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Clinical Pharmacology of Piperacillin/Tazobactam

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ABSTRACT

Piperacillin extends the spectrum of activity of ampicillin to include most strains of *Pseudomonas aeruginosa, Enterobacteriaceae* (non-β-lactamase-producing), many Bacteroides species, and *Escherichia faecalis.* Combined with the β-lactamase inhibitor tazobactam, piperacillin/tazobactam has the broadest antibacterial spectrum of penicillins including activity against methicillin-susceptible *Streptococcus aureus, Haemophilus influenzae, Bacillus fragilis, most Escherichia coli,* and *Klebsiella.* Piperacillin is only available for parenteral administration. Piperacillin is an important agent for treatment of patients with serious infections caused by gram-negative bacteria including bacteraemias, pneumonias, infections following burns, and urinary-tract infections owing to microorganisms resistant to ampicillin and the bacteria responsible include *Pseudomonas aeruginosa,* indole-positive strains of Proteus, and Enterobacter species. The efficacy and safely of piperacillin/tazobactam have been reviewed and piperacillin and tazobactam concentrate in tissues in significant amounts. The elimination half-life of piperacillin and tazobactam is about 1 and 1.8 hours, respectively. The prophylaxis, treatment, and trials with piperacillin/tazobactam have been reviewed. Piperacillin/tazobactam may induce nephrotoxicity or neutropenia in some patients. The penetration of piperacillin into the central nervous system is good but tazobactam reaches concentrations in the cerebrospinal fluid inadequate to protect piperacillin by organisms producing β-lactamases and piperacillin/tazobactam treats bacterial meningitis. Piperacillin and tazobactam freely cross the human placenta. The aim of this study is to review piperacillin/tazobactam efficacy and safely, prophylaxis, treatment, trials, treatment of meningitis, and piperacillin and tazobactam pharmacokinetics, penetration into the body-tissues and into the cerebrospinal fluid, transfer across the human placenta, and metabolism of piperacillin.

Keywords

Cerebrospinal-fluid, Efficacy-safely, Meningitis, Metabolism, Pharmacokinetics, Piperacillin/Tazobactam, Placenta, Prophylaxis, Toxicity, Treatment, Trials

Introduction

Pharmacological Properties of Piperacillin

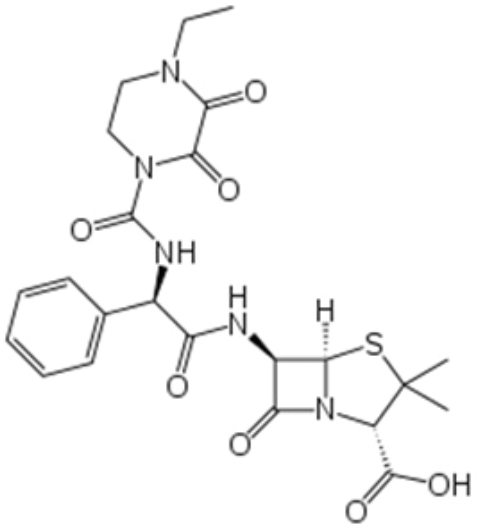
Piperacillin extends the spectrum of activity of ampicillin to include most strains of *Pseudomonal aeruginosa, Enterobacteriaceae* (non-β-lactamase-producing), many Bacteroides species, and *Escherichia faecalis.* Combined with the β-lactamase inhibitor tazobactam, piperacillin/tazobactam has the broadest antibacterial spectrum of penicillins including activity against methicillin-susceptible *Streptococcus aureus, Haemophilus influenzae, Bacillus fragilis, most Escherichia coli,* and *Klebsiella*. Piperacillin is only available for parenteral administration and achieves high biliary concentrations. The penetration of piperacillin into the central nervous system is good but the concentration of tazobactam in the cerebrospinal fluid may be inadequate to protect piperacillin by organisms producing β-lactamases. Piperacillin is eliminated renally and requires adjustment in renal dysfunction [1].

Therapeutic Indications of Piperacillin

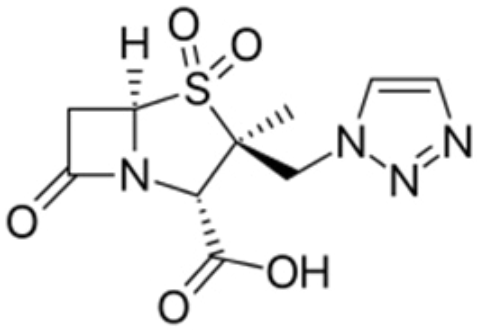
Piperacillin is an important agent for the treatment of patients with serious infections caused by gram-negative bacteria including infections often acquired in the hospital. Therefore, piperacillin finds its greatest use in treating bacteraemias, pneumonias, infections following burns, and urinary-tract infections owing to microorganisms resistant to ampicillin; the bacteria responsible include *Pseudomonas aeruginosa,* indole-positive strains of Proteus, and Enterobacter species. Because Pseudomonas infections are common in neutropenic patients, therapy for severe bacterial infections in such individuals should include a β-lactam antibiotic such as piperacillin with good activity against these organisms. Because of piperacillin/tazobactam has good activity against *Escherichia faecalis* and *Bacillus fragilis* this drug also has utility in mixed intraabdominal infections [1].

Literature Search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "piperacillin efficacy and safely", "piperacillin metabolism", "piperacillin tissue concentration", "piperacillin pharmacokinetics", "piperacillin prophylaxis", "piperacillin treatment", "piperacillin trial", "piperacillin toxicity", "piperacillin CSF", "piperacillin meningitis", and "piperacillin placental transfer". In addition, the book "The pharmacological basis of therapeutics" [1] has been consulted.



Piperacillin molecular structure (molecular weight=516.548 grams/mole)



Tazobactam molecular structure (molecular weight=300.289 grams/mole)

Results

Efficacy and Safely of Piperacillin/Tazobactam

Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily effectively and safely teats most hospital-acquired infections [2], complicated skin and soft-tissue infections [3], and adult and paediatric patients with febrile neutropenia [4]. Piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams thrice-daily for 5 days effectively and safely treats hospitalized patients with lower respiratory-tract infections caused by sensitive organisms [5]. Cefoperazone/sulbactam is efficacy and safe as piperacillin/tazobactam in treating elderly patients with severe community-acquired pneumonia [6]. Cefepime is efficacious and safe as piperacillin/tazobactam in treating paediatric patients with febrile neutropenia [7], and cefoperazone/sulbactam is safe and effective as piperacillin/tazobactam in treatment of febrile neutropenia in children with cancer [8].

Metabolism of Piperacillin

In literature there is only one study on the metabolism of piperacillin and it has been reported by Ghibellini et al. [9]. The metabolism of piperacillin was studied *in-vitro* using human liver microsomes and *in-vivo* in healthy volunteers. Piperacillin is converted into desethylpiperacillin which is glucuronidated and desethylpiperacillin-glucuronide is excreted into the bile.

Penetration of Piperacillin and Tazobactam in Body-Tissues

A single intravenous dose of 4/0.5 grams of piperacillin/tazobactam was administered to 5 patients undergoing thoracotomy. The peak concentration of piperacillin is 176 ± 105 µg/gram in infected lung and 326 ± 60.6 µg/ml in serum. The area under the concentration-time curve of piperacillin is 288 ± 167 µg*h/gram in infected lung and 470 ± 142 µg*h/ml in serum. The intrapulmonary concentration of piperacillin exceeds the minimum inhibitory concentration of most relevant

Table 1: Pharmacokinetic parameters of piperacillin and tazobactam which have been obtained in 56 patients with complicated intraabdominal infection. Piperacillin/tazobactam was administered by a continuous infusion at a dose of 2/0.25 grams over 30 min once-daily to 26 patients or by intermittent infusion at a dose of 3/0.375 grams once-daily to 30 patients. Values are the mean ± SD, by Li et al. [13].

Parameter	Continuous infusion (N=26)	Intermittent infusion (N=30)
Piperacillin		
Total body clearance (L/h)	16.0 ± 5.71	13.7 ± 4.31
Distribution volume (L)	22.2 ± 4.54	22.4 ± 6.18
Elimination half-life (h)	1.08 ± 0.45	1.24 ± 0.64
Peak concentration (µg/ml)	Not available	122 ± 30.4
Concentration at the steady-state (µg/ml)	35.6 ± 12.1	Not available
Tazobactam		
Total body clearance (L/h)	10.7 ± 8.42	11.0 ± 3.82
Distribution volume (L)	22.8 ± 4.69	23.2 ± 8.87
Elimination half-life (h)	1.88 ± 1.04	1.73 ± 1.34
Peak concentration (µg/ml)	Not available	15.7 ± 4.84
Concentration at the steady-state (µg/ml)	7.29 ± 3.28	Not available

bacteria for 4 to 6 hours after treatment [10]. Piperacillin/tazobactam was administered intravenously at a dose of 2.5/0.62 grams once-daily to 7 patients undergoing surgery and the mean peak concentration of piperacillin is 123 µg/gram and that of tazobactam is 30.3 µg/gram in the gallbladder. In these patients, the mean peak concentration of piperacillin is 60.2 µg/ml and that of tazobactam is 14.4 µg/ml in the ascites and the mean peak concentration of piperacillin is 66.5 µg/ml and that of tazobactam is 8.5 µg/ml in the bile [11]. Piperacillin was administered intravenously at a dose of 2 grams once-daily to 13 patients undergoing surgery. The median concentration of piperacillin in the subcutaneous-tissue is 2.4 µg/gram on day 1 of treatment and 5.5 µg/gram on day 2 of treatment [12].

Pharmacokinetics of Piperacillin and Tazobactam in Patients with Complicated Intraabdominal Infection

Li et al., [13] studied the pharmacokinetics of piperacillin and tazobactam in 56 patients with complicated intraabdominal infection who had a median age of 52 years (range, 18 to 82). Twenty-six patients received a daily dose of 2/0.25 grams of piperacillin/tazobactam by continuous infusion over 30 min and 30 patients received a daily dose of 3/0.375 grams of piperacillin/tazobactam by intermittent infusion. Both continuous infusion and intermittent infusions were administered to a minimum of 4 days and not more than 14 days.

Table 1 shows that the pharmacokinetic parameters of piperacillin and tazobactam obtained following continuous infusion are not different from those obtained following intermittent infusion and there is a remarkable variability of the pharmacokinetic parameters. This variability is accounted by the wide variation in the patient's age and disease.

Prophylaxis with Piperacillin/Tazobactam

Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams thrice-daily reduces post-operative site infection in adult patients [14], prevents the infection in patients undergoing radical cystectomy [15], and the infection in patients with high-risk febrile neutropenia [16]. A single intravenous dose of 2.25/0.56 grams of piperacillin/tazobactam is more effective than placebo in preventing postoperative infection in patients undergoing breast surgery and in patients undergoing hernia repair [17]. The administration of a single intravenous dose of 4.5/0.5 grams of piperacillin/tazobactam along with a standard dose of fluoroquinolone prevents the risk of serious bacterial infection in patients undergoing prostate biopsy [18]. Prophylaxis with piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams thrice-daily prevents the infection in patients undergoing blood stem cell transplantation [19], the infection in women undergoing gynaecological surgery [20], and the infection in patients undergoing prostate biopsy [21].

Treatment of Bacterial Infections with Piperacillin/Tazobactam

Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily treats the infection caused by *Pseudomonas aeruginosa* [22], wound infection in patients undergoing head and neck surgery [23], polymicrobial infections caused by aerobic or anaerobic β-lactamase-producing bacteria [24], and mixed infections of the peritoneal cavity in paediatric patients with intraabdominal infections [25]. Piperacillin/tazobactam is an antimicrobial agent with enhanced activity against most β-lactamase-producing organisms [26]. Piperacillin/tazobactam is especially useful in treatment of infections caused by organisms with plasmid-mediated β-lactamases [27]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams thrice-daily effectively treats 94.3% cases of pneumonia and 100% cases of bronchitis caused by *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa,* Enterobacter species, or by *Escherichia coli* [28], soft-tissue bacterial infections [29], serious infections of soft-tissue caused by group A streptococci or by *Pseudomonas aeruginosa* [30], and patients with polymicrobial infections [31]. Intravenous imipenem/cilastatin effectively treats febrile neutropenia in paediatric patients as intravenous piperacillin/tazobactam [32]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily is safe and effective as cefepime administered intravenously at a dose of 2 grams thrice-daily in treatment of high-risk febrile neutropenic patients with cancer [33], and piperacillin/tazobactam administered intravenously at a dose of 3/0.375 grams 4 times-daily is more effective than ticarcillin/clavulanate administered intravenously at a dose of 3 grams/100 milligrams 4 time-daily in treatment of lower respiratory-tract infections [34].

Trials with Piperacillin/Tazobactam

Piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams 4 times-daily effectively treats patients with infection caused by gram-negative organisms as imipenem/cilastatin/relebactam administered intravenously at a dose of 500 mg/500 mg/250 mg 4 times-daily [35], and piperacillin/tazobactam administered by continuous infusion at a dose of 4.5/0.5 grams 4 times-daily effectively treats patients with infections caused by gram-negative bacteria [36]. Piperacillin/tazobactam administered intravenously at a dose 337.5/80 mg/kg daily is effective and safe as cefepime administered intravenously at a dose of 100 mg/kg daily in treatment of children with febrile neutropenia [37]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily treats febrile patients with severe neutropenia as cefepime administered intravenously at a dose of 2 grams thrice-daily plus amikacin administered intravenously at a dose of 20 mg/kg once-daily [38], and piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams thrice-daily is more effective than imipenem/cilastatin administered intravenously at a dose of 2/0.5 grams thrice-daily in treatment of severe diabetic foot infections [39]. Ertapenem administered intravenously at a dose of 1 gram once-daily is efficacy and safe as piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams thrice-daily in treatment of complicated infections caused by gram-negative bacteria [40], and ertapenem administered intravenously at a dose of 1 gram once-daily is efficacy as piperacillin/tazobactam administered intravenously at a dose of 3.375/0.85 grams 4 times-daily in treatment of intraabdominal infections [41]. Intravenous piperacillin/sulbactam treats community-acquired respiratory-tract and urinary-tract infections caused by β-lactamase-producing organisms as intravenous piperacillin/tazobactam

[42]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily plus amikacin administered intravenously at a dose of 7.5 mg/kg twice-daily treats ventilator-associated pneumonia in adult patients as ceftazidime administered intravenously at a dose of 1 gram 4 times-daily plus amikacin administered intravenously at a dose of 7.5 mg/kg twice-daily [43]. Piperacillin/tazobactam administered intravenously at a dose of 4/0.5 gram 4 times-daily effectively treats complicated urinary-tract infections [44], and piperacillin/tazobactam administered intravenously at a dose of 4/0.5 gram thrice-daily is more effective than imipenem/cilastatin administered intravenously at a dose of 500/500 mg thrice-daily in treatment of intraabdominal infections caused by sensitive organisms [45].

Toxicity Caused by Piperacillin/Tazobactam

The combination of vancomycin plus piperacillin/tazobactam increases the odds of acute kidney injury [46]. Piperacillin/tazobactam induces nephrotoxicity in paediatric oncology patients with fever plus neutropenia [47]. Piperacillin/tazobactam induces nephrotoxicity in 18% of elderly patients with pneumonia [48]. Of 41 patients with bone-related infection who were treated with piperacillin/tazobactam intravenously at a dose of 4.5/0.5 grams thrice-daily for 10 days, 14 patients (34.1%) developed neutropenia which increases with increasing the cumulative dose of piperacillin/tazobactam [49].

Penetration of Piperacillin and Tazobactam into the Cerebrospinal Fluid (CSF)

Placzek et al., [50] described the penetration of piperacillin into the CSF of 70 infants with meningitis caused by Escherichia coli or by Pseudomonas aeruginosa. Infants received piperacillin intravenously at a dose of 100 mg/kg twice-daily and flucloxacillin intravenously at a dose of 25 mg/kg twice-daily. Table 2 summarizes the concentration of piperacillin in CSF and in blood.

Table 2: Concentrations of piperacillin in the Cerebrospinal Fluid (CSF) and in blood which were obtained in 70 infants who received piperacillin intravenously at a dose of 100 mg/kg twice-daily. Values are the minimum, maximum, mean, and ± SD, by Placzek et al. [50].

Value	Time after piperacillin injection (h)	Number of doses	Piperacillin concentration in CSF (µg/ml)	Piperacillin concentration in blood (µg/ml)	
				1 hour after dosing	12 hours after dosing
Minimum	2.5	1	2.6	90	50
Maximum	24	20	190	800	180
Mean	10.4	7.1	51.1	262	98.3
± SD	2.6	2.5	46.3	137	41.1

Table 2 shows that the concentration of piperacillin in CSF and in blood is variable. The minimum inhibitory concentration of *Escherichia coli* and *Pseudomonas* is 10 µg/ml. The mean concentration of piperacillin in CSF is 51.1 µg/ml thus piperacillin administered at a dose of 100 mg/kg twice-daily yields concentration in CSF higher the minimum inhibitory concentration of Escherichia coli and Pseudomonas aeruginosa and these bacteria were eradicated from the CSF. Piperacillin/tazobactam was administered intravenously at a mean dose of 113/96.7 mg/kg thrice-daily to 5 children, aged 6 to 59 months, with meningitis caused by *Haemophilus influenzae.* The concentration of piperacillin and tazobactam was measured in CSF 0 to 105 min after dosing. The concentration of piperacillin in the CSF ranges from 2.54 to 7.74 µg/ml and that of tazobactam ranges from 0.32 to 1.32 µg/ml, and this dosing regimen eradicated *Haemophilus influenzae* from the CSF [51]. Following the administration of the first intravenous dose of piperacillin/tazobactam of 6/0.5 grams to 9 adult patients with non-inflammatory occlusive hydrocephalus the peak concentration of piperacillin in CSF ranges from 8.67 to < 0.37 µg/ml (median, 3.42) and that of tazobactam ranges from 1.37 to 0.11 µg/ml (median, 0.45). The peak concentration of piperacillin and tazobactam is observed 1.5 and 2 hours, respectively, after dosing. The elimination half-life of piperacillin is 5.9 hours in CSF and 1.47 hours in serum and that of tazobactam is 6.1 hours in CSF and 1.4 hours in serum. The ratio of the area under the concentration-time curve (AUC) of tazobactam in CSF to the AUC in serum is approximately 3 times lower than that for piperacillin (median, 0.034 versus 0.106). The tazobactam concentrations in CSF of 4 µg/ml is inadequate for treatment of intracranial infections caused by organisms producing β-lactamases and a dose of 0.5 grams thrice-daily is necessary to combat infections of the central nervous system caused by these organisms [52]. Ten adult patients with haemorrhagic stroke (subarachnoid haemorrhage N=6 and intracerebral haemorrhage N=4) received piperacillin/tazobactam intravenously at a dose of 4/0.5 grams thrice-daily. The mean peak concentration of unbound piperacillin in brain interstitial space fluid is 1.6 µg/ml (range, 0.08 to 3.59) and 2.78 µg/ml (range, 0.47 to 7.53) after the first administration and after multiple doses, respectively. The median estimate of transfer-rate of piperacillin from plasma to brain is 0.32 h^{-1} and the median estimate of transfer-rate of piperacillin from brain to plasma is 7.31 h^{-1}. Simulations suggested that the probability of target attainment would exceeds 90% for the minimum inhibitory concentration of 0.5 and 1 µg/ml at a daily dose of piperacillin of 12 to 16 grams and 24 grams, respectively [53]. Ten adult patients with purulent meningitis caused by gram-negative organisms received 3 intravenous doses of 4 grams of piperacillin. The mean piperacillin concentration in the CSF is 9.2 µg/ml, the mean piperacillin penetration-rate is 22.7%, and the meningitis was cured after 10 to 20 days of treatment [54]. These results indicate that piperacillin penetrates into the CSF in significant amounts.

Treatment of Bacterial Meningitis with Piperacillin/Tazobactam

Adult patients had the meningitis caused by *Streptococcus*

pneumoniae, Neisseria meningitides, Haemophilus influenzae, Staphylococcus, or by *Escherichia coli.* Piperacillin/tazobactam was administered intravenously at a dose of 4.5/0.5 grams 4 times-daily and the meningitis was cured in all patients [55]. A male patient, aged 23 years, with meningitis caused by *Elizabethkingia meningoseptica* received piperacillin/tazobactam intravenously at a dose of 4.5/0.5 grams 4 times-daily and vancomycin and clotrimazole orally and the cerebrospinal fluid became sterile after 21 days of treatment [56]. One-hundred-one cases of post-surgical meningitis and 10 cases of nosocomial meningitis caused by *Pseudomonas meningitis* were diagnosed. Piperacillin/tazobactam was administered intravenously at a dose of 4.5/0.5 grams 4 times-daily and this treatment cured 50% of cases [57].

Transfer of Piperacillin and Tazobactam across the Human Placenta

The transfer of piperacillin and tazobactam across the human placenta was studied in 6 pregnant women at delivery. Piperacillin/tazobactam was administered intravenously at a dose of 4/0.5 grams 4 times-daily and both piperacillin and tazobactam freely crossed the human placenta [58]. Piperacillin was administered intravenously at a dose of 4 grams 4 times-daily to 10 pregnant women at delivery and piperacillin promptly crossed the human placenta [59].

Discussion

Piperacillin extends the spectrum of activity of ampicillin to include most strains of *Pseudomonas aeruginosa, Enterobacteriaceae* (non-β-lactamase-producing), many Bacteroides species, and *Escherichia faecalis.* Combined with the β-lactamase inhibitor tazobactam, piperacillin/tazobactam has the broadest antibacterial spectrum of penicillins including activity against methicillin-susceptible *Streptococcus aureus, Haemophilus influenzae, Bacillus fragilis, most Escherichia coli* and *Klebsiella.* Piperacillin is only available for parenteral administration and achieves high biliary concentrations. Piperacillin and tazobactam penetrate into the body-tissues in significant amounts. Piperacillin penetrates into the central nervous system well but the concentration of tazobactam in the cerebrospinal fluid is inadequate to protect piperacillin by organisms producing β-lactamases. Piperacillin is eliminated renally and requires adjustment in renal dysfunction. Piperacillin is an important agent for treatment of patients with serious infections caused by gram-negative bacteria including infections often acquired in the hospital. Therefore piperacillin finds its greatest use in treating bacteraemias, pneumonias, infections following burns, and urinary-tract infections caused by microorganisms resistant to ampicillin and the bacteria responsible include *Pseudomonas aeruginosa,* indole-positive strains of Proteus, and Enterobacter species. Because of piperacillin/tazobactam has good activity against *Escherichia faecalis* and *Bacillus fragilis* this drug also has utility in mixed intraabdominal infections [1]. The efficacy and safely of piperacillin/tazobactam have been reviewed. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily effectively and safely treats most hospital-acquired infections [2], complicated skin and soft-tissue infections [3], and adult and paediatric patients with febrile neutropenia [4]. Piperacillin/tazobactam administered at a dose of 4/0.5 grams trice-daily for 5 days effectively and safely treats lower respiratory-tract infections caused by sensitive organisms [5], and cefoperazone/sulbactam is efficacy and safe as piperacillin/tazobactam for treatment of elderly patients with severe community-acquired pneumonia [6]. Cefepime is efficacy and safe as piperacillin/sulbactam for treatment of paediatric patients with febrile neutropenia [7], and cefoperazone/sulbactam is efficacy and safe as piperacillin/tazobactam in treatment of febrile neutropenia in children with cancer [8]. The metabolism of piperacillin has been studied and piperacillin is metabolised into desethylpiperacillin, desethylpiperacillin is glucoronated, and desethylpiperacillin-glucuronide is excreted into the bile [9]. The penetration of piperacillin and tazobactam into body-tissues has been reviewed. Following a single intravenous dose of 4/0.5 grams of piperacillin/tazobactam to 5 patients undergoing thoracotomy the mean peak concentration of piperacillin is 176 μg/gram in infected lung and 326 μg/ml in serum and the mean area under the concentration-time curve of piperacillin is 288 μg*h/gram in the infected lung and 470 μg*h/ml in serum [10]. Following the intravenous administration of piperacillin/tazobactam at a dose of 2.5/0.62 grams once-daily to 7 patients undergoing surgery the mean peak concentration of piperacillin in the gallbladder is 123 μg/gram and that of tazobactam is 30.3 μg/gram, the mean peak concentration of piperacillin in ascites is 60.2 μg/ml and that of tazobactam is 14.4 μg/ml, and the mean peak concentration of piperacillin in the bile is 66.5 μg/ml and that of tazobactam is 8.5 μg/ml [11]. Following the administration of piperacillin intravenously at a dose of 2 grams once-daily to 13 patients undergoing surgery the median concentration of piperacillin in subcutaneous-tissue is 2.4 μg/gram on day 1 of treatment and 5.5 μg/gram on day 2 of treatment [12]. These results indicate that piperacillin and tazobactam penetrate into body-tissues in significant amounts. The pharmacokinetics of piperacillin and tazobactam have been studied by Li et al., [13] in 56 patients with complicated intraabdominal infection. Twenty-six patients received a daily dose of 2/0.25 grams of piperacillin/tazobactam by continuous infusion and 30 patients received a daily dose of 3/0.375 grams of piperacillin/tazobactam by intermittent infusion. The mean elimination half-life of piperacillin is 1.08 hours following the administration of piperacillin/tazobactam by continuous infusion and 1.24 hours following the administration of piperacillin/tazobactam by intermittent infusion. The mean elimination half-life of tazobactam is 1.88 hours following the administration of piperacillin/tazobactam by continuous infusion and 1.73 hours following the administration of piperacillin/tazobactam by intermittent infusion. These results indicate that the elimination half-life of piperacillin and tazobactam is similar according the two infusion regimens. The prophylaxis with piperacillin/tazobactam has been reviewed. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams thrice-daily reduces post-operative site infection [14], prevents the infection in patients undergoing radical cystectomy [15], and in patients with high-risk febrile neutropenia [16]. A single intravenous dose of 2.25/0.56 grams of piperacillin/tazobactam prevents the infection in patients undergoing breast surgery and in patients undergoing hernia repair [17]. The administration of a single intravenous dose of 4.5/0.5 grams of piperacillin/

tazobactam along with a standard dose of fluoroquinolone prevents the infection in patients undergoing prostate biopsy [18]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams thrice-daily prevents the infection in patients undergoing blood stem cell transplantation [19], in women undergoing gynaecological surgery [20], and in patients undergoing prostate biopsy [21]. These results indicate that piperacillin/tazobactam prevents different infections. The treatment of bacterial infections with piperacillin/tazobactam has been reviewed. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily treats patients infected by Pseudomonas aeruginosa [22], wound infection in patients undergoing head and neck surgery [23], polymicrobial infections caused by aerobic and anaerobic bacteria producing β-lactamases [24], and mixed infections of the peritoneal cavity of paediatric patients with intraabdominal infections [25]. Piperacillin/tazobactam has enhanced activity against most organisms producing β-lactamases [26], and treats infections caused by organisms with plasmid-mediated β-lactamases [27]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams thrice-daily treats pneumoniae and bronchitis caused by *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, Enterobacter species,* or by *Escherichia col*i [28], soft-tissue bacterial infections [29], serious infections of soft-tissue caused by group A streptococci or by *Pseudomonas aeruginosa* [30], and polymicrobial infections [31]. Intravenous imipenem/cilastatin treats febrile neutropenia in paediatric patients as intravenous piperacillin/tazobactam [32]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily treats high-risk febrile neutropenic patients with cancer as 2 grams of intravenous cefepime administered thrice-daily [33], and piperacillin/tazobactam administered intravenously at a dose of 3/0.375 grams 4 times-daily is more effective than ticarcillin/clavulanate administered intravenously at a dose of 3 grams/100 milligrams 4 times-daily in treatment of lower respiratory-tract infections [34]. These results indicate that piperacillin/tazobactam treats different infections. The trials with piperacillin/tazobactam have been reviewed. Piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams 4 times-daily treats patients infected by gram-negative organism as imipenem/cilastatin/relebactam administered intravenously at a dose of 500 mg/500 mg/250 mg 4 times-daily [35], and piperacillin/tazobactam administered by continuous infusion at a dose of 4.5/0.5 grams 4 times-daily treats patients infected by gram-negative bacteria [36]. Piperacillin/tazobactam administered intravenously at a dose of 337.5/80 mg/kg daily is effective as cefepime administered intravenously at a dose of 100 mg/kg daily in treatment of children with febrile neutropenia [37]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily treats febrile patients with severe neutropenia as cefepime administered intravenously at a dose of 2 grams thrice-daily plus amikacin administered intravenously at dose of 20 mg/kg once-daily [38], and piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams thrice-daily is more effective than imipenem/cilastatin administered intravenously at a dose of 2/0.5 grams thrice-daily in treatment of severe diabetic foot infection [39]. Ertapenem administered intravenously at a dose of 1 gram once-daily is efficacy as piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams thrice-daily in treatment of complicated infections caused by gram-negative bacteria [40], and ertapenem administered intravenously at a dose of 1 gram once-daily is efficacy as piperacillin/tazobactam administered intravenously at a dose of 3.375/0.85 grams 4 times-daily in treatment of intraabdominal infections [41]. Intravenous piperacillin/sulbactam treats community-acquired respiratory-tract and urinary-tract infections caused by β-lactamase producing organisms as intravenous piperacillin/tazobactam [42]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams 4 times-daily plus amikacin administered intravenously at a dose of 7.5 mg/kg twice-daily treats ventilator-associated pneumoniae as ceftazidime administered intravenously at a dose of 1 gram 4 times-daily plus amikacin administered intravenously at a dose of 7.5 mg/kg twice-daily [43]. Piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams 4 times-daily treats complicated urinary-tract bacterial infections [44], and piperacillin/tazobactam administered intravenously at a dose of 4/0.5 grams thrice-daily is more effective than imipenem/cilastatin administered intravenously at a dose of 500/500 mg thrice-daily in treatment of intraabdominal infections caused by sensitive organisms [45]. These results indicate that trials with piperacillin/tazobactam co-administered with other drugs treat different infections. Little is known about the toxicity induced by piperacillin/tazobactam. The combination of vancomycin plus piperacillin/tazobactam increases the odds of acute kidney injury [46]. Piperacillin/tazobactam induces nephrotoxicity in paediatric oncology patients with fever plus neutropenia [47], and induces nephrotoxicity in 18% of elderly patients with pneumonia [48]. Piperacillin/tazobactam administered intravenously at a dose of 4.5/0.5 grams thrice-daily for 10 days to patients with bone-related infections induces neutropenia in 34.1% of patients and the neutropenia increases with increasing the cumulative dose of piperacillin [49]. These results indicate that piperacillin/tazobactam my induce nephrotoxicity of neutropenia in some patients. The penetration of piperacillin and tazobactam into the cerebrospinal fluid has been reviewed. Piperacillin was administered intravenously at a dose of 100 mg/kg twice-daily to 70 infants with the meningitis caused by Escherichia coli or by Pseudomonas aeruginosa the mean concentration of piperacillin in the cerebrospinal fluid is 51.1 µg/ml and this concentration is higher than the minimum inhibitory concentration of bacteria causing the meningitis and the bacteria were eradicated from the cerebral spinal fluid [50]. Piperacillin/tazobactam was administered intravenously at a dose of 113/96.7 mg/kg thrice-daily to 5 children with meningitis caused by *Haemophilus influenzae.* The concentration of piperacillin and tazobactam in the cerebrospinal fluid ranges from 2.54 to 7.74 µg/ml and from 0.32 to 1.32 µg/ml, respectively, and this treatment eradicates *Haemophilus influenzae* from the cerebrospinal fluid [51]. Following the administration of the first intravenous dose of 6/0.5 grams of piperacillin/tazobactam to 9 patients with non-inflammatory occlusive hydrocephalus the peak concentration of piperacillin and tazobactam in the cerebrospinal fluid ranges from 8.67 to < 0.37 (median, 3.42) and from 1.37 to 0.11 µg/ml (median, 0.45), respectively.

Piperacillin and tazobactam are slowly eliminated from the cerebrospinal fluid and the elimination half-life of piperacillin and tazobactam from the cerebrospinal fluid is 5.9 and 6.1 hours, respectively. The concentration of tazobactam of 4 µg/ml is inadequate to treat cranial infections caused by organisms producing β-lactamases and a dose of 0.5 grams thrice-daily is necessary to combat infections of the central nervous system caused by these organisms [52]. Six patients with subarachnoid haemorrhage and 4 patients with intracerebral haemorrhage received piperacillin/tazobactam intravenously at a dose of 4/0.5 grams thrice-daily. The mean peak concentration of unbound piperacillin in brain interstitial space is 1.6 and 2.78 µg/ml after the first administration and multiple doses, respectively. Simulations suggested that the probability of target attainment would exceeds 90% for the minimum inhibitory concentration of 0.5 and 1 µg/ml at a daily dose of piperacillin of 12 to 16 grams and 24 grams, respectively [53]. Ten adult patients with purulent meningitis caused by gram-negative organisms received 3 intravenous doses of 4 grams of piperacillin, the mean concentration of piperacillin in the cerebrospinal fluid is 9.2 µg/ml, the mean piperacillin penetration-rate is 22.7%, and the meningitis was cured after 10 to 20 days of treatment [54]. These results indicate that piperacillin penetrates into the cerebrospinal fluid in significant amounts. Little is known about the treatment of meningitis with piperacillin/tazobactam. Piperacillin/tazobactam was administered intravenously at a dose of 4.5/0.5 grams 4 times-daily to adult patients with the meningitis caused by *Streptococcus pneumoniae, Neisseria meningitis, Haemophilus influenzae, Staphylococcus,* or by *Escherichia coli* and the meningitis was cured [55]. A patient with meningitis caused by *Elizabethkingia meningoseptica* received piperacillin/tazobactam intravenously at a dose of 4.5/0.5 grams 4 times-daily plus vancomycin and clotrimazole orally and this treatment sterilized the cerebrospinal fluid [56]. Post-surgical meningitis was diagnosed in 101 cases and 10 cases had the nosocomial meningitis caused by *Pseudomonas meningitis.* Piperacillin/tazobactam was administered intravenously at a dose of 4.5/0.5 grams 4 times-daily and the meningitis was cured in 50% of cases [57]. The transfer of piperacillin and tazobactam across the human placenta has been reviewed. Piperacillin/tazobactam was administered intravenously at a dose of 4/0.5 grams 4 times-daily to 6 pregnant women at delivery and both piperacillin and tazobactam freely cross the human placenta [58]. Piperacillin was administered intravenously at a dose of 4 grams 4 times-daily to pregnant women at delivery and piperacillin promptly crossed the human placenta [59].

In conclusion, piperacillin extends the spectrum of activity of ampicillin and combined with tazobactam, piperacillin/tazobactam has the broadest antibacterial spectrum of penicillins. Piperacillin is metabolized into desethylpiperacillin, desethylpiperacillin is glucoronated, and desethylpiperacillin-glucuronide is excreted into the bile. Piperacillin and tazobactam penetrate into body-tissues in significant amounts. The pharmacokinetics of piperacillin and tazobactam have been studied in patients with complicated intraabdominal infection who received piperacillin/tazobactam by a continuous infusion or by intermittent infusion. The elimination half-lifeof piperacillin and that of tazobactam is similar according to the two regimens of infusion and is about 1 and 1.8 hours, respectively. The efficacy and safely, prophylaxis, treatment, and trials with piperacillin/tazobactam have been reviewed and piperacillin/tazobactam may induce nephrotoxicity or neutropenia in some patients. The penetration of piperacillin and tazobactam into the cerebrospinal fluid has been reviewed. Piperacillin penetrates into the cerebrospinal fluid in significant amounts whereas tobramycin reaches lower concentrations in the cerebrospinal fluid, piperacillin/tazobactam treats bacterial meningitis, and piperacillin and tazobactam freely cross the human placenta. The aim of this study is to review the clinical pharmacology of piperacillin.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

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References

1. MacDougal C. "Penicillins, Cephalosporin, and Other β-Lactam Antibiotics". In The Goodman & Gilman's. The Pharmacological Basis of the Therapeutics, Brunton Hilal-dandan LL, Knollmann BC, editors. Mc Graw Hill, 13th Edition, USA, New York. 2018;1023-1038.

2. Machado-Albaa JE, Gaviria-Mendozab A, Machado-Duque ME. Results of the effectiveness of two piperacillin–tazobactam molecules in the real world. *Int J Infect Dis.* 2018;76(6):91-96.

3. Takimoto K, Wang Q, Suzuki D, et al. Clinical efficacy of piperacillin/tazobactam in the treatment of complicated skin and soft-tissue infections. *Expert Opin Pharmacother.* 2017;18(10):1027-1034.

4. Tamura K, Akiyama N, Kanda Y, et al. Efficacy and safely of tazobactam/piperacillin as an empirical treatment for the patients of adult and child with febrile neutropenia in Japan. *J Infect Chemother.* 2015;21(9):654-662.

5. Charoenpong L, Tongsai S, Thamlikitkul V. Effectiveness and safely of generic formulation of piperacillin/tazobactam (Astaz-P) for treatment of infected patients at Siriraj Hospital. *J Med Assoc Thai.* 2013;96(Suppl 2):S104-S110.

6. Mouton Y, Leroy O, Beuscart C, et al. Efficacy, safely and tolerance of parenteral piperacillin/tazobactam in the treatment of patients with lower respiratory tract infections. *J Antimicrob Chemother.* 1993;31(Suppl A):87-95.

7. Huang CT, Chen CH, Chen WC, et al. Clinical effectiveness of cefoperazone-sulbactam vs. piperacillin-tazobactam for the treatment of pneumonia in elderly patients. *Int J Antimicrob Agents.* 2022;59(1):106491

8. Aamir M, Abrol P, Sharma D, et al. A clinical evaluation of efficacy and safely of cefepime monotherapy versus piperacillin-tazobactam in patients of paediatric age group with febrile neutropenia in a tertiary care centre of north India. *Trop Doct.* 2016;46(3):142-148.

9. Ghibellini G, Bridges AS, Generaux CN, et al. In vitro and in

vivo determination of piperacillin metabolism in humans. *Drug Metab Dispos*. 2007;35(3):345-249.

10. Tomaselli F, Dittrich P, Maier A, et al. Penetration of piperacillin and tazobactam into pneumonic human lung tissue measured by in vivo microdialysis. *Br J Clin Pharmacol.* 2003;55(6):620-624.

11. Tanimura H. Tissue concentrations and clinical effect of tazobactam/piperacillin in surgical infections. *Chemother.* 1994;(suppl 2):612-628.

12. Roberts JA, Roberts MS, Robertson TA, et al. Piperacillin penetration into tissue of critically ill patients with sepsis--bolus versus continuous administration? *Crit Care Med.* 2009;37(3):926-933.

13. Li C, Kuti JL, Nightingale CH, et al. Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intraabdominal infection. *J Antimicrob Chemother*. 2005;56(2):388-395.

14. De Pastena M, Paiella S, Azzini AM, et al. Antibiotic Prophylaxis with Piperacillin-Tazobactam Reduces Post-Operative Infectious Complication after Pancreatic Surgery:An Interventional, Non-Randomized Study. *Surg Infect (Larchmt).* 2021;22(5):536-542.

15. Shigemura K, Tanaka K, Hamasuna R, et al. Efficacy of Prophylactic Antimicrobial Administration of Tazobactam/Piperacillin for Radical Cystectomy with Urinary Diversion:A Multicenter Study. *Urol Int.* 2019;102(3):293-298.

16. Viscoli C, Cometta A, Kern WV, et al. Piperacillin-tazobactam monotherapy in high-risk febrile and neutropenic cancer patients. *Clin Microbiol Infect.* 2006;12(3):212-216.

17. Esposito S, Leone S, Noviello S, et al. Antibiotic prophylaxis in hernia repair and breast surgery:a prospective randomized study comparing piperacillin/tazobactam versus placebo. *J Chemother.* 2006;18(3):278-284.

18. Remynse LC 3rd, Sweeney PJ, Brewton KA, et al. Intravenous piperacillin/tazobactam plus fluoroquinolone prophylaxis prior to prostate ultrasound biopsy reduces serious infectious complications and is cost effective. *Open Access J Urol.* 2011;17(3):139-143.

19. Solano C, Gutierrez A, Martine M, et al. Prophylaxis of early bacterial infections after autologous Peripheral Blood Stem Cell Transplantation (PBSCT):a matched-pair study comparing oral fluoroquinolones and intravenous piperacillin-tazobactam. *Bone Marrow Transplant.* 2005;36(1):59-65.

20. Trimbos JB, van Lindert AC, Heintz AP, et al. Piperacillin for prophylaxis in gynecological surgery. *Eur J Obstet Gynecol Reprod Biol.* 1989;30(2):141-149.

21. Yasuda M, Nakane K, Yamada Y, et al. Clinical effectiveness and safely of tazobactam/piperacillin 4.5 g for the prevention of febrile infectious complication after prostate biopsy. *J Infect Chemother.* 2014;20(10):631-634.

22. Cotrina-Luque J, Gil-Navarro MV, Acosta-García H, et al. Continuous versus intermittent piperacillin/tazobactam infusion in infection due to or suspected pseudomonas aeruginosa. *Int J Clin Pharm.* 2016;38(1):70-79.

23. Rodrigo JP, Sŭrez C, Bernaldez R, et al. Efficacy of piperacillin-tazobactam in the treatment of surgical wound infection after clean-contaminated head and neck oncologic surgery. *Head Neck.* 2004;26(9):823-828.

24. Perry CM, Markham A. Piperacillin/tazobactam:an updated review of its use in the treatment of bacterial infections. *Drugs.* 1999;57(5):805-843.

25. Arguedas A, Sifuentes-Osornio J, Loaiza C, et al. An open, multicenter clinical trial of piperacillin/tazobactam in the treatment of pediatric patients with intraabdominal infections. *J Chemother.* 1996;8(2):130-136.

26. Schoonover LL, D Occhipinti J, Rodvelderly KA, et al. Piperacillin/tazobactam:a new beta-lactam/beta-lactamase inhibitor combination. *Ann Pharmacother.* 1995;29(5):501-514.

27. Sanders WE Jr , Sanders CC. Piperacillin/tazobactam:a critical review of the evolving clinical literature. *Clin Infect Dis.* 1996;22(1):107-123.

28. Sifuentes-Osornio J, Ruíz-Palacios GM, Jakob E, et al. Piperacillin/tazobactam in the treatment of lower respiratory tract infections:an open non-comparative and multicentered trial. Latin American Clinical Research Group. *J Chemother.* 1994;6(3):197-203.

29. Tassler H, Cullmann W, Elhardt D. Therapy of soft-tissue infections with piperacillin/tazobactam. *J Antimicrob Chemother.* 1993;31(Suppl A):105-112.

30. Gould IM, Ansari A, Harvey G, et al. Piperacillin/tazobactam in the treatment of serious acute soft-tissue infection. *Drugs Exp Clin Res.* 1991;17(3):187-190.

31. Bryson HM, Brogden RN. Piperacillin/tazobactam. A review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. *Drugs.* 1994;47(3):506-535.

32. Vural S, Erdem E, Gulec SG, et al. Imipenem-cilastatin versus piperacillin-tazobactam as monotherapy in febrile neutropenia. *Pediatr Int*. 2010;52(2):262-267.

33. Bow EJ, Rotstein C, Noskin GA, et al. A randomized, open-label, multicenter comparative study of the efficacy and safely of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. *Clin Infect Dis.* 2006;43(4):447-459.

34. Shlaes DM, Baughman R, Boylen CT, et al. Piperacillin/tazobactam compared with ticarcillin/clavulanate in community-acquired bacterial lower respiratory tract infection. *J Antimicrob Chemother.* 1994;34(4):565-577.

35. Titov I, Wunderink RG, Roquilly A, et al. A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safely of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study). *Clin Infect Dis*. 2021;73(11):e4539-e4548.

36. Hagel S, Fiedler S, Hohn A, et al. Therapeutic drug monitoring-based dose optimisation of piperacillin/tazobactam to improve outcome in patients with sepsis (TARGET):a prospective, multi-centre, randomised controlled trial. *Trials.* 2019;20(1):330.

37. Sano H, Kobayashi R, Suzuki D, et al. Comparison between piperacillin/tazobactam and cefepime monotherapies as an empirical therapy for febrile neutropenia in children with hematological and malignant disorders:A prospective,

randomized study. *Pediatr Blood Cancer.* 2015;62(2):356-358.

38. Sanz MA, López J, Lahuerta JJ, et al. Cefepime plus amikacin versus piperacillin-tazobactam plus amikacin for initial antibiotic therapy in haematology patients with febrile neutropenia:results of an open, randomized, multicentre trial. *J Antimicrob Chemother.* 2002;50(1):79-88.

39. Saltoglu N, Dalkiran A, Tetiker T, et al. Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections:a prospective, randomized clinical trial in a university hospital. *Clin Microbiol Infect.* 2010;16(8):1252-1257.

40. An MM, Zou Z, Shen H, et al. Ertapenem versus piperacillin/tazobactam for the treatment of complicated infections:a meta-analysis of randomized controlled trials. *BMC Infect Dis.* 2009;9(12):193.

41. Solomkin JS, Yellin AE, Rotstein OD, et al. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections:results of a double-blind, randomized comparative phase III trial. *Ann Surg.* 2003;237(2):235-245.

42. Zhiyong Z, Xiaoju L, Yanbin L, et al. Piperacillin-sulbactam versus piperacillin-tazobactam:a multicentre, randomised, single-blind, controlled clinical trial. *Int J Antimicrob Agents.* 2005;26(1):22-27.

43. Brun-Buisson C, Sollet JP, Schweich H, et al. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin versus ceftazidime/amikacin:a multicenter, randomized controlled trial. VAP Study Group. *Clin Infect Dis.* 1998;26(2):346-354.

44. Sifuentes-Osornio J, Jakob E, Clara L, et al. Piperacillin/tazobactam in the treatment of hospitalized patients with urinary tract infections:an open non-comparative and multicentered trial. *J Chemother.* 1996;8(2):122-129.

45. Eklund AE, Nord CE. A randomized multicenter trial of piperacillin/tazobactam versus imipenem/cilastatin in the treatment of severe intraabdominal infections. Swedish Study Group. *J Antimicrob Chemother.* 1993;31(Suppl A):79-85.

46. Luther MK, Timbrook TT, Caffrey AR, et al. Vancomycin Plus Piperacillin-Tazobactam and Acute Kidney Injury in Adults:A Systematic Review and Meta-Analysis. *Crit Care Med.* 2018;46(1):12-20.

47. Pratt JA, Stricherz MK, Verghese PS, et al. Suspected piperacillin-tazobactam induced nephrotoxicity in the pediatric oncology population. *Pediatr Blood Cancer.* 2014;61(2):366-368.

48. Karino F, Nishimura N, Ishihara N, et al. Nephrotoxicity induced by piperacillin–tazobactam in late elderly Japanese patients with nursing and healthcare associated pneumonia. *Biol Pharm Bull*. 2014;37(12):1971-1976.

49. Peralta FG, Sánchez MB, Roíz MP, et al. Incidence of neutropenia during treatment of bone-related infections with piperacillin-tazobactam. *Clin Infect Dis.* 2003;37(11):1568-1572.

50. Placzek M, Whitelaw A, Want S, et al. Piperacillin in early neonatal infection. *Arch Dis Child.* 1983;58(12):1006-1009.

51. Fukasawa C, Hoshino T, Hoshino T, et al. Concentration of tazobactam/piperacillin in the Cerebrospinal Fluid of Patients with Haemophilus influenzae Type B Meningitis. *Infect Dis.* 2013;87(5):590-595.

52. Nau R, Kinzig-Schippers M, Sörgel F, et al. Kinetics of piperacillin and tazobactam in ventricular cerebrospinal fluid of hydrocephalic patients. *Antimicrob Agents Chemother.* 1997;41(5):987-991.

53. Ullah S, Beer R, Fuhr U, et al. Brain Exposure to Piperacillin in Acute Hemorrhagic Stroke Patients Assessed by Cerebral Microdialysis and Population Pharmacokinetics. *Antimicrob Agents Chemother.* 1997;33(3):740-748.

54. Decazes JM, Meulemans A, Bure A, et al. Penetration of piperacillin into the cerebrospinal fluid of patients with purulent meningitis. *Presse Med.* 1984;13(5):261-264.

55. Mengistu A, Gaeseb J, Uaaka G, et al. Antimicrobial sensitivity patterns of Cerebrospinal Fluid (CSF) isolates in Namibia:implications for empirical antibiotic treatment of meningitis. *J Pharm Policy Pract.* 2013;6:4.

56. Tak V, Mathur P, Varghese P, et al. Elizabethkingia meningoseptica:an emerging pathogen causing meningitis in a hospitalized adult trauma patient. *Indian J Med Microbiol.* 2013;31(3):293-295.

57. Juhi T, Bibhabati M, Archana T, et al. Pseudomonas aeruginosa meningitis in post neurosurgical patients. *Neurol Asia.* 2009;14(2):95-100.

58. Bourget P, Sertin A, Lesne-Hulin A, et al. Influence of pregnancy on the pharmacokinetic behaviour and the transplacental transfer of the piperacillin-tazobactam combination. *Eur J Obstet Gynecol Reprod Biol.* 1998;76(1):21-27.

59. Brown CE, Christmas JT, Bawdon RE. Placental transfer of cefazolin and piperacillin in pregnancies remote from term complicated by Rh isoimmunisation. *Am J Obstet Gynecol.* 1990;163(3):938-943.