), (2) immunosuppression status for animals, (3) delivery of dose (e.g., PI vs SI), (4) type of β -lactam

on $fT_{>MIC}$ required (carbapenems $<$ penicillins $<$ cephalosporins), (5) starting bacterial inoculum, (6) pathogen gram stain type and further genus, species, and even isolate, (7) infection type (e.g., pneumonia vs thigh infection), (8) amount of kill targeted (stasis vs 1-log vs 2-log vs 3-log "cidal"), and (9) length of time that the experiment was run. The latter is addressed more specifically as regrowth and emergence of resistance separately below. Most studies assessing bacterial killing utilized 10^5 – 10^9 bacteria for initial inoculum loads. Multiple PK/PD parameters have been suggested to correlate to bacterial killing and thus serve as targets. Such targets include $fT_{>MIC}$ between 40% and 70% for SI and up to 4-h EI and fC_{ss} greater than 4 to 8 \times MIC for CI. A meta-regression²³ attempted to quantify the impact of many of the aforementioned variables on bacterial load reduction (i.e., CFU/mL). To combine multiple PK/PD endpoints, the study utilized a free drug area under the concentration curve for 24h ($fAUC_{24}/MIC$) to control for the magnitude of drug exposure. This study found that $fAUC_{24}/MIC$ predicted lower CFU/mL only in the in vitro studies (vs in vivo studies). As such, and in conjunction with the studies identified in this literature search, we also suggest target $fT_{>MIC}$ of 40%–70% for preclinical studies and C_{ss}/MIC ratios of 4–8 for CI as targets. Although the meta-regression suggests that these targets are agnostic to other variables (pathogen, β -lactam class, etc.), data remain limited in this regard and trends exist with class effects such that carbapenems likely require less $fT_{>MIC}$ than penicillins and cephalosporins (i.e., carbapenems \sim 40% $fT_{>MIC}$, cephalosporins \sim 70% $fT_{>MIC}$, and penicillins falling between those two targets (i.e., 40%–70% $fT_{>MIC}$). Some cephalosporins such as cefiderocol required slightly higher exposures.²⁴ It is not clear if this is a pathogen, class effect, or experimental variation. Thus, targets are not absolute.

Resistance suppression was evaluated in a fewer number of studies. Resistance has been defined phenotypically (e.g., growth on 3 \times MIC plates) as well as with genotypic mutations. Generally, minimum targets for resistance suppression for timelines up to 5 days were most frequently identified at trough concentrations of four to six times the MIC.^{15–18} Notably, these concentrations do not invariably prevent the emergence of resistance, thus like targets for bacterial killing, they are not universal nor absolute. Most resistance studies have been performed in vitro (as opposed to in vivo), and the translational relevance such as when immune function is retained is less clear. Thus, these models might serve as "worst-case scenarios" in which only the antibiotic is involved in bacterial killing.

3.1.3 | Future research needs

In order to compare studies from disparate labs, standardization is needed to limit the number of impacting variables. For instance, HFIM models should standardize the number of CFUs as a starting point and use standardized growth media, and animal models should use common outbred animal strains. Once standardization is complete, more data comparing pathogens and β -lactam class are

expected to be informative to understanding nuances in the targets according to variables. Presently, these endpoints have been created sans assessment of toxicity, which should also be performed to help inform the therapeutic window. Additionally, further study is needed to evaluate the generalizability of a target C_{ss} of 4 times the MIC for continuous infusion across organisms other than *Pseudomonas aeruginosa*.

3.2 | Background question II

Does PI of β -lactams result in enhanced bacterial killing relative to SI in preclinical PK/PD models of infections?

3.2.1 | Background consensus statement 2

In vitro and animal data, predominately with gram-negative bacteria, demonstrated equivalent or better killing for PI compared to SI; this is likely attributable to greater $fT_{>MIC}$ with PI compared with SI.

3.2.2 | Evidence summary

Preclinical PK/PD infection model studies were identified that compared the bactericidal activity of the same total daily exposures of a β -lactam administered as either an SI or a PI. Studies were in vitro PK/PD models of infection^{13,17,18,25-37} and animal studies of pneumonia,^{21,38,39} infective endocarditis,^{40,41} and neutropenic mouse thigh.⁴² *P. aeruginosa*,^{13,17,18,21,25,26,28,32,35,38-40,42} *Klebsiella pneumoniae*,^{27,34,36} *Staphylococcus aureus*,^{29,30,41} *Acinetobacter baumannii*,³¹ *Haemophilus influenzae*,³³ and *Bacillus anthracis* were studied.³⁷ The β -lactams examined were ceftazidime,^{21,25,26,32,38,40} meropenem,^{17,29,31,36} piperacillin-tazobactam,^{13,28,34} cefepime,^{30,35} doripenem,^{18,39,42} ceftazidime-avibactam,²⁷ methicillin,⁴¹ cefprozil,³³ and amoxicillin.³⁷

Overall, the results can be summarized as demonstrating similar or enhanced bacterial killing^{13,25,32-35,42} and regrowth/resistance suppression^{17,34} with PI relative to SI for β -lactam regimens with equivalent daily dosing.^{18,21,25-27,29-31,36,38-40} Only one study observed reduced bacterial killing and lower survivorship with CI relative to SI (methicillin in a rabbit infective endocarditis model of *S. aureus*).⁴¹ Although there is considerable heterogeneity in observed results, most preclinical PK/PD infection model studies that showed equivalent efficacy between PI and SI examined organisms with lower MIC values and/or higher β -lactam doses. Increased bacterial killing with PIs relative to SI at equivalent total daily exposures is only likely to be observed when there is an increased ability to achieve critical PK/PD targets with the PI regimen relative to the SI regimen. These observations are consistent with a meta-regression, which reported that the mode of infusion has minimal effect on bacterial killing when corrected for antibiotic exposure, provided that the appropriate antibiotic exposure is achieved in both arms (e.g., 40%–70% $fT_{>MIC}$ for SI and a C_{SS}/MIC ratio of >4 for CI).²³

The observed pattern between PK/PD target achievement and bacterial killing is best illustrated across the published in vitro PK/PD infection models for each evaluated β -lactam class (i.e., cephalosporins, penicillins, and carbapenems). In a 48-h in vitro infection model study of *P. aeruginosa* (starting inoculum of 10^6 CFU/mL), no significant difference was observed in time to 99.9% killing between 6 g/day of ceftazidime administered as an SI or a CI against a ceftazidime-susceptible *P. aeruginosa* strain (MIC of 1.56 mg/L), an organism for which both infusion modalities achieved concentrations four to five times above the MIC for the entire dosing interval.²⁶ In contrast, substantial regrowth was observed with both regimens at hour 48 against the ceftazidime-resistant *P. aeruginosa* strain with a MIC of 50 mg/L.²⁶ For this isolate, both regimens had concentration–time profiles that were well below critical PK/PD exposures required for effect. A 36-h two-compartment in vitro model of *P. aeruginosa* (starting inoculum of 5×10^5 CFU/mL) found enhanced killing at the end of the study and less regrowth with CI of ceftazidime relative to SI against two of the three strains tested with MIC values of 1 and 4 mg/L, respectively.³² The difference in killing between infusion modalities was attributed to having concentrations more than four times the minimum concentration (C_{min})/MIC ratio with CI versus SI. Similar rates of bacterial killing and resistance suppression were observed with ceftazidime/avibactam 6 g/day administered as a 2- or 4-h infusion every 8 h or CI in a 10-day HFIM study of KPC-2 *K. pneumoniae* (two strains: MICs of 0.5/4.0 mg/L and 0.125/4.0 mg/L).²⁷ All regimens in this study had ceftazidime and avibactam exposures above their respective PK/PD targets ($fT_{>MIC}$ for ceftazidime and time >4 mg/L for avibactam).

The dependency of bacterial killing for each infusion modality based on the ability to achieve PK/PD exposures was also demonstrated with piperacillin-tazobactam. In an HFIM study of *P. aeruginosa* that tested two starting inoculums ($\sim 10^4$ CFU/mL and 10^7 CFU/mL), SI and CI were equivalent in terms of the antibacterial effect for the lower starting inoculum as both regimens had exposures above the PK/PD targets identified for each infusion modality (the PK/PD target for 3-log reduction in total CFU/mL was a C_{min}/MIC of 2.4 for SI and C_{min}/MIC of 6.7 for CI).²⁸ In the high bacterial density study, stasis was observed for SI and CI, and this was the only critical PK/PD target readily achieved by both infusion strategies. The PK/PD target for stasis was a C_{min}/MIC of 3.2 for SI and a C_{min}/MIC of 8.3 for CI. In a 6–8 h one-compartment in vitro pharmacodynamic study of *P. aeruginosa* (starting inoculum of 1×10^6 CFU/mL), there was no increased initial killing with EI compared with SI of piperacillin-tazobactam (3.375 g intravenously every 6 h for 0.5- and 3-h infusions and 3.375 g intravenously every 8 h for 4-h infusions) for isolates with MICs of 8 or 16 mg/L. However, bacterial killing at the end of the dosing interval was significantly greater for both EI regimens relative to SI against isolates with MIC values of 32 mg/L and this was attributed to insufficient $fT_{>MIC}$ with SI versus EI.¹³ Similarly, both EI and CI demonstrated greater bacterial killing and less resistance emergence than SIs against the CTX-M-14 extended spectrum β -lactamase (ESBL)-producing isolate in a 7-day HFIM (initial inoculum $\sim 10^7$ CFU/mL) of *K. pneumoniae*.³⁴ Although the PK/PD target

associated with the effect was not ascertained in this study, it was most likely a function of the higher C_{\min}/MIC exposures achieved with PIs (C_{\min}/MIC of 3.18 and 34.11, respectively, for EI and CI) relative to SI (C_{\min}/MIC of 1.09).

Similar exposure effect findings for PI and SI were observed for carbapenems. In a 32-h HFIM of *P. aeruginosa* (starting inoculum of 10^8 CFU/mL), similar mean reductions in the initial inoculum were observed at the end of the study with SI (2g every 8h) and CI (6g every 24h) of meropenem against *P. aeruginosa* with meropenem MICs of 8–16 mg/L.²⁵ However, there was less regrowth with CI relative to SI for the *P. aeruginosa* isolate with an MIC of 32 mg/L at the end of the study and this was attributed to greater $fT_{>\text{MIC}}$ and $C_{\min}/\text{MIC} > 2.5$ with PI versus SI. The findings of this study aligned with a neutropenic murine thigh infection model (starting inoculum of 10^6 CFU/mL) with doripenem against 24 clinical *P. aeruginosa* isolates with a wide range of MICs. In this study, bacterial killing at hour 24 was similar between doripenem 500mg intravenously every 8h administered as a 1- or 4-h infusion for isolates with MIC values up to 2 mg/L.⁴² However, the 4-h infusion regimen displayed enhanced activity for three of the four isolates with an MIC of 4 mg/L. The advantages of EI versus SI of doripenem align with a 10-day HFIM of *P. aeruginosa* (PAO1 wild-type isolate, stably derepress *ampC* mutant, *oprD* isogenic mutant).¹⁸ In this study, 4-h infusions of doripenem 500mg intravenously every 8h demonstrated greater killing relative to 1-h infusions of the same doripenem regimen. Finally, similar bacterial killing between SI (0.5 h) and EI (3 h) regimens of meropenem 1g every 8h was observed in a 24-h HFIM study of *K. pneumoniae* for isolates with MIC values (0.031 mg/L and 8 mg/L) in which there was sufficient $fT_{>\text{MIC}}$ with both SI and EI.³⁶

Although in vitro PK/PD studies demonstrated some trends to increase bacterial killing for PI, data from animal studies are less conclusive. However, it is difficult to fully mimic humanized exposures for PI in animal studies. In a rabbit pneumonia model of *P. aeruginosa*, humanized SI ceftazidime (2g three times daily) and CI ceftazidime (4g daily) against *P. aeruginosa* with a ceftazidime MIC of 1 mg/L had a similar bacterial effect in the lung but enhanced bacterial killing and sterilization were observed in the spleen with CI versus SI.³⁸ A similar reduction in lung bacterial burden between SI and CI ceftazidime was observed in a pig pneumonia model of *P. aeruginosa* (ceftazidime MIC of 16 mg/L).²¹ Doripenem 500mg every 8h also had a similar reduction in pulmonary bacterial loads and similar spleen and blood sterilization rates as doripenem 1.5g daily as a CI in a rabbit pneumonia model of *P. aeruginosa*.³⁹ In a *P. aeruginosa* rabbit infective endocarditis study, equivalent daily doses of ceftazidime administered as CI (6g daily) and SI (2g every 8h) resulted in similar bacterial count reductions in vegetations at hour 24 for four strains of *P. aeruginosa* with ceftazidime MIC ranging from 1 to 8 mg/L.⁴⁰

3.2.3 | Future research needs

Additional adequately powered, preclinical PK/PD studies with formalized statistical analysis plan that mimic humanized

concentration–time profiles of SI or PI β -lactams are needed to properly ascertain if there are differential rates of bacterial killing and regrowth/resistance suppression between SI or PI β -lactams. A diverse array of pathogens should be included in future studies, including isolates with emerging resistance mechanisms and higher MIC values. Emphasis should be placed on studying isolates in which there are distinctive differences in $fT_{>\text{MIC}}$ profiles between SI and PI as any potential differences in bacterial killing and regrowth/resistance suppression between infusion modalities are likely to be elucidated in these strains.

As part of these studies, there should be a focus on evaluating exposures associated with maximal daily doses of β -lactams shown to be safe and efficacious in humans. Additionally, there is a need to evaluate concentration–time profiles achieved with candidate dosing regimens across the range of patients in clinical practice (i.e., augmented renal function, normal renal function, impaired renal function, obesity, etc.) in both the bloodstream and difficult-to-treat infection sites (e.g., epithelial lining fluid and central nervous system) for older, recently approved, and investigational β -lactams. When feasible, starting bacterial inoculums should mirror the bacterial burden encountered in practice for the intended indication (e.g., skin infections vs ventilator-associated bacterial pneumonia), and study durations should be consistent with current treatment practices (e.g., 5 days for skin infections vs 7–10 days for ventilator-associated bacterial pneumonia).

3.3 | Background question III

Do PI β -lactams minimize resistance emergence relative to SI in pre-clinical PK/PD models of infections?

3.3.1 | Background consensus statement 3

β -lactams given by PI may reduce the emergence of resistance. β -lactam agent, the bacterial species, MIC, and initial inoculum are important factors affecting the emergence of resistance.

3.3.2 | Evidence summary

Relatively little preclinical data exist on the potential benefits of PI compared to SI with regard to suppression of resistance. One study demonstrated suppression of regrowth with meropenem at concentrations mimicking plasma concentration in humans with CI, but not at concentrations simulating SI, against *P. aeruginosa* in HFIM experiments.¹⁷ Piperacillin–tazobactam has been studied as a simulated 12g daily CI compared to 4g every 8h administered as a 4-h infusion against ESBL-producing *K. pneumoniae*.³⁴ In this study, suppression of resistance after 72h of experiments was only achieved with CI. However, other studies failed to show such associations, for example, in a rabbit pneumonia model using

P. aeruginosa, where neither CI nor SI of ceftazidime had an impact on resistance development regardless of the dosing regimen.³⁸ With doripenem, $fT > 6.2$ times the MIC has been found to be correlated with suppression of resistance in *P. aeruginosa* HFIM experiments, and achievement of this target was maximized with EI.¹⁸ This finding might indirectly support the use of PI as these administration modes increase the time above this threshold compared to SI, assuming the same daily dose is used. However, another study identified different PK/PD targets for SI and CI regimens in *P. aeruginosa* HFIM experiments to suppress the emergence of resistance – C_{min}/MIC of 3.4 with SI and C_{min}/MIC of 10.4 with CI,²⁸ suggesting different targets may exist. Finally, cefepime showed similar antibacterial effects during the first 12 h of experiments mimicking cefepime 1 g every 12 h SI versus 1 g bolus dose followed by 2 g daily as a CI.³⁵ Regrowth was observed during experiments with SI but not with CI, which may be partly the result of a higher total dose during the first 24 h of experiments. No resistance development was observed in the study.

Very few preclinical studies investigated the emergence of resistance with β -lactam infusions in combination with other agents. PK profiles representing augmented renal clearance (creatinine clearance [CrCl] 250 mL/min) were simulated in an HFIM for meropenem (1–2 g every 8 h over 30 min or 3–6 g daily CI) and tobramycin (7 mg/kg every 24 h over 30 min) over a 7-day total duration of therapy. Two carbapenem-resistant *P. aeruginosa* isolates were studied with an initial inoculum of $\sim 10^7$ CFU/mL and MICs 8 mg/L and 32 mg/L. The only regimen that suppressed the regrowth of resistant subpopulation was meropenem 6 g/day CI with tobramycin in the isolates with MIC 8 mg/L. In the less susceptible population (MIC 32 mg/L), no regimen suppressed the growth of resistant bacterial population.⁴³ A similar study investigated imipenem–tobramycin combination against *A. baumannii* (MICs 0.25, 4, and 32 mg/L) and initial inoculum of $\sim 10^7$ CFU/mL. The investigators combined the mechanism-based combination PD model with the published PK models of tobramycin and imipenem in critically ill patients, and simulated imipenem (1 g every 6–8 h over 1 h and 1 g loading dose followed by 3–4 g/day CI) and tobramycin (5–7 mg/kg every 24 h over 30 min) regimens. The regimen with the highest probability of success for eradication of *A. baumannii*-resistant isolates (MIC 32 mg/L) was imipenem 4 g/day CI plus tobramycin 7 mg/kg/day.⁴⁴ The PD of meropenem and polymyxin B combination against *A. baumannii* (MIC 16 mg/L and initial inoculum 10^8 CFU/mL) has been evaluated. The comparative approach identified a preference for meropenem regimens which improve the $fT_{>MIC}$ by prolonging the infusion time or shortening the dosing interval. The best-simulated regimen was meropenem 19.6 g/day as a 2-h infusion every 5 h plus polymyxin B 5.17 mg/kg/day every 6 h to eradicate *A. baumannii* from initial inoculum of 10^8 CFU/mL to zero.⁴⁵

3.3.3 | Future research needs

Additional preclinical studies are needed to better understand if differences exist between SI and PI schemes. Greater diversity of

bacterial species and baseline resistance profiles encompassing a heterogeneity of phenotypic and genotypic differences are needed. Starting inocula should mimic bacterial loads from the intended infection types.

3.4 | Background question IV

Is there a role for TDM of PI β -lactams?

3.4.1 | Background consensus statement 4

We suggest that β -lactam TDM and personalized dosing may be considered on a patient-by-patient, indication-by-indication, drug-by-drug basis until further evidence is available. We cannot recommend for or against routine TDM for PI β -lactams at this time. (Consensus recommendation).

3.4.2 | Evidence summary

Three randomized controlled studies have evaluated the impact of β -lactam TDM on PK/PD exposure and clinical outcomes (Table S4).^{46–48} Adverse effects and resistance development were not reported in any of these studies. A single-center, open-label RCT in critically ill adults ($n=41$) who received meropenem or piperacillin–tazobactam by EI were randomized to daily TDM or standard of care.⁴⁶ The primary outcome was the proportion of patients achieving the PK/PD target of 100% $fT > 4$ times the MIC at 72 h. At baseline, only 21% of patients receiving piperacillin–tazobactam and 0% of those receiving meropenem reached this exposure threshold. At 72 h, 58% and 16% of patients in the TDM and standard-of-care groups, respectively, achieved 100% $fT > 4$ times the MIC ($p=0.007$). There was no difference between groups in mortality, treatment failure, or bacterial persistence.

A second single-center, open-label RCT enrolled patients with febrile neutropenia receiving piperacillin–tazobactam and randomized them to TDM or standard of care.⁴⁸ All patients ($n=32$) initially received piperacillin–tazobactam by SI; EIs could be used as a strategy to increase exposure in those randomized to TDM. The primary outcome was the proportion of patients achieving the PK/PD target of 100% $fT_{>MIC}$ on day 3. Overall, only 22% of patients reached the target at baseline. On day 3, 69% of patients in the TDM group compared with 19% of those in the standard-of-care group achieved 100% $fT_{>MIC}$ ($p=0.012$). There was no difference in the duration of fever or time to recovery from neutropenia.

The third single-center, open-label RCT focused on critically ill burn patients ($n=38$).⁴⁷ Patients were allocated to groups where they received alternate β -lactams; all were administered by SI during the first 3 years of the study and by EI during the final 2 years. PK/PD targets varied by the agent but, in general, were close to 100% $fT_{>MIC}$. Less than 60% of patients reached the targets at baseline. There was no difference between groups in the primary outcome of time

to reach the PK/PD target (hazard ratio [HR] 1.39 [95% confidence interval 0.81–2.39]) although patients randomized to TDM had fewer trough concentrations below and more days spent above the PK/PD target. Daily defined doses, as a measure of antibiotic consumption, were not different between groups. The resolution of signs and symptoms of infection occurred in over 90% of patients in both groups.

Collectively, these studies demonstrate that β -lactam TDM in high-risk populations displaying altered PK increases the achievement of PK/PD target exposures. However, none of the studies were designed or powered to demonstrate benefits in important patient-centered outcomes (decreased mortality, improved clinical cure, decreased adverse effects) or public health endpoints (decreased emergence of antimicrobial resistance). In addition, the trials have important limitations: all were small, open-label, single-center studies; two^{47,48} measured total rather than free β -lactam concentrations; not all patients had isolates available for MIC testing and epidemiological cut-off values or MIC₉₀ were used as surrogates; target exposures differed; TDM may not have been performed frequently enough in patients with rapidly changing PK^{47,48}; and protocol violations in the standard of care arm may have diluted the effect of TDM.⁴⁷ None of the studies consistently used PIs at baseline; it is possible that these infusion strategies would increase exposure sufficiently to obviate the need for β -lactam TDM.

There may be potential utility of TDM in individual patients with disease states that cause altered β -lactam PK. Critically ill patients regularly display altered PK and PD as a function of infections with high MIC isolates, the rapid development of resistant organisms, and the increased clearance of β -lactam antibiotics resulting in the lack of optimization of the $fT_{>MIC}$.^{46,48–51} Of note, clinical studies have compared the use of TDM to the standard dosing protocol in patients who are critically ill and receiving PI β -lactam therapy.^{46,50–52} These clinical studies relied heavily on higher targets as markers required for β -lactam clinical success and each of the studies indicated that TDM was required to achieve the therapeutic targets. Nevertheless, the defined PK/PD targets were not linked to improved patient outcomes when comparing those individuals who received the prolonged β -lactam infusion therapy to those that did not.

The potential utility of TDM for adequate target attainment in patients with augmented renal function receiving PI has been described. Notably, greater than 40% of study patients did not achieve specified targets, and 80% of those individuals had documented renal clearances >130 mL/min; thereby placing them at risk for treatment failure.⁵² Although TDM adjustments are absent from this clinical study, it attests to the potential utility of adjusting therapy to meet PK/PD targets. With that, the strongest predictor for subtherapeutic β -lactam exposure in a prospective observational study was augmented renal function, defined as a CrCl >130 mL/min.⁵⁰ The authors indicated that 103/330 (31.2%) of the included patients with augmented renal function required TDM to achieve the predefined PK/PD targets, but the most appropriate PK/PD target and association with clinical outcomes remains unknown.

In patients with CF, PK uncertainties further complicate the probability of target attainment (PTA). Increased volume of

distribution and total body clearance of β -lactam antibiotics may consequently require higher doses in patients with CF compared with healthy patients.⁵³ As a result, people with CF may not be able to achieve PK/PD goals with standard dosing.^{54–56} The ability to achieve PK/PD goals has been demonstrated in people with CF utilizing PIs of β -lactams.^{57–60} Employing TDM with a PI of β -lactams may be beneficial in patients with CF. An increase in forced expiratory volume over 1 s (FEV₁) % predicted, forced expiratory flow at 25%–75% (FEF_{25%–75%}), and FEV₁/forced vital capacity (FVC) ratio was described when therapeutic β -lactam PD indices were achieved compared to when they were not.⁶¹

3.4.3 | Further research needs

Future prospective randomized studies are needed to determine which, if any, patients derive benefit from TDM and dose optimization of β -lactam PI. Currently, most data on the potential utility of PI β -lactam TDM exists for patients who are critically ill. Thus, priority patient groups, in which information regarding prolonged β -lactam infusion is scarce, would include those that are obese, pediatric, pregnant, immunocompromised, renally impaired, on extracorporeal membrane oxygenation, at high risk of gram-negative infections, patients with CF, or individuals known to be infected with bacteria demonstrating high MICs (i.e., intermediately susceptible with MICs near the recommended breakpoint) to the selected β -lactam. Additionally, future studies should evaluate the role of TDM based on free versus total drug concentrations, the utility of Bayesian modeling, and the optimal sampling strategy.

3.5 | Background question V

What β -lactam concentration or exposure should be targeted when performing TDM?

3.5.1 | Background consensus statement 5

There is insufficient evidence to recommend a single concentration or exposure to target when performing β -lactam TDM; however, evidence does exist for minimum exposure. When TDM is performed, we suggest minimum plasma exposures of at least 50%–70% $fT_{>MIC}$ be targeted for β -lactams when administered as SI and EI. For β -lactams administered as CI, we suggest 100% $fT_{>MIC}$ with concentrations at least four times the MIC.

3.5.2 | Evidence summary

The majority of data to support PD thresholds for individual antibiotic/bacteria combinations, especially for newer antibiotics, is generated during preclinical development using various in vitro and

in vivo models. Most notably, the neutropenic murine thigh infection model is frequently employed by drug developers to establish thresholds for stasis, 1-log and 2-log reductions in CFU.⁶² These thresholds are often quoted as being the minimum drug exposure required that should translate to clinical efficacy in most human infections, with 1- or 2-log reduction thresholds preferred for serious infections such as pneumonia and bloodstream infections; exposures resulting in stasis may be sufficient for less serious infections such as skin and skin structure infections and urinary tract infections.⁶³ As a result, dosing regimens designed to achieve these thresholds in humans frequently lead to noninferiority and successful application for approval by the United States Food and Drug Administration (FDA). For most β -lactam antibiotics, exposures of 50%–70% $fT_{>MIC}$ achieve at least 1-log reductions in CFU against gram-negative bacteria in the neutropenic murine thigh infection model.⁴ It should be noted that in some preclinical murine experiments, certain β -lactams required less than 50% $fT_{>MIC}$ to achieve 1-log reductions in CFU (e.g., ceftolozane against *P. aeruginosa*), while others required >70% (e.g., cefiderocol against *A. baumannii*).

Outside of preclinical data, limited exposure-response studies are conducted in humans and only a few Phase 3 studies identify a relationship between β -lactam $fT_{>MIC}$ and the selected clinical endpoint. For example, ceftobiprole did not achieve its predefined noninferiority margin when studied in Phase 3 trials for nosocomial pneumonia, thereby providing an opportunity to evaluate the efficacy of lower exposures.⁶⁴ For patients with pathogens identified, 51% $fT_{>MIC}$ was identified as the threshold associated with eradication of the baseline pathogen by the end of treatment. Additionally, 62.2% $fT_{>MIC}$ was identified as the threshold associated with the eradication of any pathogen by the end of therapy. Ceftaroline exposure-response relationships were defined for patients treated during the acute bacterial skin and skin structure clinical trials.⁶⁵ Classification and regression tree analyses identified 54.2% and 55% $fT_{>MIC}$ as thresholds predictive of microbiological success in all patients and those specifically with *S. aureus* infections, respectively.

Unfortunately, the majority of non-registrational clinical studies assessing exposure-response relationships are fraught with assumptions and limitations, most notably, small numbers, receipt of other active antibiotics concomitantly, multiple different infection types, limited to no actual concentration data from the included patients, and no MIC data available for the causative pathogen. Endpoints also vary across these studies. Despite these limitations, the majority of studies identified congruent thresholds between ~50% and 70% as being predictive of success (i.e., clinical response, microbiological eradication, survival, etc.).⁶⁶ However, some studies have suggested higher thresholds, such as 100% $fT_{>MIC}$ or 100% $fT > 4$ times the MIC as preferred targets, especially in critically ill patients.⁶⁶ Among these human studies, and at the time of the literature search, only two studies determined actual plasma concentrations from participants and performed MICs for causative pathogens.^{67,68} One study evaluated 20 patients treated with cefepime plus an aminoglycoside who were infected with various gram-negative pathogens from a

mixture of infection sources; the most common infection was of the respiratory tract.⁶⁷ Microbiological success (defined as eradication or presumed eradication) was 89% when total drug $T_{>MIC}$ was 100%, and 0% when total drug $T_{>MIC}$ was <100% ($p=0.032$); however, only two patients had less than 100% $T_{>MIC}$. When Classification and Regression Tree was employed, a C_{min}/MIC of 4.3 was significantly associated with microbiological success. The final logistic regression model predicted 80% and 90% success when $T > 4.3$ times the MIC was 83% and 95% of the dosing interval, respectively.

The second study was of 15 pediatric patients with CF acute pulmonary exacerbations who were receiving meropenem as EI.⁶⁸ All patients received either an aminoglycoside or fluoroquinolone concomitantly. The primary endpoint was relative improvement in the FEV₁. A maximum effect model identified $fT_{>MIC}$ as a significant predictor of improved FEV₁, and Classification and Regression Tree identified a $fT_{>MIC}$ exposure cutoff at 65% to predict this improvement. Patients achieving >65% $fT_{>MIC}$ had FEV₁ median improvement of 28% whereas those who did not only observed a median improvement of 7.8%.

Each of these two studies reported different $fT_{>MIC}$ thresholds for their respective β -lactam and used different endpoints, thereby making it difficult to derive a consensus for target exposure. Because murine-based preclinical studies consistently demonstrate ~50%–70% $fT_{>MIC}$ is associated with 1-log reductions in CFU, we suggest this be the minimum exposure threshold used when conducting β -lactam TDM, particularly for regimens, where the β -lactam is administered as an SI or an EI (i.e., 3–4 h). However, when administered as a CI, free concentrations can only be \geq or $<$ MIC for the entire dosing interval with this dosing strategy. For β -lactams administered as CI, we suggest a threshold of at least 100% $fT_{>MIC}$ with steady-state concentrations exceeding a minimum of four times the MIC. Higher exposure thresholds may be necessary for individual patients based on the site of infection (e.g., consideration of penetration), interpretation of MIC (e.g., known variability in MIC across different testing methods), or unknown factors (e.g., inter-isolate variability in required $fT_{>MIC}$ thresholds). However, when clinicians aim to target efficacious therapy, they should remain cognizant about limiting maximum doses.

Although well-tolerated, β -lactams are not spared from dose-related adverse events. Notably, higher exposures can be associated with neurotoxicity and bone marrow abnormalities.⁶⁹ In contrast, nephrotoxicity and hepatotoxicity appear to be unrelated to exposure. Small studies have attempted to evaluate the threshold for specific agents that are associated with these toxicities (e.g., cefepime-induced neurotoxicity). Most of these studies associate toxicity with the serum trough concentration, and reported thresholds vary widely between studies and specific β -lactams. For example, cefepime neurotoxicity has been reported with mean trough concentrations between 22 and 63 mg/L,⁶⁹ and one study observed no neurotoxicity only when the trough was <7.5 mg/L.⁷⁰ For this reason, it is difficult to set a strict therapeutic range for β -lactams, and therefore routine TDM is not recommended. However, TDM may be useful in individual patients who develop neurotoxicity and bone marrow abnormalities while receiving β -lactams to aid in therapeutic

management, including dosage reductions or discontinuation of the offending β -lactam.

Finally, recommendations for how to conduct β -lactam TDM are outside the scope of this guidance and can vary from institution to institution, depending on available drug assays and software used to estimate individual PK parameters. Interpretation of MICs as a part of TDM requires careful consideration of many factors to ensure appropriate use. Limitations to interpreting a single MIC value include assay variability, laboratory variability (incubation time, inoculum size, etc.), variation by strain, and potential discordance between *in vitro* MICs and *in vivo* concentrations at the site of infection, leading to uncertainty in the interpretation of a single MIC value and possibly inappropriate dose adjustment.⁷¹ We refer the reader to robust reviews of β -lactam TDM,^{66,72} which discuss practical approaches for day-to-day implementation, and a suggested approach for interpreting single MICs.⁷¹ In brief, all MIC testing should be completed using a method calibrated to reference methodology. When MICs are below the epidemiological cut-off value for susceptible strains (i.e., wild type), the MIC of the epidemiological cut-off value should be used. If the strain has an MIC above the epidemiological cut-off value, the utilized MIC should be inflated by one dilution step.⁷¹

3.5.3 | Future research needs

It remains possible that no single $fT_{<MIC}$ or fC_{ss}/MIC threshold will apply uniformly across all β -lactam agents, organisms, and infection types. Future studies in patients are needed to confirm the optimal exposure required for β -lactam TDM, including exposures associated with dose-related toxicities. We recommend that such studies include monotherapy, when possible, a similar infection type, and importantly collect actual plasma concentration and MIC data to determine observed individual exposure. Finally, the sample size should be sufficient to include patients with exposures over a broad range of $T_{>MIC}$.

3.6 | Background question VI

Are there stability concerns when delivering PI β -lactam infusions?

3.6.1 | Background consensus statement 6

There are general stability concerns that should be considered on a drug-by-drug basis when delivering β -lactams by PI.

3.6.2 | Evidence summary

Stability data are primarily derived from three main sources: pharmaceutical industries, manufacturers of infusion-related

devices (e.g., elastomeric pumps), or individual research groups with an active interest in this area. These data are usually based on simulation/modeling/degradation studies or patient case series. Although valuable, several limitations arise from these data, including no independent verification of the data, no international consensus on the acceptable limits or tolerances, laboratory-based conditions that do not depict real-life situations, and evaluated concentrations and time points that are not always relevant to clinical situations.⁷³ As expected, no RCTs were identified in this area.

Of the agents reviewed, β -lactam stability data exist to varying degrees around amoxicillin,^{74,75} ampicillin,^{76,77} benzylpenicillin,^{76,78-80} cefepime,^{73,81} cefoxitin,⁸⁰ ceftaroline,⁸² ceftazidime,^{83,84} ceftolozane/tazobactam,⁸⁵ flucloxacillin,^{73,80,86} piperacillin-tazobactam,^{73,87,88} and meropenem.⁸⁹⁻⁹² In recent years, there is emerging evidence to suggest that a number of key pharmaceutical criteria are important and should be explored when considering stability concerns. The final concentration of drug recovered in the device can potentially be altered by temperature, pH changes and associated buffers, altering the starting drug concentration of the solution, degradant rate, formation of toxic impurities, and altered flow rates of devices.^{75,80,88,93-95} These variables are particularly important if infusions are going to be utilized outside of an inpatient setting and not for immediate use. These variables can impact the logistics of manufacturing and delivery of infusions, particularly when the shelf life of the product could be days or even weeks. In addition, there is further evidence to suggest in an outpatient setting that temperature (due to the device being worn close to the body) can potentially accelerate the degradation of antimicrobials.⁹³

Stability data for agents such as flucloxacillin, piperacillin-tazobactam, and cefepime have been evaluated recently. Buffered flucloxacillin,^{73,86} buffered piperacillin-tazobactam,^{73,87} and cefepime⁸¹ PIs appear to be supported by reproducible stability data at 24 h or more, depending on temperature storage conditions. Meropenem⁸⁹⁻⁹² appears to be stable between 6 and 12 h and ceftaroline and⁸² ceftolozane/tazobactam⁸⁵ appear stable between 12 and 24 h depending on the percentage of drug degradation. Increased degradation rates have been reported with amoxicillin, ampicillin, benzylpenicillin, and ceftazidime.^{74,77,78,83} One potential solution to this is to undertake TDM to assess for therapeutic effect; however, it is noted that this is not universally available.⁷⁷

3.6.3 | Future research needs

There is insufficient evidence to suggest a “one size fits all” strategy for overcoming stability concerns when delivering PI β -lactams as there are inconsistencies in how antimicrobial stability studies are carried out globally. The United Kingdom has led in publishing open-access drug stability data which meets pharmaceutical critique.^{94,96} However, these studies are costly, and while some intercountry

differences may exist, it may set a standard for global collaboration and consensus when delivering β -lactams by PI. It is suggested that this be a focus of further research to allow for consistency, safe practice, and dose optimization.

3.7 | PICO question VII

Should PI β -lactam antibiotics be preferred over SI dosing in severely ill adult patients to improve mortality or clinical cure?

3.7.1 | Recommendation 7

We suggest PI β -lactam antibiotics over SI to reduce mortality or increase clinical cure among severely ill adult patients, particularly those with gram-negative infections. (Conditional recommendation; very low certainty of evidence).

3.7.2 | Evidence summary

Severely ill patients are defined as those with a high risk of mortality (i.e., median Acute Physiology and Chronic Health Evaluation II [APACHE II] ≥ 15 , Sequential Organ Failure Assessment [SOFA] ≥ 9 , or critically ill). Mortality was evaluated in severely ill patients in 20 RCTs, including one RCT with cancer patients exclusively, but only one single-center pilot study suggested a mortality benefit with CI compared with SI β -lactam therapy.⁹⁷ This study only included 21 patients with suspected sepsis, resulting in a wide confidence interval, limited external validity, and mortality was not the primary outcome. Collectively, the mortality rate across all RCTs was numerically lower with prolonged administration methods, but the difference was not statistically significant (RR 0.86 [95% confidence interval 0.72 to 1.02; $I^2=0$])^{49,97-115} (Figure S1). CI was used in 13 studies, whereas EI was used in the remaining 7 studies. Agents studied included piperacillin-tazobactam,^{49,100,108-113,116,117} meropenem^{49,108,110,114,115} cefepime,^{99,110,118} ceftazidime,^{97,116,119} ticarcillin-clavulanate,^{49,108} doripenem,¹⁰⁶ imipenem-cilastatin,¹⁰⁷ and ceftriaxone.¹⁰² RCTs that provided a weight greater than 10% in the meta-analyses are summarized.

The β -lactam Infusion Group II (BLING II) study,¹⁰⁸ which had the largest weight on the overall effect size, was conducted in 25 intensive care units (ICUs) in Australia, New Zealand, and Hong Kong. It randomized 212 patients with severe sepsis to receive CI of β -lactams and 220 patients to receive SI. About 70% of patients received piperacillin-tazobactam, 28% received meropenem, and the remaining 2% received ticarcillin-clavulanate. The study did not find a statistically significant difference in 90-day mortality (HR 0.91 [95% confidence interval 0.63 to 1.31], $p=0.61$) or clinical cure (odds ratio [OR] 1.12 [95% confidence interval 0.77 to 1.63], $p=0.56$) between patients receiving CI or SI. Although half of the patients had a lung infection and a quarter had an intraabdominal infection, only

19% of patients had a pathogenic organism identified, and about 26% of patients received continuous or intermittent renal replacement therapy.

A nested cohort study of BLING-II is the only prospective randomized trial that compared β -lactam CI to SI in patients with augmented renal clearance (ARC), defined as an 8-h urinary CrCl >130 mL/min ($n=45$, median CrCl 165 mL/min, interquartile range 144–198 mL/min).¹²⁰ CI was administered in 42% of patients with ARC and no difference in 90-day mortality (11% vs 15%, $p=0.6$) nor clinical cure (74% vs 73%, $p=0.96$) was observed between the CI and SI groups, respectively.

The β -Lactam Infusion in Severe Sepsis (BLISS) study,¹¹⁰ conducted in two ICUs in Malaysia, randomized 70 patients with severe sepsis to receive CI of β -lactams and 70 patients to receive SI. No patients received renal replacement therapy. About 60% of patients received piperacillin-tazobactam, 30% meropenem, and 10% cefepime. Similar to BLING II, about 59% of patients had lung infections and 19% had intraabdominal infections. The study did not find a statistically significant difference in 30-day mortality (absolute difference 11%; 95% confidence interval -0.3% to 0.1%), but it did find a significant increase in clinical cure (absolute difference 22%; 95% confidence interval -0.4% to -0.1%) with CI.

A single-center study¹¹² conducted in an ICU in Hong Kong randomized 185 patients to receive EI (4h) piperacillin-tazobactam and 182 patients to receive SI (0.5h) piperacillin-tazobactam. About 73% of patients had respiratory infections and 18% had intraabdominal infections. About 28% of patients received continuous renal replacement therapy. Again, this study did not find a statistically significant difference in 14-day mortality (11.5% EI vs 15.7% SI, $p=0.29$). Clinical cure was not an outcome of this study.

Patients with cancer were evaluated in a single-center study in China.¹¹³ It randomized 32 patients with hospital-acquired pneumonia to receive EI (3h) of piperacillin-tazobactam and 35 patients to receive SI (0.5h) piperacillin-tazobactam. Patients with CrCl <20 mL/min or acute kidney disease were excluded. The study showed significant improvement in clinical efficacy (78.13% EI vs 57.14% SI, $p=0.007$) and no difference in 28-day mortality.

Several retrospective studies have demonstrated a reduced rate of mortality with PI β -lactam antibiotics, predominantly among severely ill patients. Although not all patients were in an ICU, most had APACHE II scores above 14.¹²¹⁻¹²⁴ Additionally, in most trials in which decreased mortality was observed, patients had documented gram-negative infection, including *P. aeruginosa*.¹²¹⁻¹²⁶ Most evidence reporting statistically significant mortality reductions with PIs of β -lactams were from studies with retrospective designs.

Clinical efficacy was evaluated in 14 RCTs, 10 of which reported clinical cure and the remaining 4 reported clinical success as either clinical cure or clinical improvement. One study included cancer patients exclusively.¹¹³ Collectively, the studies demonstrated a beneficial effect of PI β -lactam antibiotics compared with SI, mostly among those with pulmonary infections (RR 1.10 [95% confidence interval 1.03 to 1.19; $I^2=33$])^{49,99,102-106,108,110,111,113-115,127,128} (Figure S2). However, there was significant publication bias ($p=0.02$)

and the adjusted pooled estimate was not statistically significant (RR 0.97 [95% confidence interval 0.83–1.12]) (Figure S2). Most RCTs and observational studies supporting clinical success used continuous infusion.^{49,102,110,124,128-131} Studies that did not find a difference had a low incidence of resistant organisms^{105,114} or were underpowered.^{104,111,115,127}

Two RCTs among patients receiving PI β -lactam therapy found improved microbiological success compared with SI β -lactam administration.^{105,113} Four other RCTs^{102,114,115,128} failed to find significant differences in microbiological outcomes with PI β -lactam therapy. Meta-analysis of the six studies collectively demonstrated an advantage with the use of PI administration methods among severely ill patients (RR 1.21 [95% confidence interval 1.08–1.35], $I^2=0\%$) (Figure S3). The GRADE evidence summary for mortality, clinical cure, and microbiological cure among severely ill adult patients is in Table S1.

Limitations exist in the studies reviewed. Most studies included empirically treated patients without proven infection, thus requiring extrapolation of pathogens and resistance profiles. Additionally, the majority of pathogens were gram-negative organisms and a mismatch between selected antibiotic agents or doses and pathogen resistance profiles existed in some studies. While outside of our search timeline, we reviewed the recent multicenter, double-blind, RCT, which concluded no improvement in clinical outcomes with continuous infusion meropenem over short infusion among critically ill patients with presumed sepsis. Unfortunately, patients that could benefit from PI did not comprise a large portion of the enrolled patients (i.e., ~30% of patients had no identified causative pathogens, ~30% had meropenem-resistant organisms, and ~36% had gram-positive organism identified. By enrolling patients that prim.

3.8 | PICO question VIII

Should PI β -lactam antibiotics be preferred over SI in nonseverely ill adult patients to improve mortality and clinical cure?

3.8.1 | Recommendation 8

We cannot recommend for or against PI β -lactam antibiotics over SI to reduce mortality and increase clinical cure among nonseverely ill adult patients. (Conditional recommendation; very low certainty of evidence).

3.8.2 | Evidence summary

Nonseverely ill patients are defined as those with a low risk of mortality (i.e., median APACHE II <15, SOFA <9, or not critically ill). Six RCTs evaluating mortality among nonseverely ill patients found no difference in survival between the use of PI β -lactam

antibiotics versus SI with an overall RR of 1.06 (95% confidence interval 0.52–2.18), $I^2=0\%$ ^{113,116-118,132,133} (Figure S4). Half of these studies used CI of β -lactam therapy^{117,132,133} and the other half used EI β -lactams.^{113,116,118} Agents studied included cefoperazone,¹³² cefepime,¹¹⁸ piperacillin-tazobactam,^{113,116,117,133} and only a few patients received ceftazidime.¹¹⁶ In a multicenter RCT of 258 patients with intra-abdominal infection and a median APACHE II score of 7, only four deaths occurred (one received CI piperacillin-tazobactam and three received SI).¹¹⁷ The most common causative pathogens were *Escherichia coli* and *Bacteroides fragilis*, but MICs were generally low. In another RCT, 78 patients with suspected *Pseudomonas* infection were treated with either CI or SI piperacillin-tazobactam with only one reported death in the SI group, which was not thought to be infection related.¹³³ Of note, only 20% had sepsis and about 90% of patients were treated empirically with only 24 positive cultures of which *Pseudomonas* was isolated from 8 cultures.

Patients with cancer were assessed in the other four single-center RCTs^{113,116,118,132} as well as in two retrospective studies^{134,135} and similarly demonstrated no significant difference in mortality between infusion strategies. CI versus SI cefoperazone was evaluated in 45 patients with gram-negative bacteremia, most with cancer (80%), and nine deaths were reported of which seven were attributed to treatment failure (three in the CI group versus four in the SI group).¹³² Over half of the patients did not have a site of infection identified, 12 had a urinary tract infection with *E.coli* being the most frequently isolated pathogen, and all but three strains were sensitive to cefoperazone. EI versus SI piperacillin-tazobactam was compared in patients with cancer and hospital-acquired pneumonia where the cohort was further divided into those with mild ($n=53$) or severe disease ($n=67$) based on a SOFA cutoff of 9.¹¹³ No deaths occurred among those with SOFA less than 9 while six deaths occurred in those with SOFA of at least 9 (five of which were in the SI group). Another study randomized 105 patients with febrile neutropenia to EI or SI piperacillin-tazobactam or ceftazidime and observed few deaths (1 vs 2 in the EI and SI groups, respectively).¹¹⁶ Most did not have a clinically documented infection and of the <8% that were microbiologically documented, *E. coli* (sensitive to piperacillin-tazobactam) was the causative pathogen in most cases. Among patients with febrile neutropenia randomized to EI or SI cefepime, numerically greater deaths were found in the group receiving EI compared with those who received SI cefepime (5 vs 3, $p=0.46$, respectively).¹¹⁸ However, cefepime did not have activity against more identified pathogens in the EI group (e.g., methicillin-resistant *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, vancomycin-resistant *Enterococcus faecium*, and extended-spectrum β -lactamase *E. coli*).

Only one multicenter, observational study identified reduced mortality among patients treated with PI β -lactams including piperacillin-tazobactam, imipenem-cilastatin, and meropenem (HR 0.28, 95% confidence interval 0.10–0.88).¹³⁶ All patients had cirrhosis and bacteremia, and despite increased isolation of multidrug-resistant and nonfermenting gram-negative pathogens in the PI group, PI in patients with gram-negative bacteremia was associated with fewer deaths. Although no mortality benefit was demonstrated

among those with gram-positive infections, this subgroup was underpowered.¹³⁶

Eight RCTs evaluating clinical cure among nonseverely ill patients found no significant benefit with the use of PI β -lactam antibiotics with a RR of 1.00 (95% confidence interval% 0.95–1.06), $I^2=32\%$ (Figure S5). These studies included piperacillin–tazobactam^{114,116,117,133,137} and cephalosporins (cefuroxime,¹³⁸ cefotaxime,¹³⁹ cefepime,¹¹⁸ and ceftazidime¹¹⁶). Most trials utilized CI^{117,133,137–139} and the three RCTs in cancer patients utilized EI.^{113,116,118} A few reported only the combined outcome of both clinical cure and clinical improvement,^{116,117,139} and one study evaluated clinical efficacy without a definition.¹¹³ A significant overall response with EI piperacillin–tazobactam or ceftazidime over SI was found among those with documented infection, especially pneumonia.¹¹⁶ Of note, among patients with complicated intraabdominal infections, >90% received a laparotomy, which may have driven treatment success for these patients.¹¹⁷ Additionally, many patients were not microbiologically evaluable^{116,118,133,138} or pathogens were highly susceptible with low MICs.^{113,117,137,139}

Six RCTs^{113,116,117,133,137,138} compared microbiological cure between nonseverely ill patients who received PI β -lactam therapy versus SI and none demonstrated a difference, though a trend toward improved bacteriological success with PI β -lactam antibiotics was still observed among nonseverely ill patients (RR 1.06 [95% confidence interval 0.99–1.15], $I^2=27\%$) (Figure S6). The GRADE evidence summary for mortality, clinical cure, and microbiological cure among nonseverely ill adult patients is shown in Table S2.

Patients with CF hospitalized with acute pulmonary exacerbations are often nonseverely ill and there is currently limited evidence on the clinical impact of PI β -lactam antibiotics in this patient population. To date, the largest multicentered, randomized, cross-over trial evaluating CI versus SI β -lactams in patients with CF compared ceftazidime delivered via CI versus three times daily SI and concluded no significant differences between regimens with respect to the primary outcome of change in FEV₁.⁵⁴ However, the mean change in FEV₁% predicted was significantly better with CI over SI in patients with resistant bacteria. In addition, the mean difference in time to the next intravenous antibiotics was 0.4 months longer with CI versus SI ($p=0.04$). Another multicentered, randomized, cross-over study of ceftazidime-delivered CI versus SI found no difference in leukocyte counts, FEV₁, *Pseudomonas* density, and inflammatory biomarkers in patients with CF.¹⁴⁰ Similarly, a prospective cross-over study found no difference in white blood cell counts, *Pseudomonas* density, and pulmonary function in patients with CF treated with CI or SI ceftazidime.¹⁴¹ Cefepime delivered as CI versus SI was investigated in patients with CF where no difference in bacterial density, inflammatory mediators, or pulmonary function was observed.⁵⁷ There are currently no comparative trials evaluating PI versus SI with other antipseudomonal β -lactam antibiotics (i.e., aztreonam, ceftazidime–avibactam, ceftolozane–tazobactam, doripenem, imipenem–cilastatin, meropenem, meropenem–vaborbactam, piperacillin–tazobactam) in patients with CF for the treatment of an acute pulmonary exacerbation.

3.8.3 | Future research needs (Recommendations 7 and 8)

Regarding mortality, all RCTs were underpowered to detect a difference. Further research is needed to determine if the benefit depends upon organism, infection type, method of PI (extended vs continuous), as well as the duration of EI (e.g., 3 vs 4 h), but future studies should be powered for outcomes in patients with a documented infection. In most RCTs of nonseverely ill patients, MICs may have been too low for infusion time to affect clinical outcomes and many studies lacked MIC data. Larger RCTs are needed in hospitalized patients as well as patients in the outpatient setting to determine the role of PI β -lactams. Adequately powered research is also needed to elucidate the clinical effects of PI β -lactams in patients with cancer, febrile neutropenia, augmented renal clearance, and impaired renal function, including those requiring renal replacement therapy.

Most studies were underpowered for microbiological outcomes because few patients have causative organisms isolated and without bacteriologic documentation, patients are not microbiologically evaluable. Additionally, repeat cultures are not often recommended to assess the resolution of infection. Larger studies are needed to better elucidate the effect of PI β -lactam therapy on microbiologic response relative to short β -lactam infusions; however, clinical outcomes should take precedence in clinical decision making.

In nonseverely ill patients, if no differences in clinical outcomes exist, differences in patient/caregiver-oriented endpoints such as line compatibility, nursing time, quality of life measures, and other practical considerations should be taken into account.

3.9 | PICO question IX

Is the use of PI β -lactam antibiotics safer than SI among adult and pediatric patients?

3.9.1 | Recommendation 9

We cannot recommend for or against the use of PI over SI to provide a safety advantage and reduce adverse effects of β -lactam antibiotics. (Conditional recommendation; very low certainty of evidence).

3.9.2 | Evidence summary

Currently, no clinical trials have demonstrated a safety advantage for PI β -lactam antibiotics when compared to administration via SI. Various adverse events within 18 RCTs^{49,102,105,108,110–112,115–117,127,128,133,137–139,142,143} and 8 observational studies^{122,144–150} include acute kidney injury, diarrhea (including *Clostridioides difficile* infection), phlebitis or infusion-related infections, and transaminitis, with no apparent difference when administration time is prolonged. However, with most studies not

designed specifically to evaluate safety, the reporting of adverse events was inconsistent including the type of adverse events or their severity. Thus, no signal of differences in safety has been detected between administration methods.

Clinical experience with the administration of β -lactams as PI in pediatrics is increasing. In general, longer infusions are well tolerated. Observational studies (e.g., PK studies, retrospective cohort studies) have also not reported any major safety concerns. Although comparative studies evaluating the safety of PI versus SI are largely unavailable in children, the use of PI in children in the inpatient setting appears similar to SI overall from a safety standpoint.

Two randomized trials in children have compared PI to SI and reported safety outcomes.^{151,152} In one trial,¹⁵¹ adverse events did not differ by the duration of infusion of cefotaxime in children with meningitis. However, in the trial comparing meropenem infusion durations among neonates with late-onset gram-negative sepsis,¹⁵² acute kidney injury was significantly less frequent in recipients of EI meropenem (6% EI vs 23.5% SI, $p=0.02$), whereas other adverse events were not different between the groups. In a population PK study of SI versus EI of meropenem in very-low-birth-weight infants,¹⁵³ no side effects of drug-related laboratory abnormalities occurred in either group. In a retrospective comparison of outcomes among 21 children treated with EI cefepime and 46 treated with SI cefepime, adverse effects developed in two (9.5%) of the EI recipients and three (6.5%) of the SI recipients ($p>0.05$).¹⁵⁴ Table S3 shows the GRADE evidence summary for safety data (adverse events) from comparative studies of PIs and SIs in pediatric patients.

3.9.3 | Future research needs

Very few studies have evaluated safety as a primary outcome and so additional research designed specifically to compare the safety profile associated with PI versus SI may be necessary. As clinical experience with PIs in children increases, observational studies will be important to inform the safety, tolerability, and practical considerations of their use, particularly in the absence of trial data.

3.10 | PICO question X

Should a loading dose be administered over no loading dose when using PI β -lactam antibiotics in adults to improve mortality or clinical cure?

3.10.1 | Recommendation 10

We suggest the use of a loading dose over no loading dose when initiating CI β -lactam antibiotics to improve clinical success and we cannot recommend for or against a loading dose with EI (Conditional recommendation; very low certainty of evidence).

3.10.2 | Evidence summary

Loading doses are administered to improve time to therapeutic drug concentrations when initiating therapy and prevent delays in reaching target attainment.¹⁵⁵ About 71% (15 of 21) of the RCTs evaluating clinical cure utilized a loading dose.^{49,102,104,105,108,110,114,116-118,128,133,137-139} Subgroup analysis showed that a loading dose significantly improved clinical cure with an RR of 1.10 (95% confidence interval 1.03–1.18), though, there was heterogeneity across studies ($I^2=50\%$) (Figure S7). The three RCTs that found improvement in clinical cure included severely ill patients and used the CI dosing strategy with a loading dose.^{49,102,110} In the six RCTs where no loading dose was administered, no significant difference in clinical cure was observed (RR 1.01 [95% confidence interval 0.92–1.10], $I^2=12\%$).^{99,103,106,111,113,115} Categorization by severity of illness demonstrated significant benefit with use of a loading dose among severely ill patients (RR 1.19 [95% confidence interval 1.08–1.31], $I^2=26\%$) (Figure S8), but statistical significance was not met among nonseverely ill patients (RR 1.00 [95% confidence interval 0.94–1.06], $I^2=42\%$) (Figure S9).

Of the 25 RCTs evaluating mortality, 18 studies utilized a loading dose and demonstrated no survival benefit with an RR of 0.90 (95% confidence interval 0.74 to 1.10), $I^2=0\%$ and similar results observed among severely ill and nonseverely ill patients (Figures S10–S12).^{49,97,98,100-102,104,105,107,108,110,114,116-118,132,133,156}

Given a loading dose was administered prior to initiation of CI β -lactam dosing in all except one RCT⁹⁹ and in three out of nine studies that utilized EI,^{107,116,118} it would be prudent to utilize loading doses until further studies can clarify the implications of this practice.

In studies with CI, the maintenance dose was initiated immediately after the completion of the loading dose.^{49,97,98,100-102,104,105,108,110,114,117,132,133,156} In two of the three studies using EI, the first maintenance dose corresponded with the dosing interval of either every 6 or 8h.^{107,118} The other study utilized an every 8-h maintenance dose that was initiated 6h after the loading dose.¹¹⁶

3.10.3 | Future research needs

Although challenging to perform adequately powered studies to address the remaining questions for the use of loading doses, future research may evaluate differences in clinical outcomes (i.e., both safety and efficacy) between the use of a loading dose and no use of the loading dose, especially with respect to the severity of illness as well as different PI administration methods (CI vs EI). It is unclear whether the first maintenance dose should be initiated at the time of the next dosing interval or earlier and whether that timing may impact clinical efficacy and safety outcomes. Thus, the optimal timing for the initiation of maintenance dosing requires further investigation. Additionally, it is unknown what dose is required for each β -lactam and whether the optimal dose for a given

loading dose varies depending on the time interval between the end of a loading dose infusion and the start of a prolonged infusion. Furthermore, studies should be conducted to determine the best infusion time for administration of a loading dose (e.g., 3-min bolus vs 30-min infusion).

3.11 | PICO question XI

Should PI β -lactam antibiotics be used in children versus SI to improve efficacy?

3.11.1 | Recommendation 11

We cannot recommend for or against routine use of PI for any specific clinical situations or in any specific patient populations (e.g., severely ill, obese, neonates) to improve the efficacy of β -lactam agents in the pediatric population. (Conditional recommendation, very low certainty of evidence).

3.11.2 | Evidence summary

Evidence to support the routine use of PI of β -lactam agents in children is lacking. Through our systematic review, we identified only five published studies that have compared the efficacy of PI to SI in children,^{83,151,152,154,157} and one additional study was published after the performance of the initial systematic literature review¹⁵⁸ (Table S5). Among the studies that were identified, there were three RCTs,^{151,152,157} two retrospective analyses of children treated with prolonged or SIs per standard of care,^{154,158} and one prospective nonrandomized trial of ceftazidime in children with CF that first treated children with bolus infusions followed 4–9 months later by use of CI.⁸³ The β -lactam agents studied include cefepime,^{154,158} ceftazidime,⁸³ cefotaxime,¹⁵¹ meropenem,^{152,158} and piperacillin-tazobactam.^{157,158} The GRADE evidence summary for efficacy outcomes (mortality, clinical cure, and microbiological cure) among pediatric patients is shown in Table S3.

The three RCTs comparing PI to SI evaluated the use of cefotaxime in pediatric meningitis,¹⁵¹ meropenem in neonates with gram-negative late-onset sepsis,¹⁵² and piperacillin-tazobactam in children with febrile neutropenia.¹⁵⁷ One RCT found that EI of meropenem was associated with a significantly higher rate of clinical improvement (61% vs 33%, $p=0.009$) and microbiological eradication at 7 days (82% vs 57%, $p=0.009$), as well as significantly shorter duration of respiratory support (median 4 days vs 12.5 days, $p=0.03$) and lower mortality (14% vs 31%, $p=0.03$) compared with SI, respectively, among neonates with gram-negative late-onset sepsis.¹⁵² Meanwhile, the other two RCTs found no difference in efficacy outcomes based on infusion duration.^{151,157} Among children with bacterial meningitis in Angola administered CI or SI cefotaxime, mortality and neurologic sequelae

were comparable between the treatment groups.¹⁵¹ Similarly, there were no differences in clinical cure, mortality, or fever duration among children with febrile neutropenia treated with CI piperacillin-tazobactam.¹⁵⁷

Observational studies also have failed to identify a significant benefit from the administration of PI of β -lactams in children. In a retrospective study of 67 children with gram-negative bacteremia treated with cefepime, clinical outcomes were similar among 21 children who were treated with a EI compared to 46 who received SI cefepime.¹⁵⁴ The authors used a composite outcome definition of infection-related mortality, bacteremic relapse, and treatment failure and few patients in either group met this outcome (2 [9.5%] in the EI group versus 3 [6.5%] in the SI group, $p>0.05$).¹⁵⁴ In a larger retrospective analysis,¹⁵⁸ the authors evaluated hospital length of stay, hospital readmission, and 30-day all-cause mortality among 258 children who were treated with an EI of either meropenem, cefepime, or piperacillin-tazobactam as the standard of care following implementation of a system-wide change to use of EIs compared to 293 children treated with the same drugs via SI prior to the system-wide change. On univariate analyses, these three outcomes were comparable (i.e., not statistically significantly different) between the groups. On subset analyses, all-cause mortality was lower among critically ill children who were treated with EIs (2.1% vs 19.6%, $p=0.006$), but multivariable or other analytic approaches to account for confounding and potential differences between groups were not performed.¹⁵⁸ Finally, a study treated children with CF with SI dosing of ceftazidime followed a “few months later” by CI of ceftazidime⁸³; amikacin was co-administered with both treatment courses. The authors found that patients similarly improved with both treatment regimens, including on assessment of pulmonary function and laboratory inflammation.⁸³

Ultimately, few studies have been conducted that have compared clinical and microbiologic outcomes among children treated with PI to those treated with SI β -lactams. Although a single RCT provided evidence for improved outcomes with EI of meropenem in septic neonates,¹⁵² other RCTs have found comparable outcomes among children treated with PI and SI.^{151,157} Similarly, a few observational studies have reported comparable outcomes regardless of infusion duration. Ultimately, the heterogeneity of populations, drugs studied, and outcome definitions employed across studies limit the interpretation of current evidence. As a result, there is currently insufficient evidence to support the routine use of PI of β -lactams for any specific clinical situation/s in children.

Numerous studies have evaluated the PK of β -lactams in children and simulations based on population PK analyses have consistently shown an improved PTA with PI when treating less susceptible bacterial pathogens.^{55,159-174} In fact, we did not identify a single population PK analysis in which simulations failed to show improved PTA in serum with the use of PI. It is noteworthy that a large population PK study of meropenem in infants with late-onset sepsis or meningitis found (via simulation) that increasing infusion times increased PTA in serum but decreased the percentage of time above MIC in the cerebrospinal fluid (CSF).¹⁷⁵

Ultimately, few studies have compared the real-world attainment of specific concentration-based targets in pediatric patients. Serum concentrations have been compared among very-low-birth-weight neonates treated with 20mg/kg of meropenem every 12h via SI (30min; $n=9$) and EI (4h; $n=10$).¹⁵³ Although steady-state clearance estimates assessed via noncompartmental analysis were similar for the two groups, all of the patients ($n=9$) in the SI group and 80% ($n=8/10$) in the EI group achieved a $fT_{>MIC}$ of 100% for an MIC of 2mg/L.¹⁵³ In another trial,⁸³ 14 children with CF were treated with intravenous ceftazidime. Each child was sequentially given ceftazidime via bolus infusion followed a few months later by ceftazidime via CI. None of the children had trough concentrations below the MIC for their *P. aeruginosa* isolates with the use of CI but 32% were below the MIC with SI.⁸³ Meanwhile, the successful treatment of a 2-year-old child with *Serratia marcescens* ventriculitis via CI of meropenem was reported.¹⁷⁶ Serum and CSF concentrations were maintained above the MIC only after changing from SI to CI, although the daily dose was also increased with the change in infusion duration.¹⁷⁶

Although simulations performed based on population PK analyses of various β -lactam agents have consistently found that use of PIs increases the PTA in children compared with SI, there have been relatively few real-world studies to verify these findings. Based on the preponderance of simulation-based data, it is reasonable to conclude that the time above MIC in serum is optimized by the administration of PIs.

3.11.3 | Future research needs

It is exceedingly difficult to design RCTs in children that seek to test the superiority of PIs in children. Because children tend to have more susceptible infections than adults, the potential advantage of extending infusion durations is muted when used broadly across all pediatric patients. Children also seem to have better outcomes than adults for the same infections (e.g. bacteremia, meningitis, etc.), thereby minimizing the impact of target attainment on clinical outcomes. Novel trial designs involving specific pediatric populations that would most benefit from optimized drug exposures (i.e., severe sepsis, multidrug-resistant infections) may be necessary to properly evaluate the value of prolonged β -lactam infusions. Many simulation-based studies have demonstrated improved PTA with prolonged versus SI in children, particularly when treating more resistant bacterial pathogens. However, very few studies have confirmed these findings prospectively. Although simulations based on appropriately performed population PK analyses tend to be reliable, the specific dosing and infusion schemes evaluated in these studies must be validated prior to clinical use.

Because of the challenges to conducting pediatric studies defined above, extrapolation of adult data to children can be useful, and sometimes necessary. For instance, the pathophysiology of many bacterial infections is similar among adults and older children (e.g., meningitis, pneumonia, bacteremia), and the mechanism

of antibacterial killing by β -lactams is the same in children as in adults. Therefore, the PD advantage of PIs remains relevant for children when considering optimal dosing strategies, even if pediatric-specific data are lacking. The crux of the issue in pediatrics is that fewer children than adults would benefit from the advantages that PIs impart and so the magnitude of benefit at a population level is smaller. Similarly, drug toxicities are more frequent in adults and therefore the safety margins of β -lactams are wider in children. This has created resistance to the routine clinical use of PIs in children, even though there may be a theoretical advantage to PI versus SI, which has contributed to the paucity of observational pediatric data. Unless pediatric centers implement PI of β -lactams more regularly, the specific populations, infection types, pathogens, and patient conditions that most justify the use of PIs may remain undefined.

3.12 | PICO question XII

Should PI β -lactam antibiotics be used in obese patients versus SI to improve efficacy?

3.12.1 | Recommendation 12

We cannot recommend for or against the routine use of PI to improve the efficacy of β -lactam agents in obese patients (Consensus recommendation).

3.12.2 | Evidence summary

A few small studies have examined the impact of obesity on β -lactam disposition, and even fewer studies have looked at whether PIs result in better outcomes in obesity compared with SI dosing.

Piperacillin-tazobactam is one of the most studied β -lactams in obesity, yet the literature primarily reports the impact of obesity on drug disposition compared with nonobese. One study evaluated the population PK/PD of piperacillin-tazobactam administered by EI in obese and nonobese patients.¹⁷⁷ Twenty-seven patients (16 obese, 11 nonobese) received 4.5g or 6.75g piperacillin-tazobactam every 8h over 4h, and serum concentrations were measured. Clearance and volume of distribution for piperacillin were significantly different between obese and non-obese patients; body mass index (BMI) was a significant covariate on clearance and total body weight (TBW) was significant on volume of distribution. At MICs ≥ 16 mg/L, larger doses were necessary in obese patients to meet PTA $>90\%$; doses of at least 3.375g every 8h over 4h in nonobese patients and at least 4.5g every 8h over 4h in obese patients. As such, 4.5g every 8h infused over 4h was recommended for empiric therapy in obese patients, though no outcome data for this dose recommendation was provided. In a separate population PK study,¹⁷⁸ obese patients were more likely than nonobese patients to experience piperacillin underdosing

when treating high MIC pathogens (≥ 64 mg/L) using CI dosing. The authors suggested that piperacillin TDM might be necessary in obese critically ill patients.¹⁷⁸ Similar results were found in another population PK analysis of nonobese, obese, and morbidly obese critically ill patients who received piperacillin-tazobactam administered by SI.¹⁷⁹ The authors found increased clearance and volume of distribution in obesity and reported from Monte Carlo simulation data that PI greatly improved the PTA in the presence of different BMIs and CrCl.¹⁷⁹ The authors commented that their findings were consistent with the available literature,^{117,180,181} which indicate that PI can improve achievement of PD goals.

Numerous studies have explored the impact of obesity on the dosing of β -lactams through the use of population PK modeling and simulation. One study developed a population PK model of doripenem in critically ill patients with nosocomial pneumonia and then used Monte Carlo dosing simulations to procure clinically relevant dosing recommendations for that population.¹⁸⁰ Creatinine clearance was an influential covariate on doripenem clearance, whereas body weight influenced drug peripheral volume of distribution. As with piperacillin-tazobactam above, the authors concluded that the administration of doripenem via EI negated most of the variability in target attainment caused by alterations in body weight and renal function. An additional population PK study demonstrated that renal function, critical illness, and obesity were all associated with doripenem PK: CrCl was a significant covariate on clearance, critical illness and TBW were influential covariates on central volume, and TBW was influential on peripheral volume.¹⁸² Through Monte Carlo simulations, the authors found that using a SI regimen (500 mg every 8 h infused over 1 h) was adequate for the treatment of susceptible bacteria (MIC ≤ 2 mg/L) but that PIs and/or larger-than-standard doses would be needed for treatment of less susceptible bacteria. Other studies have evaluated meropenem in obesity via population PK modeling in an attempt to provide dosing guidance.^{183,184} In a study of nine morbidly obese, critically ill patients, the PK of meropenem was comparable to that reported in nonobese patients, although steady-state volume of distribution was larger in the morbidly obese patients.¹⁸³ Meanwhile, another study found that meropenem PK was comparable among nonobese, obese, and morbidly obese adults.¹⁸⁴ Although these authors concluded that standard doses would be adequate for the treatment of susceptible bacteria using lower PK/PD targets (e.g., 40% $fT_{>MIC}$), higher doses or PIs would be necessary for less susceptible pathogens.^{183,184}

Finally, there is a growing body of literature on cefazolin administered as a CI during bariatric surgery. Previous studies have reported that SI of 2 g of cefazolin at surgical incision may fail to provide adequate tissue concentrations to prevent surgical site infections in obese patients.^{185,186} As a result, the use of alternative dosing strategies (e.g., larger doses and/or PI) for surgical prophylaxis may be necessary in obese patients. The concentration of cefazolin in adipose tissue of 18 patients undergoing bariatric surgery who were administered intravenous cefazolin as a bolus dose of 2 g in anesthetic induction, followed by CI of cefazolin 1 g has been reported.¹⁸⁷ Adipose tissue samples were collected for measures of cefazolin

concentrations soon after the incision ("initial") and before the skin synthesis ("final"). Patients with a normal BMI had significantly higher initial and final cefazolin concentrations in those samples than patients with BMI ≥ 40 kg/m².¹⁸⁷ The authors concluded that there was an inverse correlation between BMI and cefazolin adipose tissue concentrations. Another prospective, cross-sectional study of 896 Roux-en-Y gastric bypasses compared the incidence of surgical site infection among three groups of patients according to the perioperative antibiotic prophylaxis administered.¹⁸⁸ Group I consisted of 194 patients treated with two 3 g doses of ampicillin/sulbactam, Group II consisted of 303 patients treated with a single 1 g dose of ertapenem, and Group III was comprised of 399 patients treated with a 2 g dose of cefazolin at anesthesia induction followed by a CI of cefazolin 1 g throughout the surgical procedure.¹⁸⁸ The rates of surgical site infection were 4.16%, 1.98%, and 1.55%, respectively ($p > 0.05$).¹⁸⁸ The authors concluded that the prophylactic use of CI cefazolin in surgeries for morbid obesity showed promising results. Lastly, a population PK study evaluated 117 morbidly obese patients (mean BMI 46.95 kg/m²) treated with 4 g of cefazolin before sleeve gastrectomy was conducted.¹⁸⁹ Monte Carlo simulations were performed to determine PTA based on simulated subcutaneous tissue concentrations above the MIC throughout the surgical procedure. The authors found that a cefazolin 3 g loading dose followed by a CI of 1 g/h achieved the target (90% PTA for MIC 4 mg/L until 4 h after the loading dose), as did a 4 g SI dosage scheme, whereas the 2 g and 3 g SI doses did not achieve sufficient concentrations.¹⁸⁹ They concluded that for shorter surgeries, an initial administration of cefazolin 4 g was sufficient, but for extended surgeries, CI should be considered.

In summary, there is a growing body of literature studying the impact of obesity on β -lactam concentrations. Based on population PK studies and simulations, PI may overcome some of the effects of body weight leading to suboptimal concentrations in the blood of obese patients. As with nonobese patients, the use of PI along with larger-than-normal doses may be necessary for the treatment of infections caused by less susceptible pathogens. Meanwhile, for prophylaxis during gastric bypass surgery, the use of CI along with larger cefazolin doses (> 2 g) may help ensure adequate tissue concentrations to prevent skin and soft tissue infections, particularly, for longer surgeries. Presently, no studies demonstrate the superiority of PI versus SI β -lactam dosing in obese patients regarding clinical outcomes, although few comparative effectiveness trials have been performed.

3.12.3 | Future research needs

Body weight and body habitus have important effects on the PK of β -lactams. The use of PIs may be a reliable approach to improve $fT_{>MIC}$ and ensure adequate serum concentrations in obese patients. But, larger-than-standard doses are often also needed in obese patients, obscuring the specific benefit of PI versus SI. Given the spectrum of obesity, however, it would be most beneficial for studies to focus on the relationship between increased body weight/BMI and

drug PK rather than simply comparing PK in obese versus nonobese patients. This will promote the derivation of more accurate dosing and drug infusion strategies.

4 | CONCLUSION

In conclusion, β -lactam agents have been given as SI and PIs in a large number of clinical cohorts and trials. Both administration schemes demonstrate their role in the treatment of many bacterial infections due to their broad spectrum of activity and relative safety profiles. Efficacy for both is maximized pharmacodynamically by optimizing the $fT_{>MIC}$. Elucidating exact targets will require more clinical trials; however, the body of evidence suggests improved efficacy and similar safety when similar doses are administered as PI (compared with SI). Because of substantial inter- and inpatient PK variability, optimizing the administration strategy of these agents to achieve PD targets may be important for bacterial killing and resistance suppression, but the overall quality of evidence for clinical outcomes is low, particularly among patient populations who would be expected to benefit. The use of PIs has become more prevalent in recent years; however, greater uptake is possible and could be recommended in many situations outlined within these guidelines. Many questions remain. The specific need for TDM should be better defined in patients with known altered PK due to acute illness and/or underlying conditions, as well as those infected with bacteria demonstrating high MICs to the selected β -lactam. Further studies are needed to evaluate the role of PI of β -lactam agents in special populations, define the role of TDM, assess the need for a loading dose, determine optimal PI methods, and identify strategies and global consensus for improving the stability of these agents within inpatient and outpatient settings. To address challenges ahead, future research should also evaluate patient/caregiver-oriented endpoints such as line compatibility, nursing time, quality of life measures, and other practical considerations.

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CONFLICT OF INTEREST STATEMENT

Author's personal and financial relationships with industry and other entities are detailed in [Appendix 1](#).

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REFERENCES

- MacGowan A. Revisiting Beta-lactams – PK/PD improves dosing of old antibiotics. *Curr Opin Pharmacol*. 2011;11:470-476.
- Drusano GL. Pharmacokinetics and pharmacodynamics of antimicrobials. *Clin Infect Dis*. 2007;45(Suppl 1):S89-S95.
- Grupper M, Kuti JL, Nicolau DP. Continuous and prolonged intravenous beta-lactam dosing: implications for the clinical laboratory. *Clin Microbiol Rev*. 2016;29:759-772.
- Turnidge JD. The pharmacodynamics of beta-lactams. *Clin Infect Dis*. 1998;27:10-22.
- Eagle H, Fleischman R, Levy M. "Continuous" vs. "discontinuous" therapy with penicillin; the effect of the interval between injections on therapeutic efficacy. *N Engl J Med*. 1953;248:481-488.
- Vinks AA, Brimicombe RW, Heijerman HG, Bakker W. Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. *J Antimicrob Chemother*. 1997;40:125-133.
- Yusuf E, Spapen H, Pierard D. Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: a narrative and systematic review. *J Crit Care*. 2014;29:1089-1095.
- Craig WA, Ebert SC. Continuous infusion of beta-lactam antibiotics. *Antimicrob Agents Chemother*. 1992;36:2577-2583.
- De Waele J, Carlier M, Hoste E, et al. Extended versus bolus infusion of meropenem and piperacillin: a pharmacokinetic analysis. *Minerva Anesthesiol*. 2014;80:1302-1309.
- Roberts JA, Lipman J, Blot S, Rello J. Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients? *Curr Opin Crit Care*. 2008;14:390-396.
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
- Zelenitsky S, Nash J, Weber Z, Iacovides H, Ariano R. Targeted benefits of prolonged-infusion piperacillin-tazobactam in an in vitro infection model of *Pseudomonas aeruginosa*. *J Chemother*. 2016;28:390-394.
- Caballero VR, Abuhussain SA, Kuti JL, Nicolau DP. Efficacy of human-simulated exposures of ceftolozane-tazobactam alone and in combination with amikacin or colistin against multidrug-resistant *Pseudomonas aeruginosa* in an in vitro pharmacodynamic model. *Antimicrob Agents Chemother*. 2018;62:e02384-17.
- Bergen PJ, Bulitta JB, Kirkpatrick CMJ, et al. Substantial impact of altered pharmacokinetics in critically ill patients on the antibacterial effects of meropenem evaluated via the dynamic hollow-fiber infection model. *Antimicrob Agents Chemother*. 2017;61:e02642-16.
- Rees VE, Yadav R, Rogers KE, et al. Meropenem combined with ciprofloxacin combats Hypermutable *Pseudomonas aeruginosa* from respiratory infections of cystic fibrosis patients. *Antimicrob Agents Chemother*. 2018;62:11.
- Tam VH, Schilling AN, Neshat S, Poole K, Melnick DA, Coyle EA. Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2005;49:4920-4927.

18. Louie A, Bied A, Fregeau C, et al. Impact of different carbapenems and regimens of administration on resistance emergence for three isogenic *Pseudomonas aeruginosa* strains with differing mechanisms of resistance. *Antimicrob Agents Chemother.* 2010;54:2638-2645.
19. Bulik CC, Christensen H, Li P, Sutherland CA, Nicolau DP, Kuti JL. Comparison of the activity of a human simulated, high-dose, prolonged infusion of meropenem against *Klebsiella pneumoniae* producing the KPC carbapenemase versus that against *Pseudomonas aeruginosa* in an in vitro pharmacodynamic model. *Antimicrob Agents Chemother.* 2010;54:804-810.
20. Bergeron MG, Nguyen BM, Gauvreau L. Influence of constant infusion versus bolus injections of antibiotics on in vivo synergy. *Infection.* 1978;6:38-46.
21. Girardi C, Tonnellier M, Goldstein I, et al. Lung deposition of continuous and intermittent intravenous ceftazidime in experimental *Pseudomonas aeruginosa* bronchopneumonia. *Intensive Care Med.* 2006;32:2042-2048.
22. Chavanet P, Dalle F, Delisle P, et al. Experimental efficacy of combined ceftriaxone and amoxicillin on penicillin-resistant and broad-spectrum cephalosporin-resistant *Streptococcus pneumoniae* infection. *J Antimicrob Chemother.* 1998;41:237-246.
23. Dhaese S, Heffernan A, Liu D, et al. Prolonged versus intermittent infusion of beta-lactam antibiotics: a systematic review and meta-regression of bacterial killing in preclinical infection models. *Clin Pharmacokinet.* 2020;59:1237-1250.
24. Nakamura R, Ito-Horiyama T, Takemura M, et al. In vivo pharmacodynamic study of cefiderocol, a novel parenteral siderophore cephalosporin, in murine thigh and lung infection models. *Antimicrob Agents Chemother.* 2019;63:e02031-18.
25. Alou L, Aguilar L, Sevilano D, et al. Is there a pharmacodynamic need for the use of continuous versus intermittent infusion with ceftazidime against *Pseudomonas aeruginosa*? An in vitro pharmacodynamic model. *J Antimicrob Chemother.* 2005;55:209-213.
26. Cappelletty DM, Kang SL, Palmer SM, Rybak MJ. Pharmacodynamics of ceftazidime administered as continuous infusion or intermittent bolus alone and in combination with single daily-dose amikacin against *Pseudomonas aeruginosa* in an in vitro infection model. *Antimicrob Agents Chemother.* 1995;39:1797-1801.
27. Drusano GL, Shields RK, Mtchedlidze N, et al. Pharmacodynamics of ceftazidime plus avibactam against KPC-2-bearing isolates of *Klebsiella pneumoniae* in a hollow fiber infection model. *Antimicrob Agents Chemother.* 2019;63:e00462-19.
28. Felton TW, Goodwin J, O'Connor L, et al. Impact of bolus dosing versus continuous infusion of Piperacillin and Tazobactam on the development of antimicrobial resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother.* 2013;57:5811-5819.
29. Firsov AA, Mattie H. Relationships between antimicrobial effect and area under the concentration-time curve as a basis for comparison of modes of antibiotic administration: meropenem bolus injections versus continuous infusions. *Antimicrob Agents Chemother.* 1997;41:352-356.
30. Huang V, Rybak MJ. Pharmacodynamics of cefepime alone and in combination with various antimicrobials against methicillin-resistant *Staphylococcus aureus* in an in vitro pharmacodynamic infection model. *Antimicrob Agents Chemother.* 2005;49:302-308.
31. Li X, Wang L, Zhang XJ, et al. Evaluation of meropenem regimens suppressing emergence of resistance in acinetobacter baumannii with human simulated exposure in an in vitro intravenous-infusion hollow-fiber infection model. *Antimicrob Agents Chemother.* 2014;58:6773-6781.
32. Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. *Antimicrob Agents Chemother.* 1994;38:931-936.
33. Smith PF, Tsuji B, Booker BM, et al. Pharmacodynamics of ceftazidime against *Haemophilus influenzae* in an in vitro pharmacodynamic model. *Diagn Microbiol Infect Dis.* 2006;56:379-386.
34. Sumi CD, Heffernan AJ, Naicker S, et al. Pharmacodynamic evaluation of intermittent versus extended and continuous infusions of piperacillin/tazobactam in a hollow-fiber infection model against *Klebsiella pneumoniae*. *J Antimicrob Chemother.* 2020;75:2633-2640.
35. Tessier PR, Nicolau DP, Onyeji CO, Nightingale CH. Pharmacodynamics of intermittent- and continuous-infusion cefepime alone and in combination with once-daily tobramycin against *Pseudomonas aeruginosa* in an in vitro infection model. *Chemotherapy.* 1999;45:284-295.
36. Vourli S, Tsala M, Kotsakis S, et al. Comparison of short versus prolonged infusion of standard dose of meropenem against carbapenemase-producing *Klebsiella pneumoniae* isolates in different patient groups: a pharmacokinetic-pharmacodynamic approach. *J Pharm Sci.* 2016;105:1513-1518.
37. Louie A, Vanscoy B, Liu W, Kulawy R, Drusano GL. Hollow-fiber pharmacodynamic studies and mathematical modeling to predict the efficacy of amoxicillin for anthrax postexposure prophylaxis in pregnant women and children. *Antimicrob Agents Chemother.* 2013;57:5946-5960.
38. Croisier D, Martha B, Piroth L, Chavanet P. In vivo efficacy of humanised intermittent versus continuous ceftazidime in combination with tobramycin in an experimental model of pseudomonal pneumonia. *Int J Antimicrob Agents.* 2008;32:494-498.
39. Bretonniere C, Jacqueline C, Caillon J, et al. Efficacy of doripenem in the treatment of *Pseudomonas aeruginosa* experimental pneumonia versus imipenem and meropenem. *J Antimicrob Chemother.* 2010;65:2423-2427.
40. Robaux MA, Dube L, Caillon J, et al. In vivo efficacy of continuous infusion versus intermittent dosing of ceftazidime alone or in combination with amikacin relative to human kinetic profiles in a *Pseudomonas aeruginosa* rabbit endocarditis model. *J Antimicrob Chemother.* 2001;47:617-622.
41. Gengo FM, Mannion TW, Nightingale CH, Schentag JJ. Integration of pharmacokinetics and pharmacodynamics of methicillin in curative treatment of experimental endocarditis. *J Antimicrob Chemother.* 1984;14:619-631.
42. Kim A, Banevicius MA, Nicolau DP. In vivo pharmacodynamic profiling of doripenem against *Pseudomonas aeruginosa* by simulating human exposures. *Antimicrob Agents Chemother.* 2008;52:2497-2502.
43. Yadav R, Bergen PJ, Rogers KE, et al. Meropenem-tobramycin combination regimens combat carbapenem-resistant *Pseudomonas aeruginosa* in the hollow-fiber infection model simulating augmented renal clearance in critically ill patients. *Antimicrob Agents Chemother.* 2019;64:e01679-e01619.
44. Yadav R, Landersdorfer CB, Nation RL, Boyce JD, Bulitta JB. Novel approach to optimize synergistic carbapenem-aminoglycoside combinations against carbapenem-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother.* 2015;59:2286-2298.
45. Smith NM, Lenhard JR, Boissonneault KR, et al. Using machine learning to optimize antibiotic combinations: dosing strategies for meropenem and polymyxin B against carbapenem-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect.* 2020;26:1207-1213.
46. De Waele JJ, Carrette S, Carlier M, et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. *Intensive Care Med.* 2014;40:380-387.
47. Fournier A, Eggimann P, Pantet O, et al. Impact of real-time therapeutic drug monitoring on the prescription of antibiotics in burn patients requiring admission to the intensive care unit. *Antimicrob Agents Chemother.* 2018;62:e01818-17.

48. Sime FB, Roberts MS, Tiong IS, et al. Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial. *J Antimicrob Chemother.* 2015;70:2369-2375.
49. Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis.* 2013;56:236-244.
50. Wong G, Briscoe S, McWhinney B, et al. Therapeutic drug monitoring of β -lactam antibiotics in the critically ill: direct measurement of unbound drug concentrations to achieve appropriate drug exposures. *J Antimicrob Chemother.* 2018;73:3087-3094.
51. Scharf C, Paal M, Schroeder I, et al. Therapeutic drug monitoring of meropenem and piperacillin in critical illness-experience and recommendations from one year in routine clinical practice. *Antibiotics (Basel).* 2020;9:9.
52. Carlier M, Carrette S, Roberts JA, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? *Crit Care.* 2013;17:R84.
53. Akkerman-Nijland AM, Akkerman OW, Grasmeyer F, et al. The pharmacokinetics of antibiotics in cystic fibrosis. *Expert Opin Drug Metab Toxicol.* 2021;17:53-68.
54. Hubert D, Le Roux E, Lavrut T, et al. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother.* 2009;53:3650-3656.
55. Pettit RS, Neu N, Cies JJ, et al. Population pharmacokinetics of meropenem administered as a prolonged infusion in children with cystic fibrosis. *J Antimicrob Chemother.* 2016;71:189-195.
56. Thompson RZ, Martin CA, Burgess DR, Rutter WC, Burgess DS. Optimizing beta-lactam pharmacodynamics against *Pseudomonas aeruginosa* in adult cystic fibrosis patients. *J Cyst Fibros.* 2016;15:660-663.
57. Han EE, Beringer PM, Falck P, et al. Pilot study of continuous infusion cefepime in adult patients with cystic fibrosis. *J Antimicrob Chemother.* 2006;57:1017-1019.
58. Vinks AA, van Rossem RN, Mathot RA, Heijerman HG, Mouton JW. Pharmacokinetics of aztreonam in healthy subjects and patients with cystic fibrosis and evaluation of dose-exposure relationships using Monte Carlo simulation. *Antimicrob Agents Chemother.* 2007;51:3049-3055.
59. Bulitta JB, Duffull SB, Kinzig-Schippers M, et al. Systematic comparison of the population pharmacokinetics and pharmacodynamics of piperacillin in cystic fibrosis patients and healthy volunteers. *Antimicrob Agents Chemother.* 2007;51:2497-2507.
60. Bulitta JB, Landersdorfer CB, Huttner SJ, et al. Population pharmacokinetic comparison and pharmacodynamic breakpoints of ceftazidime in cystic fibrosis patients and healthy volunteers. *Antimicrob Agents Chemother.* 2010;54:1275-1282.
61. Hahn A, Jensen C, Fanous H, et al. Relationship of pulmonary outcomes, microbiology, and serum antibiotic concentrations in cystic fibrosis patients. *J Pediatr Pharmacol Ther.* 2018;23:379-389.
62. Bulitta JB, Hope WW, Eakin AE, et al. Generating robust and informative nonclinical In vitro and In vivo bacterial infection model efficacy data to support translation to humans. *Antimicrob Agents Chemother.* 2019;63:e02307-18.
63. Kawaguchi N, Katsube T, Echols R, Wajima T. Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection. *Antimicrob Agents Chemother.* 2020;65:e01437-20.
64. Muller AE, Punt N, Mouton JW. Exposure to ceftobiprole is associated with microbiological eradication and clinical cure in patients with nosocomial pneumonia. *Antimicrob Agents Chemother.* 2014;58:2512-2519.
65. Bhavnani SM, Hammel JP, Van Wart SA, et al. Pharmacokinetic-pharmacodynamic analysis for efficacy of ceftaroline fosamil in patients with acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother.* 2015;59:372-380.
66. Fratoni AJ, Nicolau DP, Kuti JL. A guide to therapeutic drug monitoring of β -lactam antibiotics. *Pharmacotherapy.* 2021;41:220-233.
67. Tam VH, McKinnon PS, Akins RL, Rybak MJ, Drusano GL. Pharmacodynamics of cefepime in patients with Gram-negative infections. *J Antimicrob Chemother.* 2002;50:425-428.
68. Kuti JL, Pettit RS, Neu N, et al. Meropenem time above the MIC exposure is predictive of response in cystic fibrosis children with acute pulmonary exacerbations. *Diagn Microbiol Infect Dis.* 2018;91:294-297.
69. Barreto EF, Webb AJ, Pais GM, Rule AD, Jannetto PJ, Scheetz MH. Setting the beta-lactam therapeutic range for critically ill patients: is there a floor or even a ceiling? *Crit Care Explor.* 2021;3:e0446.
70. Boschung-Pasquier L, Atkinson A, Kastner LK, et al. Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study. *Clin Microbiol Infect.* 2020;26:333-339.
71. Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. MIC-based dose adjustment: facts and fables. *J Antimicrob Chemother.* 2018;73:564-568.
72. Abdul-Aziz MH, Alfenaar JC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. *Intensive Care Med.* 2020;46:1127-1153.
73. Voumard R, Gardiol C, Andre P, et al. Efficacy and safety of continuous infusions with elastomeric pumps for outpatient parenteral antimicrobial therapy (OPAT): an observational study. *J Antimicrob Chemother.* 2018;73:2540-2545.
74. Arlicot N, Marie A, Cade C, Laffon M, Antier D. Stability of amoxicillin in portable pumps is drug concentration dependent. *Pharmazie.* 2011;66:631-632.
75. Binson G, Grignon C, Le Moal G, et al. Overcoming stability challenges during continuous intravenous administration of high-dose amoxicillin using portable elastomeric pumps. *PLoS One.* 2019;14:e0221391.
76. Nakamura T, Enoki Y, Uno S, et al. Stability of benzylpenicillin potassium and ampicillin in an elastomeric infusion pump. *J Infect Chemother.* 2018;24:856-859.
77. Parsonson F, Legg A, Halford M, McCarthy K. Contemporaneous management of ampicillin infusions in the outpatient setting through the use of therapeutic drug monitoring. *Int J Antimicrob Agents.* 2020;55:105975.
78. Neffel KA, Walti M, Schulthess HK, Gubler J. Adverse reactions following intravenous penicillin-G relate to degradation of the drug in vitro. *Klin Wochenschr.* 1984;62:25-29.
79. Vella-Brincat JW, Begg EJ, Gallagher K, et al. Stability of benzylpenicillin during continuous home intravenous therapy. *J Antimicrob Chemother.* 2004;53:675-677.
80. Perks SJ, Lanskey C, Robinson N, Pain T, Franklin R. Systematic review of stability data pertaining to selected antibiotics used for extended infusions in outpatient parenteral antimicrobial therapy (OPAT) at standard room temperature and in warmer climates. *Eur J Hosp Pharm.* 2020;27:65-72.
81. Sprauten PF, Beringer PM, Louie SG, Synold TW, Gill MA. Stability and antibacterial activity of cefepime during continuous infusion. *Antimicrob Agents Chemother.* 2003;47:1991-1994.
82. Al Madfai F, Zaidi STR, Ming LC, Wanandy T, Patel RP. Physical and chemical stability of ceftaroline in an elastomeric infusion device. *Eur J Hosp Pharm.* 2018;25:e115-e119.
83. Rappaz I, Decosterd LA, Bille J, Pilet M, Belaz N, Roulet M. Continuous infusion of ceftazidime with a portable pump is as effective as thrice-a-day bolus in cystic fibrosis children. *Eur J Pediatr.* 2000;159:919-925.
84. Bourget P, Amin A, Dupont C, et al. How to minimize toxic exposure to pyridine during continuous infusion of ceftazidime

- in patients with cystic fibrosis? *Antimicrob Agents Chemother.* 2014;58:2849-2855.
85. Jamieson C, Drummond F, Hills T, et al. Assessment of ceftolozane/tazobactam stability in elastomeric devices and suitability for continuous infusion via outpatient parenteral antimicrobial therapy. *JAC Antimicrob Resist.* 2021;3:dlab141.
 86. Allwood MC, Stonkute D, Wallace A, et al. Assessment of the stability of citrate-buffered flucloxacillin for injection when stored in two commercially available ambulatory elastomeric devices: INFusor LV (Baxter) and Accufuser (woo Young medical): a study compliant with the NHS yellow cover document (YCD) requirements. *Eur J Hosp Pharm.* 2020;27:90-94.
 87. Jamieson C, Ozolina L, Seaton RA, et al. Assessment of the stability of citrate-buffered piperacillin/tazobactam for continuous infusion when stored in two commercially available elastomeric devices for outpatient parenteral antimicrobial chemotherapy: a study compliant with the NHS yellow cover document requirements. *Eur J Hosp Pharm.* 2020;29:212-216.
 88. Perks SJ, Pain T, Franklin R. Total intended antibiotic delivery related to drug concentration affecting the flow rate of elastomeric devices used in outpatient parenteral antimicrobial therapy (OPAT). *J Pharm Pract Res.* 2019;49:349-355.
 89. Chen IH, Martin EK, Nicolau DP, Kuti JL. Assessment of meropenem and vaborbactam room temperature and refrigerated stability in polyvinyl chloride bags and elastomeric devices. *Clin Ther.* 2020;42:606-613.
 90. Fawaz S, Barton S, Whitney L, Swinden J, Nabhani-Gebara S. Stability of meropenem after reconstitution for administration by prolonged infusion. *Hosp Pharm.* 2019;54:190-196.
 91. Manning L, Wright C, Ingram PR, et al. Continuous infusions of meropenem in ambulatory care: clinical efficacy, safety and stability. *PLoS One.* 2014;9:e102023.
 92. Jamieson C, Allwood MC, Stonkute D, et al. Investigation of meropenem stability after reconstitution: the influence of buffering and challenges to meet the NHS yellow cover document compliance for continuous infusions in an outpatient setting. *Eur J Hosp Pharm.* 2020;27:e53-e57.
 93. Docherty T, Montalto M, Leslie J, King K, Niblett S, Garrett T. Temperature profiles of antibiotic-containing elastomeric infusion devices used by ambulatory care patients. *Am J Health Syst Pharm.* 2017;74:992-1001.
 94. Jenkins A, Hills T, Santillo M, Gilchrist M. Extended stability of antimicrobial agents in administration devices. *J Antimicrob Chemother.* 2017;72:1217-1220.
 95. NHS Pharmaceutical Quality Assurance Committee. *A standard protocol for deriving and assessment of stability. Part 1 - aseptic preparations (small molecules).* 5th ed. NHS Pharmaceutical Quality Assurance Committee; 2019. Accessed December 21, 2021. <https://www.sps.nhs.uk/wp-content/uploads/2013/12/Stability-part-1-small-molecules-5th-Ed-Sept-19.pdf>
 96. British Society for Antimicrobial Chemotherapy UK OPAT Initiative. Accessed September 10, 2021. www.e-opat.com
 97. Angus BJ, Smith MD, Suputtamongkol Y, et al. Pharmacokinetic-pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicemic melioidosis. *Br J Clin Pharmacol.* 2000;50:184-191.
 98. Cousson J, Floch T, Vernet-Garnier V, et al. Pharmacodynamic interest of ceftazidime continuous infusion vs intermittent bolus administration in patients with severe nosocomial pneumonia. *Pathol Biol (Paris).* 2005;53:546-550.
 99. Georges B, Conil JM, Cougot P, et al. Cefepime in critically ill patients: continuous infusion vs. an intermittent dosing regimen. *Int J Clin Pharmacol Ther.* 2005;43:360-369.
 100. Rafati MR, Rouini MR, Mojtahedzadeh M, et al. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. *Int J Antimicrob Agents.* 2006;28:122-127.
 101. Sakka SG, Glauner AK, Bulitta JB, et al. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomized, controlled trial. *Antimicrob Agents Chemother.* 2007;51:3304-3310.
 102. Roberts JA, Boots R, Rickard CM, et al. Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. *J Antimicrob Chemother.* 2007;59:285-291.
 103. Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med.* 2008;36:1089-1096.
 104. Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Piperacillin penetration into tissue of critically ill patients with sepsis-bolus versus continuous administration? *Crit Care Med.* 2009;37:926-933.
 105. Chytra I, Stepan M, Benes J, et al. Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. *Crit Care.* 2012;16:R113.
 106. Kollef MH, Chastre J, Clavel M, et al. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. *Crit Care.* 2012;16:R218.
 107. Lipš M, Siller M, Strojil J, Urbánek K, Balík M, Suchánková H. Pharmacokinetics of imipenem in critically ill patients during empirical treatment of nosocomial pneumonia: a comparison of 0.5-h and 3-h infusions. *Int J Antimicrob Agents.* 2014;44:358-362.
 108. Dulhunty JM, Roberts JA, Davis JS, et al. A multicenter randomized trial of continuous versus intermittent β -lactam infusion in severe sepsis. *Am J Respir Crit Care Med.* 2015;192:1298-1305.
 109. Jamal JA, Mat-Nor MB, Mohamad-Nor FS, et al. Pharmacokinetics of meropenem in critically ill patients receiving continuous venovenous haemofiltration: a randomised controlled trial of continuous infusion versus intermittent bolus administration. *Int J Antimicrob Agents.* 2015;45:41-45.
 110. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, et al. Beta-lactam infusion in severe sepsis (BLISS): a prospective, two-Centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med.* 2016;42:1535-1545.
 111. Bao H, Lv Y, Wang D, Xue J, Yan Z. Clinical outcomes of extended versus intermittent administration of piperacillin/tazobactam for the treatment of hospital-acquired pneumonia: a randomized controlled trial. *Eur J Clin Microbiol Infect Dis.* 2017;36:459-466.
 112. Fan SY, Shum HP, Cheng WY, Chan YH, Leung SM, Yan WW. Clinical outcomes of extended versus intermittent infusion of piperacillin/tazobactam in critically ill patients: a prospective clinical trial. *Pharmacotherapy.* 2017;37:109-119.
 113. Lyu Y, Yang Y, Li X, et al. Selection of piperacillin/tazobactam infusion mode guided by SOFA score in cancer patients with hospital-acquired pneumonia: a randomized controlled study. *Ther Clin Risk Manag.* 2018;14:31-37.
 114. Zhao HY, Gu J, Lyu J, et al. Pharmacokinetic and pharmacodynamic efficacies of continuous versus intermittent administration of meropenem in patients with severe sepsis and septic shock: a prospective randomized pilot study. *Chin Med J (Engl).* 2017;130:1139-1145.
 115. Ammar M, Abdalla W. Effect of extended infusion of meropenem and nebulized amikacin on Gram-negative multidrug-resistant ventilator-associated pneumonia. *Saudi J Anaesthesia.* 2018;12:89-94.
 116. Ram R, Halavy Y, Amit O, et al. Extended vs bolus infusion of broad-spectrum β -lactams for febrile neutropenia: an unblinded. *Randomized Trial Clin Infect Dis.* 2018;67:1153-1160.

117. Lau WK, Mercer D, Itani KM, et al. Randomized, open-label, comparative study of piperacillin-tazobactam administered by continuous infusion versus intermittent infusion for treatment of hospitalized patients with complicated intra-abdominal infection. *Antimicrob Agents Chemother.* 2006;50:3556-3561.
118. Wrenn RH, Cluck D, Kennedy L, Ohl C, Williamson JC. Extended infusion compared to standard infusion cefepime as empiric treatment of febrile neutropenia. *J Oncol Pharm Pract.* 2018;24:170-175.
119. Cousson J, Floch T, Guillard T, et al. Lung concentrations of ceftazidime administered by continuous versus intermittent infusion in patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother.* 2015;59:1905-1909.
120. Udy AA, Dulhunty JM, Roberts JA, et al. Association between augmented renal clearance and clinical outcomes in patients receiving β -lactam antibiotic therapy by continuous or intermittent infusion: a nested cohort study of the BLING-II randomised, placebo-controlled, clinical trial. *Int J Antimicrob Agents.* 2017;49:624-630.
121. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis.* 2007;44:357-363.
122. Bauer KA, Gentene AJ, West JE, Shidham G, Goff DA. An antimicrobial stewardship program's evaluation of the safety and efficacy of continuous infusion of nafcillin in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteremia. *Infect Dis Clin Pract.* 2013;21:111-113.
123. Yost RJ, Cappelletty DM. The retrospective cohort of extended-infusion piperacillin-tazobactam (RECIPT) study: a multicenter study. *Pharmacotherapy.* 2011;31:767-775.
124. Ahmed N, Jen SP, Altschuler D, Papadopoulos J, Pham VP, Dubrovskaya Y. Evaluation of meropenem extended versus intermittent infusion dosing protocol in critically ill patients. *J Intensive Care med.* 2020;35:763-771.
125. Ibrahim MM, Tammam TF, Ebaed MED, Sarhan HA, Gad GF, Hussein AK. Extended infusion versus intermittent infusion of imipenem in the treatment of ventilator-associated pneumonia. *Drug Des Devel Ther.* 2017;11:2677-2682.
126. Lee GC, Liou H, Yee R, Quan CF, Neldner K. Outcomes of extended-infusion piperacillin-tazobactam: a retrospective analysis of critically ill patients. *Clin Ther.* 2012;34:2297-2300.
127. McNabb JJ, Nightingale CH, Quintiliani R, Nicolau DP. Cost-effectiveness of ceftazidime by continuous infusion versus intermittent infusion for nosocomial pneumonia. *Pharmacotherapy.* 2001;21:549-555.
128. Nicolau DP, McNabb J, Lacy MK, Quintiliani R, Nightingale CH. Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. *Int J Antimicrob Agents.* 2001;17:497-504.
129. Lorente L, Jimenez A, Palmero S, et al. Comparison of clinical cure rates in adults with ventilator-associated pneumonia treated with intravenous ceftazidime administered by continuous or intermittent infusion: a retrospective, nonrandomized, open-label, historical chart review. *Clin Ther.* 2007;29:2433-2439.
130. Lorente L, Lorenzo L, Martin MM, Jimenez A, Mora ML. Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to gram-negative bacilli. *Ann Pharmacother.* 2006;40:219-223.
131. Lorente L, Jimenez A, Martin MM, Iribarren JL, Jimenez JJ, Mora ML. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. *Int J Antimicrob Agents.* 2009;33:464-468.
132. Lagast H, Meunier-Carpentier F, Klustersky J. Treatment of gram-negative bacillary septicemia with cefoperazone. *Eur J Clin Microbiol.* 1983;2:554-558.
133. Cotrina-Luque J, Gil-Navarro MV, Acosta-Garcia H, et al. Continuous versus intermittent piperacillin/tazobactam infusion in infection due to or suspected *Pseudomonas aeruginosa*. *Int J Clin Pharm.* 2016;38:70-79.
134. Feher C, Rovira M, Soriano A, et al. Effect of meropenem administration in extended infusion on the clinical outcome of febrile neutropenia: a retrospective observational study. *J Antimicrob Chemother.* 2014;69:2556-2562.
135. Przybylski DJ, Reeves DJ. Extended versus intermittent infusions of cefepime for the treatment of febrile neutropenia. *Infect Dis Clin Pract.* 2018;26:154-158.
136. Bartoletti M, Giannella M, Lewis RE, et al. Extended infusion of beta-lactams for bloodstream infection in patients with liver cirrhosis: an observational multicenter study. *Clin Infect Dis.* 2019;69:1731-1739.
137. Grant EM, Kuti JL, Nicolau DP, Nightingale C, Quintiliani R. Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital. *Pharmacotherapy.* 2002;22:471-483.
138. Ambrose PG, Quintiliani R, Nightingale CH, Nicolau DP. Continuous vs. intermittent infusion of cefuroxime for the treatment of community-acquired pneumonia. *Infect Dis Clin Pract.* 1998;7:463-470.
139. van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH. Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. *Br J Clin Pharmacol.* 2007;63:100-109.
140. Riethmueller J, Ballmann M, Schroeter TW, et al. Tobramycin once vs thrice-daily for elective intravenous antipseudomonal therapy in pediatric cystic fibrosis patients. *Infection.* 2009;37:424-431.
141. Bosso JA, Bonapace CR, Flume PA, White RL. A pilot study of the efficacy of constant-infusion ceftazidime in the treatment of endobronchial infections in adults with cystic fibrosis. *Pharmacotherapy.* 1999;19:620-626.
142. Merchant S, Gast C, Nathwani D, et al. Hospital resource utilization with doripenem versus imipenem in the treatment of ventilator-associated pneumonia. *Clin Ther.* 2008;30:717-733.
143. Owens CA, Ambrose PG, Quintiliani R, Nightingale CH, Nicolau DP. Infusion phlebitis. Relative incidence associated with cefuroxime administered by intermittent and continuous infusion. *Clin Drug Investig.* 1998;15:531-535.
144. Cotner S, Rutter WC, Burgess DR, Martin C, Burgess DS. Influence of beta-lactam infusion strategy on acute kidney injury. *Open Forum Infect Dis.* 2016;3:3.
145. Hemvimon S, Srinithiwat P, Koomanachai P, Thamlikitkul V, Jitmuang A. Efficacy and safety of prolonged versus intermittent infusion of beta-lactam antibiotics as empirical therapy in patients with sepsis. *J Med Assoc Thai.* 2019;102:129-135.
146. Karino S, Kaye KS, Navalkele B, et al. Epidemiology of acute kidney injury among patients receiving concomitant vancomycin and piperacillin-tazobactam: opportunities for antimicrobial stewardship. *Antimicrob Agents Chemother.* 2016;60:3743-3750.
147. McCormick H, Tomaka N, Baggett S, et al. Comparison of acute renal injury associated with intermittent and extended infusion piperacillin/tazobactam. *Am J Health Syst Pharm.* 2015;72:S25-S30.
148. Mousavi M, Zapolskaya T, Scipione MR, Louie E, Papadopoulos J, Dubrovskaya Y. Comparison of rates of nephrotoxicity associated with vancomycin in combination with piperacillin-tazobactam administered as an extended versus standard infusion. *Pharmacotherapy.* 2017;37:379-385.
149. Schmees PM, Bergman SJ, Strader BD, Metzke ME, Pointer S, Valenti KM. Outcomes of an extended-infusion piperacillin-tazobactam protocol implementation in a community teaching hospital adult intensive care unit. *Am J Health Syst Pharm.* 2016;73:S100-S105.

150. Winstead EM, Ratliff PD, Hickson RP, Mueller JE, Judd WR. Evaluation of an alternative extended-infusion piperacillin-tazobactam dosing strategy for the treatment of gram-negative infections. *Int J Clin Pharmacol*. 2016;38:1087-1093.
151. Savonius O, Rugemalira E, Roine I, Cruzeiro ML, Peltola H, Pelkonen T. Extended continuous beta-lactam infusion with oral acetaminophen in childhood bacterial meningitis: a randomized, double-blind clinical trial. *Clin Infect Dis*. 2021;72:1738-1744.
152. Shabaan AE, Nour I, Elsayed Eldeglia H, Nasef N, Shouman B, Abdel-Hady H. Conventional versus prolonged infusion of meropenem in neonates with gram-negative late-onset sepsis: a randomized controlled trial. *Pediatr Infect Dis J*. 2017;36:358-363.
153. Padari H, Metsvaht T, Korgvee LT, et al. Short versus long infusion of meropenem in very-low-birth-weight neonates. *Antimicrob Agents Chemother*. 2012;56:4760-4764.
154. Beauchamp LC, Nichols KR, Knoderer CA. Outcomes of extended infusion cefepime in pediatric patients. *Infect Dis Clin Pract*. 2019;27:283-287.
155. Rhodes NJ, MacVane SH, Kuti JL, Scheetz MH. Impact of loading doses on the time to adequate predicted beta-lactam concentrations in prolonged and continuous infusion dosing schemes. *Clin Infect Dis*. 2014;59:905-907.
156. Jamal JA, Roberts DM, Udy AA, et al. Pharmacokinetics of piperacillin in critically ill patients receiving continuous venovenous haemofiltration: a randomised controlled trial of continuous infusion versus intermittent bolus administration. *Int J Antimicrob Agents*. 2015;46:39-44.
157. Solorzano-Santos F, Quezada-Herrera A, Fuentes-Pacheco Y, et al. Piperacillin/tazobactam in continuous infusion versus intermittent infusion in children with febrile neutropenia. *Rev Invest Clin*. 2019;71:283-290.
158. Zembles TN, Schortemeyer R, Kuhn EM, Bushee G, Thompson NE, Mitchell ML. Extended infusion of beta-lactams is associated with improved outcomes in pediatric patients. *J Pediatr Pharmacol Ther*. 2021;26:187-193.
159. Beranger A, Benaboud S, Urien S, et al. Piperacillin population pharmacokinetics and dosing regimen optimization in critically ill children with normal and augmented renal clearance. *Clin Pharmacokinet*. 2019;58:223-233.
160. Beranger A, Oualha M, Urien S, et al. Population pharmacokinetic model to optimize cefotaxime dosing regimen in critically ill children. *Clin Pharmacokinet*. 2018;57:867-875.
161. Bui S, Facchin A, Ha P, et al. Population pharmacokinetics of ceftazidime in critically ill children: impact of cystic fibrosis. *J Antimicrob Chemother*. 2020;75:2232-2239.
162. Cies JJ, Jain J, Kuti JL. Population pharmacokinetics of the piperacillin component of piperacillin/tazobactam in pediatric oncology patients with fever and neutropenia. *Pediatr Blood Cancer*. 2015;62:477-482.
163. Cies JJ, Moore WS 2nd, Enache A, Chopra A. Population pharmacokinetics and pharmacodynamic target attainment of meropenem in critically ill young children. *J Pediatr Pharmacol Ther*. 2017;22:276-285.
164. Cies JJ, Shankar V, Schlichting C, Kuti JL. Population pharmacokinetics of piperacillin/tazobactam in critically ill young children. *Pediatr Infect Dis J*. 2014;33:168-173.
165. De Cock P, van Dijkman SC, de Jaeger A, et al. Dose optimization of piperacillin/tazobactam in critically ill children. *J Antimicrob Chemother*. 2017;72:2002-2011.
166. Maarbjerg SF, Thorsted A, Kristoffersson A, et al. Piperacillin pharmacokinetics and target attainment in children with cancer and fever: can we optimize our dosing strategy? *Pediatr Blood Cancer*. 2019;66:e27654.
167. Nichols K, Chung EK, Knoderer CA, et al. Population pharmacokinetics and pharmacodynamics of extended-infusion piperacillin and tazobactam in critically ill children. *Antimicrob Agents Chemother*. 2016;60:522-531.
168. Rapp M, Urien S, Foissac F, et al. Population pharmacokinetics of meropenem in critically ill children with different renal functions. *Eur J Clin Pharmacol*. 2020;76:61-71.
169. Salvador E, Oualha M, Bille E, et al. Population pharmacokinetics of cefazolin in critically ill children infected with methicillin-sensitive *Staphylococcus aureus*. *Clin Microbiol Infect*. 2021;27:413-419.
170. Shi HY, Wang K, Wang RH, et al. Developmental population pharmacokinetics-pharmacodynamics and dosing optimization of cefeprozone in children. *J Antimicrob Chemother*. 2020;75:1917-1924.
171. Thibault C, Lavigne J, Litalien C, Kassir N, Theoret Y, Autmizguine J. Population pharmacokinetics and safety of piperacillin-tazobactam extended infusions in infants and children. *Antimicrob Agents Chemother*. 2019;63:e01260-19.
172. Thorsted A, Kristoffersson AN, Maarbjerg SF, et al. Population pharmacokinetics of piperacillin in febrile children receiving cancer chemotherapy: the impact of body weight and target on an optimal dosing regimen. *J Antimicrob Chemother*. 2019;74:2984-2993.
173. Wang ZM, Chen XY, Bi J, et al. Reappraisal of the optimal dose of Meropenem in critically ill infants and children: a developmental pharmacokinetic-pharmacodynamic analysis. *Antimicrob Agents Chemother*. 2020;64:e00760-20.
174. Watt KM, Hornik CP, Balevic SJ, et al. Pharmacokinetics of ticarcillin-clavulanate in premature infants. *Br J Clin Pharmacol*. 2019;85:1021-1027.
175. Germovsek E, Lutsar I, Kipper K, et al. Plasma and CSF pharmacokinetics of meropenem in neonates and young infants: results from the NeoMero studies. *J Antimicrob Chemother*. 2018;73:1908-1916.
176. Cies JJ, Moore WS 2nd, Calaman S, et al. Pharmacokinetics of continuous-infusion meropenem for the treatment of *Serratia marcescens* ventriculitis in a pediatric patient. *Pharmacotherapy*. 2015;35:e32-e36.
177. Chung EK, Cheatham SC, Fleming MR, Healy DP, Shea KM, Kays MB. Population pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese and nonobese patients. *J Clin Pharmacol*. 2015;55:899-908.
178. Jung B, Mahul M, Breilh D, et al. Repeated piperacillin-tazobactam plasma concentration measurements in severely obese versus nonobese critically ill septic patients and the risk of under- and overdosing. *Crit Care Med*. 2017;45:e470-e478.
179. Alobaid AS, Wallis SC, Jarrett P, et al. Population pharmacokinetics of piperacillin in nonobese, obese, and morbidly obese critically ill patients. *Antimicrob Agents Chemother*. 2017;61:e01276-16.
180. Roberts JA, Lipman J. Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. *Crit Care Med*. 2013;41:489-495.
181. Langgartner J, Lehn N, Gluck T, Herzig H, Kees F. Comparison of the pharmacokinetics of piperacillin and sulbactam during intermittent and continuous intravenous infusion. *Chemotherapy*. 2007;53:370-377.
182. Chung EK, Fleming MR, Cheatham SC, Kays MB. Population pharmacokinetics and pharmacodynamics of doripenem in obese, hospitalized patients. *Ann Pharmacother*. 2017;51:209-218.
183. Cheatham SC, Fleming MR, Healy DP, et al. Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit. *J Clin Pharmacol*. 2014;54:324-330.
184. Chung EK, Cheatham SC, Fleming MR, Healy DP, Kays MB. Population pharmacokinetics and pharmacodynamics of

- meropenem in nonobese, obese, and morbidly obese patients. *J Clin Pharmacol*. 2017;57:356-368.
185. Brill MJ, Houwink AP, Schmidt S, et al. Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. *J Antimicrob Chemother*. 2014;69:715-723.
186. Edmiston CE, Krepel C, Kelly H, et al. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? *Surgery*. 2004;136:738-747.
187. Anlicoara R, Ferraz AA, Coelho KP, et al. Antibiotic prophylaxis in bariatric surgery with continuous infusion of cefazolin: determination of concentration in adipose tissue. *Obes Surg*. 2014;24:1487-1491.
188. Ferraz AA, Siqueira LT, Campos JM, Araujo GC, Martins Filho ED, Ferraz EM. Antibiotic prophylaxis in bariatric surgery: a continuous infusion of cefazolin versus ampicillin/sulbactam and ertapenem. *Arq Gastroenterol*. 2015;52:83-87.
189. Gregoire M, Dumont R, Ronchi L, et al. Prophylactic cefazolin concentrations in morbidly obese patients undergoing sleeve gastrectomy: do we achieve targets? *Int J Antimicrob Agents*. 2018;52:28-34.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

AUTHOR PERSONAL AND FINANCIAL RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES

Author	Affiliation	Grant funding	Consulting fees	Lectures/ Speakers bureaus	Data safety monitoring/ Advisory board/ Employment	Materials or services
Lisa T. Hong	Loma Linda University School of Pharmacy, Loma Linda, CA, USA	None	None	None	None	None
Kevin J. Downes	Children's Hospital of Philadelphia, Philadelphia, PA, USA	Merck	None	None	None	None
Alireza FakhriRavari	Loma Linda University School of Pharmacy, Loma Linda, CA, USA	None	None	None	None	None
Jacinda Abdul-Mutakabbir	Division of Clinical Pharmacy, Skaggs School of Pharmacy, University of California San Diego, San Diego, CA, USA Division of the Black Diaspora and African American Studies	CSL Sequiris	Shionogi	None	Shionogi, Entasis Therapeutics, Innoviva Specialty Therapeutics, CSL Sequiris, Abbvie	None
Joseph Kuti	Hartford Hospital Center for Anti-Infective Research and Development, Hartford, CT, USA	bioMeriux Inc, Entasis, Merck, Shionogi, Thermo Fisher Scientific, Spero, Synthetic Biologics, Contrafact, Summit, Finch, Pfizer, Food and Drug Administration	Abbvie, bioMeriux Inc, Glaxo Smith Kline, Shionogi	Shionogi	None	None
Sarah Jorgensen	University of Toronto, ON, Canada	Canadian Immunization Research Network	None	None	None	None

Author	Affiliation	Grant funding	Consulting fees	Lectures/ Speakers bureaus	Data safety monitoring/ Advisory board/ Employment	Materials or services
David Young	University of Utah College of Pharmacy, Salt Lake City, UT, USA	Cystic Fibrosis Foundation	None	None	None	None
Mohammad H. Alshaer	University of Florida College of Pharmacy, Gainesville, FL, USA	None	None	None	None	None
Matteo Bassetti	University of Genoa, Genoa, Italy	MSD, Shionogi	Biomerieux, Gilead, Menarini, MSD, Pfizer, Shionogi	Biomerieux, Gilead, Menarini, MSD, Pfizer, Shionogi	Cidara	None
Robert Bonomo	Cleveland Veteran Affairs Medical Center, Cleveland, OH, USA Case VA CARES and Departments of Medicine, Pharmacology, Molecular Biology and Microbiology	Merit Award VHA and Senior Clinical Scientist Investigator NIAID, Merck, Venatorx, Entasis, Shionogi	None	Juvabis AG, Unilab	None	None
Mark Gilchrist	Imperial College Healthcare National Health Services Trust, London, UK	None	Pfizer, Menarini, Gilead	None	BSAC OPAT UK Initiative	None
Soo Min Jang	Loma Linda University School of Pharmacy, Loma Linda, CA, USA Loma Linda University School of Medicine, Loma Linda, CA, USA	None	None	None	None	None
Thomas Lodise	Albany College of Pharmacy and Health Sciences, Albany, NY, USA	Wockhardt, Merck, Entasis	Venatrox, Spero, Shionogi, Merck, Melinta, ICPD, Entasis, AbbVie, Ferring, GSK, Roche	Shionogi	None	None
Jason Roberts	University of Queensland Center for Clinical Research, Faculty of Medicine, Brisbane, Australia Herston Infectious Diseases Institute, Metro North Health, Brisbane, Australia Departs of Pharmacy and Intensive Care, Royal Brisbane and Women's Hospital, Brisbane, Australia Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France	MSD, The Medicines Company, Pfizer, Qpex, British Society of Antimicrobial Chemotherapy, Biomerieux	Discuva Ltd, Sandoz	MSD, Biomerieux, Pfizer	MSD, QPEX, Gilead	None

Author	Affiliation	Grant funding	Consulting fees	Lectures/ Speakers bureaus	Data safety monitoring/ Advisory board/ Employment	Materials or services
Thomas Tängdén	Department of Medical Sciences, Uppsala University, Uppsala, Sweden	None	None	None	None	None
Athena Zuppa	Children's Hospital of Philadelphia, Philadelphia, PA, USA	None	None	None	Johnson and Johnson	None
Marc H. Scheetz	Midwestern University, College of Pharmacy, Pharmacometric Center of Excellence, Downers Grove, IL, USA Northwestern Memorial Hospital, Department of Pharmacy, Chicago, IL, USA	Merck, Allecra, Nevakar, SuperTrans Medical	GSK, Entasis, Cidara, Third Pole Therapeutics, F2G, Spero, Merck, Abbvie, Takeda, Allecra, Nevakar, Guidepoint Global, Premier Healthcare Solutions	GSK	DoseMe	None

APPENDIX 2

BEATA-LACTAM AND PROLONGED INFUSION SEARCH STRATEGY

DATABASES SEARCHED

Medline (Ovid) - October 18, 2020

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 16, 2020

1	exp beta-Lactams/	129074
2	exp beta-Lactamase Inhibitors/	9358
3	(beta lactam* or b-lactam*).tw,kf.	44827
4	(ESBL or ESBLE or "CTX M" or CTXM or SHV or TEM).tw,kf.	59699
5	(carbapen* or carba-pem*).tw,kf.	16063
6	("ici 194660" or mepem* or meronem* or mero-pen* or meropen* or merrem* or "sm 7338" or sm7338).tw,kf.	7181
7	(Archifar or Bironem or Caronem or Elpenem or Enem or Eradix or Grambiot or Lanmer or Mabapenem or Mapenem or Mecapem or Meflupin or Melopen or Menem or Mepenem or Mero or Merobac or Merofen or Merogram or Meromax or Meronia or Merop or Meropedem or Meropevex or Merosan or Merosayz or Merovex or Meroxi or Merozan or Merozen or Monem or Myron or Nemmed or Newropenem or Optinem or Penomer or Pisapem or Pospnenem or Romenem or Ronem or Ropen or Tripenem or Zakster or Zaxter or Zeropenem).tw,kf.	245
8	(ertapen* or erta-pen* or invanoz or invanz or "I 749345" or "I749345" or "mk 0826" or "mk 826" or "mk0826" or "mk826" or "zd 4433" or "zd4433").tw,kf.	1641
9	(imipen* or imi-pen* or formiminothienamyc* or imipemid* or "mk 0787" or "mk 787" or mk0787 or mk787 or foramidinylthienamyc* or formimidoylthienamyc* or thienamyc*).tw,kf.	11088
10	(Anipen or Arzobema or Bacquire or Bacqure or Bidinam or Cilanem or Cilapenem or Cispenam or Imenam or Imiclast or Iminam or Iminem or Iminen or Imivex or Inem or Minem or Nemcis or Nimedine or Pelascap or Pelastin or Penam or Plastin or Premax or Prepenem or Primax or Primaxin or Sianem or Supernem or Supranem or Talispnenem or Tenacid or Tiaktam or Tienam or Tiesilan or Timipen or Tipem or Tiyenam or Vexpinam or Xerxes or Zienam).tw,kf.	574
11	Cilastatin/	957
12	(N-F-Thienamycin or N-Formimidoylthienamycin or Cilastatin or Imipemide or RAN-imipenem-cilastatin or "I 642957" or I642957 or "mk 0791" or mk0791 or mk 791 or mk791 or "7 [(2 amino 2 carboxyethyl)thio] 2 (2,2 dimethylcyclopropanecarboxamido) 2 heptenoic acid" or "s [6 carboxy 6 [(2,2 dimethylcyclopropyl)carboxamido] 5 hexenyl]cysteine" or "s [6 carboxy 6 [(2,2 dimethylcyclopropyl)carbonyl]amino] 5 hexenyl] levo cysteine").tw,kf.	1432

13	("mk 797" or mk797 or "pelastin iv" or prepenem or tenacid or tienam or zienam).tw,kf.	50
14	(doribax or doripen* or finibax or "s 4661" or "s4661").tw,kf.	687
15	(penicillin* or amdinocillin* or cyclacillin* or methicillin* or nafcillin* or nafcil or oxacillin* or cloxacillin* or dicloxacillin* or floxacillin* or sulbactam* or ticarcillin* or caprolactam* or macrocyclic lactam*).tw,kf.	100599
16	(cephalosporin* or cephalosporanic* or cefamandole* or cefazolin* or cefdinir* or cefepim* or cefonicid* or cefsulodin* or Ceftibuten* or cefuroxime* or cephaetril* or cephalixin* or cephaloridin* or cephamycin*).tw,kf.	36506
17	((pip* adj5 taz*) or (piptaz* or tazocel* or tazocillin* or tazocin* or tazonom* or tazopril* or yp14 or "yp 14" or zosyn*)).tw,kf.	4364
18	(("cl 298741" or cl298741 or "cl 307579" or cl307579 or tazobac* or "ytr 830" or "ytr 830h" or ytr830 or ytr830h) and (acopex or avocin or "cl 227 193" or "cl 227193" or "cl227 193" or cl227193 or cypercil or hishiyaclorin or ivacin or "penicillanic acid" or pentocillin or pentocillin or picillin* or pipcil or piperacil* or piperacin or piperilline or pipracil* or pipracin or pipraks or pipril or piprilin or pitamycin or "t 1220" or t1220 or taiperacillin)).tw,kf.	4363
19	(monobactam* or aztreonam* or ceftarolin* or cefiderocol*).tw,kf.	4391
20	(amoxicillin* or "26787-78-0" or "26889-93-0" or "34642-78-9" or "544y3d6myh" or "61336-70-7" or "804826j2hu" or "9em05410q9" or "actimoxi" or Amoxil or "brl 2333" or brl2333 or clamoxyl* or hydroxyampicillin* or penamox* or polymox* or trimox* or wymox* or amox? clav* or amox* potassium clav* or augmentin* or "brl 25000" or brl25000 or clavulin* or "co amoxiclav*" or coamoxiclav* or spektramox or synulox).tw,kf.	32400
21	(Ampito or Astaz-P or Aurotaz or Betamycin or Co-Tazo or Jeita or Pipertaz or Piptabac or Pletzolyn or Prizma or Pybactam or Sixacin or Tabaxin or Tasovak or Tazar or Tazepen or Tazin or Tazobak or Tazomax or Tazopen or Tazoperan or Tazopip or Tazopril or Tazorex or Tazosyn or Tazpen or Tebranic or Vigodic or Zobaction or Zopercin or Zopertsyn).tw,kf.	6
22	(ampicillin* or azlocillin* or mezlocillin* or pivampicillin* or talampicillin*).tw,kf.	25188
23	(ceftazidim* or cefidericol or cefotaxim* or cefixim* or cefmenoxim* or cefotiam* or ceftizoxime* or ceftriaxon* or ceftobipro* or ceftolozan* or cloxacillin* or dicloxacillin* or floxacillin* or flucloxacillin* or vaborbactam* or relebactam* or avibactam* or benzympenicillin*).tw,kf.	32774
24	or/1-23 [Beta lactams, other agents]	296869
25	Infusions, Intravenous/ and (prolong* or extend* or continuous* or constant).tw,kf.	12503
26	((prolong* or extend* or continuous* or continual* or constant) adj5 infus*).tw,kf.	43800
27	((prolong* or extend*) adj4 (intravenous* or intra-venous*)).tw,kf.	1567
28	or/25-27 [Prolonged Infusions]	49539
29	24 and 28 [Beta lactams, other agents & Prolonged Infusions]	1578
30	((prolong* or extend* or continu* or constant) adj5 infus*) and (beta lactam* or b-lactam* or anti-biot* or antibiot* or anti-microb* or antimicrob* or steward* or ampicillin* or aztreonam or benzympenicillin or cefazolin* or cefepime or cefidericol or cefotaxim* or ceftarolin* or ceftazidim* or avibactam* or ceftobipro* or ceftolozan* or tazobactam* or ceftriaxone or cloxacillin* or dicloxacillin* or floxacillin* or doripenem* or ertapenem* or flucloxacillin* or imipenem* or cilastatin* or relebactam* or meropenem* or vaborbactam* or nafcillin* or oxacillin or piperacillin* or penicillin* or cephalosporin* or carbapenem* or monobactam* or ceftarolin*).ti,kf.	480
31	or/29-30	1629
32	limit 31 to english	1482
33	32 not (exp Congress/ or exp Congresses as Topic/)	1481
34	remove duplicates from 33	1481
35	limit 34 to (comment or editorial or letter or news or retracted publication or "retraction of publication") [TO BE LOOKED AT IN MAIN GROUP]	53
36	34 not 35 [TO BE COMBINED WITH ALL GROUPS - Beta Lactams, other agents & prolonged infusions, without conferences]	1428
37	exp Pharmacokinetics/	311527
38	pk.fs.	295354
39	(pharmacokinetic* or pharmaco-kinetic* or pharmacodyn* or pharmaco-dyn* or "PK/PD" or (drug* adj1 kinetic*)).tw,kf.	180791
40	(absorption* or bioaccumulation* or bio-accumulation* or auc or area under curve* or biological availabilit* or biotransformation* or biotransformation* or drug* liberation* or therapeutic equivalency or tissue distribution*).tw,kf.	397380
41	(metabolic adj1 (activation or inactivation* or detoxication* or de-toxication*)).tw,kf.	8285

42	((cutaneous or hepatobiliary or intestin* or lacrimal or lacteal or pulmon* or renal or salivar*) adj1 elimination*).tw,kf.	1782
43	minimum inhibitory concentration*.tw,kf.	20057
44	or/37-43	882540
45	44 not Case Reports/	868448
46	36 and 45 [GROUP 1 Beta Lactams, other agents & prolonged infusions & PK/PD, excluding case reports]	737
47	exp Treatment Outcome/	1068782
48	exp Mortality/	386697
49	(outcome* or clinical or mortalit* or death* or survival or cure).tw,kf.	6127442
50	(complicat* or failure* or sequelae or severit* or morbidit*).ti,kf. or (complicat* or failure* or sequelae or severit* or morbidit*).ab. /freq=2	1166291
51	(safe or safety or side effect* or undesirable effect* or tolerabilit* or (adverse adj (effect or effects or reaction or reactions or event or events))).ti,kf. or (safe or safety or side effect* or undesirable effect* or tolerabilit* or (adverse adj (effect or effects or reaction or reactions or event or events))).ab. /freq=2	524117
52	ae.fs.	1748797
53	or/47-52	8287079
54	53 not Case Reports/	7419914
55	Animals/ not (Animals/ and Humans/)	4711269
56	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep*) not (human* or patient*)).ti,kf.	2145203
57	54 not (55 or 56)	6715691
58	36 and 57 [GROUP 2 Clinical Outcomes, excluding case reports and animal studies]	685
59	Drug Therapy/ or exp *Drug Therapy/	404125
60	Drug Utilization Review/	3780
61	Drug Monitoring/	21183
62	dt.fs.	2243399
63	(drug* adj2 (monitor* or therap* or stability or storage)).tw,kf.	93030
64	or/59-63	2524725
65	64 not Case Reports/	2206304
66	36 and 65 [GROUP 3 Therapeutic drug monitoring, excluding case reports]	728
67	Infusions, Parenteral/	26273
68	parenteral*.tw,kf.	56794
69	Home Infusion Therapy/	691
70	exp Home Care Services/ and exp Infusion Pumps/	213
71	((elastomeric* or infusion* or perfusion? or smart) adj3 pump?).tw,kf.	4853
72	exp Obesity/	215785
73	(obes* or overweigh* or over-weigh* or superobes*).tw,kf.	330111
74	((prolong* or extend* or continu* or constant) adj5 infus*) and (obes* or overweigh* or over-weigh* or superobes*).ti,kf.	20
75	exp pediatrics/ or adolescent/ or exp child/ or exp infant/	3602872
76	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediater* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween).tw,kf.	2519334
77	or/68-76	4690800
78	77 not (55 or 56) [Exclude Animal Studies]	4464088
79	36 and 78 [GROUP 4 - Special Population: parenteral antibiotics, obesity & pediatrics, excluding animal studies]	374
80	Critical Illness/	29750
81	(critical* adj2 ill*).tw,kf.	53044
82	Cystic Fibrosis/	35536

83	((cystic adj1 fibrosis) or (fibrocystic adj1 disease*) or mucoviscidosis).tw,kf.	47021
84	exp Renal Insufficiency, Chronic/	116287
85	(advanced* adj1 (renal or kidney*) adj1 impair*).tw,kf.	37
86	kidney diseases/ and (chronic* or long-term* or longterm* or longlast* or long-last* or longstand* or long-stand* or perpetual* or lifelong* or life-long* or endstage* or end-stage* or permanent* or progressive* or advanced).tw,kf.	18260
87	((renal or kidney*) adj1 replacement therap*).tw,kf.	13945
88	((renal* or kidney* or renovasc* or reno-vasc* or neph*) adj5 (chronic* or long-term* or longterm* or longlast* or long-last* or longstand* or long-stand* or perpetual* or lifelong* or life-long* or endstage* or end-stage* or osteodystroph* or osteo-dystroph* or permanent* or progressive*).tw,kf.	152356
89	(ckd or esrd).tw,kf.	45009
90	(IHD or SLED or CRRT).tw,kf.	8358
91	or/80-90	333035
92	91 not (55 or 56) [Exclude Animal Studies]	312501
93	36 and 91 [GROUP 5 – Special Population: Critically Ill, CF, Advanced Kidney Impairment, excluding animal studies]	316
94	46 or 58 or 66 or 79 or 93 [All Groups]	1234
95	36 not 94 [Not included in specific groups]	194
96	35 or 95 [ALL NOT LOOKED AT IN SPECIFIC GROUPS]	247
97	46 [GROUP 1 Beta Lactams, other agents & prolonged infusions & PK/PD]	737
98	58 [GROUP 2 Clinical Outcomes]	685
99	66 [GROUP 3 Therapeutic drug monitoring]	728
100	79 [GROUP 4 – Special Population: parenteral antibiotics, obesity & pediatrics]	374
101	93 [GROUP 5 – Special Population: Critically Ill, CF, Advanced Kidney Impairment]	316

Embase (Ovid) – October 18, 2020

Embase Classic + Embase 1947 to 2020 October 15

2	exp beta lactamase inhibitor/	83021
3	exp *beta lactam antibiotic/	154152
4	beta lactam antibiotic/ or carbapenem/ or carbapenem derivative/ or cephalosporin derivative/ or cilastatin plus imipenem/ or cilastatin sodium plus imipenem plus relebactam/ or clavulanate potassium/ or clavulanic acid/ or doripenem/ or ertapenem/ or imipenem/ or meropenem/ or meropenem plus vaborbactam/ or monobactam derivative/ or penicillin derivative/ or sultamicillin/ or tazobactam/	146965
5	(beta lactam* or b-lactam*).tw,kw.	57384
6	(ESBL or ESBLE or "CTX M" or CTXM or SHV or TEM).tw,kw.	70635
7	(carbapen* or carba-pem*).tw,kw.	23240
8	("ici 194660" or mepem* or meronem* or mero-pen* or meropen* or merrem* or "sm 7338" or sm7338).tw,kw.	12410
9	(Archifar or Bironem or Caronem or Elpenem or Enem or Eradix or Grambiot or Lanmer or Mabapenem or Mapenem or Mecapem or Meflupin or Melopen or Menem or Mepenem or Mero or Merobac or Merofen or Merogram or Meromax or Meronia or Merop or Meropedem or Meropevex or Merosan or Merosayz or Merovex or Meroxi or Merozan or Merozen or Monem or Myron or Nemmed or Newropenem or Optinem or Penomer or Pisapem or Pospnenem or Romenem or Ronem or Ropen or Tripenem or Zakster or Zaxter or Zeropenem).tw,kw.	297
10	(ertapen* or erta-pen* or invanoz or invanz or "I 749345" or "I749345" or "mk 0826" or "mk 826" or "mk0826" or "mk826" or "zd 4433" or "zd4433").tw,kw.	2863
11	(imipen* or imi-pen* or formiminothienamyc* or impemid* or "mk 0787" or "mk 787" or mk0787 or mk787 or foramidinylthienamyc* or formimidoylthienamyc* or thienamyc*).tw,kw.	16356
12	(Anipen or Arzobema or Bacquire or Bacqure or Bidinam or Cilanem or Cilapenem or Cispenam or Imenam or Imiclast or Iminam or Iminem or Iminen or Imivex or Inem or Minem or Nemcis or Nimedine or Pelascap or Pelastin or Penam or Plastin or Premax or Prepenem or Primax or Primaxin or Sianem or Supernem or Supranem or Talispenam or Tenacid or Tiaktam or Tienam or Tiesilan or Timipen or Tipem or Tiyanem or Vexpinam or Xerxes or Zienam).tw,kw.	1662
13	cilastatin/	2712

14	(N-F-Thienamycin or N-Formimidoylthienamycin or Cilastatin or Impipemide or RAN-imipenem-cilastatin or "I 642957" or I642957 or "mk 0791" or mk0791 or mk 791 or mk791 or "7 [(2 amino 2 carboxyethyl)thio] 2 (2,2 dimethylcyclopropanecarboxamido) 2 heptenoic acid" or "s [6 carboxy 6 [(2,2 dimethylcyclopropyl)carboxamido] 5 hexenyl]cysteine" or "s [6 carboxy 6 [(2,2 dimethylcyclopropyl)carbonyl]amino] 5 hexenyl] levo cysteine"). tw,kw.	2120
15	("mk 797" or mk797 or "pelastin iv" or prepenem or tenacid or tienam or zienam).tw,kw.	549
16	(doribax or doripen* or finibax or "s 4661" or "s4661").tw,kw.	1173
17	(penicillin* or aminocillin* or cyclacillin* or methicillin* or nafcillin* or nafcil or oxacillin* or cloxacillin* or dicloxacillin* or floxacillin* or sulbactam* or ticarcillin* or caprolactam* or macrocyclic lactam*).tw,kw.	107317
18	(cephalosporin* or cephalosporanic* or cefamandole* or cefazolin* or cefdinir* or cefepim* or cefonicid* or cefsulodin* or Ceftibuten* or cefuroxime* or cephacetril* or cephalixin* or cephaloridin* or cephamycin*).tw,kw.	50945
19	((pip* adj5 taz*) or (piptaz* or tazocel* or tazocillin* or tazocin* or tazonom* or tazopril* or yp14 or "yp 14" or zosyn*)). tw,kw.	9493
20	(("cl 298741" or cl298741 or "cl 307579" or cl307579 or tazobac* or "ytr 830" or "ytr 830h" or ytr830 or ytr830h) and (acopex or avocin or "cl 227 193" or "cl 227193" or "cl227 193" or cl227193 or cypercil or hishiyaclorin or ivacin or "penicillanic acid" or pentacillin or pentocillin or picillin* or pipcil or piperacil* or piperacin or piperilline or pipracil* or pipracin or pipraks or pipril or piprilin or pitamycin or "t 1220" or t1220 or taiperacillin)).tw,kw.	8217
21	(monobactam* or aztreonam* or ceftarolin* or cefiderocol*).tw,kw.	6281
22	(amoxicillin* or "26787-78-0" or "26889-93-0" or "34642-78-9" or "544y3d6myh" or "61336-70-7" or "804826j2hu" or "9em05410q9" or "actimoxi" or Amoxil or "brl 2333" or brl2333 or clamoxyl* or hydroxyampicillin* or penamox* or polymox* or trimox* or wymox* or amox? clav* or amox* potassium clav* or augmentin* or "brl 25000" or brl25000 or clavulin* or "co amoxiclav*" or coamoxiclav* or spektramox or synulox).tw,kw.	50074
23	(Ampito or Astaz-P or Aurotaz or Betamycin or Co-Tazo or Jeita or Pipertaz or Piptabac or Pletzolyn or Prizma or Pybactam or Sixacin or Tabaxin or Tasovak or Tazar or Tazepen or Tazin or Tazobak or Tazomax or Tazopen or Tazoperan or Tazopip or Tazopril or Tazorex or Tazosyn or Tazpen or Tebranic or Vigocid or Zobaction or Zopercin or Zopertsyn).tw,kw.	26
24	(ampicillin* or azlocillin* or mezlocillin* or pivampicillin* or talampicillin*).tw,kw.	31021
25	(ceftazidim* or cefidericol or cefotaxim* or cefixim* or cefmenoxim* or cefotiam* or ceftizoxime* or ceftriaxon* or ceftobiprol* or ceftolozan* or cloxacillin* or dicloxacillin* or floxacillin* or flucloxacillin* or vaborbactam* or relebactam* or avibactam* or benzylpenicillin*).tw,kw.	47518
26	or/1-25 [Beta lactams, other agents]	464506
27	continuous infusion/	44177
28	((prolong* or extend* or continuous* or continual* or constant) adj5 infus*).tw,kw.	57834
29	((prolong* or extend*) adj4 (intravenous* or intra-venous*)).tw,kw.	1912
30	or/27-29 [Prolonged Infusions]	88605
31	26 and 30 [Beta lactams, other agents & Prolonged Infusions]	3313
32	((((prolong* or extend* or continu* or constant) adj5 infus*) and (beta lactam* or b-lactam* or anti-biot* or antibiot* or ampicillin* or aztreonam or benzylpenicillin or cefazolin* or cefepime or cefidericol or cefotaxim* or ceftarolin* or ceftazidim* or avibactam* or ceftobiprol* or ceftolozan* or tazobactam* or ceftriaxone or cloxacillin* or dicloxacillin* or floxacillin* or doripenem* or ertapenem* or flucloxacillin* or imipenem* or cilastatin* or relebactam* or meropenem* or vaborbactam* or nafcillin* or oxacillin or piperacillin* or penicillin* or cephalosporin* or carbapenem* or monobactam* or ceftarolin*)).ti,kw.	669
33	or/31-32	3345
34	limit 33 to english	3147
35	limit 34 to (books or chapter or conference abstract or conference paper or "conference review")	471
36	34 not 35	2676
37	limit 36 to english	2676
38	limit 37 to (editorial or erratum or letter or note)	171
39	37 not 38	2505
40	remove duplicates from 39	2472

41 ("4035818" or "31697336" or "22964948" or "30364596" or "32574791" or "22898246" or "26433783" or "24951308" or "33009140" or "26754759" or "25095985" or "32535299" or "7205215" or "7872445" or "20570290" or "1889273" or "23268616" or "10586426" or "9507456" or "29954243" or "25780942" or "24770557" or "31157080" or "32832429" or "32601155" or "27139468" or "9773703" or "933218" or "28849402" or "9371344" or "8433561" or "32153771" or "26702922" or "28052849" or "15650000" or "30971094" or "26856841" or "21919869" or "22303918" or "27269810" or "8941241" or "19933800" or "29416463" or "1808044" or "29507062" or "26153194" or "24859562" or "7486219" or "10930972" or "10792202" or "24733372" or "4106894" or "6517086" or "22478986" or "24195117" or "28487584" or "29583053" or "31203809" or "3971836" or "28605490" or "21901990" or "20622257" or "23341160" or "23908259" or "27418581" or "17567657" or "24780830" or "20571462" or "9516951" or "26095008" or "20216281" or "1452502" or "7039058" or "30962339" or "7706822" or "6723636" or "3911879" or "27031898" or "16331172" or "19567350" or "27796647" or "1510432" or "971012" or "12615867" or "2365756" or "30649218" or "30221562" or "31728749" or "8063910" or "4809115" or "6968743" or "23151325" or "27584587" or "27294248" or "8821302" or "23571547" or "22949" or "20460397" or "931369" or "6929675" or "1847796" or "8141572" or "31307987" or "32461155" or "31219562" or "27485941" or "1433482" or "32066497" or "8851594" or "30306347" or "29862466" or "28980166" or "28264846" or "3488309" or "6480542" or "12760859" or "12848746" or "11864154" or "11722682" or "18791659" or "31591117" or "20176578" or "25694414" or "16127078" or "12926599" or "23132087" or "3467590" or "31427301" or "32366710" or "3370191" or "2719893" or "31419268" or "17636010" or "31839941" or "2099158" or "32406243" or "20226635" or "2729925" or "17242144" or "26303111" or "1101822" or "495630" or "1086758" or "31220258" or "11215777" or "9257947" or "8706462" or "2291659" or "10780945" or "12973166" or "18434883" or "14985960" or "10331825" or "29386022" or "11120967" or "24614367" or "9481541" or "11936353" or "3923513" or "19157801" or "7388446" or "21926549" or "21597443" or "23433439" or "2112485" or "24666465" or "4819177" or "7340882" or "4025567" or "25855703" or "10451011" or "1115440" or "9404765" or "1510418" or "12506954" or "15620828" or "9470026" or "31978581" or "32457995" or "15175266" or "11751775" or "17395686" or "19995927" or "20660688" or "17485505" or "21039762" or "21402834" or "20065059" or "30304491" or "10084455" or "19505173" or "10688391" or "10890260" or "12182254" or "25575975" or "17257093" or "17185298" or "23869050" or "23271675" or "11481316" or "20559610" or "18806062" or "9428548" or "15222672" or "15980347" or "7486921" or "21943743" or "28236797" or "6391371" or "23642005" or "24917580" or "25220554" or "30172963" or "29180280" or "11589482" or "30111350" or "8419791" or "11926000" or 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"3360694" or "3060460" or "3209527" or "2755924" or "27208142" or "14638923" or "32166286" or "18108683" or "32296502" or "28456704" or "19245363" or "8891125" or "19168542" or "31512147" or "31565960" or "25285131" or "11502544" or "21649882" or "27918382" or "23644610" or "10372723" or "32090347" or "8088980" or "2217002" or "21926550" or "10330005" or "19809009" or "19726163" or "32919007" or "20043011" or "30761114" or "17162472" or "11054234" or "23543565" or "26810655" or "31788272" or "28149601" or "27197907" or "26799442" or "28807922" or "31358583" or "26119486" or "26024868" or "24845223" or "30769293" or "16328095" or "18230687" or "28961812" or "30636060" or "6330656" or "10898132" or "14625745" or "32061797" or "16930921" or "22946869" or "1120799" or "31448789" or "23547168" or "30117081" or "31849910" or "4105353" or "16216470" or "28210888" or "16943729" or "6226720" or "12760882" or "6296967" or "8959631" or "26449198" or "15612835" or "23012385" or "28241292" or "14749346" or "16323442" or "26171974" or "300093" or "7800782" or "29452629" or "28189734" or "18752384" or "30963365" or "27747899" or "17122526" or "14287989" or "14102080" or "32585693" or "21540216" or "19260350" or "9255079" or "6682362" or "3314696" or "17974311" or "26169558" or "22958536" or "22290984" or "26831672" or "11039473" or "29348124" or "11455482" or "8604829" or "10026424" or "12120252" or "12627925" or "16304153" or "32881997" or "21407037" or "21696619" or "25408310" or "30845037" or "32916003" or "27025644" or "24657044" or "32646818" or "10394012" or "632997" or "29121839" or "31679822" or "10350382" or "3105445" or "28873292" or "31427292" or "27132188" or "29437718" or "1211961" or "31273375" or "984782" or "1137368" or "29225790" or "28578553" or "8728253" or "29778482" or "6668759" or "3470047" or "27272266" or "7805683" or "8612446" or "23124129" or "25313214" or "31515843" or "2719458" or "26275516" or "26304289" or "8017415" or "10381105" or "8592934" or "30376071" or "26697851" or "8840374" or "7264925" or "8619902" or "25957670" or "9675443" or "28286115" or "32219679" or "26869692" or "20530507" or "1283467" or "27966034" or "31005313" or "27039340" or "8703647" or "19581463" or "8529330" or "8552453" or "3116918" or "18775568" or "10660852" or "3110072" or "32627599" or "7114835" or "22747633" or "3396487" or "19448477" or "23353954" or "23249839" or "31615614" or "29102324" or "31252156" or "30244674" or "15014060" or "17223858" or "30349291" or "32653661" or "30663549" or "22005059" or "22915464" or "11057794" or "12121900" or "3778073" or "31464871" or "22230846" or "9249216" or "12543656" or "8723446" or "7974622" or "8218695" or "7633021" or "8040122" or "15504859" or "29982449" or "27019965" or "16978077" or "14152783" or "23115223" or "18150190" or "17398076" or "12593694" or "19091523" or "8375124" or "28002114" or "25798070" or "32513801" or "30710387" or "22606991" or "26909707" or "3214972" or "12741434" or "25364230" or "20441003" or "3214451" or "30472288" or "2528215" or "31585474" or "32698988" or "32862306" or "27333796" or "21507788" or "9279728" or "21282442" or "23733463" or "24379195" or "7914900" or "1510438" or "3252752" or "28077047" or "375433" or "27738856" or "33041807" or "33058798" or "11502515" or "20360589" or "31636062" or "27821448" or "28993331" or "25645842" or "27518175" or "25575030" or "2141778" or "17701132" or "20839025" or "9120813" or "16455367" or "27432414" or "26521833" or "22877766" or "21923603" or "9301994" or "19802976" or "29188736" or "9216171" or "30059536" or "25179412" or "28664350" or "6217755" or "25381169" or "10659025" or "29582764" or "21502616" or "27077931" or "20926397" or "19075069" or "26521926" or "31176931" or "32772722" or "28485312" or "21528646" or "3193364" or "23719590" or "30127628" or "3773158" or "6799585" or "27453702" or "23775821" or "23661625" or "22825925" or "21520438" or "22478987").pm.

42	40 not 41	1414
43	exp pharmacokinetics/	746036
44	pk.fs.	395922
45	1 and 44	339
46	(pharmacokinetic* or pharmaco-kinetic* or pharmacodyn* or pharmaco-dyn* or "PK/PD" or (drug* adj1 kinetic*)). tw,kw.	257213
47	(absorption* or bioaccumulation* or bio-accumulation* or auc or area under curve* or biological availabilit* or biotransformation* or biotransformation* or drug* liberation* or therapeutic equivalency or tissue distribution*). tw,kw.	471778
48	(metabolic adj1 (activation or inactivation* or detoxication* or de-toxication*)),tw,kw.	9714
49	((cutaneous or hepatobiliary or intestin* or lacrimal or lacteal or pulmon* or renal or salivar*) adj1 elimination*).tw,kw.	2175
50	minimum inhibitory concentration*.tw,kw.	26594
51	exp pharmacodynamics/	3612509
52	or/46-51	4133750
53	52 not case report/	3993788
54	42 and 53 [GROUP 1 Beta Lactams, other agents & prolonged infusions & PK/PD, excluding case reports]	611
55	exp treatment outcome/	1709168
56	exp mortality/	1100800
57	(outcome* or clinical or mortalit* or death* or survival or cure).tw,kw.	8574094
58	(complicat* or failure* or sequelae or severit* or morbidit*).ti,kw. or (complicat* or failure* or sequelae or severit* or morbidit*).ab. /freq=2	1633354
59	(safe or safety or side effect* or undesirable effect* or tolerabilit* or (adverse adj (effect or effects or reaction or reactions or event or events))).ti,kw. or (safe or safety or side effect* or undesirable effect* or tolerabilit* or (adverse adj (effect or effects or reaction or reactions or event or events))).ab. /freq=2	831466
60	ae.fs.	1241707
61	or/55-60	10812387
62	61 not case report/	9834567
63	(exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not human/	6732559
64	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep*) not (human* or patient*)).ti,kw.	2302929
65	62 not (63 or 64)	8828605
66	42 and 65 [GROUP 2 Clinical Outcomes, excluding case reports and animal studies]	669
67	drug therapy/ or exp *drug therapy/	1257322
68	"drug utilization review"/	558
69	exp drug monitoring/	54366
70	dt.fs.	3799583
71	(drug* adj2 (monitor* or therap* or stability or storage)).tw,kw.	121727
72	or/67-71	4895931
73	72 not case report/	4133047
74	42 and 73 [GROUP 3 Therapeutic drug monitoring, excluding case reports]	768
75	exp parenteral drug administration/	733911
76	parenteral*.tw,kw.	75389
77	home infusion therapy/	72
78	home intravenous therapy/	49
79	((elastomeric* or infusion* or perfusion? or smart) adj3 pump?).tw,kw.	7287
80	exp obesity/	529072
81	(obes* or overweigh* or over-weigh* or superobes*).tw,kw.	492349
82	((prolong* or extend* or continu* or constant) adj5 infus*) and (obes* or overweigh* or over-weigh* or superobes*). ti,kw.	45

83	exp pediatrics/ or exp adolescent/ or exp child/ or exp infant/	3458214
84	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediater* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween).tw,kw.	3068185
85	or/75-84	5574497
86	85 not (63 or 64) [Exclude Animal Studies]	4867471
87	42 and 86 [GROUP 4 - Special Population: parenteral antibiotics, obesity & pediatrics, excluding animal studies]	384
88	critical illness/	30148
89	(critical* adj2 ill*).tw,kw.	80843
90	cystic fibrosis/	71869
91	((cystic adj1 fibrosis) or (fibrocystic adj1 disease*) or mucoviscidosis).tw,kw.	69659
92	exp kidney failure/	370129
93	(advanced* adj1 (renal or kidney*) adj1 impair*).tw,kw.	67
94	kidney diseases/ and (chronic* or long-term* or longterm* or longlast* or long-last* or longstand* or long-stand* or perpetual* or lifelong* or life-long* or endstage* or end-stage* or permanent* or progressive* or advanced).tw,kw.	6755
95	((renal or kidney*) adj1 replacement therap*).tw,kw.	23181
96	((renal* or kidney* or renovasc* or reno-vasc* or neph*) adj5 (chronic* or long-term* or longterm* or longlast* or long-last* or longstand* or long-stand* or perpetual* or lifelong* or life-long* or endstage* or end-stage* or osteodystroph* or osteo-dystroph* or permanent* or progressive*).tw,kw.	223635
97	(ckd or esrd).tw,kw.	77491
98	(IHD or SLED or CRRT).tw,kw.	13653
99	exp renal replacement therapy/	190897
100	or/88-99	733095
101	100 not (63 or 64) [Exclude Animal Studies]	682583
102	42 and 101 [GROUP 5 - Special Population: Critically Ill, CF, Advanced Kidney Impairment, excluding animal studies]	358
103	54 or 66 or 74 or 87 or 102 [All Groups]	1119
104	42 not 103 [ALL NOT LOOKED AT IN SPECIFIC GROUPS]	295
105	54 [GROUP 1 Beta Lactams, other agents & prolonged infusions & PK/PD]	611
106	66 [GROUP 2 Clinical Outcomes]	669
107	74 [GROUP 3 Therapeutic drug monitoring]	768
108	87 [GROUP 4 - Special Population: parenteral antibiotics, obesity & pediatrics]	384
109	102 [GROUP 5 - Special Population: Critically Ill, CF, Advanced Kidney Impairment]	358

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#1	(beta lactam* or b-lactam*):ti,ab,kw	1313
#2	(ESBL or ESBLE or "CTX M" or CTXM or SHV or TEM):ti,ab,kw	756
#3	(carbapen* or carba-pem*):ti,ab,kw	537
#4	("ici 194660" or mepem* or meronem* or mero-pen* or meropen* or merrem* or "sm 7338" or sm7338):ti,ab,kw	653
#5	(Archifar or Bironem or Caronem or Elpenem or Enem or Eradix or Grambiot or Lanmer or Mabapenem or Mapenem or Mecapem or Meflupin or Melopen or Menem or Mepenar or Mero or Merobac or Merofen or Merogram or Meromax or Meronia or Merop or Meropedem or Meropevex or Merosan or Merosayz or Merovex or Meroxi or Merozan or Merozen or Monem or Myron or Nemmed or Newropenem or Optinem or Penomer or Pisapem or Pospnenem or Romenem or Ronem or Ropen or Tripenem or Zakster or Zaxter or Zeropenem):ti,ab,kw	40
#6	(ertapen* or erta-pen* or invanoz or invanz or "I 749345" or "I749345" or "mk 0826" or "mk 826" or "mk0826" or "mk826" or "zd 4433" or "zd4433"):ti,ab,kw	214
#7	(imipen* or imi-pen* or formiminothienamyc* or imipemid* or "mk 0787" or "mk 787" or mk0787 or mk787 or formamidylthienamyc* or formimidoylthienamyc* or thienamyc*):ti,ab,kw	878
#8	(Anipen or Arzobema or Bacquire or Bacquire or Bidinam or Cilanem or Cilapenem or Cispenam or Imenam or Imiclast or Iminam or Iminem or Iminen or Imivex or Inem or Minem or Nemcis or Nimedine or Pelascap or Pelastin or Penam or Plastin or Premax or Prepenem or Primax or Primaxin or Sianem or Supernem or Supranem or Talispnem or Tenacid or Tiaktam or Tienam or Tiesilan or Timipen or Tipem or Tiyenam or Vexpinam or Xerxes or Zienam):ti,ab,kw	43

#9	(N-F-Thienamycin or N-Formimidoylthienamycin or Cilastatin or Imipemide or RAN-imipenem-cilastatin or "I 642957" or I642957 or "mk 0791" or mk0791 or mk 791 or mk791 or "7 [(2 amino 2 carboxyethyl)thio] 2 (2,2 dimethylcyclopropanecarboxamido) 2 heptenoic acid" or "s [6 carboxy 6 [(2,2 dimethylcyclopropyl)carboxamido] 5 hexenyl]cysteine" or "s [6 carboxy 6 [(2,2 dimethylcyclopropyl)carbonyl]amino] 5 hexenyl] levo cysteine"):ti,ab,kw	429
#10	("mk 797" or mk797 or "pelastin iv" or prepenem or tenacid or tienam or zienam):ti,ab,kw	21
#11	(doribax or doripen* or finibax or "s 4661" or "s4661"):ti,ab,kw	91
#12	(penicillin* or amdinocillin* or cyclacillin* or methicillin* or nafcillin* or nafcil or oxacillin* or cloxacillin* or dicloxacillin* or floxacillin* or sulbactam* or ticarcillin* or caprolactam* or macrocyclic lactam*):ti,ab,kw	5839
#13	(cephalosporin* or cephalosporanic* or cefamandole* or cefazolin* or cefdinir* or cefepim* or cefonicid* or cefsulodin* or Ceftibuten* or cefuroxime* or cephacetril* or cephalixin* or cephaloridin* or cephamycin*):ti,ab,kw	5111
#14	((pip* NEAR/5 taz*) or (piptaz* or tazocel* or tazocillin* or tazocin* or tazonam* or tazopril* or yp14 or "yp 14" or zosyn*)):ti,ab,kw	587
#15	((("cl 298741" or cl298741 or "cl 307579" or cl307579 or tazobac* or "ytr 830" or "ytr 830h" or ytr830 or ytr830h) and (acopex or avocin or "cl 227 193" or "cl 227193" or "cl227 193" or cl227193 or cypercil or hishiyaclorin or ivacin or "penicillanic acid" or pentocillin or pentocillin or picillin* or pipcil or piperacil* or piperacin or piperilline or pipracil* or pipracin or pipraks or pipril or piprilin or pitamycin or "t 1220" or t1220 or taiperacillin)):ti,ab,kw	589
#16	(monobactam* or aztreonam* or ceftarolin* or cefiderocol*):ti,ab,kw	495
#17	(amoxicillin* or "26787-78-0" or "26889-93-0" or "34642-78-9" or "544y3d6myh" or "61336-70-7" or "804826j2hu" or "9em05410q9" or "actimoxi" or Amoxil or "brl 2333" or brl2333 or clamoxyl* or hydroxyampicillin* or penamox* or polymox* or trimox* or wymox* or amox? clav* or amox* potassium clav* or augmentin* or "brl 25000" or brl25000 or clavulin* or "co amoxiclav*" or coamoxiclav* or spektramox or synulox):ti,ab,kw	7390
#18	(Ampito or Astaz-P or Aurotaz or Betamycin or Co-Tazo or Jeita or Pipertaz or Piptabac or Pletzolyn or Prizma or Pybactam or Sixacin or Tabaxin or Tasovak or Tazar or Tazepen or Tazin or Tazobak or Tazomax or Tazopen or Tazoperan or Tazopip or Tazopril or Tazorex or Tazosyn or Tazpen or Tebranic or Vigocid or Zobaction or Zopercin or Zopertsyn):ti,ab,kw	1
#19	(ampicillin* or azlocillin* or mezlocillin* or pivampicillin* or talampicillin*):ti,ab,kw	2141
#20	(ceftazidim* or cefidericol or cefotaxim* or cefixim* or cefmenoxim* or cefotiam* or ceftizoxime* or ceftriaxon* or ceftobiprol* or ceftolozan* or cloxacillin* or dicloxacillin* or floxacillin* or flucloxacillin* or vaborbactam* or relebactam* or avibactam* or benzylpenicillin*):ti,ab,kw	4426
#21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	21448
#22	((prolong* or extend* or continuous* or continual* or constant) NEAR/5 infus*):ti,ab,kw	13110
#23	((prolong* or extend*) NEAR/4 (intravenous* or intra-venous*)):ti,ab,kw	234
#24	#22 OR #23	13292
#25	#21 AND #24	331
#26	((((prolong* or extend* or continu* or constant) NEAR/5 infus*) AND (beta lactam* or b-lactam* or anti-biot* or antibiot* or ampicillin* or aztreonam or benzylpenicillin or cefazolin* or cefepime or cefidericol or cefotaxim* or ceftarolin* or ceftazidim* or avibactam* or ceftobiprol* or ceftolozan* or tazobactam* or ceftriaxone or cloxacillin* or dicloxacillin* or floxacillin* or doripenem* or ertapenem* or flucloxacillin* or imipenem* or cilastatin* or relebactam* or meropenem* or vaborbactam* or nafcillin* or oxacillin or piperacillin* or penicillin* or cephalosporin* or carbapenem* or monobactam* or ceftarolin*)):ti	134
#27	#25 OR #26	336
#28	#25 OR #26 in Trials	334
#29	(pharmacokinetic* or pharmaco-kinetic* or pharmacodyn* or pharmaco-dyn* or "PK/PD" or (drug* NEAR/1 kinetic*)):ti,ab,kw	80447
#30	(absorption* or bioaccumulation* or bio-accumulation* or auc or area under curve* or biological availability* or biotransformation* or biotransformation* or drug* liberation* or therapeutic equivalency or tissue distribution*):ti,ab,kw	54386
#31	(metabolic NEAR/1 (activation or inactivation* or detoxication* or de-toxication*)):ti,ab,kw	201
#32	((cutaneous or hepatobiliary or intestin* or lacrimal or lacteal or pulmon* or renal or salivar*) NEAR/1 elimination*):ti,ab,kw	238
#33	minimum inhibitory concentration*:ti,ab,kw	1179
#34	#28 AND (#29 OR #30 OR #31 OR #32 OR #33)	184
#35	((drug*) NEAR/2 (monitor* or therap* or stability or storage)):ti,ab,kw	386520
#36	#28 AND #35	169

#37	(outcome* or clinical or mortalit* or death* or survival or cure):ti,ab,kw	1045925
#38	(complicat* or failure* or sequelae or severit* or morbidit* or safe or safety or side effect* or undesirable effect* or tolerabilit*):ti,ab,kw	616079
#39	((adverse) NEAR/1 (effect or effects or reaction or reactions or event or events)):ti,ab,kw	246317
#40	#28 AND (#37 OR #38 OR #39)	287
#41	parenteral*:ti,ab,kw	10533
#42	((elastomeric* or infusion* or perfusion? or smart) NEAR/3 pump?):ti,ab,kw	1967
#43	(obes* or overweight* or over-weigh* or superobes*):ti,ab,kw	44837
#44	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatri* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween):ti,ab,kw	291269
#45	#28 AND (339 OR #42 OR #43 OR 42)	49
#46	((cystic NEAR/1 fibrosis) or (fibrocystic NEAR/1 disease*) or mucoviscidosis):ti,ab,kw	5578
#47	(advanced* NEAR/1 (renal or kidney*) NEAR/1 impair*):ti,ab,kw	5
#48	((renal or kidney*) NEAR/1 replacement therap*):ti,ab,kw	2204
#49	((renal* or kidney* or renovasc* or reno-vasc* or neph*) NEAR/5 (chronic* or long-term* or longterm* or longlast* or long-last* or longstand* or long-stand* or perpetual* or lifelong* or life-long* or endstage* or end-stage* or osteodystroph* or osteo-dystroph* or permanent* or progressive*)):ti,ab,kw	18843
#50	(ckd or esrd):ti,ab,kw	6520
#51	(IHD or SLED or CRRT):ti,ab,kw	934
#52	#28 AND (#46 OR #47 OR #48 OR #49 OR #50 OR #51)	35
#53	#34 OR #36 OR #40 OR #45 OR #52	324
#54	#28 NOT #53	10