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Original Research

Extended infusion versus intermittent infusion of Piperacillin/tazobactam: altering current methods to optimize future outcome

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Abstract

Due to worldwide bacterial resistance, researchers and clinicians were required to optimize existing antimicrobials by influencing the pharmacokinetics and pharmacodynamics (PK/PD) features. Piperacillin/tazobactam (PIP/TZB) is one of the most frequently empirical antibiotics prescribed globally. The aim of the review was to evaluate the use of an extended infusion (EI) versus an intermittent infusion (II) of PIP/TZB in hospital settings in terms of patient safety and efficacy. Several PK/PD studies assessed the use of an extended infusion of PIP/TZB to reach different minimum inhibitory concentration (MIC) levels for many microorganisms including *Pseudomonas aeruginosa*. One of the main parameters to define the size of the effect of PIP/TZB to various microorganisms is the percentage of time the free drug concentration above MIC (%fT > MIC). Many studies have compared extended infusion (EI) versus intermittent infusion (II) in terms of mortality rate, clinical cure or efficacy, length of stay whether in an intensive care unit (ICU) or hospital, duration of therapy, and cost. The clinical data reviewed in this article include PK/PD studies, prospective trials, systematic reviews, and meta-analysis. The review emphasized the role of an extended infusion in a population with altered pharmacokinetics including patients on continuous renal replacement therapy (CRRT), critically ill patients with augmented renal clearance, and patients with cystic fibrosis. Our review reports a positive trend when using an extended infusion of PIP/TZB which encourages the adoption and implementation of the extended infusion to achieve positive patient outcomes. Nevertheless, more studies are required to attain generalizable and reliable data to determine whether an extended infusion improves patient outcomes.

Keywords: piperacillin; tazobactam; infusion; antibiotics

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INTRODUCTION

Resistance to antimicrobials has emerged as a considerable threat in recent years, specifically in a hospital setting. Infections due to gram-negative bacilli are more problematic than other pathogens, due to the high mortality rate associated with resistant infections.[1] Known risk factors for the emergence of resistance include the inappropriate use of antimicrobials and poor infection prevention and control in healthcare settings.[2] Also noteworthy is the fact that the development of novel antibiotics has declined over the last decade, resulting in limited options for the treatment of infection.[3,4] The risk of multidrug-resistant and even pan-resistant bacterial pathogens is a global threat. As a management strategy, researchers and clinicians considered optimizing the existing antimicrobial medication by manipulating the pharmacokinetic and pharmacodynamic (PK/PD) features.[5,6] Beta-lactams are considered the cornerstone antibiotic for treating severe infections including nosocomial pathogens.[7] Manipulating the infusion time can enhance the bactericidal activity of beta-lactams by maintaining the drug levels above the minimum inhibitory concentration (MIC) for an extended period.[8] Extending the infusion time is a recommended strategy supported by the Antimicrobial Stewardship Guidelines developed by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) to maximize the use of the antimicrobial.[9,10] Piperacillin/tazobactam (PIP/TZB) received considerable attention among the beta-lactams due to its

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unique features as a broad-spectrum antibiotic, anaerobic coverage, and antipseudomonal activity.

PIP/TZB is the second most frequently prescribed empirical antibiotic after Vancomycin in more than 67 intensive care units in the United States (US).[11] Several studies evaluated the effect of altering the infusion time of PIP/TZB by comparing intermittent infusion (over 30 minutes) with extended infusion (≥3 hours).[3,12-14] However, continuous infusion (24 hours) of PIP/TZB is also an accepted method to optimize PK/PD features though it is not always practical for patients who have limited intravenous access or patients who require other multiple daily infusions.[13] High rates of mortality, partial clinical cure, and the emergence of further resistance are the primary clinical outcomes that can be prevented by extending the infusion time of PIP/TZB.[11,15-17] This is specifically considerable in critically ill patients who are more exposed to these outcomes than other populations. Advantages of this dosing strategy include a shorter duration of therapy as well as a shorter hospital and intensive care unit (ICU) length of stay which ultimately may reduce the cost of treatment.[18-23] This review aims to evaluate the use of the extended versus intermittent infusion of PIP/TZB in hospital settings.

METHODOLOGY

Literature search

A comprehensive search in PubMed and Scopus was performed to identify publications using the keywords piperacillin/tazobactam, Tazocin, Zosyn, extended OR prolonged, traditional OR intermittent OR conventional OR short, infusion. The period included was from January 1st, 1995 to December 31st, 2018. Figure 1 displays the selection process of the publications included.

Study selection

All English publications reporting the comparative outcomes of patients treated with an extended infusion (or any synonyms which define the extended infusion time of ≥ 3 hours) versus intermittent infusion (or any synonyms which define ≤ 30 minutes infusion time) of PIP/TZB was considered eligible for the analysis. The exclusion criteria were pediatrics, adolescent population, animals, and retrospective studies.

Pharmacokinetic and pharmacodynamic (PK/PD) parameters

The ability of antimicrobial drugs to reach the MIC for each targeted pathogen is the key to inhibit the growth of the microorganism through different mechanisms of action.[24] It is known that beta-lactams exhibit a time-dependent mechanism, including PIP/TZB.[8] A pharmacodynamic parameter has been developed to describe this mechanism of bacterial eradication. One of the main parameters to define the size of the effect of PIP/TZB on various microorganisms is %fT > MIC which is defined as the time the free (unbound) drug remains above the MIC.[25] For gram-negative bacteria specifically, a percentage of ≥ 50% is required to achieve near maximal killing, a lower percentage is sufficient for gram-positive microbes owing to the post-antibiotic effect (PAE).[26]

With using PIP/TZB for intra-abdominal infections, a significant decrease in the penetration (30% to 50%) of the gastrointestinal tract is noticed. Consequently, the risk of treatment failure will increase, particularly for more resistant organisms such as *Pseudomonas aeruginosa*.[25] For these and other reasons, extending the infusion time can improve or achieve clinical efficacy by reaching higher concentrations above MIC.[27] The main sources to obtain reliable MIC values for most of the pathogens are The Clinical and Laboratory Standards Institute (CLSI) and The European Committee On Antimicrobial

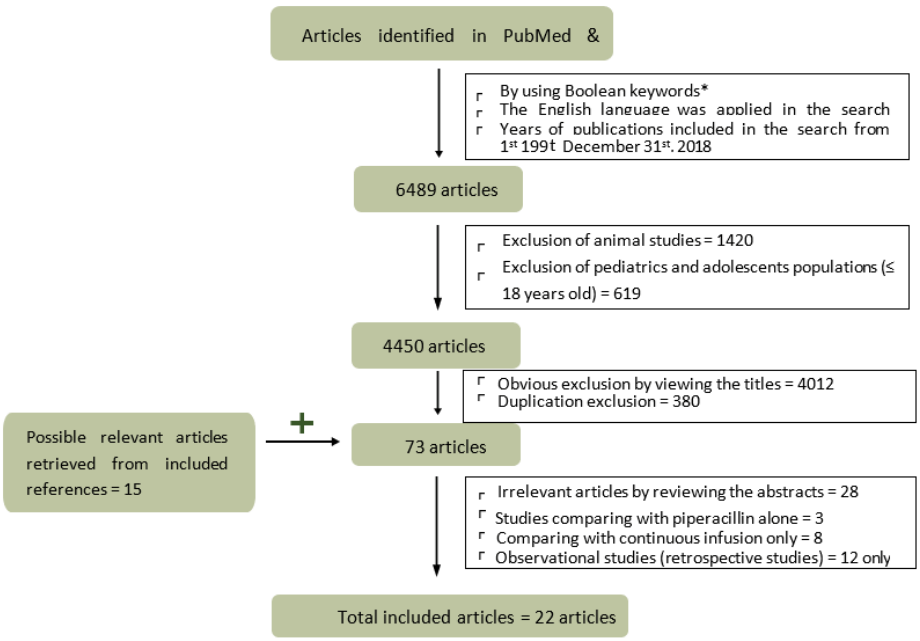

Figure 1.

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Susceptibility Testing (EUCAST).[28,29] Both the CLSI and EUCAST established that a concentration of ≥ 16 mg/L above MIC is required for the sensitivity of PIP/TZB against *P. aeruginosa* using an intermittent infusion (3.375 g every 6 hours). This however does not guarantee eradication of the pathogen, as higher concentrations above the MIC values are required to provide maximal killing. To investigate how extending the infusion time can affect the PK/PD features, population PK studies should be performed. Population PK studies are defined as the study of variability in drug concentration within a patient population receiving clinically relevant doses of a drug of interest.[30] Currently, population PK studies use the Monte Carlo simulation, a mathematical computer modeling simulation that integrates different PK/PD variables of antibiotics and their susceptibility among any microorganism.[31] This method offers a major advantage in estimating the likelihood of achieving the PK/PD targets. A concept frequently associated with Monte Carlo simulations is the probability of target attainment (PTA). A PTA of ≥ 90% indicates optimal clinical efficacy to reach certain MIC values.

Pharmacokinetics and Pharmacodynamics (PK/PD) studies

Four PK/PD studies were identified that investigated whether an extended infusion time will have a similar or better %fT > MIC percentage than an intermittent infusion using a PK model such as the Monte Carlo simulation.[32-34] The combined sample was 140 patients (Table 1). All included studies reported reaching a concentration above MIC value of 16 mg/L by using an extended infusion. The largest PK/PD study with a sample of 105 patients was done in Albany, New York and sought to examine the effect of an extended infusion of PIP/TZB on various levels of renal impairment. An extended infusion of 3.375 g for 4 hours infusion every 8 hours successfully achieved a concentration of ≤ 16 mg/L above MIC at three different creatinine clearance ranges (CrCl of 60, 40 and 20 ml/min) whereas an intermittent infusion with 3.375 g for 30 minutes every 6 hours only reached an MIC of 16 mg/L at (CrCl of 20 ml/min).[33] Another study by De Waele et al., reported that an extended infusion had a longer mean residence time (MRT) compared with an intermittent infusion in critically ill patients (extended infusion (EI) = 2.7 (2.6 - 2.8) vs. intermittent infusion (II) = 1.6 (1.4 - 1.7) *, p-value < 0.001). In three studies that reported MIC levels for *P. aeruginosa*, none of their extended regimens reached the susceptibility breakpoint.[32-35] * Data are reported as median with interquartile ranges.

Clinical trials and prospective studies

Observations and estimates from PK/PD models are often the basis for alternative dosing strategies that are assessed clinically through trials and prospective studies. Very few clinical studies were found evaluating the clinical outcomes of using an extended infusion for PIP/TZB as compared to an intermittent infusion. Multiple outcomes were investigated in these studies such as mortality rate, clinical cure or efficacy, length of stay whether in ICU or hospital, duration of therapy, and cost.[15,36-39]

The largest randomized clinical trial (RCT) was done in Hong Kong in 2017.[38] It was a single center, open-label trial that included 367 patients randomized in two groups, an extended infusion (EI) group, 182 patients = 4.5 g of PIP/TZB infused for 4 hours every 8 hours, and an intermittent infusion (II) group, 185 patients = 4.5 g of PIP/TZB infused for 30 minutes every 6 hours. The 14-day mortality rate was the primary outcome for this study. After performing a post hoc analysis, there was a significant reduction in the EI group in patients whose causing organisms were identified (9.3% in EI group vs. 22.4% in II group, p-value = 0.01) and in patients who were diagnosed with respiratory infections such as pneumonia (8.9% in EI group vs 18.7% in II group, p-value = 0.02). In addition, a numerical but not statistically significant reduction in mortality rate was also noticed in patients with *Pseudomonas* species infections (10% in EI group vs. 25.9% in II group, p-value = 0.17) possibly supporting the notion that an extended infusion is able to achieve high concentration levels compared to an intermittent infusion. In terms of secondary outcomes, a significant reduction in the time to reduce the body temperature to < 38.5°C within 24 hours was observed in the EI group (p-value = 0.01). Other secondary outcomes such as in-hospital mortality, duration of mechanical ventilation, and length of hospital/ICU stay, were not significantly different between the two groups

Table 1. Characteristics of PK/PD studies with MIC values

Study (Author, year)	Infusion Regimen			MIC Reference	MIC targets			
	Intermittent		Extended		MIC < 16		MIC ≥ 16	
(Katherine. M. Shea, 2009) (34)	3.375 g every 4 and 6 hours	4.5 g every 6 and 8 hours	2.25 g, 3.375 g, 4.5 g, and 6.75 g every 8 hours for 4-h infusion	CLSI	II: 3.375 g every 4 hours	EI: 3.375 – 4.5 g every 8 hours	II: 3.375 g every 4 hours	EI: 3.375-4.5 g every 8 hours
(N. Patel, 2010) (32)	4.5 g every 6 hours		3.375 g every 8 hours for 4 hours infusion	CLSI	II at CrCl ≤ 40 m//min	EI at CrCl ≤120 ml/min	II at CrCl ≤20 ml/min	EI at CrCl ≤ 60 ml/min
(T. W. Felton, 2012) (33)	4.5 g every 6 or 8 hours for 30 minutes infusion		4.5 g every 6 or 8 hours for 3 to 4 hours infusion	CLSI	EI		EI (every 6 hours for 3 hours infusion)	
(J.DE WAELE, 2014) (35)	4.5 g every 6 hours for 30 minutes		4.5 g every 6 hours for 3 hours infusion	EUCAST	II and EI		EI	

CLSI; The Clinical & Laboratory Standards Institute, EUCAST; The European Committee on Antimicrobial Susceptibility Testing, MIC; minimum inhibitory concentration, II; Intermittent infusion, EI; Extended Infusion

(p-value > 0.05). The conclusion of this study was that the clinical effect of an extended infusion is more pronounced in patients with a respiratory tract infection. However, the risk of bias cannot be overlooked, as the investigators of the study were not blinded.

Another RCT with a smaller number of enrolled patients (n = 50) similarly evaluated the clinical outcomes of an extended PIP/TZB infusion in patients with a diagnosis of hospital-acquired pneumonia (HAP) (15). Patients were randomized in the following groups: EI: 4.5 g over 3 hours every 6 hours, number of patients = 25 vs II: 4.5 over 30 minutes every 6 hours, number of patients = 25. The main outcomes in this study were the %fT > MIC, clinical success rate, clinical failure rate, drug-related adverse events, and the cost of therapy. The extended infusion resulted in a high plasma concentration with a mean %fT > MIC of 100%, 98.73%, and 93.04% for pathogens with MICs of 4, 8, and 16 mg/L, respectively compared to a %fT > MIC of 81.48%, 53.29%, and 42.15% in the intermittent arm for micro-organisms with MICs of 4, 8, and 16 mg/L, respectively. The high levels did not reflect a significant difference in the clinical success or the clinical failure rate. However, the extended infusion enabled a significant reduction in the cost of therapy ($1351.72 ± 120.39 for EI vs. $1782.04 ± 164.51 for II, p-value = 0.001) with a saving of about $430.32 per patient. From a safety perspective, the study reported a similar number of patients who experienced drug-related adverse events (mostly gastrointestinal adverse effects) in both groups (19 patients in the EI arm vs. 23 patients in the II arm). It should be noted that the patients included in the study had a low illness severity, which contrasts with previously published studies.

The final RCT identified compared alternative modes of administration of PIP/TZB, included 120 cancer patients with a postoperative HAP.[39] Patients were randomized in the following groups: EI group = 4.5 g for 3 hours every 6 hours and II group = 4.5 g for 30 minutes every 6 hours. Subsequently, the patients were categorized depending on the sequential organ failure assessment score (SOFA) into a mild disease group (SOFA<9) and a severe disease group (SOFA≥9). The authors found that the patients in the severe disease group who received an extended infusion had a longer %fT > MIC which is reflected in a significant reduction in the 28-day mortality rate (3.12% vs. 14.29%, p-value = 0.027). In addition, a statistically significant reduction in the antibiotic duration with an estimated difference of two days (p-value = 0.01) and a major decline in mechanical ventilation time was observed for the extended infusion group with high disease severity (126.09 ± 12.91 hours vs. 169.36 ± 16.45 hours, p-value = 0.043). These results can add valuable evidence supporting the use of extended infusion, however, the population chosen for this trial is a particular group of patients with restricted inclusion criteria, which limits generalizability to a larger population.

Two prospective studies evaluated the clinical outcomes of extending the infusion time of PIP/TZB and had similar negative results.[36,37] The mortality rate was the primary outcome in both studies, which was not significantly different for the two infusion methods. Clinical cure, length of hospital stays, ICU stay, and duration of treatment were all nonsignificant. The main limitation for one of the studies was not using a randomized design for comparing the regimens.[37] The design weakness of the second study was not performing a comparative controlled trial.[36]

Patients with altered pharmacokinetics

Renally Impaired Patients on Continuous Renal Replacement Therapy (CRRT): Many patients with critical illness develop acute kidney injury, acute renal failure, or volume overload due to various reasons, which necessitate the use of CRRT during hospitalization.[40] Extensive drug elimination can occur in patients receiving CRRT due to the ability to maximize the removal of excess fluids and toxic substances.[41] An increased elimination rate of medication can result in sub-therapeutic levels which may jeopardize patient outcomes. According to literature, the modalities of CRRT (e.g., continuous veno-venous hemofiltration, continuous veno-venous hemodialysis, etc.) do not affect the PK/PD of PIP/TZB in extended doses.[40,42] Only two studies evaluated the effect of an extended infusion of PIP/TZB to prevent sub-therapeutic levels in patients on CRRT. Awissi and colleagues assessed the PK/PD parameters to predict if the extended infusion can cause bacteriological eradication by reaching very high MIC values, specifically for a very resistant pathogen such as *P. aeruginosa* with an MIC of 64 mg/L (according to the institution sensitivity profile) in critically ill patients.[40] Twenty patients were included, and they were infused with 4.5 g PIP/TZB for 4 hours every 8 hours. The study did not compare with an intermittent arm as they already implemented the extended infusion protocol in their institution. They found that 90% of the patients reached an MIC of 64 mg/L in 50% of the dosing time interval. This study suggested that a dose of 4.5 g is sufficient to eradicate *P. aeruginosa*, usually the cause of aggressive infections. It is noteworthy that by using this mode of administration, an early therapeutic target was reached in the first 48 hours. Another similar cohort study was done in the US, in three different centers.[42] The authors compared the use of an extended infusion vs. an intermittent infusion in critically ill patients receiving CRRT. Two centers provided the standard intermittent infusion - 2.5 g or 3.375 g administered over 30 minutes scheduled every 6, 8, or 12 hours - (n = 54) and the third used the alternative extended dosing - 240 minutes (4 g) every 8 hours - (n = 14). According to the study, the likelihood of target attainment was significantly higher with EI than II, 12 g/d of PIP/TZB was associated with 95% target attainment.

Critically Ill patients with augmented renal clearance: Two of the main PK factors that are altered in critically ill patients, due to the nature of their critical illness, are the volumes of distribution and the elimination rate. Drug concentration can be affected and result in unpredictable and negative outcomes.[43] Augmented renal clearance (ARC) is a phenomenon of enhanced renal function observed in critically ill patients. It is defined as CrCl > 130 ml/min/1.73 m^2, through which acute infections have been associated with its occurrence.[44] Using unadjusted antimicrobial doses, eliminated by the kidneys, can cause treatment failure and poor patient outcomes.

The use of the extended infusion of PIP/TZB in this population may delay the effect of ARC and restore normal drug concentration with a high %fT > MIC.[45] Carlier and colleagues assessed the effect of this phenomena to reach a %fT > MIC of 50% and 100% of the dosing interval in 60 critically ill patients with ARC.[45] The MIC target of 16 mg/L for this study was for *P. aeruginosa*. The authors reported that 86% of the patients were able to reach 50% of the %fT > MIC (p-value < 0.045) and 55% achieved 100% of %fT > MIC (p-value < 0.02). Only one study was found focusing on the ARC population, making the interpretation of such results in practice problematic.

Cystic fibrosis patients: Cystic fibrosis (CF) is a progressive, genetic disease, which affects mainly the lungs, causes persistent lung infections, and limits the ability to breathe.[43] Respiratory infections are the leading cause of death in patients with cystic fibrosis. The most identified microorganism in this population is *P. aeruginosa,* which is usually treated empirically with PIP/TZB.[43] Extending the infusion time can improve infection eradication in this specific population and decrease the mortality rate. One study evaluated the effect of an extended infusion of PIP/TZB on the PK/PD characteristics. Butterfield and colleagues studied nine CF patients with an acute pulmonary exacerbation who were treated with an extended infusion of PIP/TZB (3.375 g infusion for 4 hours every 8 hours).[43] Monte Carlo 249 simulations that integrated intermittent infusion with extended or continuous infusion were done to estimate the PTA for the different levels of MIC. An acceptable PTA (>90%) was achieved with 251 at an MIC of 8 mg/L with the extended infusion. Higher doses with more frequent 252 intervals achieved a PTA of 89% at MIC levels of 16 mg/L. However, none of the evaluated regimens achieved an acceptable PTA for MICs > 16 mg/L.

Systematic reviews and meta-analysis

High-quality systematic reviews and meta-analysis are considered as reliable evidence to obtain strong recommendations with an accurate estimation of the true effect for any intervention investigated. Our search yielded four meta-analyses and two qualitative systematic reviews.[16,17,46-49] All the studies evaluated similar primary and secondary endpoints such as mortality, clinical cure, microbiological cure, length of hospital stays, ICU stay, drug-related adverse events, and cost.

Table 2 displays a summary of all the systematic reviews and meta-analysis included comparing the intermittent infusion with the extended infusion of PIP/TZB. We could not display statistical data for all the studies as the majority had mixed results with other antibiotics (e.g., carbapenems) or other dosing strategies (e.g., continuous infusion) which can overestimate the actual effect of an extended infusion of PIP/TZB. Regarding mortality, all the reviews described positive outcomes with the use of an extended infusion compared to an intermittent infusion. The

Table 2. Summary of systematic reviews and meta-analysis of extended infusion vs. intermittent infusion of piperacillin-tazobactam (PIP/TZB)

(Author, Year) Study	**Included studies**	**Mortality**	**Clinical Cure**	**Microbiological Cure**	**Length of stay in Hospital/ICU**	**Drug related Adverse events**	**Cost**
(Matthew,2012) Meta-analysis	2 out of 14 studies reported extended PIP/TZB	Mortality rates were lower among patients who received PIP/TZB by extended infusion.	No significant difference	Not reported	Not reported	No significant difference	Not reported
(Greg T, 2012) Qualitative systematic review	5 out of 12 studies reported extended PIP/TZB	Mortality rates were lower among patients who received PIP/TZB by extended infusion.	No significant difference	Extended PIP/TZB achieves higher PK/PD targets compared to intermittent infusion	Not reported	Not reported	Not reported
(Erlangga, 2014) Narrative systematic review	8 studies reported extended PIP/TZB	Mortality rates were lower among patients who received PIP/TZB by extended infusion.	Clinical cure rates were higher among patients who received PIP/TZB by extended infusion.	Not reported	Shorter length of hospital-stay	Not reported	Not reported
(Hui, 2015) Meta-analysis	7 out of 14 studies reported extended PIP/TZB	Mortality rates were lower among patients who received PIP/TZB by extended infusion.	Clinical cure rates were higher among patients who received PIP/TZB by extended infusion.	No significant difference	Not reported	No significant difference	Not reported
(Hui, 2016) Meta-analysis	9 out of 15 studies reported extended PIP/TZB	Mortality rates were lower among patients who received PIP/TZB by extended infusion.	No significant difference	Not reported	No significant difference	Not reported	Significant difference in healthcare costs in favor of extended infusion
(Nathaniel, 2017) Meta-analysis	18 studies reported extended PIP/TZB	Mortality rates were lower among patients who received PIP/TZB by extended infusion. (OR, 0.69; 95% CI, 0.56– 0.84).	Clinical cure rates were higher among patients who received PIP/TZB by extended infusion. (OR,1.77; 95% CI, 1.24–2.53).	No significant difference	No significant difference	Not reported	Not reported

most recent meta-analysis with the highest number of studies included reported an odds ratio of 0.69 (95%CI 0.56:0.84) in favor of extending the infusion time, with a low heterogenicity (I2 = 0%) found across the analyzed publications.[17] Clinical cure was also a frequent outcome observed in most of the studies with favorable outcomes. Clinical cure had different definitions for each study, but a unified matched definition from the studies is a complete resolution of all the signs and symptoms of infection or improvement of the clinical signs and symptoms of the infection. Other positive outcomes demonstrated were not consistently present in all the studies, such as a cost reduction, reported in only one meta-analysis, which showed a significant cost benefit in the cohort study subgroups with moderate heterogenicity (I2=43%).[46] The length of hospital stay was also evaluated in one study reporting a shorter duration of stay in favor of the extended infusion, however, there was a numerical but not statistically significant difference with moderate heterogenicity (I_2 = 39%).

DISCUSSION

Limited novel antimicrobials and emergence of resistance mandates the optimization of existing antimicrobials. This updated review aimed to present acceptable and comprehensive evidence of the comparison of PIP/TZB extended infusion vs. intermittent infusion. The authors emphasized the role of the PK/PD parameters in the patients' clinical outcomes. Although not supported by all the studies in the review, a trend towards favorable outcomes with the extended infusion was noticed, supported by the findings in another review article.[6] Extended infusion offers benefits over intermittent infusion in terms of %fT > MIC. Several PK/PD studies consistently reported significantly longer %fT > MIC of 16 mg/L, demonstrating a clear superiority of the extended infusion compared with the intermittent infusion. However, achieving the MIC levels for *P. aeruginosa* is still a challenge and a controversial issue.

Interestingly, only one study reported that half of the patients achieved a %fT>4x MIC (64 mg/l) vs. none in the intermittent group.[35] It must be noted that a firm conclusion cannot be drawn from a single study. All PK/PD studies reported that extending the infusion time improved the antibiotic exposure and increased the PTA percentage with a lower total daily dose compared to the intermittent infusion.

In patients with altered pharmacokinetics, obese and morbidly obese patients are at a higher risk of infection and increased mortality and morbidity.[50] This population was not included in the review, as the literature search did not yield eligible studies. One study focused the use of an extended infusion in critically ill obese patients. However, extracting data relevant to the comparison was difficult as the analysis combined multiple variables (for example use of other antibiotics and use of continuous infusion).[50] More research is required in this population as they represent a significant proportion of critically ill patients.

Regarding clinical outcomes, few clinical trials and prospective studies were identified, and most had conflicting results, limiting a substantive deduction. It is worth mentioning that none of the evaluated studies stated any negative outcomes associated with an extended infusion, except one prospective study reporting a longer time to mortality in the intermittent infusion group, which was contradictory to findings in multiple meta-analyses.[36] In terms of systematic reviews and meta-analysis, most of the studies included were observational with limited RCT studies. A well-designed controlled RCT with a large sample size is required to obtain generalizable and reliable data. More clinical trials are already being conducted to define the exact effect of an extended infusion of PIP/TZB.[51-53]

LIMITATIONS

Our study has several limitations, both in terms of the methodology we used to select the studies and the way they were evaluated. However, our literature search revealed a comprehensive descriptive search of the extended infusion compared to the intermittent infusion of Piperacillin/Tazobactam. Despite this review, we were unable to generate a high level of evidence, but we provided an overview to the health care providers.

CONCLUSION

In conclusion, our review reports a positive trend when using an extended infusion of PIP/TZB, clinicians may be encouraged to adopt and implement the extended infusion to achieve positive patient outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this review article. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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