Dose optimization of β-lactams antibiotics in pediatrics and adults: A systematic review

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Background: β-lactams remain the cornerstone of the empirical therapy to treat various bacterial infections. This systematic review aimed to analyze the data describing the dosing regimen of β-lactams.

Methods: Systematic scientific and grey literature was performed in accordance with Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The studies were retrieved and screened on the basis of pre-defined exclusion and inclusion criteria. The cohort studies, randomized controlled trials (RCT) and case reports that reported the dosing schedule of β-lactams are included in this study.

Results: A total of 52 studies met the inclusion criteria, of which 40 were cohort studies, 2 were case reports and 10 were RCTs. The majority of the studies (34/52) studied the pharmacokinetic (PK) parameters of a drug. A total of 20 studies proposed dosing schedule in pediatrics while 32 studies proposed dosing regimen among adults. Piperacillin (12/52) and Meropenem (11/52) were the most commonly used β-lactams used in hospitalized patients. As per available evidence, continuous infusion is considered as the most appropriate mode of administration to optimize the safety and efficacy of the treatment and improve the clinical outcomes.
Introduction

In the past few years, increasing trend of antibiotic resistance challenges the efficacy of currently available antibiotics. It is because of the global dissemination of multi-drug resistant (MDR) microorganisms causing more than 23,000 death annually in the United States (Pacios et al., 2020). The higher mortality rates associated with methicillin-resistant Staphylococcus aureus (MRSA) were observed in East Africa (Wangai et al., 2019). A study reported that about 96,000 patients were died due to MDR infection in Southern Asia (Khan et al., 2016). Similarly, the morbidity rates associated with MDR are also high, particularly in low- and middle-income countries (LMICs) due to lack of resources, inadequate microbiological testing methods and treatment interventions (Atif et al., 2020). According to the Centers of Disease Control and Prevention (CDC), the economic burden associated with drug-resistant infections estimated US$3.5 billion annually (Caron et al., 2010). One of the major causes for the spread of these infections is the injudicious use of antibiotics. The injudicious use of antibiotics can contribute to increased mortality, morbidity, and overall healthcare costs (Lesprit and Brun-Buisson, 2008). The use of unnecessarily broad-spectrum antibiotics is common in empirical as well as targeted therapy (Mettler et al., 2007). Many healthcare professionals have limited knowledge regarding antibiotic use and resistance and do not follow guidelines. Expert-based strategies and policies regarding the initiation and implementation of an antibiotic stewardship program (ASP) are recommended by different organizations such as World Health Organization (WHO), CDC, and Infectious Diseases Society of America (IDSA) (van Limburg et al., 2014; Gross et al., 2019).

Antibiotic stewardship program (ASP) is one of the main effective approaches to promote the rational use of antibiotics and combat antibiotic resistance. ASP also helps to optimize the treatment of infectious diseases, improve prescribing behavior, ensure cost-effective therapy, minimize the side effects related to antibiotic use, including resistance (Pollack and Srinivasan, 2014). Lee and his colleagues implemented ASP in children’s hospital that results in the reduction of antibiotic acquisition costs of about US$200,000 (Lee et al., 2017). Data published on ASP in intensive care units have demonstrated significant improvement in antibiotic consumptions (Kaki et al., 2011; Haseeb et al., 2020; Haseeb et al., 2021a; Alghamdi et al., 2021). To optimize the antibiotic use, many strategies in ASP intervention including identification of patient with bacterial infection, appropriate selection of treatment using pharmacokinetics-pharmacodynamic (PK-PD) characteristic to optimize the antibiotic dosing and modalities, de-escalation of antibiotics and shortening of therapy duration were employed (Luyt et al., 2014).

Dose optimization includes optimization of antibiotic dosing based on patient characteristics (e.g., weight, age, renal/liver function), PK-PD parameters of the drug (e.g., concentration or time-dependent activity), and causative microorganisms (Haseeb et al., 2021b; Haseeb et al., 2022). An appropriate dosing is the mainstay of antibiotic therapy, which intensifies the PK and PD profiles of drugs and has a huge impact on therapeutic outcomes, dose-dependent toxicity as well as the emergence of antibiotic resistance (He et al., 2020). For instance, administering single dose of aminoglycosides instead of multiple doses not only improve bacterial eradication but also reduces the risk of ototoxicity and nephrotoxicity. The continuous infusion or prolonged/extended infusion of β-lactams instead of administering bolus is recommended as an advanced dose optimization strategy. This strategy not only improves therapeutic outcomes but also reduce the mortality rates for all patients infected with resistant pathogens. Multisite studies reported that for some particular antibiotics, PD profiles can be assessed to improve the efficacy by changing the mode of administration (Felton et al., 2012; Georges et al., 2012; Falagas et al., 2013). The awareness regarding how dosing strategies are employed is needed for the selection of appropriate antibiotics (Roberts et al., 2014).

The selection of dosing regimen for antibiotics are usually based on summary endpoints such as PK/PD indices and point estimates of effect in terms of MIC. Multisite studies documented that antibiotics have been categorized in accordance with the relationship between effect and three PK/PD indices: 1) the ratio of the maximal unbound (free) drug concentration to MIC (fCmax/MIC), 2) the ratio of area under the drug-concentration-time curve to the MIC (AUC/MIC), or 3) the percentage of a 24-h time interval that unbound drug concentration exceeds to MIC (f>MIC) (Andes and Craig, 2002; MacGowan and Bowker, 2002; Nielsen et al., 2011). These indices are commonly utilized as targets in the dose selection process. In
Monte Carlo simulations, between-patient variability in PK-PD parameters is considered and the probability of the target attainment (PTA) is estimated on the basis of stochastic simulations from the model (Mouton et al., 2004; Owens Jr et al., 2005). On the basis of existing literature, the activities of β-lactams antibiotics have been categorized as being dependent on the $f_T$/MIC (Leggett et al., 1989; Gustafsson et al., 2001).

β-lactams (penicillins, cephalosporins and carbapenems) are broad-spectrum antibiotics that are used widely to treat various bacterial infections in healthcare settings particularly in intensive care units (ICUs) and may be targeted by antibiotic stewardship initiatives (Masich et al., 2018b). Optimal treatment needs appropriate dosage, modes of administration and dosing schedules (Delattre et al., 2017). The clinician’s knowledge concerning dose optimization of β-lactams is broadened but still faces some issues in implementing dosing-based approaches (Grupper et al., 2016). The initiation and implementation ASP and guidelines for β-lactams can improve the clinical outcomes and decrease the spread or emergence of antibiotic resistance (Hammond et al., 2019). Therefore, optimization of antibiotic therapy is an important consideration for clinician worldwide (Cotta et al., 2015). This systematic review was aimed to assess the data describing the dose optimization of β-lactams.

Materials and methods

Data sources and searches

We performed systematic scientific and grey literature search according to Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines from October 2021 to January 2022 (Moher et al., 2015). Two independent approaches were followed. Comprehensive grey literature and peer-reviewed literature were performed independently by two reviewers. The reference lists of the relevant articles and related reviews were also searched manually for additional studies. Complementary research was also performed to identify the most recent studies. The search items included “antibiotic” or “dose optimization” or “pharmacokinetic” or “pharmacodynamic” or “drug administration” or “β-lactams” or “penicillins” or “cephalosporins” or “carbapenems” or “ampicillin,” “amoxicillin,” or “piperacillin,” or “ceftriaxone” or “cefuroxime” or “cefixime” or “ceftaroline” or “ceftazidime” or “meropenem” or imipenem” or “doripenem” or “astreneram.”

Inclusion and exclusion criteria

All the studies found were reviewed for eligibility. The studies retrieved from the aforementioned search strategies were combined and duplicates were removed. Full-text articles on dose optimization of antibiotics were included in this review. The inclusion criteria include articles written in English and published in peer-reviewed journals. Articles published after 2000 were included in this review to ensure the current dosing recommendation. However, the exclusion criteria were review articles, letters to editor, animal studies, no full-text availability, conference abstracts, and in vitro studies. Two reviewers screened titles and abstracts as per eligibility criteria to identify potential publications independently at first. Then full-text was assessed for final inclusion. The disagreements were resolved by discussion between 2 reviewers or by consulting third reviewers. The type of studies included were cohort study, case reports and randomized controlled trial (RCT).

Quality assessment

The quality assessment was carried out using New Castle-Ottawa Scale (NOS) scale for cohort studies and Cochrane bias tool for randomized controlled trials. The NOS scale categorizes the data into three subscales, i.e., selection, comparability and outcomes (Wells et al., 2014). However, the Cochrane assessment tool validates the randomized controlled studies (RCT) by assessing the risk of bias in each study (Higgins et al., 2019). This tool is structured into domains (random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data and other bias) through which bias of each included study might be introduced in the results. The judgment is generally based on “high risk,” “low risk” and “unclear.” Each article was independently assessed by two experts. Reviewers compared their results and differences were then sorted by discussion.

Data extraction

The data was extracted from text, table and graph from each included study and was recorded in the pre-specified data collection form. This customized data form includes the following information; study characteristics (author’s name, year of publication, design, and sample size), patient characteristics (patient clinical condition, prescribed antibiotics, dosing regimen, outcomes of interests, and dosing recommendation). Data extraction was completed by one reviewer and it was then reviewed by another reviewer. Disagreements were addressed by discussion between two reviewers or consultation with the third reviewer if necessary.
| Antibiotics + clavulanic acid | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameters | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-----------------------------|----------------|---------|--------------|-------------|-----------------------------|----------------|--------------|-----------------------------------------------------|----------------------|
| Amoxicillin + clavulanic acid | De Cock et al. (2015) | Belgium | Cohort | 50 | Patients with mixed conditions | 25–30 mg/kg every 6 h intravenously | Amoxicillin CI (17.97 L/h/70 kg), V1 (9.07 L/70 kg)/V2 (5.43 L/kg), V3 (11.24 L/kg) Clavulanic acid CI (12.20 L/h/70 kg), V (11.60 L/70 kg), V2 (9.8 L/kg) | For prophylaxis The clinical failure rate was 32%; for treatment it was 34.4% | 25 mg/kg every 4 h intravenously. 1-h infusion was preferred to bolus dosing for patients with augmented renal function | (Continued on following page) |
| Antibiotics and dose | Author and Year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameters | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|----------------------|----------------|---------|--------------|-------------|-----------------------------|----------------|--------------|------------------------------------------------|---------------------|
| Piperacillin + tazobactam | Béranger et al. (2019) | France | Cohort, PK population model | 50 | Patients with pneumonia, peritonitis, BSI, mediastinitis, UTIs, skin abscess | 300 mg/kg/day, intermittent infusions every 6 h | Half-life (0.9 h); Cl (2.6 L/hr/70 kg); Vd (4.6 L/70 kg) | Extended or continuous infusions attained PK targets (50% fT [MIC] or 100% fT [MIC]), 100 mg/kg every 6 h administered as a 3-h prolonged infusion achieved 77.7% PTA and 400 mg/kg administered as a 24-h continuous infusion achieved 74.8% PTA | Continuous or extended infusions were the most adequate administration regimens for treatment of various infection |
| Piperacillin + tazobactam | Cies et al. (2014) | Pennsylvania | Cohort | 13 | Patients with febrile neutropenia, pneumonia, burn, sepsis, enterocolitis | 400 mg/kg/day in 4 divided doses | Vp (0.262 + 0.177 L/kg); Vc (0.249 L/kg); Vd (0.511 L/kg); Cl (0.296 L/kg); Half-life (1.39 ± 0.62 h) | 100 mg/kg every 6 h administered as a 3-h prolonged infusion or as continuous infusion 400 mg/kg/day in continuous or extended infusions, for children with augmented renal clearance | |
| Piperacillin + tazobactam | Nichols et al. (2016) | United States | Cohort | 12 | Patients with pneumonia, VAP, sepsis, typhilitis | 100/12.5 mg/kg TID infused over 4 h | Piperacillin Cmax (11.9 + 3.63 mg/L); Cmin (5.55 + 11.0 mg/L); Cl (0.22 + 0.07 L/hr/kg); Vd (0.43 + 0.16 L/kg) Tazobactum Cmax (17.6 mg/L); Cmin (2.4 + 2.0 mg/L); Cl (0.19 + 0.007 L/hr/kg); Vd (0.37 + 0.14 L/kg) | All extended-infusion dose regimens achieved PTAs of > 90% at MICs of <16 mg/L. Only the 3-h infusion regimens given every 6 h achieved PTAs of > 90% at an MIC of 32 mg/L | The doses of above 80/10 mg/kg given every 8 h and infused over 4 h achieve adequate PD targets in critically pediatrics |
| Piperacillin + tazobactam | De Cock et al. (2017) | Belgium | Cohort, Pharmacokinetic study | 47 | Patients with TRIs, GIT, burns, postoperative, oncology, neurological disorders | 300 mg/kg/day in 4 doses, infusion in 3–30 min | Piperacillin Cl (0.25 L/kg/h); V1 (0.13 L/kg); V2 (0.11 L/kg) Tazobactum Cl (0.13 L/kg/h); V1 (0.13 L/kg); V2 (0.11 L/kg) | For intermittent dosing regimens the PTA was of 90% (75 mg/kg piperacillin every 4 h, infusion over 2 h, 100 mg/kg every 4 h over 1 or 2 h). For continuous dosing regimens, PTA was 100% after loading dose | A loading dose of 75 mg/kg over 1 h followed by continuous infusion 300–450 mg/day is recommended |

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| Antibiotics | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameters | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-------------|-----------------|---------|--------------|-------------|-----------------------------|----------------|--------------|------------------------------------------------|----------------------|
| Cefazolin   | Cies et al. (2019) | United States | Cohort, prospective open-label pharmacokinetic study | 41 | Patients with perioperative surgical prophylaxis | 25 mg/kg as a bolus over 5 min within 60 min of the first surgical incision and an additional 25 mg/kg dose to a maximum of 1,000 mg was added to the CPB priming solution | Birth–6 months CL 0.009 ml/min/kg; Vd 0.598 L/kg; 7 months–3 years CL 0.01 ml/min/kg; Vd 0.786 L/kg; 4–16 years CL (0.007 ml/min/kg); Vd (3.4 L/kg) | - | mixing cefazolin in the CPB circuit priming solution was effective in maintaining cefazolin serum concentrations during surgery |
| Cefazolin   | De Cock et al. (2016) | Belgium | Cohort, prospective pharmacokinetic study | 56 | Patients with Cardiac surgery | 25 mg/kg with maximum of 2000 mg/dose, IV as a bolus, 4 doses in total before, during and after surgery | CI (0.229 L/h/kg); V1 (0.284 L/kg); V2 (0.351 L/kg) | The study dosing regimen was between 62% and 70% achieved PD targets during surgery and 89–98% after surgery while the PTA of proposed regimen was 88–99% | The dosing regimen (40 mg/kg, 30 min before surgical incision; 20 mg/kg, at start of CPB; 20 mg/kg, at the start of rewarming on CPB; 40 mg/kg, 8 h after the third dose; 40 mg/kg 8 h after the fourth dose) was considered effective undergoing cardiac surgery |
| Cefotaxime  | Béranger et al. (2018) | France | Cohort | 64 | Patients with mixed conditions | 100 mg/kg/day–300 mg/kg/day in 4 doses, in patients > 50 kg the adult dose of 3 d 1,000 mg was Used | CI (14.7 L/h/kg); Vd (21.4 L); t½ (0.34–1.15 h) | The PTA was 100% using dosing regimen 100 mg/kg/day as continuous infusion | 100 mg/kg/day as continuous infusion is recommended |
| Cefotaxime  | Hartman et al. (2019) | Nederland | RCT | 37 | Patients with Meningococcal septic shock | 100–150 mg/kg/day in 3–4 doses | - | PTA ranged from 14.7% for MIC 16 mg/L to 95.6% for MIC of 0.125 mg/L | Not given |
| Ceftaroline | Cies et al. (2018b) | Pennsylvania | Cohort | 7 | Patient with MRSA infections | 60 mg/kg/day (1 patient with 54 mg/kg/day) in 4 doses | Vd (0.17–0.84 L/kg); CI (1.57–6.11 ml/min/kg); t½ (0.98–2 h); k (0.50.33–0.64 h) | All patients needed a dose alteration or non-standard dose to reach the target of fT > 4–6 × MIC 40% | For bloodstream infections, pneumonia, and meningitis with MRSA, dosing every 6 h is advised. For patients with increased Vd, a dose of 15 mg/kg is advised |

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TABLE 1 (Continued) Dose optimization of β-lactams among pediatrics.

| Antibiotics   | Author and year | Country       | Study design          | Sample size | Characteristics of patients | Dosing practice | Pk parameters | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|---------------|-----------------|---------------|-----------------------|-------------|-----------------------------|----------------|---------------|-------------------------------------------------|-----------------------|
| Cefuroxime    | Olguin et al. (2008) | Mexico        | Cohort                | 11          | Patients with septicemia and septic shock | 100 mg/kg every 6 h by intravenous infusion for 30 min | Control Vd (1.5 L/kg), Cl (0.55 L/kg/h); AUC (116.4 µg/ml/h) severely ill Vd (1.6 L/kg); Cl (0.48 L/kg/h); AUC (121.6 µg/ml/h) very severely ill Vd (3.1 L/kg); Cl (1.87 L/kg/h); AUC (190.7 µg/ml/h) | - | Not given |
| Ceftriaxone   | Fukumoto et al. (2009) | Japan         | Cohort                | 21          | Patients with pneumonia     | 50 mg/kg/day, intravenously at a constant rate about 60-min period | Cpeak (546 µg/ml); Ctrough (25.0 µg/ml); Half-life (4.87 h); Vd (0.128 L/kg), Cl (0.0179 L/h/kg) | - | - |
| Ceftriaxone   | Khan et al. (2020)   | China         | Cohort Open-label pharmacokinetic study | 99          | Patients with CAP           | 50–100 mg/kg once a day (QD) or two times a day (BID) over 30 min as intravenous infusion | At a steady state, Cl (0.03 L/h/kg); Vd (0.16 L/kg), AUC0–24 (460.42291.3 mg*h/L) | Using 60% ft > MIC as the PD target, the PTA was 99.4% for dosing regimen 50 mg/kg QD; 51.2% for 50 mg/kg QD; 100% for 75 mg/kg BID; 68.9% for 75 mg/kg QD; 100% for 100 mg/kg BID; 81.8% for 100 mg/kg QD. | The administration of ceftriaxone once daily to pediatric population with pneumonia was shown to be effective bacteriologically as well and pharmacokinetically A dosing regimen of 100 mg/kg every 24 h produced satisfactory target attainment rates |
| Carbapenems   | Giannoni et al. (2006) | Switzerland   | Cohort                | 19          | Patient with mixed conditions | 100 mg/kg/day in 3–4 doses, qh8 and qh6 infusion in 30 min | after first dose: T1/2 (1.22 h ± 0.47), Cl (0.27 L/kg/h ± 0.11), Vd (0.42 L/kg ± 0.13), Vss (0.30 ± 0.1) Steady state T1/2 (1.35 h ± 0.38), Cl (0.34 L/kg/h ± 0.14), Vd (0.64 L/kg ± 0.3), Vss (0.46 ± 0.25) | The dose regimen (100 mg/kg/day) prescribed by the physicians ensured a T1/2 > MIC of 70%–100% for all recovered pathogens except the methicillin-resistant S epidermidis isolate | The higher-range dose of 100 mg/kg/day was uniformly appropriate over the whole pediatric population tested, irrespective of the q8h or q6h administration schedule |

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| Antibiotics | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameters | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-------------|----------------|---------|--------------|-------------|-----------------------------|----------------|--------------|--------------------------------------------------|----------------------|
| Meropenem   | Cies et al. (2015) | Pennsylvania | Case report | 1 | Patient with Ventriculitis | 40 mg/kg intravenously every 6 h, infused over 30 min | Intermittent dosingCp (12 μg/ml after 2 h) Ccsf (1 μg/ml after 2 h and 0.5 μg/ml after 4 h) Continuous dosingCp (15 μg/ml), Ccsf (0.5 μg/ml) | Continuous infusion gave PTA of 100% | The continuous-infusion dosing regimen allowed for 100% PTA in the serum and CSF and a successful clinical outcome |
| Meropenem   | Cies et al. (2017b) | Pennsylvania | Cohort | 9 | mixed | 40 mg/kg/day to 160 mg/kg/day over 2–4 doses, infusion in 30 min 1 patient received continuous dosing of 200 mg/kg/day 1 patient received 100 mg/kg/day in 2 doses with prolonged infusion of 4 h | Meropenem Cl: 6.99 ml/kg/min ± 2.5Vc: 0.57 L/kg ± 0.47Kcp: 2.512 h⁻¹ ± 1.449Kpc: 3.268 h⁻¹ ± 1.667Total Vd 0.78 L/kg ± 0.73 | Target: fT > MIC 40% and 80% for MICs from 0.03–32 mg/L PTA of 90% defined as optimal |
| Meropenem   | Tan et al. (2018) | Singapore | prospective single-center, pharmacokinetic study | 9 | Patients with sepsis | 40 mg/kg q12 h over a 30 min infusion | Cl: (0.091 L/h/kg), half-life (3.98) | 32% patients achieve PD targets by using standard dose regimen (of 40 mg/kg/dose q12 h over a 30 mins infusion) while 90% of patient achieved 100%/T>MIC using dose (20 mg/kg q8h over 4-h infusion or 40 mg/kg q8h over 2-h infusion) | 20 mg/kg dose q8h over a 4-h infusion or 40 mg/kg q8h over 2-h infusion gives optimal antibiotic coverage for susceptible pathogens |

Cl: Clearance, V1: volume of distribution in central compartment, V2: volume of distribution in peripheral compartment, Vd: Volume of distribution, Cmax: maximum concentration of drug, Cmin AUC: area under curve, t1/2 = half-life, MIC: minimum inhibitory concentration, T>MIC: time above minimum inhibitory concentration, TID: three times a day, BID: two times a day, OD: once daily, Ke: Elimination rate constant, PK: Pharmacokinetic, PD: Pharmacodynamic, CPB: Cardiopulmonary bypass, BSI: Blood stream infections, UTI: Urinary tract infections, PTA: Probability of target attainment, VAP: Ventilator-acquired pneumonia, CAP: Community acquired pneumonia, GIT: Gastrointestinal tract infections.
Results

Characteristics of selected studies

Of the 1,136 relevant published articles identified, 181 articles were initially proved eligible after duplicates were removed and abstracts screened. Various articles were retrieved from reference lists of the selected studies, other systematic reviews, and personal files. Majority of the studies were excluded some are Monte Carlo simulation studies where there were no patients involved. Of 127 articles, the data were not retrieved from 23 articles, therefore, excluded. After screening of articles, 104 articles met the eligibility criteria. A total of 52 studies were excluded due to following reasons: inappropriate intervention (N = 12), literature reviews (N = 6), non-English (N = 7), no full-text available (N = 9), and non-β-lactams (N = 18). The 52 articles met the inclusion criteria for this systematic review. The PRISMA flow diagram for studies selection is shown in Figure 1. Data extraction was performed for 47 full text articles with data on β-lactams. A complete list of all 47 articles and extracted Pk-data is presented in Tables 1, 2. All the 47 articles included were published in English of which 12 were RCT and 18 were cohort studies. The quality of case reports was not assessed because no validated tool is available. Therefore, we used Joanna Briggs institute (JBI) critical checklist for case reports (Ma et al., 2020).

Dose optimization of β-lactams in pediatrics

A total of twenty studies were reported among pediatrics (Table 1). Of 20 studies, eight studies were reported on penicillins
| Antibiotics                  | Author and year                | Country       | Study design | Sample size | Characteristics of patients                                                                 | Dosing practice                                                                 | Pk parameter                                                                 | Patients achieving targets (PAT)/Clinical outcomes                                                                 | Dosing recommendation                                                                                   |
|-----------------------------|--------------------------------|---------------|--------------|-------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Penicillins                 |                                |               |              |             |                                                                                                |                                                                                 |                                                                                  |                                                                                                                                                                           |                                                                                                                                                           |
| Temocillin                  | Laterre et al. (2015)          | Belgium       | RCT          | 32          | Patients with intra-abdominal and LRTIs                                                                                                                  | Loading dose: 750 mg followed by continuous infusion of 750 mg/24 h             | CI (3.69 L/h/kg); V1 (14.0 L); V2 (21.7 L); AUC0-24 (1764 mg.h/L); Cmax (170 mg/L); Cmin (51 mg/L) | A target of 80% fT > MIC was achieved using MIC of 16 mg/L                                                                     | The dosing regimen of 6 g OD by CI improve PK/PD target using a MIC of 16 mg/L                                                                                   |
| Ampicillin + sulbactam      | Yokoyama et al. (2015)         | Japan         | Cohort       | 8           | Patients undergoing cardiovascular surgery with CBP                                                                                                        | 1 g every 3, 4, 6 and 12 h                                                     | Vd (15.8 L); ke (0.505 h⁻¹); half-life (1.52 h); CI (7.72 L/h)                                                                 | -                                                                                                                                                            | Dosing interval should be adjusted to optimize the efficacy and safety of treatment                                                                             |
| Ampicillin + sulbactam      | Yokoyama et al. (2016)         | Japan         | Cohort       | 5           | Anuric dialysis patients undergoing cardiac surgery                                                                                                        | 1 g every 3, 4, 6 and 12 h                                                     | Vd (8.9 L); ke (0.18 h⁻¹); half-life (4.23 h); CI (1.69 L/h)                                                                 | -                                                                                                                                                            | Dose should be given IV every 12 h to maintain a free drug concentration of more than 12 µg/ml                                                              |
| Piperacillin and tazobactum | Dow et al. (2011)              | Wisconsin     | Retrospective cohort | 129        | Patients with UTIs, pulmonary, BSIs and intra-abdominal infections                                                                                      | Piperacillin-tazobactam infused over 4 hCrCl > 20 ml/min; 3.375 g IV every 8 hCrCl ≤ 20 ml/min; 3.375 g IV every 12 hHemodialysis/ peritoneal dialysis; 3.375 g IV every 12 h | -                                                                                   | -                                                                                                                                                            | The utilization of prolonged infusions demonstrated the favorable outcomes                                                                                   |
| Piperacillin and tazobactum | Yost and Cappelletty, (2011)   | Ohio          | Retrospective cohort | 359        | Patients with UTIs, BSIs, RIs and skin and soft tissues infections                                                                                        | 4.5 g every 12 h as a 30-min infusion; 3.375 g every 8 h as a 4-h infusion; 3.375 g every 12 h as a 4-h infusion | -                                                                                   | -                                                                                                                                                            | PD dosing using extended-infusion piperacillin + tazobactam improves the clinical outcomes                                                      |
| Piperacillin and tazobactum | Lodise et al. (2007)           | United States | Cohort       | 194         | Patients with pseudomonas aeruginosa infections                                                                                                          | Group I:II (3.375 g intravenously for 30 min every 4 or 6 h)Group II:II (3.375 g intravenously for 4 h every 8 h) | -                                                                                   | A 50% fT > MIC was achieved using dosing regimen 4-h infusion of 3.375 g of piperacillin-tazobactam administered intravenously every 8 h | The II of drug showed to be more effective over Iı dosing regimen                                                                                 |

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TABLE 2 (Continued) Dose optimization of β-lactams among adults.

| Antibiotics     | Author and year       | Country  | Study design | Sample size | Characteristics of patients                                                                 | Dosing practice                                                                 | Pk parameter                                                                 | Patients achieving targets (PAT)/Clinical outcomes                                                                 | Dosing recommendation                                                                 |
|-----------------|-----------------------|----------|--------------|-------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Piperacillin     | Sime et al. (2015b)   | Australia| RCT          | 39          | Febrile neutropenic patients with hematological malignancies                                 | 4.5 g of piperacillin/tazobactam every 8 h or every 6 h                        |                                                                              | 1st TDM 22% patients achieved 100% \(T > MIC\) and 38% patients achieved 50% \(T > MIC\) 2nd TDM 69% of intervention patients and 19% of control patients attained 100% \(T > MIC\), and 15/16 (94%) of intervention patients versus 5/16 (31%) of control patients achieved 50% \(T > MIC\). 3rd TDM, the proportion of patients attaining 100% \(T > MIC\) in 73% patients in the intervention group and 7% in the control group | TDM provides useful feedback of dosing adequacy to guide dose optimization |
| Piperacillin-    | Roberts et al. (2010) | Australia| Cohort       | 16          | Patients with sepsis                                                                          | Piperacillin dose For bolus 229 mg/kg/day For continuous 168 mg/kg/day          | BolusCmax (266.6 mg/L), Cmin (7.2 mg/L), Cmin (day 2) 6.2 mg/L, ContinuousCmax (144 mg/L), Cmin (day 1) 7.1 mg/L, Cmin (day 2) 21.2 mg/L | The PTA was 93% using 16 g/day by CI and 53% using bolus dosing (4 g every 6 h) | The administration of piperacillin by CI achieved PD targets                   |
| tazobactam      |                       |          |              |             |                                                                                                |                                                                              |                                                                              |                                                                                 |                                                                                  |
| Lorente et al.  | (2009)                | Spain    | cohort       | 87          | Patients with VAP                                                                            | II (4.0/5.5 g infused over 30 min every 6 h) CI (LD 4.0/5.5 g over 30 min, followed by 4.0/5.5 g infused over 360 min every 6 h) | -                                                                            | The %T>MIC was 100% for a MIC ≤ 16 mg/L for CI, the %T>MIC for II was 100% for a MIC ≤ 2 mg/L, 90% for a MIC of 4 mg/L, 70% for a MIC of 8 mg/L and 55% for a MIC of 16 mg/L | Both doses (16/2 g and 12/1.5 g) achieve serum concentrations far above the 35–40 mg/L threshold |
| Wael et al. (2014)  | Belgium, RCT          |          |              | 49          | Patients’ pneumonia CAP, HAP, Tracheobronchitis RSI, Peritonitis, Febrile neutropenia         | LD (4 g infused over 30 min, followed by EI dose of either antibiotic (4 g PTZ) at 6-h (PTZ) dosing interval. EI doses were administered over 3 h | -                                                                            | 94.7% of the intervention patients achieved 100% \(T > MIC\) as compared to control groups (68.4%). For the target of 100 % \(T > 4xMIC\), PTA rates were higher in the intervention group | A strategy of dose optimization based on daily TDM results in an increase in PK/PD target attainment compared to conventional dosing |

(Continued on following page)
TABLE 2 (Continued) Dose optimization of β-lactams among adults.

| Antibiotics | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameter | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-------------|----------------|---------|--------------|-------------|-----------------------------|----------------|--------------|---------------------------------|---------------------|
| Piperacillin | De Waele et al. (2014a) | Belgium | RCT | 33 | Patient with normal renal functions | LD (1 g meropenem or 4 g piperacillin) administered over 30 min, followed by EI dose of either antibiotic (4 g PTZ) at 6-h (PTZ) dosing intervals. EI doses were administered over 3 h | Extended infusion Cmax (76.2 mg/L); Cmin (14.7 mg/L); CI (13.2 L/h); Vd (0.33 L/kg); Bolus infusion Cmax (240.2 mg/L); Cmin (5.9 mg/L); CI (16.2 L/h); Vd (0.36 L/kg) | Compared to bolus infusion, ∫ T>MIC using extended infusion was higher for i.e. 96% compared to 77% for piperacillin | EI led to improved PK/PD target attainment |

Cephalosporins

| Cefuroxime | Carlier et al. (2014) | Belgium | RCT | 20 | Patients with pulmonary infections | II (1.5 g infused every 8 h or 1.5 g every 6 h); CILD 750 mg over 0.5 h constant infusion over 24 h 4.5 g over 24 h; 7.5 g over 24 h; 9.0 g over 24 h | Fixed effects CL (9.0 L/h); V convicted (10.5 L); Vp (12.0 L); intercompartmental CL (16.7 L/h); Random effects, CL (28.0 L/h); Vd (23.7 L); Vp (29.5 L) | The standard dose of 1.5 g TID leads to an 87% PTA for patients with a Cl Cr of 50 ml/min and organism MIC of 8 mg/L | - |

| Cefazidime | Cousson et al. (2015) | France | RCT | 34 | Patients with Ventilator-associated pneumonia | CI (LD of 20 mg/kg followed by 60 mg/kg/day); II (20 mg/kg over 30 min every 8 h) | For CI Vd (0.4 L/kg); AUC0-48 (1.348 mg.h/L); For II Cmax (95 mg/L); Cmin (6 mg/L); V (0.3 L/kg); AUC0-48 (1.361 mg.h/L) | CI presents PK/PD advantages and predictable efficacy | - |

| Cefazidime | Nicolau et al. (2001) | United States | RCT | 35 | Patients with nosocomial infection | CI (3 g/day); II (2 g every 8 h) | - | CI presents optimal PD targets in terms of efficacy | - |

| Cefazidime | Lorente et al. (2007) | Spain | Retrospective, cohort | 121 | Patients with VAP | II (2 g infused over 30 min every 12 h); CI (LD of 1 g over 30 min followed by 2 g infused over 720 min every 12 h) | - | The mean time that Cp of ceftazidime increased the MIC was higher for CI (100%) than for II (99.8%, 69.0%, and 47.6% for susceptible, intermediate, and resistant strains, respectively); Cefazidime administered by continuous infusion had greater clinical efficacy than ceftazidime administered by intermittent infusion | - |

(Continued on following page)
| Antibiotics | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameter | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-------------|-----------------|---------|--------------|-------------|-----------------------------|----------------|--------------|------------------------------------------------|---------------------|
| Ceftazidime | Buijk et al. (2002) | Netherlands | RCT and non RCT | 18 | Patients with peritonitis | For non RCT: 1 g IV loading dose followed 4.5 g IV continuous infusion or RCT: 1 g IV followed by 4.5 g IV continuous infusion as above or 1.5 g IV bolus TDS for 10 days | Serum RCT AUC0-24 (1,131 mg.h/L); CL (4.1 L/h); Non-RCT: Cmax (88.7 mg/L); AUCO-24 (1,064 mg.h/L); Vd (0.279 L/kg); Half-life (4.2 h); CL (5.1 L/h) | CI resulted in mean serum concentration >40 mg/L and a T4xMIC for most pathogens encountered in severe IAI due to >90% of the course of the therapy both serum and peritoneal exudate | CI resulted in more favorable concentration in serum and peritoneal exudate |
| Ceftazidime | Hanes et al. (2000) | United States | Cohort | 31 | Patients with nosocomial pneumonia | 2 g intravenously every 8 hours 2 g an intravenous bolus followed by 60 mg/kg per day as a continuous intravenous infusion | For continuous ceftazidime Cmax (19.2 mg/ml); Cl (2.45 ± 0.76 L/h) for intermittent Cmax (44.3 mg/ml); Cmin (3.7 6 mg/ml); V (0.32 + 0.14 L); Half-life (1.72 + 0.71 h); Cl (2.33 + 1.06 L/h) | Both the CI and II dosing regimen maintained drug concentrations above the MIC 100% of the dosing interval in all patients | Both CI and II dosing regimens were equally effective to treat nosocomial pneumonia |
| Cefepime | Chapuis et al. (2010) | Switzerland | Cohort | 91 | Patients with mixed conditions | 2 g every 12 h for CLcr ≥ 50 ml/min IV; 2 g every 24 h or 36 h for CLcr < 50 ml/min IV | 1st dose Cmax (105 ± 22 mg/L); Cmin (7.6 ± 2 mg/L); V (0.513 ± 0.180 L/kg); Vss (0.413 ± 0.118 L/kg); AUC (370 ± 360 mg.h/L); Half-life (4.03 ± 3.19 h); Steady state Cmax (97 ± 8 mg/L); Cmin (2.68 ± 3.06 mg/L); Vb (0.513 ± 0.80 L/kg); Vss (0.413 ± 0.118 L/kg); AUC (226 ± 107 mg.h/L); Half-life (4.33 ± 4.32 h) | All study population had appropriate duration of cefepime concentrations above the MIC (T>MIC>50%) for the pathogens recovered (MIC ≤ 4 mg/L), but only 45–65% of them had appropriate coverage for potential pathogens using MIC > 8 mg/L | The dose of 2 g every 12 h provides the safety and efficacy window in patients with a CLcr ≥ 50 ml/min infected by pathogens with cefepime MICs ≤ 4 mg/L |
| Ceftriaxone | Joynt et al. (2001) | Hong Kong | Cohort | 12 | Patients with pneumonia, septic shock, sepsis, bacteremia | 2 g OD as an infusion over 30 min | Cmax (204.9 mg/L); Vc (5.9 L); Vss (19.9 L); Cl (41.3 ml/min); | - | Decrease in dosing interval or CI should be evaluated further in patients with normal renal function |
| Ceftriaxone | Jason et al., 2007 | Australia | RCT | 57 | Patients with sepsis | 2 g administered once a day as a bolus 2 g as a 24 h infusion | - | - | Improvement in the primary endpoints in terms of efficacy was observed for patients receiving CI for 4 or more days |

(Continued on following page)
TABLE 2 (Continued) Dose optimization of β-lactams among adults.

| Antibiotics | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameter | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-------------|-----------------|---------|--------------|-------------|----------------------------|-----------------|--------------|---------------------------------------------------|-----------------------|
| Ceftriaxone And Cefepime (Lodise et al., 2007b) | Lodise et al. (2007) | Germany | Cohort | 14 | Patients with extracerebral infections | Ceftriaxone 2 g IV q12 h and cefepime 2 g IV q8h | - | For ceftriaxone, The PTA of achieving 50% and 100% ∫T>MIC in the CSF were 76% and 65% respectively. For cefepime, the PTA at 50% and 100% ∫T>MIC in the CSF was 91.8% and 82%, respectively | The CSF PD against S. pneumoniae for cefepime were superior to that of ceftriaxone |
| Cefpirome Kang et al. (2020) | Kang et al. (2020) | Republic of Korea | Cohort | 15 | Patients receiving Extracorporeal oxygenation | 2 g cefpirome every 12 h (q12 h) as an intravenous bolus injection | Based model population estimateCl (3.6 L/h); Vc (10.3 L); Vp (19.5 L) | 2 g cefpirome q8h (6 g/day) for IV bolus or 2 g every 12 h for EI over 4 h is recommended | |
| Carbapenems | | | | | | | | |
| Meropenem Dow et al. (2011b) | Rebekka et al., 2011 | United States | Cohort, Retrospective | 121 | Patients with UTIs, pulmonary, SIs and intra-abdominal infections | Meropenem infused over 3 hClCr > 36 ml/min (500 mg IV every 6 h); ClCr 26–35 ml/min (500 mg IV every 8 h); ClCr 10–25 ml/min (500 mg IV every 12 h); ClCr 10 ml/min (500 mg IV every 24 h); Hemodialysis/peritoneal dialysis (500 mg every 24 h) | - | The mean drug exposures (% T>MIC) above the MICs of 4 and 1 mg/L of 47.27% and 71.44% of the dosage interval | The prolonged infusions showed to be effective and improve clinical outcomes in critically ill patients |
| Meropenem Yokoyama et al. (2018) | Yokoyama et al. (2018) | Japan | Cohort | 4 | Patients receiving hemodialfiltration | 0.5 g OD (1 h infusion) | Vd (15.80 L); CLnon-I-HDF (1.05 ± 0.27 L/h); CLI-HDF (5.78 ± 1.03 L/h) | Dosing regimens of 0.25 g OD for a MIC of 8 mg/ml and of 0.5 g once daily for a MIC of 16 mg/ml achieved 40% T>MIC | 0.5 g OD is considered an appropriate regimen for empirical treatment |
| Meropenem Crandon et al. (2011) | Crandon et al. (2011) | United States | Cohort | 21 | Patient with VAP | 0.5 g q6h (0.5 h inf)1 g q8h (0.5 h inf)2 g q8h (0.5 h inf)2 g q8h (3 h inf) | - | At MICs up to 8 mg/L, the PTA using 40% T>MIC was 96%, 90%, and 61% for 3 h infusions of 2 g q8h, 1 g q8h, and 1 g q12 h in patients with ClCr ≥50, 30–49, and 10–29 | Meropenem doses of 2 g every 8 h (3 h infusion) were required to achieve predictable PTA against MICs ≥8 μg/ml | (Continued on following page)
| Antibiotics | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameter | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-------------|----------------|---------|--------------|-------------|-----------------------------|----------------|--------------|------------------------------------------------|----------------------|
| Meropenem   | Lorente et al. (2006) | Spain   | Cohort       | 89          | Patient with VAP             | CI (1 g over 360 min every 6 h (1 g over 30 min every 6 h) | -             | The group receiving CI showed greater clinical rate (90.47%) than another group receiving II (59.57%) | CI may have more clinical efficacy in the treatment of VAP. |
| Meropenem   | Lu et al. (2016)     | China   | Cohort       | 42          | Patients with post neurosurgery, meningitis | 1 g every 8 h (q8h)1 g q6h2 g q8h | Clc (22.2 L/h), Clp (1.79 L/h), Vc (17.9 L); Vp (3.84 L) | A 4-h infusion with a limited CSF drainage rate has a >90% probability of achieving 40% T>MIC for MICs of ≤8 mg/L. In CSF, it had a >90% PTA of achieving 50% and 100% T>MIC for MICs of ≤0.5 mg/L and ≤0.25 mg/L, and has a >80% PTA of achieving 50% and 100% T>MIC for MICs of ≤1 mg/L and ≤0.5 mg/L | 2 g every 8 h, administered as a 4-h infusion with a limited CSF drainage rate (less than 150 ml/day), may provide the highest possibility of target attainment |
| Meropenem   | Kothekar et al. (2020) | India   | Cohort       | 25          | Patients with severe sepsis and septic shock | 1,000 mg as a 3 h Extended Infusion (Q8H) | Day 1Cmax (15.36 µg/ml); AUC (57.92 µg/h/ml); Half-life (1.31 h); Cl (17.26 L/h); Vd (32.61 L) Day 3Cmax (14.14 µg/ml); AUC (43.82 µg-h/ml); Half-life (0.6 h); Cl (22.86 L/h); Vd (19.83 L) | 100% patients achieved targets of 40% fT>MIC while 66.7% patients achieved targets of 40% fT >2×MIC | It requires a bolus of 500 mg followed by El of 1,500 mg Q8H. While fT > 8 µg/ml > 40 require escalation of El dose, fT > 4 µg/ml = 100 and fT > 8 µg/ml = 100 require escalation of both El dose and frequency |
| Meropenem   | Cheatham et al. (2008) | Indiana | Prospective, open-label, steady-state pharmacokinetic study | 20          | Patients with bacterial infection | 30-min infusions of meropenem 500 mg every 6 h (group 1) every 8 h (group 2)every 12 h (group 3) | Group 1Cmax (29.2 µg/ml); Cmin (2.4 µg/ml); Half-life (2.5 h); Cl (10.7 L/h); AUC (49.1 µg-h/ml); V (29.3 L) Group 2Cmax (33.2 µg/ml); Cmin (3.8 µg/ml); Half-life (3.4 h); Cl (6.4 L/hr); AUC (86.2 µg-h/ml); V (23.8 L) Group 3Cmax (133.5 µg/ml); Cmin (4.9 µg/ml); Half-life (6.1 h); Cl (3.7 L/hr); AUC (140.2 µg-h/ml); V (0.38 L) | At 40% T>MIC, the PTA was 90.2%, 95.6%, and 99.5% for groups 1, 2, and 3, respectively | PD analysis suggest that regimens of meropenem 500 mg every 6, 8, or 12 h, adjusted for renal function, are sustainable for treatment of infectious diseases |
| Antibiotics | Author and year | Country | Study design | Sample size | Characteristics of patients | Dosing practice | Pk parameter | Patients achieving targets (PAT)/Clinical outcomes | Dosing recommendation |
|-------------|----------------|---------|--------------|-------------|-----------------------------|----------------|-------------|------------------------------------------------|----------------------|
| Meropenem   | De Waele et al. (2014a) | Belgium | RCT         | 33          | Patient with renal function | LD 1 g followed EI dose of 1 g every 8 hours; EI doses are administered over 3 h | Extended infusion | Cmax (17 mg/L); Cmin (14.7 mg/L); Cl (15.9 L/hr); Vd (0.39 L/kg); Bolus infusion; Cmax (85.2 mg/L); Cl (15.7 L/hr); Vd (0.24 L/kg) | Compared to bolus infusion, $fT_{MIC}$ using EI was higher for 82% compared to 51% | EI led to improved PK/PD target attainment |
| Imipenem    | Sakka et al. (2007) | Germany | RCT         | 20          | Patients with nosocomial pneumonia | LD of 1 g/1 g imipenem and cilastatin (as a short-term infusion) followed by 2 g/2 g imipenem-cilastatin per 24 h as a CI for 3 days | - | - | II of 1 g q8h had a 90% PTA for achieving $fT_{MIC}$ of 20% at MIC of 8 mg/L, while this was 4 mg/L for the $fT_{MIC}$ target of 30% and 1–2 mg/L for the $fT_{MIC}$ target of 40% (88% probability at 2 mg/L). For CI, all three targets were achieved at the 90% probability level at an MIC of 2–4 mg/L (86% at 4 mg/L) | It provides robust coverage for the most common nosocomial pathogens when administered either in II or CI. |
| Doripenem   | Hsaiky et al. (2013) | United States | Cohort study | 200         | Patients with pneumonia, SSTIs, intraabdominal infections | Clcr > 50 ml/min (500 mg every 8 h); Clcr 30 ml/min or more to 50 ml/min or less (250 mg every 8 h); Clcr 10–30 ml/min (125 mg every 12 h); Clcr less than 10 ml/min (500 mg after hemodialysis) | - | - | The PTA of 100% for serum and presumed ELF concentration above the MIC for at least 40% of the dosing interval | Doripenem should be administered via prolonged infusion when required |
| Aztreonem   | Cies et al. (2017a) | United States | Case report  | 1           | Patient with injury, chronic respiratory failure, and a tracheostomy | 2 g IV every 6 h (each dose infused over 4 h) and polymyxin B 1,000,000 units IV every 12 h (each dose infused over 30 min) on 3rd day | - | - | A prolonged infusion regimen of aztreonam 2 g every 6 h (each dose infused over 4 h) was effective in this complex patient with MDR P aeruginosa empyema | - |

Cl: Clearance, V1: volume of distribution in central compartment, V2: volume of distribution in peripheral compartment, Vd: Volume of distribution, Cmax: maximum concentration of drug, Cmin AUC: Area under curve, $t_{1/2}$: half-life, MIC: Minimum inhibitory concentration, LD: Loading dose, TID: three times a day, BID: Two times a day, OD: once daily, Ke: Elimination rate constant, PK: Pharmacokinetic, PD: Pharmacodynamic, CPB: Cardiopulmonary bypass, BSI: Blood stream infections, UTI: Urinary tract infections, PTA: Probability of target attainment, VAP: Ventilator-acquired pneumonia, CAP: Community acquired pneumonia, GIT: Gastrointestinal tract infections, LRTIs: Lower respiratory tract infections, MDR: Multi-drug resistant, Clcr: Creatinine clearance, SSTIs: Skin and Soft tissue infections, HAP: Hospital-acquired pneumonia, TDM: Therapeutic drug monitoring, RCT: Randomized Controlled Trials, CI: continuous infusion, II: Intermittent infusion, EI: Extended infusion.
| References                              | Selection | Comparability of cohort studies on basis of design | Outcomes | Adequacy of follow-up | Quality score |
|----------------------------------------|-----------|---------------------------------------------------|----------|-----------------------|--------------|
| Tang et al. (2019)                     | *         | *                                                 | *        | *                     | 7            |
| Wu et al. (2021)                       | *         | *                                                 | *        | *                     | 7            |
| D’Agate et al. (2020)                  | *         | *                                                 | *        | *                     | 7            |
| De Cock et al. (2015)                  | *         | *                                                 | *        | *                     | 7            |
| Agathe Béranger et al. (2019)          | *         | *                                                 | *        | *                     | 7            |
| Cies et al. (2014)                     | *         | *                                                 | *        | *                     | 7            |
| Nichols et al. (2016)                  | *         | *                                                 | *        | *                     | 7            |
| De Cock et al. (2017)                  | *         | *                                                 | *        | *                     | 7            |
| Cies et al. (2019)                     | *         | *                                                 | *        | *                     | 7            |
| De Cock et al. (2016)                  | *         | *                                                 | *        | *                     | 7            |
| Olgui et al. (2008)                    | *         | *                                                 | *        | *                     | 6            |
| Fukumoto et al. (2009)                 | *         | *                                                 | *        | *                     | 6            |
| Khan et al. (2020)                     | *         | *                                                 | *        | *                     | 7            |
| Giannoni et al. (2006)                 | *         | *                                                 | *        | *                     | 7            |
| Tan et al. (2018)                      | *         | *                                                 | *        | *                     | 7            |
| Yokoyama et al. (2015)                 | *         | *                                                 | *        | *                     | 6            |

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TABLE 3 (Continued) Quality assessment of cohort studies.

| References                        | Selection | Representaive of exposed studies | Selection of non-exposed studies | Ascertainment of exposure | Demonstration of outcome | Comparability of cohort studies on basis of design | Outcomes | Adequacy of follow-up | Quality score |
|-----------------------------------|-----------|----------------------------------|----------------------------------|---------------------------|-------------------------|-----------------------------------------------|----------|-----------------------|--------------|
| Yokoyama et al. (2016)            | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 6            |
| Yokoyama et al. (2016)            |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Dow et al. (2011)                 | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 8            |
| Dow et al. (2011)                 |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Yost & Cappelletty, (2011)        | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Yost and Cappelletty, (2011)      |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Lodise et al. (2007)              | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 8            |
| Lodise et al. (2007a)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| J. A. Roberts et al., 2010        | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Roberts et al. (2010)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Lorente et al. (2009)             | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 8            |
| Lorente et al. (2009)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Lorente et al. (2007)             | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 8            |
| Lorente et al. (2007)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Buijk et al. (2002)               | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Buijk et al. (2002)               |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Hanes et al. (2000)               | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Hanes et al. (2000)               |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Chapuis et al. (2010)             | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Chapuis et al. (2010)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Joynt et al. (2001)               | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Joynt et al. (2001)               |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Lodise et al. (2007)              | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Lodise et al. (2007b)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Kang et al. (2020)                | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Kang et al. (2020)                |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Yokoyama et al. (2018)            | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 8            |
| Yokoyama et al. (2018)            |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Crandon et al. (2011)             | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Crandon et al. (2011)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Lorente et al. (2006)             | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 8            |
| Lorente et al. (2006)             |           |                                  |                                   |                           |                         |                                                |          |                       |              |
| Lu et al. (2016)                  | *         | *                                | -                                | -                         | -                       | **                                            | *        | *                     | 7            |
| Lu et al. (2016)                  |           |                                  |                                   |                           |                         |                                                |          |                       |              |

(Continued on following page)
| References                     | Selection                                                                 | Comparability                                                                  | Outcomes                                                                 |
|-------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|
|                               | Representative of exposed studies<sup>a</sup> | Selection of non-exposed<sup>b</sup> | Ascertainment of exposure<sup>c</sup> | Demonstration of outcome<sup>d</sup> | Comparability of cohort studies on basis of design<sup>e</sup> | Assessment of outcomes<sup>f</sup> | Adequacy of follow-up<sup>g</sup> | Quality score |
| Kothekar et al. (2020)        | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 7            |
| Kothekar et al. (2020)        | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 7            |
| Cheatham et al. (2008)        | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 7            |
| Cheatham et al. (2008)        | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 7            |
| Hsaiky et al. (2013)          | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 7            |
| Cies et al. (2017)            | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 7            |
| Cies et al. (2017a)           | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 7            |
| Cies et al. (2018)            | *                                                                         | *                                                                             | *                                                                          | *                                                                          | *                                                                             | *                                                             | *                                                             | 8            |

<sup>a</sup> * = truly representative or somewhat representative of average in target population.
<sup>b</sup> * = Drawn from the same community.
<sup>c</sup> * = Secured record or structured review.
<sup>d</sup> * = Yes, - = No.
<sup>e</sup> * = Study controls for age, gender, and other factors.
<sup>f</sup> * = Record linkage or blind assessment, ** = Both.
<sup>g</sup> * = follow-up of all subjects.
Cies et al., 2014; De Cock et al., 2015; Nichols et al., 2016; De Cock et al., 2016; Cies et al., 2018a; Béranger et al., 2018; Cies et al., 2019; Hartman et al., 2019) and 4 on caripenem (Giannoni et al., 2006; Cies et al., 2015; Cies et al., 2017b; Tan et al., 2018). Four studies were reported on amoxicillin (De Cock et al., 2015; Tang et al., 2019; D’Agate et al., 2020; Wu et al., 2021). The normal dose for amoxicillin in selected studies ranged from 25 mg/kg to 125 mg/kg. Wu and his colleagues recommended to use other broad-spectrum antibiotic instead of amoxicillin for the treatment of E. coli infections. Another study reported that treatment of dose (25 mg/kg every 6 h) of amoxicillin + clavulanic acid was stopped due to clinical failure in critically ill pediatrics with augmented renal functions (De Cock et al., 2015). The dose optimization and PK/PD parameters of piperacillin/tazobactam were discussed in four cohort studies (Cies et al., 2014; Nichols et al., 2016; De Cock et al., 2017; Béranger et al., 2019). The recommended dose of piperacillin range was from 150 mg/kg to 450 mg/kg. The continuous or extended infusion of piperacillin was shown to be effective in terms of safety and efficacy. De Cock et al. reported that loading dose followed by continuous infusion may improve the PD targets (De Cock et al., 2017).

Two cohort studies on cefazolin were reported in pediatrics (De Cock et al., 2016; Cies et al., 2019). The authors proposed a dose of 25 mg/kg by assessing the PK parameters using the Monta Simulation Model. The authors recommended that
mixing cefazolin in the CPB circuit priming solution was effective in maintaining cefazolin serum concentration during surgery (De Cock et al., 2016). Two cefotaxime studies were included in this review (Béranger et al., 2018; Hartman et al., 2019). The recommended dose of cefotaxime ranges from 100 mg to 300 mg/kg as a continuous infusion that achieved 100% probability target attainment (PTA). Olguin et al. (2008) studied the PK parameters of cefuroxime on 11 patients with septicemia and septic shock. The authors recommended the dose of 100 mg/kg of body weight, administered every 6 h by intravenous infusion for 30 min. Cies et al. (2018a) discussed the PK-PD characteristics of Ceftaroline on 7 patients with MRSA infection. In this study, majority of the patients did not require additional alteration to achieve target attainment while a dose of 15 mg/kg was recommended for patients with increased volume of distribution.

One cohort study was reported on imipenem (Giannoni et al., 2006). All patients using dose regimen 100 mg/kg/day reached $T > \text{MIC}$ of 70%–100% for all isolated pathogens except meticillin-resistant *staphylococcus epidermidis* pathogen. Three studies were found reporting meropenem using the same dose (40 mg/kg) in pediatrics (Cies et al., 2015; Cies et al., 2017b). However, these studies recommended the continuous dosing regimen resulted in effective therapy.

### Dose optimization of β-lactams in adults

A total of 32 studies were reported in adults, of which 11 articles were on penicillins (Lodise et al., 2007a; Lorente et al., 2009; Roberts et al., 2010; Dow et al., 2011b; Yost and Cappelletty, 2011; De Waele J. et al., 2014; De Waele J. J. et al., 2014; Sime F. B. et al., 2015; Laterre et al., 2015; Yokoyama et al., 2015; Yokoyama et al., 2016), 11 on cephalosporin (Hanes et al., 2000; Joynt et al., 2001; Nicolau et al., 2001; Buijk et al., 2002; Lodise et al., 2007b; Lorente et al., 2007; Roberts et al., 2007; Chapuis et al., 2010; Carlier et al., 2014; Cousson et al., 2015; Kang et al., 2020), 10 on carbapenems (Lorente et al., 2006; Sakka et al., 2007; Cheatham et al., 2008; Dow et al., 2011a; Crandon et al., 2011; Hsaiky et al., 2013; De Waele J. J. et al., 2014; Lu et al., 2016; Yokoyama et al., 2018; Kothekar et al., 2020) and 1 on other β-lactams (aztreonam) (Cies et al., 2017a) (Table 2). One randomized controlled trial was conducted on temocillin in patients with intra-abdominal and lower respiratory tract infections (Laterre et al., 2015). A target of 80% $T > \text{MIC}$ was reached for the mean population for a MIC of 16 mg/L and a target of around 40 was reached for the mean population for a MIC of 32 mg/L. Two cohort studies were performed on patients receiving ampicillin + sulbactam (Yokoyama et al., 2015; Yokoyama et al., 2016). The standard dose of 1 g/0.5 g intravenously seemed to be adequate in terms of efficacy. However, dosing intervals can be increased to optimize the safety and efficacy of the treatment. Six studies were documented on piperacillin with or without combination with tazobactam, out of which two are randomized controlled trials (RCT) (Lodise et al., 2007a; Lorente et al., 2009; Roberts et al., 2010; Dow et al., 2011b; Yost and Cappelletty, 2011; Sime F. B. et al., 2015). Most of the studies recommended the dose of piperacillin of 4.5 g every 6 h or 8 h infused over 30 min. The administration of piperacillin + tazobactam using extended or continuous infusion achieve superior PK/PD targets.

For ceftazidime, one RCT was reported (Carlier et al., 2014). The standard dose of ceftazidime prescribed by physicians was 1.5 g TID. Carrier et al. recommended that high-dose continuous infusion is more likely to reach PK/PD targets. The standard dose leads to 87% probability of target attainment (PTA) for patients with creatinine clearance (CLCr) of 50 ml/min and pathogen of MIC 8 mg/ml. Five studies were reported on cefazidime (Hanes et al., 2000; Nicolau et al., 2001; Buijk et al., 2002; Lorente et al., 2007; Cousson et al., 2015). All these studies recommended the continuous infusion regimen that presents PK/PD advantages and predictable efficacy. Lorente et al. (2007) reported that the meantime that plasma cefazidime concentration exceeded the MIC was higher for continuous infusion (100%) for susceptible, intermediate and resistant strains over intermittent infusion. Chapuis and his colleagues studied the PK/PD parameters of cefepime which identified a safety and efficacy window for a dose of 2 g every 12 h in patients with CLCr > 50 ml/min infected by pathogens with cefepime < 4 mg/ml. The dose of ceftriaxone included in three studies was 2 g once daily (Chapuis et al., 2010).

Eight studies were reported on dose optimization and PK/PD characteristics of meropenem (Lorente et al., 2006; Cheatham et al., 2008; Dow et al., 2011b; Crandon et al., 2011; De Waele J. J. et al., 2014; Lu et al., 2016; Yokoyama et al., 2018; Kothekar et al., 2020). In Cheatham et al. (2008) study, the PK/PD analysis recommended that dosing regimen of meropenem 500 mg every 6, 8, or 12 h, adjusted for the renal function is considered for treatment of various infection. Similarly, Kothekar et al. reported that dose optimization of meropenem is required in patients with severe sepsis and septic shock. The prescribed was 100 mg as 3 h extended infusion. The PTA was 100% at 40% $T > \text{MIC}$ and 66.7% at 40% $T > 2\times\text{MIC}$. Sakka et al. (2007) reported that imipenem-colistin provide robust coverage for most common nosocomial pathogens when administered either in intermittent or continuous infusion of 1 g q8h or in a continuous infusion of 2 g/day. Hsaiky et al. (2013) reported that doripenem should be administered via prolonged infusion regimen to optimize the efficacy of the treatment. The dose of aztreonam 2 g every 6 h was effective in patients with pseudomonas aeruginosa empyema (Cies et al., 2017a).

### Quality assessment

In NOS, a maximum of 13 stars assigned to each study. According to Agency for Healthcare Research and Quality (AHRQ) standards, a study who scored 3 or 5 stars in...
selection, 1 or 2 stars in comparability group and 2 or 3 stars in outcome groups is of good quality, study who scored 2 stars in selection domain, 1 or 2 stars in comparability domain and 2 or 3 stars in outcome domain is of fair quality, study who scored 0 or 1 start in selection group of 0 stars in comparability group or 0 or 1 star in outcome group is of poor quality. In this systematic review, out of 52 studies, 50 studies are of good quality and the remaining two studies are of fair quality (Table 3). The Cochrane bias tool assessed that all RCT studies are at lower risk of bias and all domains were discussed in Table 4. The two case reports included in the systematic review are of good quality (Table 5).

Discussion

Inappropriate antibiotic treatment is most often the result of inappropriate dose, delayed administration or more often an underestimation of current trends in resistance (Sulis et al., 2020). The bactericidal activity of antibiotics depends on the concentration of the drug with regards to the minimum inhibitory concentration (MIC) and the time that this exposure can be sustained (Kuti, 2016). The MIC represents the most fundamental PD measure for antibiotics against pathogens, presenting the potency of administered antibiotics (Onufrik et al., 2016). The dose optimization based on MIC would seem to provide rectification in the PD characteristics and target attainment (Hartman et al., 2020). However, the demerits using MIC values to optimize the dosing regimens were highlighted by Mouton et al. (2018). Therefore, MIC variation must be examined to avoid potential underdosing of the patient. Moreover, alteration in PK measure may affect the PD characteristics. In our systematic review, we have gathered information regarding the dosing pattern of β-lactams from 52 studies. The majority of the studies were carried out in intensive care units. Although antibiotic use is the cornerstone of intensive care treatment for critically ill patients with suspected infection (Pickens and Wunderink, 2019).

β-lactams include penicillins, cephalosporins, and carbapenems are widely used in the management and treatment of serious infection particularly in critically ill patients (Thakuria et al., 2013; Bozcal et al., 2017). All β-lactams showed time-dependent bactericidal activity, which is determined by the free antibiotic concentration-time above the MIC for microorganisms identified (% T>MIC) (Masich et al., 2018a; Pandey and Casella, 2020). The optimal clinical outcomes may differ depending on the β-lactams, for example, the target attainment goals for piperacillin + tazobactam, cephalosporins and carbapenems were 50% T>MIC, 60% T>MIC and 40% T>MIC, respectively (Masich et al., 2018a). Moreover, the maximal bactericidal activity can be achieved by increasing the drug levels i.e., four to five times above MIC, even so, the interaction to improved clinical outcomes is inconsistent. The specific percentage of dosing interval T>MIC needed for optimal activity differs for different β-lactam classes. The variation in percentages have been associated with variation in the rate of killing and the post-antibiotic effect. Majority of the studies documented the clinical pharmacodynamic parameters of β-lactams against gram-negative bacteria (Manduru et al., 1997; Tam et al., 2002). Several studies suggested that the amount of time the plasma concentration of the drug remains 4-6 fold greater than MIC has to be maintained for 100% of the dosing time period, however other studies have reported a target of 60% T>MIC depending on clinical outcome measures (clinical cure vs. reduced bacterial resistance) (Manduru et al., 1997; Tam et al., 2002; Crandon et al., 2010).

As per available evidence, the current knowledge of PK and target attainment is often suboptimal in patients following the standard dosing regimen of β-lactams. Most of the studies provide data on PK parameters (34/52). It is evident that changes in PK parameters occur in patients. Cies et al. (2018a) reported that volume of distribution was increased in 86% of patients and clearance was increased in 71% of patients receiving ceftaroline. Piperacillin (12/52) was the most commonly used β-lactams, followed by meropenem (11/52), and ceftazidime (5/52). Piperacillin and meropenem are widely used to treat various infections among the hospitalized patients because of their susceptibility against many gram-positive and gram-negative pathogens (Shah and Ryzner, 2013; Xu et al., 2019).

The common mode of administration of antibiotics recommended by many clinicians was intermittent intravenous administration (Kasiakou et al., 2005). However, optimal dosing strategies for the treatment of various infectious diseases remain controversial. Most of the β-lactams were administered as an intermittent bolus. However, on the basis of strong PK/PD data, the administration of antibiotics by continuous infusion is more effective than administration by intermittent infusion (Dulhunty et al., 2013). Many of included studies found that continuous or extended infusion increased the survival rates among hospitalized patients especially critically ill patients. The administration of β-lactams as continuous infusion increased blood and interstitial fluid concentration with greater time above the MIC as compared to intermittent dosing, especially for pathogens with MIC values, which are frequent in ICUs (Dulhunty et al., 2013). The potential benefits to patients as well as the healthcare system by implementing improved approaches of antibiotic delivery are substantial. In an era of increasingly expensive treatments, the administration of β-lactams are cost-effective in terms of drug costs and labor costs (Mouton and Vinks, 2007).

β-lactams are frequently recommended by international and national treatment guidelines, have been prescribed for various infectious diseases. Therefore, ASPs should be implemented that helps the clinicians to use antibiotic appropriately from a pharmacological point of view that means excluding the
pharmacological factors that potentially increase the risk of spread of resistance (Adembri et al., 2020). More accurately, antibiotics should be administered following PK/PD principles. When selecting the appropriate dosing regimen by keeping in view the PK/PD principles, the specified pathophysiological changes must be taken into consideration (Roberts et al., 2014). Moreover, multiple PK/PD software using a combination of TDM, Bayesian forecasting and PopPK can be utilized by pharmacists, clinical pharmacologists, and clinicians to maintain optimal target attainment (Abdulla et al., 2021). The guidelines on the use of TDM including an overview of suggested PD targets for several B-lactams antibiotics is also recommended by the French Society Anesthesia and Intensive Care Medicine (SFAR) (Guilhaumou et al., 2019). However, various softwares such as MIPD, NONMEM, MWP’HARM++, ID-ODS, InsightRx Nova and AutoKinetics are available, close collaboration between pharmacists and clinicians are required to implement this feature to optimize the patient target attainment (Sime F. et al., 2015; Kantasiripitak et al., 2020). Model-informed precision dosing (MIPD) is an emerging approach that improves TDM process. This approach estimates the PK variability utilizing population PK model and predict the probability of target attainment for various dosing regimen (Gijsen et al., 2022). Despite of its advantages and availability of softwares, adoption of MIPD in clinical settings has been limited to date (Neely et al., 2018; Frymoyer et al., 2020).

The present study has some limitation that should be acknowledged when evaluating the data from included studies. Firstly, this study used limited databases with specific focus on titles describing the dose optimization of β-lactams antibiotics as no quantitative analysis was carried out. Moreover, limited grey literature search was conducted using additional search terms that identified relevant data. Secondly, some studies included the co-administration of two or more β-lactams antibiotics may alter the PK/PD parameters of both drugs. Thirdly, the difficulty in the assessment of efficacy concerning MIC was observed due to under-reporting.

Conclusion

This systematic review showed that appropriate antibiotic therapy is challenging due to a wide range of pathophysiological change among different age groups. This challenging perspective requires close collaboration between clinicians, pharmacists and clinical pharmacologists to optimize the effective treatment and improve the clinical outcome. The PK/PK analysis can be utilized to support alternative dosing regimens such as increase in dosing interval, continuous infusion, and increased bolus doses. The current study aimed to inspire both researchers and clinicians to identify and resolve these differences, not only by elucidating PK/PD parameters, but also providing guidelines for implementation in the healthcare settings, as this data is important to optimize antibiotic treatment in patient populations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization, AH, HF, SA, MA, and AS; methodology, AH, SA, ME, SAA, AFA, and ZS; review, AH, SA, and ZS; analysis, AH, SAA, and AZ; resources, AH, ME, SAA, and NO; writing—original draft preparation, AH, NO, SAA, AM, SSA, AK, and NO; writing—review and editing, AS, ZS, HF, and AK; supervision, HF, MA, and AS; funding acquisition, AH, AFA, NO, ME, and HF. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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