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Piperacillin–tazobactam: a β -lactam/ β -lactamase inhibitor combination

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Piperacillin–tazobactam is a β -lactam/ β -lactamase inhibitor combination with a broad spectrum of antibacterial activity that includes Gram-positive and -negative aerobic and anaerobic bacteria. Piperacillin–tazobactam retains its *in vitro* activity against broad-spectrum β -lactamase-producing and some extended-spectrum β -lactamase-producing Enterobacteriaceae, but not against isolates of Gram-negative bacilli harboring AmpC β -lactamases. Piperacillin–tazobactam has recently been reformulated to include ethylenediaminetetraacetic acid and sodium citrate; this new formulation has been shown to be compatible *in vitro* with the two aminoglycosides, gentamicin and amikacin, allowing for simultaneous Y-site infusion, but not with tobramycin. Multicenter, randomized, double-blinded clinical trials have demonstrated piperacillin–tazobactam to be as clinically effective as relevant comparator antibiotics. Clinical trials have demonstrated piperacillin–tazobactam to be effective for the treatment of patients with intra-abdominal infections, skin and soft tissue infections, lower respiratory tract infections, complicated urinary tract infections, gynecological infections and more recently, febrile neutropenia. Piperacillin–tazobactam has an excellent safety and tolerability profile and continues to be a reliable option for the empiric treatment of moderate-to-severe infections in hospitalized patients.

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Piperacillin–tazobactam is a β -lactam/ β -lactamase inhibitor combination with broad-spectrum antibacterial activity against Gram-positive and -negative aerobic and anaerobic bacteria [1]. Piperacillin, a ureidopenicillin, demonstrates *in vitro* activity against members of the family Enterobacteriaceae and *Pseudomonas aeruginosa* [2]. The addition of tazobactam to piperacillin inactivates β -lactamases produced by Enterobacteriaceae as well as other Gram-negative and -positive aerobic and anaerobic pathogens [1,3]. Tazobactam extends piperacillin's spectrum of activity, permitting its use in various clinical infections [4]. Piperacillin–tazobactam is less active *in vitro* against *Escherichia coli*, *Klebsiella* spp. and other Enterobacteriaceae-producing extended-spectrum β -lactamases (ESBLs) than against isolates not producing ESBLs [5]. Piperacillin–tazobactam

has been clinically proven to be effective for the treatment of patients with intra-abdominal infections, skin and soft tissue infections, lower respiratory tract infections, complicated urinary tract infections, gynecological infections and febrile neutropenic patients [4].

The purpose of this article is to provide an updated review of the chemistry, mechanism of action and resistance, microbiology and pharmacokinetics/pharmacodynamics of piperacillin–tazobactam. Recent (2000 to present) clinical trials assessing the efficacy and safety of piperacillin–tazobactam will also be considered.

Chemistry

Penicillins are a large group of bicyclic ring compounds containing a 4-membered β -lactam ring fused to a 5-membered thiazolidine ring [6].

Addition of substituents to the 6-amino group of 6-aminopenicillanic acid has resulted in the development of various semi-synthetic penicillins such as piperacillin [6]. The specific substituent added determines the characteristics of the penicillin, including resistance to β -lactamases, acid stability and spectrum of antimicrobial activity [7].

Piperacillin, a ureidopenicillin, is derived from D(-)- α -aminobenzyl-penicillin (ampicillin) by the addition of a hydrophilic heterocyclic group to the α -amino group of ampicillin (FIGURE 1). This substituent improves the activity of piperacillin against Gram-negative bacteria, partly due to increased affinity for penicillin-binding protein (PBP)-3, and thus leads to a broader spectrum of activity [7]. Tazobactam is a penicillanic acid sulfone derivative that has a similar chemical structure to that of sulbactam, another β -lactamases inhibitor [8]. The penicillanic acid sulfone nucleus of tazobactam contains a triazolymethyl substituent at position 2 (FIGURE 1). The structure of sulbactam differs in that it has a methyl group at this position [9]. The addition of tazobactam to piperacillin allows for greater stability of piperacillin against β -lactamases including β -lactamase-producing staphylococci, Enterobacteriaceae, *Haemophilus influenzae* and *Bacteroides* spp. [4]. Tazobactam alone lacks any intrinsic antibacterial activity [10].

Both piperacillin and tazobactam are supplied as a sodium salt in an 8:1 piperacillin:tazobactam ratio. In the USA and Canada, piperacillin–tazobactam (Zosyn[®], Tazocin[®]) has been recently reformulated to include ethylenediaminetetraacetic acid (EDTA) and sodium citrate [11]. This new formulation has been shown to be compatible *in vitro* with the two aminoglycosides, gentamicin and amikacin, allowing for simultaneous Y-site infusion. It is not compatible with tobramycin and its compatibility with other aminoglycosides has not been

established [11]. The addition of EDTA has also allowed for lactated Ringer's solution to be included as a compatible solution [11]. The new formulation increases the sodium content by 0.4 mEq/g compared with the previous product [11].

Mechanism of action

β -lactam antibiotics, including piperacillin, are bactericidal due to the irreversible inhibition of PBP enzymes [3]. PBPs are critical enzymes of the bacterial cell that catalyze the final cross-linkage between peptidoglycan strands [12]. Peptidoglycan is an essential component of the bacterial cell wall, which protects the cell from osmotic rupture, maintains the cell shape and is integral for cell growth and division [7]. Individual peptidoglycan strands consist of a polysaccharide chain composed of *N*-acetyl glucosamine residues alternating with *N*-acetyl muramic acid residues [12]. Attached to each *N*-acetyl muramic acid residue is a pentapeptide chain that terminates with a D-alanine residue linked to another D-alanine residue [12]. The active site of PBPs contains a serine residue that targets the terminal D-alanine–D-alanine bond of the pentapeptide chains [12,13]. These enzymes cleave the terminal D-alanine residue of a peptide chain and catalyze formation of a new peptide bond between the remaining D-alanine residue and the peptide chain of an adjacent peptidoglycan strand [12,13].

Due to the stereochemical similarity between piperacillin and the D-alanine–D-alanine substrate of PBPs, piperacillin is able to inhibit these enzymes by forming a covalent complex with the serine residue at the enzymes' active site [12]. The formation of this penicilloyl–enzyme complex interferes with the normal transpeptidase reaction resulting in a loss of integrity to the cell wall [12]. Through a complex mechanism, autolysins are released after the PBP binding, which leads to lysis of the bacterial cell wall [3].

Various β -lactam antibiotics demonstrate different affinities towards various PBPs [14]. Piperacillin's broader spectrum of activity against Gram-negative bacteria is primarily due to increased affinity towards PBP-3 [7]. Piperacillin has been shown to bind quite selectively to PBP-3 in *E. coli* [15,16]. Studies have demonstrated that binding to PBP-3 appears to interfere with septation, thereby inhibiting cell division and causing elongated filament formation [15,16]. Piperacillin also binds moderately to PBP-2 and -7 in *E. coli* [15]. Piperacillin has been shown to bind with high affinity to all *Streptococcus pneumoniae* PBPs [14]. Studies have reported that piperacillin demonstrates comparable *in vitro* activity with cefotaxime and ceftriaxone against β -lactamase-negative ampicillin-resistant *H. influenzae* due to potent affinities towards PBP-2, PBP-3a and PBP-3b [17].

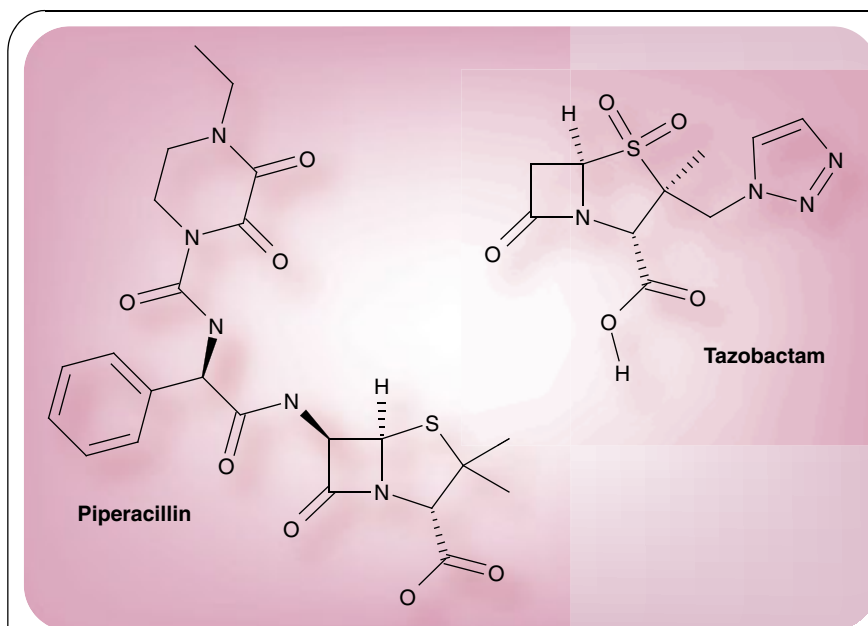


Figure 1. Piperacillin and tazobactam.

Certain β -lactamase enzymes (Ambler Class A, C and D) contain a serine residue at the active site, similar to PBPs. These enzymes are capable of hydrolyzing the β -lactam ring of many penicillin antibiotics [12]. A temporary acyl-enzyme intermediate is formed during the process of hydrolysis. Tazobactam inactivates β -lactamase enzymes by irreversibly binding to them through the formation of a stable acyl-enzyme complex (acyl enzyme then highly reactive imine followed by an enamine). This complex is identical to the acyl-enzyme intermediate formed with the normal β -lactam substrates of these enzymes [10]. The tazobactam– β -lactamase complex protects piperacillin from the hydrolytic activity of β -lactamases [10].

Mechanism of resistance

The four potential mechanisms of resistance to piperacillin–tazobactam include β -lactamase enzyme production, alteration of the target site (PBPs), a change in membrane permeability or an increase in the membrane efflux [18]. Production of β -lactamase enzymes by Gram-negative bacteria is the major mechanism of resistance towards piperacillin [19]. Tazobactam inhibits Ambler Class A β -lactamases, but is not active against Class B metallo- β -lactamases as they are intrinsically resistant to β -lactamase inhibitors leading to resistance with piperacillin–tazobactam [10,19]. Acquired metallo- β -lactamases are now being observed in species such *P. aeruginosa* and *Klebsiella pneumoniae* [19].

The prevalence of ESBL-producing organisms is increasing [20,21]. ESBLs are β -lactamase enzymes that are capable of hydrolyzing an expanded substrate spectrum, including the extended-spectrum (third-generation) cephalosporins, cefotaxime and ceftazidime. These enzymes result from genetic mutations in more narrow-spectrum β -lactamases, especially those of the TEM and SHV type. ESBLs are most often found in *K. pneumoniae*, *Klebsiella oxytoca* and *E. coli* [5]. Piperacillin–tazobactam is significantly less active against *Klebsiella* spp. and *E. coli* isolates that produce an ESBL [21,22]. Owing to resistance concerns and a lack of published clinical data supporting their efficacy, it is controversial as to whether β -lactam/ β -lactamase inhibitor combinations should be used against ESBL-producing strains [22–25]. Some *in vitro* data suggest that piperacillin–tazobactam should not be used against ESBL-producing *K. pneumoniae* due to limited activity at high inoculum [24,26]. Piperacillin–tazobactam has been demonstrated *in vitro* to be less effective against ESBL-producing *Klebsiella* spp. than ESBL-producing *E. coli* [22].

The use of piperacillin–tazobactam in the treatment of infections caused by Gram-negative bacteria that produce an AmpC β -lactamase is also potentially problematic as hyperproduction of these enzymes generally confers resistance to β -lactamase inhibitors [5,19]. Chromosomally encoded, inducible AmpC β -lactamases are present in several clinically important Gram-negative bacteria, including *Citrobacter freundii*, *Acinetobacter* and *Enterobacter* spp. Plasmid-mediated AmpC β -lactamases are now appearing in other species that do not naturally produce the AmpC enzyme, such as *Klebsiella* spp., *Proteus*

mirabilis and *Salmonella* spp. [19,27]. *In vitro*, it has been found that increasing the relative proportion of tazobactam in the piperacillin–tazobactam combination increased the effectiveness of this antibiotic against AmpC-producing *E. coli* that were resistant to ceftazidime [28]. In one study, the development of AmpC-mediated resistance to piperacillin was shown to be suppressed by tazobactam but not clavulanic acid. This suppressive effect was mediated primarily by the β -lactamase inhibitory activity of tazobactam [29].

The major mechanism conferring resistance to piperacillin–tazobactam in Gram-positive bacteria is alteration of the PBPs [13]. While piperacillin–tazobactam exhibits a broad spectrum of antibacterial activity, some Gram-positive bacteria demonstrate intrinsic resistance to the antibiotic. Low affinity of *Enterococcus faecium* PBP-5 as well as methicillin-resistant *Staphylococcus aureus* (MRSA) PBP-2a for piperacillin is associated with resistance to the combination of piperacillin–tazobactam [30,31]. Mutations of PBP-2b in *S. pneumoniae* significantly decreases the affinity of this PBP for piperacillin, thereby causing a decrease in the autolytic response [14].

While changes in membrane permeability are not a common mechanism conferring resistance to piperacillin–tazobactam, studies of *K. pneumoniae* have reported that an increase in SHV-1 β -lactamase production may be accompanied by decreased permeability to the antibiotic [18,32]. The decrease in permeability here is thought to contribute to an increase in resistance [32]. Resistance–nodulation–cell division-type multidrug efflux systems (such as MexAB–OmpM) have been shown to accommodate β -lactams. However, efflux systems are rarely implicated as the main cause of β -lactam resistance [19,33].

Microbiology

Piperacillin–tazobactam displays broad-spectrum *in vitro* activity against Gram-positive and -negative aerobic and anaerobic bacteria (TABLES 1–3). Piperacillin–tazobactam is active against methicillin-susceptible *S. aureus* (MSSA), but clinically inactive against MRSA, as are all β -lactams (TABLE 1) [34]. Piperacillin–tazobactam displays decreased potency against penicillin-intermediate and -resistant streptococci, consistent with altered PBPs. Although piperacillin–tazobactam is active against *Enterococcus faecalis*, it is clinically inactive against *E. faecium* due to its intrinsic resistance to β -lactams [30,34].

Piperacillin–tazobactam demonstrates high potency against *H. influenzae* [34]. ESBL-producing Enterobacteriaceae are an increasingly concern. The carbapenems retain their *in vitro* potency against ESBL-producing organisms (TABLE 2) [21,34]. Piperacillin–tazobactam displays less potent *in vitro* activity against ESBL-producing *E. coli* and *K. pneumoniae* than against non-ESBL-producing isolates (TABLE 2) [22]. Data from surveillance studies indicate that piperacillin–tazobactam susceptibility has remained stable for most species of Enterobacteriaceae [36]. Various studies have also demonstrated the sustained potency of piperacillin–tazobactam against *P. aeruginosa* [34,37].

Table 1. *In vitro* activity of piperacillin–tazobactam and comparator β -lactams against Gram-positive aerobes.

Bacteria	Piperacillin–tazobactam (mg/l)			Amoxicillin–clavulanic acid (mg/l)		Meropenem (mg/l)		Ceftriaxone (mg/l)	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Staphylococcus aureus</i> (MS)	1	2	0.03 to 128	1	2	0.12	0.12	4	4
<i>S. aureus</i> (MR)	16	>32	1 to >256	8	16	16	32	>32	>32
<i>Staphylococcus epidermidis</i>	0.5	2	0.03 to >128	1	8	0.06	0.12	1	2
<i>Streptococcus pyogenes</i>	0.06	0.12	0.03 to 4	0.03	0.03	≤0.03	≤0.03	≤0.03	≤0.03
<i>Streptococcus agalactiae</i>	0.25	0.5	0.12 to 16	0.06	0.12	0.06	0.06	0.06	0.12
<i>Streptococcus pneumoniae</i> (PS)	0.03	1	0.03 to 2	0.03	0.03	≤0.03	0.03	≤0.03	0.25
<i>S. pneumoniae</i> (PI)	≤1	2	≤1 to 2	0.25	1	0.12	0.5	0.25	0.5
<i>S. pneumoniae</i> (PR)	2	4	1 to 16	2	8	0.5	1.0	1	2
<i>Enterococcus faecalis</i>	4	8	0.06 to 64	1	1	4	16	>32	>32
<i>Enterococcus faecium</i>	32	>128	0.5 to >256	32	128	>32	>32	>32	>32

Clinical and Laboratory Standards Institute (CLSI) susceptible breakpoints for *Staphylococcus* spp.: piperacillin–tazobactam ≤8/4 mg/l, amoxicillin–clavulanic acid ≤4/2 mg/l, meropenem ≤4 mg/l and ceftriaxone ≤8 mg/l [106].

CLSI susceptible breakpoints for *Streptococcus* spp. other than *Streptococcus pneumoniae*: meropenem ≤0.5 mg/l and ceftriaxone ≤0.5 mg/l; breakpoints for piperacillin–tazobactam and amoxicillin–clavulanic acid are not published [106].

CLSI susceptible breakpoints for *S. pneumoniae*: amoxicillin–clavulanic acid ≤2/1 mg/l, meropenem ≤0.25 mg/l, and ceftriaxone ≤1 mg/l (nonmeningitis); breakpoints for piperacillin–tazobactam are not published [106].

CLSI breakpoints for piperacillin–tazobactam, amoxicillin–clavulanic acid, meropenem and ceftriaxone are not published for *Enterococcus* spp. [106].

MIC₅₀: Minimum inhibitory concentration that inhibited the growth of 50% of isolates tested; MIC₉₀: Minimum inhibitory concentration that inhibited the growth of 90% of isolates tested; MR: Methicillin resistant; MS: Methicillin susceptible; PI: Penicillin intermediate (penicillin MIC 0.12–1 mg/l); PR: Penicillin resistant (penicillin MIC ≥2 mg/l); PS: Penicillin susceptible (penicillin MIC ≤0.06 mg/l).

Data presented adapted from [34,38,107–122].

β -lactamase production is common among *Bacteroides fragilis*, and is becoming increasingly observed in other anaerobes such as *Prevotella* spp., *Fusobacterium* and *Clostridium* spp. [40]. Piperacillin–tazobactam, amoxicillin–clavulanic acid and meropenem all demonstrate more potent *in vitro* activity against anaerobic organisms than ceftriaxone (TABLE 3) [38,41].

Pharmacokinetics

The pharmacokinetics of piperacillin–tazobactam obtained from healthy volunteers and patients are presented in TABLES 4 AND 5. Piperacillin and tazobactam are not absorbed in the gastrointestinal tract and must be administered intravenously via infusion or as a slow bolus injection [4]. Over the past two decades, there has been ongoing controversy regarding whether piperacillin displays linear or nonlinear pharmacokinetics; to date, consensus has not been reached [42,43]. Tazobactam pharmacokinetics appear to be dose dependent when administered as a single agent in healthy volunteers [44].

In combination, piperacillin pharmacokinetics appear not to be affected by coadministration of tazobactam [44]. By contrast, the coadministration of piperacillin increased the maximum concentration of tazobactam in plasma (C_{max}), its area under the curve (AUC) and its half-life [44–46]. In a study comparing two piperacillin–tazobactam high-dose regimens, tazobactam half-life was prolonged compared with conventional piperacillin–tazobactam regimens, suggesting nonlinear tazobactam pharmacokinetics. The increase in tazobactam half-life may be as a result of competitive inhibition of tazobactam renal elimination by piperacillin [44–46]. Examination of the penetration of the antibiotic into the inflammatory exudates of healthy male subjects displayed the percentage of tazobactam penetration to be higher when coadministered with piperacillin (67.7%) than when administered alone (46.7%) [46].

Children aged 2 months to 12 years administered either low-dose 50/6.25-mg/kg or high-dose 100/12.5-mg/kg piperacillin–tazobactam showed no statistically significant difference in pharmacokinetic parameters relative to dose with the

Table 2. *In vitro* activity of piperacillin–tazobactam and comparator β -lactams against Gram-negative aerobes.

Bacteria	Piperacillin–tazobactam (mg/l)			Amoxicillin–clavulanic acid (mg/l)		Meropenem (mg/l)		Ceftriaxone (mg/l)	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter</i> spp.	16	128	≤0.008 to 256	4	32	0.5	>8	16	>32
<i>Citrobacter freundii</i>	2	32	0.12 to 256	32	>32	0.03	0.06	0.12	32
<i>Enterobacter aerogenes</i>	2	32	0.25 to 256	>32	>32	≤0.03	0.06	0.12	32
<i>Escherichia coli</i>	1	4	≤0.06 to >128	4	16	≤0.06	≤0.06	0.06	≤0.25
<i>E. coli</i> (ESBL)	8	64	1 to 128	16	32	0.06	0.06	>32	>32
<i>Haemophilus influenzae</i>	0.06	0.125	0.03 to 1	0.5	1	0.03	0.25	≤0.03	0.26
<i>Klebsiella pneumoniae</i>	4	64	0.03 to 256	2	8	0.03	0.06	0.06	0.25
<i>K. pneumoniae</i> (ESBL)	32	128	1 to >256	16	>32	0.125	0.125	>32	>32
<i>Klebsiella oxytoca</i>	1	64	≤0.06 to 256	2	16	0.03	0.12	0.06	8
<i>Klebsiella</i> spp.	2	8	≤0.25 to >128	2	8	0.03	0.03	≤0.25	0.5
<i>Morexella catarrhalis</i>	0.25	0.25	0.25 to 8	0.12	0.25	≤0.03	≤0.03	0.12	0.5
<i>Morganella morganii</i>	0.25	0.5	0.25 to 32	>32	>32	0.25	0.25	0.12	8
<i>Proteus mirabilis</i>	0.25	0.5	0.03 to 256	1	2	0.06	0.06	0.03	0.12
<i>Proteus vulgaris</i>	0.25	2	0.03 to 16	8	8	0.12	0.12	>32	>32
<i>Pseudomonas aeruginosa</i>	4	>64	0.12 to >128	>16	>16	0.5	8	>32	>32
<i>Salmonella</i> spp.	2	16	0.25 to 256	1	1	0.03	0.06	0.06	0.125
<i>Serratia marcescens</i>	2	8	0.03 to 256	>32	>32	0.03	0.06	0.25	0.5
<i>Shigella</i> spp.	0.5	1	0.03 to 128	4	32	0.03	0.06	0.03	0.06
<i>Stenotrophomonas maltophilia</i>	>128	>128	32 to >256	32	>32	>32	>32	>32	>32

Clinical and Laboratory Standards Institute (CLSI) susceptible breakpoints for Enterobacteriaceae: piperacillin–tazobactam ≤16/4 mg/l, amoxicillin–clavulanic acid ≤8/4 mg/l, meropenem ≤4 mg/l and ceftriaxone ≤8 mg/l [106].

CLSI susceptible breakpoints for *Pseudomonas aeruginosa* and other non-Enterobacteriaceae: piperacillin–tazobactam ≤16/4 mg/l, meropenem ≤4 mg/l and ceftriaxone ≤8 mg/l; breakpoints for amoxicillin–clavulanic acid are not published [106].

ESBL: Extended-spectrum β -lactamase; MIC₅₀: Minimum inhibitory concentration that inhibited the growth of 50% of isolates tested; MIC₉₀: Minimum inhibitory concentration that inhibited the growth of 90% of isolates tested.

Data presented adapted from [21,22,38,39,107–114,116,117,120,122–128].

exception of AUC, C_{max} and C_{min} values [47]. Younger infants (<6 months) were shown to have a prolonged elimination half-life and a decreased clearance compared with older infants (>6 months) indicating that dosage adjustment may be required for infants less than 6 months [4,47]. Elimination half-life decreased and clearance increased with increasing age, however, the volume of distribution of piperacillin–tazobactam remained constant in both younger and older children [47]. Over 6 h, 70% of the administered dose was collected unchanged in the urine demonstrating renal clearance to account for a majority of the drug clearance [47]. As with adults, the elimination was shown to be highly dependant on renal function [47].

Distribution

The volume of distribution of piperacillin–tazobactam ranges from 15 to 18 l in healthy adults and patients (TABLE 4) [4]. Distribution into various tissue sites is generally regarded as good (with the exception of fat tissue) due to the hydrophilic nature of the two compounds [4,44,48]. Piperacillin–tazobactam concentrations in skin, muscle, lung, gallbladder and intestinal mucosa were 16–85% of those concentrations found in plasma, often exceeding the MIC₉₀ of common pathogens [44]. Similar to other β -lactam antibiotics, piperacillin–tazobactam penetration into fatty tissue is lower (~10% of plasma concentrations) compared with other tissues [48]. In a study of a blister model,

Table 3. *In vitro* activity of piperacillin–tazobactam and comparator β -lactams against anaerobes.

Bacteria	Piperacillin–tazobactam (mg/l)			Amoxicillin–clavulanic acid (mg/l)		Meropenem (mg/l)		Ceftriaxone (mg/l)	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Bacteroides fragilis</i>	0.5	4	≤0.008 to >128	0.25	1	0.12	0.5	32	64
<i>B. fragilis</i> group	4	16	≤0.125 to 64	2	4	0.25	0.5	64	>64
<i>Bacteroides ovatus</i>	4	8	≤0.06 to 32	0.25	1	0.25	0.5	>64	>64
<i>Bacteroides uniformis</i>	0.2	16	≤0.06 to >128	1	8	0.25	0.5	32	>128
<i>Bacteroides vulgatus</i>	2	16	≤0.06 to 32	4	16	0.25	0.5	16	>64
<i>Bacteroides thetaiotaomicron</i>	8	32	≤0.06 to 32	1	16	0.25	0.5	>64	>64
<i>Bacteroides distasonis</i>	4	8	≤0.06 to >128	8	16	0.25	0.5	32	>64
<i>Clostridium difficile</i>	8	16	2 to 32	0.25	2	2	4	32	64
<i>Clostridium perfringens</i>	0.25	0.5	≤0.06 to 1	0.06	0.25	0.016	0.03	2	8
<i>Fusobacterium</i> spp.	≤0.06	0.12	≤0.06 to 8	0.25	2	0.03	0.12	0.125	4
<i>Lactobacillus</i> spp.	2	4	0.06 to >128	0.25	2	8	>8	64	>64
<i>Peptostreptococcus</i> spp.	0.125	2	≤0.06 to 16	0.25	0.25	0.06	0.5	0.5	8
<i>Prevotella</i> spp.	≤0.06	≤0.06	≤0.006 to >128	0.03	0.25	0.06	0.25	0.5	32

Clinical and Laboratory Standards Institute susceptible breakpoints for anaerobes: piperacillin–tazobactam ≤32/4 mg/l, amoxicillin–clavulanic acid ≤4/2 mg/l, meropenem ≤4 mg/l and ceftriaxone ≤16 mg/l [128,129].

MIC₅₀: Minimum inhibitory concentration that inhibited the growth of 50% of isolates tested; MIC₉₀: Minimum inhibitory concentration that inhibited the growth of 90% of isolates tested.

Data presented adapted from [38,113,114,117,121,123,126,127,130–137].

tazobactam was shown to penetrate rapidly and to a greater extent when coadministered with piperacillin (67.7 vs 46.7% alone) [46]. The protein binding of piperacillin and tazobactam is low at 20–30% and 20–25%, respectively [43,49].

Metabolism & elimination

The major route of elimination of both piperacillin and tazobactam is renal, predominantly through active tubular secretion and glomerular filtration. Approximately 70–80% of the piperacillin dose eliminated in the urine is unmetabolized [50]. Piperacillin was shown to decrease the extent of renal elimination of tazobactam over 24 h from 63.7% of the administered dose to 56.8% [46]. Nonrenal elimination via hepatobiliary excretion also occurs but to a lesser extent [44]. Westphal and colleagues noted that the concentration of piperacillin in the bile was markedly higher than that of tazobactam, suggesting piperacillin only is actively secreted into the biliary tract [51]. Piperacillin and tazobactam undergo cleavage of their β -lactam rings

forming *N*-desethyl-piperacillin (minor active metabolite) and M₁ (inactive metabolite), respectively [49]. In subjects receiving ¹⁴C-labeled tazobactam, 26% were recovered as an inactive metabolite [52].

Renal insufficiency

The volume of distribution of piperacillin–tazobactam remains similar for patients with renal dysfunction and for those with normal renal function [50,53]. However the elimination half-life of piperacillin and tazobactam increases three- to fivefold in patients with decreased renal function compared with those with normal renal function [53]. In patients with creatinine clearance (CrCl) between 10 and 30 ml/min, renal excretion of piperacillin decreased to 35% of the administered dose [53]. In patients with CrCl less than 20 ml/min, the average AUC of piperacillin and tazobactam are threefold and four- to fivefold higher, respectively, than subjects with normal renal function [44]. The decrease in renal clearance appears to

Table 4. Pharmacokinetic parameters of piperacillin and tazobactam*.

Parameter	Dose	Piperacillin	Tazobactam	Ref.
Area under the curve (mg/l*h)	4/0.5 g	278	41	[51]
	4/0.5 g	296.0 (83.9)	43.6 (16.4)	[50]
	4/0.5 g	361 (80.3)	47.6 (13.3)	[47]
Maximum concentration (mg/l)	4/0.5 g	277	34	[51]
	4/0.5 g every 8 h	264.44 (50.5)	29.12 (5.59)	[45]
	4/0.5 g	259 (81.8)	27.9 (7.67)	[47]
Apparent plasma clearance (l/h)	4/0.5 g every 6 h	14.5	12.1	[51]
	4/0.5 g every 8 h	10.9 (1.17)	11.09 (1.1)	[47]
Apparent renal clearance (l/h)	4/0.5 g every 6 h	6.5	6.2	[51]
	4/0.5 g every 8 h	6.15 (0.55)	7.52 (0.67)	[47]
Apparent nonrenal clearance (l/h)	4/0.5 g every 6 h	8.0	5.9	[51]
Volume of distribution at steady state (l)	4/0.5 g every 6 h	15	18	[51]
Plasma half-life (h)	4/0.5 g	0.83	0.78	[51]
	4/0.5 g every 6 h	0.91	0.80	

*Mean ($\pm$ standard deviation) pharmacokinetic parameters for total (protein bound and unbound) drug.

have a greater effect on tazobactam than piperacillin due to the normally higher excretion of tazobactam than piperacillin in healthy individuals [44].

Modification of the dose of piperacillin–tazobactam is necessary in patients with severe renal impairment [4,50,53]. The manufacturer recommends that the piperacillin–tazobactam dose be reduced and/or interval extended in patients with CrCl less than 40 ml/min with the reduction dependent upon the degree of renal insufficiency (e.g., 20–40 vs <20 ml/min) [11]. Alternative dosage suggestions include extending the dosage interval in patients with a CrCl less than 20 ml/min to every 12 h [4]. In patients receiving hemodialysis, a supplemental dose of piperacillin–tazobactam 0.75 g is recommended after hemodialysis since 30–50% of the piperacillin–tazobactam dose may be removed [4,44]. With regards to peritoneal dialysis, supplemental dosing of piperacillin–tazobactam is not required since only 6 and 13% of piperacillin and tazobactam, respectively, are removed [44].

Hepatic insufficiency

Patients with hepatic insufficiency do not show a significant alteration of the piperacillin–tazobactam pharmacokinetics [4].

Pharmacodynamics

β -lactam antibiotics generally exhibit time-dependent antibacterial activity as opposed to the concentration-dependent bacterial killing demonstrated by aminoglycosides and fluoroquinolones [54,55]. The time the antibiotic concentration in the serum exceeds the MIC ($T_{>MIC}$) for a pathogen correlates best with the microbiological and clinical efficacy of piperacillin–tazobactam [55,56]. While a rise in bactericidal activity

is noted with increasing concentration, this only occurs until the concentration of piperacillin–tazobactam is four- to five-times the pathogen's MIC, after which bacterial killing plateaus [57]. The maximal activity against Gram-negative bacteria is obtained with a $T_{>MIC}$ of 60–70% of the dosing interval and 40–50% for Gram-positive bacteria [54,57]. The pharmacodynamic parameter that best describes tazobactam's activity is not fully elucidated, although the AUC appears to be important in describing β -lactam/ β -lactamase inhibitor activity [58].

A comparison of two common piperacillin–tazobactam dosage regimes, 3.375 g every 6 h and 4.5 g every 8 h, found both regimens provided a $T_{>MIC}$ of more than 60% of the 24-h period for the *E. coli*, *S. aureus*, *K. pneumoniae* and *P. aeruginosa* (all isolates were susceptible to piperacillin) isolates studied [45]. Using Monte Carlo simulation, the Optimizing Pharmacodynamic Target Attainment using the MYSTIC Antibigram (OPTAMA) program found that the probability of target attainment (for susceptible pathogens) for piperacillin–tazobactam 3.375 g every 6 h and 4.5 g every 8 h for treatment of the following infections was: skin and soft tissue (>90 and 88.7%, respectively), secondary peritonitis (92.9 and 85.2%, respectively) and nosocomial bloodstream infections (97.9 and 95%, respectively) [59–61]. Against pathogens commonly isolated in nosocomial pneumonia, the probability of target attainment of 50% $T_{>MIC}$ was found to be greater than 90% for both piperacillin–tazobactam 3.375 g every 6 h and 4.5 g administered every 6 h [62]. No data exist regarding the pharmacodynamics of piperacillin–tazobactam against piperacillin–tazobactam-resistant pathogens.

Table 5. Pharmacokinetic parameters of piperacillin–tazobactam versus comparators.

Drug	iv. dosage (g)	C _{max} (mg/l)*	AUC (mg/h/l)*	Half-life (h)	Vd (l/kg)*	Protein binding (%)	Excreted unchanged (%)	Dosing interval	Ref.
Piperacillin–tazobactam	3.375	262.67 (28.68)	278	0.76–0.93	0.21	20–23	70	t.i.d.–q.i.d.	[4,45,50]
Meropenem	0.5	26	27.2–32.4	1	0.23–0.35	2	70	t.i.d.–q.i.d.	[137,138]
	1	61.6	77.5						
Ceftriaxone	1	136.4 (21.2)	1075.4 (191.76)	7.5 (0.6)	0.12 (0.02)	85–95 [†]	60	o.d.	[138,139]

*Mean or range with or without $\pm$ standard deviation.[†]Concentration dependent.AUC: Area under the concentration–time curve; C_{max}: Peak concentration reached in the plasma/serum; iv.: Intravenous; o.d.: Once daily; q.i.d.: Four-times daily; t.i.d.: Three-times daily; Vd: Volume of distribution.

There has been active discussion as to how to best optimize β -lactam pharmacodynamics by either continuous infusion versus traditional intermittent administration [63,64]. Several studies have evaluated piperacillin–tazobactam by traditional, high-dose extended-interval intermittent or continuous infusion to optimize pharmacodynamics [56,58]. Serum concentrations achieved with continuous infusion (8.1 g over 24 h or 13.5 g over 24 h) often exceeded MICs (all susceptible) of pathogens such as *C. freundii*, *K. pneumoniae* and *E. faecalis* based on pharmacokinetic analyses and pharmacodynamic modeling [43,56]. A recent clinical trial comparing piperacillin–tazobactam 13.5 g/day by intermittent administration against continuous infusion for complicated intra-abdominal infections reported no differences in clinical outcome between the two administration methods [65]. A pharmacodynamic assessment of this intra-abdominal trial determined intermittent and continuous infusion pharmacodynamic indices were well above the MICs of pathogens documented [43]. The pharmacodynamic characteristics of high-dose, extended-interval administration of piperacillin–tazobactam has been reported by Kim and associates [58]. Piperacillin–tazobactam 6.75 g every 12 h and 8.1 g every 12 h provided a 50% T_{>MIC} for organisms with MIC values less than or equal to 16 and 32 mg/l, respectively [58]. Other methods of intermittent administration have included administering traditional intermittent doses of piperacillin–tazobactam over a 4-h infusion resulting in probability of target attainment of 92% with organisms with a MIC of 16 mg/l [63,64]. By contrast, with respect to ESBL-producing pathogens, Reese and colleagues found using Monte Carlo simulation that neither intermittent (3.375 g every 4 h) nor continuous infusion (13.5 g over 24 h) of piperacillin–tazobactam achieved adequate pharmacodynamic targets (T_{>MIC} >50%) for these pathogens [66]. The probability of T_{>MIC} greater than 50% was 57% when piperacillin–tazobactam 3.375 g every 6 h for ESBL-producing *K. pneumoniae* was calculated [22].

In summary, depending on the pathogen and desired pharmacodynamic target, piperacillin–tazobactam meets or exceeds target attainment (against susceptible pathogens) at

different intermittent dosages and administration, or by continuous infusion. However, these methods do not appear to achieve the desired T_{>MIC} (depending on the target) for ESBL-producing pathogens.

Clinical trials

Over the past two decades, the use of piperacillin–tazobactam for intra-abdominal infections, respiratory tract infections and febrile neutropenia has been extensively studied through large randomized controlled trials, open-label comparative trials as well as several noncomparative trials. These trials have been summarized previously [4,49]. Since 1999, several randomized control trials have been published evaluating piperacillin with various comparators for the management of a variety of infections including intra-abdominal, skin and soft tissue, pelvic, nosocomial pneumonia and febrile neutropenia (TABLES 6 & 7). Clinical trials involving piperacillin–tazobactam published from 2000 to present will be briefly reviewed. The clinical trials discussed below have all been performed with the old formulation, not the new formulation with EDTA and sodium citrate.

Complicated intra-abdominal infection

The efficacy of piperacillin–tazobactam for the management of complicated intra-abdominal infections has been well established in Phase III and open-label clinical trials. Clinical response rates in several open-label studies comparing piperacillin–tazobactam with various antimicrobial regimens for intra-abdominal infections reported response rates ranging from 80 to 100% (TABLE 6) [67–69]. Newer agents/regimens such as ertapenem and moxifloxacin have used piperacillin–tazobactam as the comparator agent in large, double-blind, randomized controlled clinical trials. Cohn and colleagues compared ciprofloxacin–metronidazole with piperacillin–tazobactam [70]. Response rates in evaluable patients were 74 and 63%, respectively, favoring ciprofloxacin–metronidazole (95% confidence interval [CI]: 0.3%, 23.1%; $p = 0.047$) [70]. The modified intent-to-treat (MITT) analyses, however, were similar between

Table 6. Recent (2000–present) piperacillin–tazobactam clinical trials in intra-abdominal, pelvic and complicated skin and soft tissue infections.

Author	Regimen (iv.)	No. randomized	Duration of parenteral treatment* (days: range)	Test of cure (no. of days post-therapy)	% favorable response (no. of evaluable patients)			Ref.
					Clinical	Micro.	Clinical + micro.	
Intra-abdominal								
Solomkin <i>et al.</i>	P/T 3.375 g every 6 h	633	7.8 (4–18)	28–42	n.d.	n.d.	81.2 (193)	[71]
	ERT 1 g o.d.				7.6 (4–17)	n.d.	n.d.	
Cohn <i>et al.</i>	P/T 3.375 g every 6 h	459	10	21–35	63 (116)	71 (96)		[70]
	CIP 400 mg every 12 h + MTR 500 mg every 6 h		9		74 (134)	77 (102)		
Malagoni <i>et al.</i>	P/T 3.375 g every 6 h	656	n.d.	25–50	78 (196)	77 (163)		[72]
	MOX 400 mg o.d.				80 (183)	78 (150)		
Ohlin <i>et al.</i>	P/T 4.5 g every 8 h	269	5	28–42	88 (105)	n.d.		[92]
	CXM 1.5 g every 8 h + MTR 1.5 g every 24 h		6		83 (100)	n.d.		
Jaccard <i>et al.</i>	P/T 4.5 g every 8 h	159	8.2	14–28	95 (72)	n.d.		[67]
	IMI/CIL 0.5 g every 6 h		8.5		93 (77)	n.d.		
Maltzou <i>et al.</i>	P/T 100/12.5 mg/kg every 8 h	70	5 (5–9)	14–28	100 (35)	97 (30)		[69]
	CEF + MTR 50/7.5 mg/kg every 8 h		5 (5–9)		100 (34)	100 (31)		
Pelvic								
Roy <i>et al.</i>	P/T 3.375 g every 6 h	412	4 (3–12)	14–28	91.5 (153)	93.8 (129)		[77]
	ERT 1 g o.d.				4 (2–12)	93.9 (163)	93.7 (128)	
Skin and soft tissue								
Graham <i>et al.</i>	P/T 3.375 g every 6 h	540	9.8 (3–18)	10–21	84.4 (174)	83.4 (151)	82.1 (151)	[90]
	ERT 1 g o.d.				9.1 (3–16)	82.4 (185)	82.6 (155)	
Lipsky <i>et al.</i>	P/T 3.375 g every 6 h	586	11.3	10	83 (196)	81		[73]
	ERT 1 g o.d.		11.1		87 (206)	93		
Giordano <i>et al.</i>	P/T 3.375 g every 6 h	617	6	10–42	82 (187)	85.77		[76]
	MOX 400 mg o.d.		6		79 (180)	85.70		
Siami <i>et al.</i>	P/T 3.375 g every 6 h	409	13	6–14	65.2 (135)	57.2		[75]
	CFX 200 mg every 12 h		13		68.8 (144)	61.5		

CEF: Cefotaxime; CFX: Clinafloxacin; CIL: Cilastatin; CIP: Ciprofloxacin; CTX: Ceftriaxone; CXM: Cefuroxime; ERT: Ertapenem; IMI: Imipenem; iv.: Intravenous; Micro.: Microbiological; MOX: Moxifloxacin; MTR: Metronidazole; n.d.: No data; o.d.: Once daily; P/T: Piperacillin–tazobactam.

ciprofloxacin–metronidazole and piperacillin–tazobactam at 75 versus 69% (95% CI: -3.4%, 15.6%), respectively. The end of therapy bacteriological eradication rates were similar, 77 and 71% for the ciprofloxacin–metronidazole and

piperacillin–tazobactam groups, respectively (95% CI: -5.1%, 19.4%) [70]. In a trial comparing ertapenem with piperacillin–tazobactam, the test of cure (TOC) rates for clinical and microbiologic response were 86.7 and 81.2% for ertapenem

Table 7. Recent (2000–present) piperacillin–tazobactam clinical trials in febrile neutropenia and nosocomial pneumonia.

Author	Regimen	No. randomized	Duration of parenteral treatment (days: mean range)	Test of cure (no. of days post therapy)	% favorable response (no. of evaluable patients)			Ref.
					Clinical	Micro.	Clinical + micro.	
Febrile neutropenia								
Rossini <i>et al.</i>	P/T 200 mg/kg/day + AMI 20 mg/kg/day	252	11 (1–28)	4	52.9 (121)	50 (38)		[79]
	CTX 30 mg/kg/day + AMI 20 mg/kg/day		12 (1–26)		50.8 (122)	46 (37)		
Harter <i>et al.</i>	P/T 4.5 g every 8 h	219	8 (2–23)	3	53 (87)	48 (50)		[80]
	CZD 2 g every 8 h		8 (1–29)		55 (74)	57 (44)		
Del Favero <i>et al.</i>	P/T 4.5 g every 8 h	760	n.d.	n.d	49 (364)	n.d.		[83]
	P/T 4.5 g every 8 h + AMI 7.5 mg/kg every 12 h		53 (369)		n.d.			
Sanz <i>et al.</i>	P/T 4.5 g every 6 h + AMI 20 mg/kg/day	343	n.d.	7	31.2 (141)	25 (24)		[78]
	IMI/CIL 500 mg		41.6 (149)		14.3 (14)			
Cometta <i>et al.</i>	P/T 4.5 g every 6 h	165	n.d.	4	46 (79)	n.d.		[84]
	P/T 4.5 g every 6 h + VAN 15 mg/kg every 12 h		49 (86)		n.d.			
Sanz <i>et al.</i>	P/T 4.5 g every 6 h + AMI 20 mg/kg/day	969	15.7	4	54	39	51 (435)	[81]
	CPM 2 g every 8 h + AMI 20 mg/kg/day		15.8		47	40	49 (432)	
Bow <i>et al.</i>	P/T 4.5 g every 6 h	528	9.9 (1–23)	7	26.8 (265)	n.d.		[82]
	CPM 2 g every 8 h		9 (1–26)		20.5 (263)	n.d.		
Nosocomial pneumonia								
Joshi <i>et al.</i>	P/T 3.375 g every 4 h + TOB 5 mg/kg/day	300	9	7–24	74 (78)	65 (78)		[86]
	CZD 2 g every 8 h + TOB 5 mg/kg/day		9		50 (58)	50 (58)		
Alvarez-Lerma <i>et al.</i>	P/T 4.5 g every 6 h + AMI 15 mg/kg	124	10.8	10–14	51.8 (83)	62 (50)		[87]
	CZD 2 g every 8 h + AMI 15 mg/kg		9.5		53.8 (26)	65 (20)		
Joshi <i>et al.</i>	P/T 4.5 g every 6 h + TOB 5 mg/kg/day	437	10.2	14 (±7)	68.4 (98)	63.9 (97)		[88]
	IMI 500 mg every 6 h + TOB 5 mg/kg/day		10.6		60.6 (99)	58.6 (99)		

AMI: Amikacin; CIL: Cilastatin; CIP: Ciprofloxacin; CPM: Cefepime; CTX: Ceftriaxone; CZD: Ceftazidime; IMI: Imipenem; Micro.: Microbiological; MOX: Moxifloxacin; n.d.: No data; P/T: Piperacillin–tazobactam; TOB: Tobramycin; VAN: Vancomycin.

and piperacillin–tazobactam, respectively (5.5% difference; 95% CI: -2.2%, 13.1%) meeting predefined definitions of therapeutic equivalency [71]. MITT results were also similar, 79.3% (ertapenem) and 76.2% (piperacillin–tazobactam), for the two groups [71].

Recently, moxifloxacin was compared with piperacillin–tazobactam for complicated intra-abdominal infections. Of the subset of patients with hospital-acquired intra-abdominal infections, Malagoni and colleagues reported that efficacy and microbiologic eradication was higher with moxifloxacin compared with piperacillin–tazobactam [72]. The primary TOC analyses found clinical and microbiologic cure rates in evaluable patients were similar between moxifloxacin and piperacillin–tazobactam, 80 and 78%, respectively (95% CI: -7.4%, 9.3%) for efficacy and 78 and 77%, respectively (95% CI: -9.9%, 8.7%) for microbiologic eradication [72]. Overall, comparative studies have supported the continued use of piperacillin–tazobactam for the management of intra-abdominal infections with clinical and microbiologic response rates similar to the comparators.

Complicated skin & skin structure infections

Similar to complicated intra-abdominal studies, piperacillin–tazobactam has been used as a comparator in large, double-blinded, randomized controlled studies involving ertapenem or broad-spectrum fluoroquinolones for the management of complicated skin and soft tissue infections. In a Phase III clinical trial comparing ertapenem and piperacillin–tazobactam for complicated skin and skin structure infections (e.g., abscesses, lower extremity), efficacy rates for evaluable patients at TOC were similar between ertapenem and piperacillin–tazobactam, 82.4 versus 84.4%, respectively (95% CI: -10.2%, 6.2%) [73]. Clinical and microbiologic response rates were also similar when adjusted for patient strata, 81.9 and 82.1% (95% CI: -9.3%, 9.0%) for ertapenem and piperacillin–tazobactam, respectively [73]. A subset analysis of patients receiving outpatient antibiotic therapy (OPAT) with ertapenem or piperacillin–tazobactam also found similar rates of efficacy [74]. In patients with moderate-to-severe diabetic foot infections, outcomes were found to be similar in a study by Lipsky and colleagues comparing ertapenem and piperacillin–tazobactam [73]. Clinical response at the time of discontinuation of intravenous therapy (primary end point) adjusted for baseline severity was 94 and 92% (95% CI: -2.9%, 6.9%) for the ertapenem and piperacillin–tazobactam arms, respectively [73]. There was no difference in the response rate by grade of severity or pathogen.

When compared with broad-spectrum fluoroquinolones, clinical response rates were similar between the fluoroquinolones and piperacillin–tazobactam in patients with severe skin and soft tissue infections. Siami and colleagues found clinical response rates (68 and 65.2% [95% CI: -7.5%, 14.6%]) and microbiologic response rates (61.5 and 57.2% [95% CI: -4.4%, 13.0%]) to be similar in patients receiving ciprofloxacin or piperacillin–tazobactam, respectively [75]. In a recent study comparing moxifloxacin and piperacillin–tazobactam, the TOC clinical response rates were 79 and 82%, respectively

(95% CI: -12.4%, 3.29%) [76]. There were no differences in response rates based on type of infection or baseline pathogens. In the subset of patients with abscess however, the clinical response rate was observed to be higher in patients receiving piperacillin–tazobactam compared with moxifloxacin (93 vs 78%, respectively; $p = 0.04$). After adjusting for resistance, number of surgeries and MRSA, no differences were found [76].

In summary, studies to date continue to support the use of piperacillin–tazobactam for complicated skin and soft tissue infections including diabetic foot infections.

Gynecological infections

In contrast to other infections, only a few studies have formally evaluated piperacillin–tazobactam for the treatment of acute pelvic infections such as endometritis. In a recent study, Roy and associates found clinical TOC response rates similar between ertapenem and piperacillin–tazobactam, 93.9 versus 91.5% (95% CI: -4.0%, 8.8%), respectively [77]. Response rates were also similar between the two groups when stratified based on the diagnosis, severity of infection or population (obstetric vs gynecologic). Microbiologic response rates in clinically evaluable patients did not differ between the ertapenem and piperacillin–tazobactam groups (93.7 vs 93.8%, respectively).

Febrile neutropenia

Previous studies have compared piperacillin–tazobactam monotherapy or combination therapy (e.g., aminoglycoside or vancomycin) with other antibiotics (monotherapy or combination) in the febrile neutropenic population generally in large, open-label prospective trials [4]. Recent trials have compared a carbapenem or third/fourth-generation cephalosporin with piperacillin–tazobactam with or without an aminoglycoside (TABLE 7). In a nonrandomized observational study, Sanz and colleagues reported similar response rates between imipenem–cilastatin and piperacillin–tazobactam plus amikacin (500 mg every 12 h) in patients with febrile neutropenia, 42 and 31%, respectively (95% CI: -0.01%, 21.47%; $p = 0.06$) [78]. There were no differences in time to defervescence or other secondary analyses between the two groups.

With respect to the cephalosporin trials, piperacillin–tazobactam was compared with ceftriaxone (both with amikacin) for the empiric management of febrile neutropenia in patients with primarily hematologic malignancies [79]. Clinical response rates were similar between the two groups, 52.9 and 50.8% ($p > 0.2$), respectively. By contrast, an open-label study reported higher response rates (defervescence at 72 h) with piperacillin–tazobactam monotherapy than with the combination of ceftriaxone plus gentamicin (57.1 vs 35.3%, respectively; $p = 0.0047$).

Compared with ceftazidime, Harter and associates found no difference in clinical response rates in evaluable patients (those on high-dose chemotherapy or peripheral blood stem cell transplants) receiving ceftazidime 2 g every 8 h or piperacillin–tazobactam 4.5 g every 8 h as monotherapy (55 and 53%, respectively; $p = 0.9$) [80]. When therapy was evaluated based on modification (e.g., addition of vancomycin), there were no

differences between the two groups. Piperacillin–tazobactam was considered noninferior to ceftazidime. Two trials have evaluated cefepime 2 g every 8 h and piperacillin–tazobactam 4.5 g every 6 h as empiric therapy for patients with febrile neutropenia. Sanz and colleagues compared the two regimens, which included amikacin 20 mg/kg/day in both study arms in a randomized prospective trial [81]. The response rates were 49 and 52% for the cefepime and piperacillin–tazobactam arms, respectively. There was no difference in response when analyzed by antibiotic modification, documented infection (clinical or microbiologic) or infection type. Recently, Bow and colleagues reported response rates at TOC of 26.8 and 20.5% (odds ratio [OR]: 1.42; 95% CI: 0.95–2.12; $p = 0.09$) for the piperacillin–tazobactam and cefepime monotherapy arms, respectively, in a noninferiority MITT analysis [82]. Clinical response favored piperacillin–tazobactam (57.7%) at a 72-h assessment compared with cefepime (48.3%; $p = 0.04$). Treatment failures were noted to be lower among piperacillin–tazobactam recipients compared with those receiving cefepime (51.7 vs 61.2%; OR: 0.68; 95% CI: 0.48–0.96; $p = 0.027$). Multivariate analysis observed allocation to piperacillin–tazobactam predicted treatment success (OR: 1.65; 95% CI: 1.04–2.64; $p = 0.0354$) [82].

Piperacillin–tazobactam monotherapy has been evaluated in previous studies [4]. Two recent studies have evaluated piperacillin–tazobactam monotherapy in double-blind, randomized controlled trials. Del Favero and associates compared piperacillin–tazobactam (4.5 g every 8 h) with or without amikacin (7.5 mg/kg every 12 h) in patients receiving chemotherapy or autologous bone marrow transplantation due to hematologic or other malignancies [83]. Overall clinical success (49 vs 53%; $p = 0.2$; 95% CI: -11%, 3%) and microbiologic success (32% both arms $p = -0.9$; 95% CI: -10%, 10%) was similar between monotherapy and combination therapy, respectively. There were no differences in time to defervescence, time to failure or treatment modification between the two groups. A European Organisation for Research and Treatment of Cancer (EORTC) study evaluating piperacillin–tazobactam monotherapy with or without concomitant vancomycin noted no difference in resolution of fever, time to defervescence, treatment modification or mortality between the two groups [84]. A subsequent ITT and per protocol analysis confirmed the use of piperacillin–tazobactam monotherapy for the empiric management of the febrile neutropenia [85].

In summary, although there may be variation in study design and definitions, clinical outcomes with piperacillin–tazobactam are generally similar to comparator agents in studies of febrile neutropenia. Piperacillin–tazobactam may be considered as effective to comparator agents as monotherapy or in combination with an aminoglycoside for the empiric management of the febrile neutropenic patient.

Nosocomial pneumonia

Recent nosocomial pneumonia studies involving piperacillin–tazobactam have generally evaluated piperacillin–tazobactam and comparators in combination with an aminoglycoside.

The efficacy of piperacillin–tazobactam versus ceftazidime with tobramycin in both arms was evaluated in hospitalized patients with nosocomial pneumonia primarily not admitted to the intensive care units [86]. In evaluable patients, clinical and microbiologic success was higher in the piperacillin–tazobactam combination arm compared with the ceftazidime group, 74 versus 50% ($p = 0.006$; 95% CI: -42%, -7%) and 65 versus 38% ($p = 0.003$), respectively [86]. By contrast, the efficacy of piperacillin–tazobactam versus ceftazidime both in combination with tobramycin in primarily mechanically ventilated patients with nosocomial pneumonia was found to be similar [87]. In clinically evaluable patients, the response rate was 63.9 versus 61.5% (OR: 1.1, 95% CI: 0.44%, 2.75%; $p = 0.831$) in the piperacillin–tazobactam and ceftazidime combination groups, respectively [87]. There were no differences in microbiologic success.

Two recent double-blind, randomized control trials have compared piperacillin–tazobactam with imipenem. Joshi and colleagues compared the efficacy of piperacillin–tazobactam and tobramycin versus imipenem and tobramycin in hospitalized patients with nosocomial pneumonia including those on mechanical ventilation [88]. Clinical efficacy at TOC was similar between the piperacillin–tazobactam and imipenem groups in clinically evaluable patients, 68.4 and 60.6% (95% CI: -6.6%, 22.1%; $p = 0.256$), respectively. Microbiological response was 64 versus 59% ($p = 0.445$; 95% CI: -9.3%, 20%) in the piperacillin–tazobactam and imipenem groups, respectively. Similar comparative efficacy was reported in a study that was terminated early to due lack of recruitment [89]. Although not powered for statistical evaluation, the authors concluded piperacillin–tazobactam and imipenem were equally effective in the treatment of severe nosocomial pneumonia [89].

In summary, current comparative studies support the use of piperacillin–tazobactam in combination with an aminoglycoside for the treatment of nosocomial pneumonia. The clinical efficacy of piperacillin–tazobactam was similar to comparator agents in hospitalized patients and those on mechanical ventilation with nosocomial pneumonia.

Adverse effects

Piperacillin–tazobactam is generally a well-tolerated antibiotic. The most common adverse effects associated with piperacillin–tazobactam reported in clinical studies were gastrointestinal or dermatologic reactions [4,49]. Recent studies comparing piperacillin–tazobactam and ertapenem demonstrated no significant difference in the safety and tolerability of both treatment groups [71,73,77,90]. The incidence of one or more clinical adverse effects reported was 23.3% in the piperacillin–tazobactam group and 23.2% in the ertapenem group [91]. Adverse effects reported in both treatment groups included diarrhea, infused vein reaction, nausea and headache, most of which were considered mild or moderate (TABLE 8) [91].

Diarrhea was the most common gastrointestinal symptom associated with piperacillin–tazobactam reported in clinical trials [4,49]. Other gastrointestinal adverse effects include

Table 8. Adverse effects of piperacillin–tazobactam versus ertapenem.

Adverse effect	Piperacillin–tazobactam (n = 774)*	Ertapenem (n = 802)*
Diarrhea	7.0 (12.1)	5.0 (10.3)
Infused vein complication	5.5 (7.9)	4.5 (7.1)
Nausea	3.4 (8.7)	2.5 (8.5)
Headache	1.2 (5.4)	1.9 (5.6)
Phlebitis/thrombophlebitis	1.3 (2.7)	1.6 (1.9)
Pruritus	1.2 (2.6)	1.2 (2.0)
Rash	1.8 (3.1)	1.1 (2.5)
Abdominal pain	0.5 (4.8)	0.7 (3.6)
Vomiting	1.7 (5.3)	0.9 (3.7)
Oral candidiasis	1.2 (1.3)	0.1 (0.1)
Vaginitis	0.7 (1.0)	0.9 (1.4)

Adapted from [91].

*Incidence (%) of adverse effects occurring with a frequency of at least 1% during the study therapy plus the 14-day follow-up in patients receiving either piperacillin–tazobactam or ertapenem, which were considered by the investigator to be possibly, probably or definitely related to the study drug therapy. The values in parentheses are those that were reported without regards to the relation to the study therapy.

constipation, nausea and vomiting [76,77,91,92]. Generally, the incidence of gastrointestinal adverse effects appear similar between piperacillin–tazobactam and other comparative agents [71,72,76,82] depending on the clinical trial and population evaluated.

Skin rash was the most common dermatologic adverse effect associated with piperacillin–tazobactam [4,82,85]. Local infusion-related reactions such as pain, phlebitis and erythema are also common adverse events that have been observed [4]. Neurologic adverse effects have included headaches and insomnia [4]. Other adverse effects reported have included transient, mild-to-moderate elevation of aminotransferase levels and positive Coomb's tests [4]. Infrequent neutropenia, elevated eosinophil and platelet counts, hypokalemia and elevated bleeding times have also been observed [4].

Development of pseudomembranous colitis has been reported in patients treated with piperacillin–tazobactam [4,80]. It has been suggested that use of piperacillin–tazobactam may decrease the risk or prevalence of *Clostridium difficile* diarrhea (CDD) [93–95]. Two studies reported increased CDD rates by 200% or more during a recent shortage of piperacillin–tazobactam and resultant change in antibiotic utilization [93,94]. By contrast, Mendez and colleagues reported that CDD rates at their institution decreased by 47% during the same piperacillin–tazobactam shortage [96]. It is unclear precisely why

piperacillin–tazobactam is less likely to cause CDD or whether piperacillin–tazobactam may affect rates of CDD in the presence of other interventions (e.g., changes in antibiotic prescribing, infection control practices, environmental cleaning etc.).

Drug interactions

As with other penicillin antibiotics, the coadministration of piperacillin with aminoglycoside antibiotics can lead to the inactivation of the aminoglycoside [11]. The recent reformulation of piperacillin–tazobactam with EDTA has increased compatibility *in vitro* with amikacin and gentamicin, allowing for simultaneous Y-site infusion [11]. The new formulation is not compatible with tobramycin for coadministration through Y-site infusion [11].

Since piperacillin and tazobactam are both excreted through renal tubular secretion, there is an interaction with probenecid, which is also eliminated through the same mechanism [44]. Administration of a single dose of probenecid 1000 mg 1 h before infusion of piperacillin–tazobactam resulted in reduction of piperacillin and tazobactam renal clearance by 21 and 71%, respectively [44]. There is some evidence suggesting that piperacillin–tazobactam may decrease the clearance of methotrexate (MTX). Animal studies have shown that the concomitant administration of MTX with piperacillin–tazobactam leads to an increase in mean residence time and AUC values of MTX due to a decrease in the total body clearance [97]. High sustained MTX concentrations were reported in a patient receiving MTX and piperacillin–tazobactam that declined upon discontinuation of piperacillin–tazobactam [98]. MTX concentrations and signs and symptoms of toxicity should be closely monitored when piperacillin–tazobactam is given concurrently. Similar to other antibiotics, coagulation parameters should be monitored regularly when piperacillin–tazobactam is administered to patients receiving anticoagulants or antiplatelet agents [11].

Pharmacoeconomics

Due to the growing cost of antibiotic use, pharmacoeconomic evaluations of antibiotic treatments are becoming increasingly important. As well as the drug acquisition costs, there are many other factors of the drug processing and administration process that contribute to the total cost of antibiotic therapy [4,99]. Some of these additional costs include pharmacy preparation time, nursing time, cost of materials required for the drug preparation and administration, maintenance of the intravenous site, waste disposal as well as therapeutic drug monitoring [99]. While drug acquisition costs may not change, other factors such as drug preparation, administration method and dosage frequency could be influenced to reduce the total costs associated with therapy. The pharmacoeconomic considerations of piperacillin–tazobactam in relation to data published before 2000 has been previously discussed [4].

The use of continuous infusion of piperacillin–tazobactam compared with intermittent administration has been widely published by investigators from Hartford Hospital in the USA [43,100–102]. In addition to pharmacodynamic optimization,

proposed advantages include decreased drug, preparation and administration, and labor (nursing and pharmacy) costs. A time-motion study suggested that depending on the comparative total daily dose of piperacillin-tazobactam administered intermittently, continuous infusion was more cost efficient on a daily, 5- or 10-day course [100,101]. Depending on the admixture system (e.g., vials vs ADD-Vantage®), the cost differential between intermittent administration and continuous infusion decreased if the total daily dose was the same between the two groups. Estimated nursing time freed up for other patient care activities was 12.7–17.4 min/patient/day [100,101]. By contrast, a pharmacoeconomic analysis [102] of a comparative trial of continuous infusion versus intermittent administration of piperacillin-tazobactam (total 13.5 g/day) in patients with complicated intra-abdominal infections [65] did not identify any cost savings between the two administration methods. In addition, potential supply and personnel cost savings did not translate economically in favor of continuous infusion [102]. Although promising, there is insufficient evidence to support continuous infusion as a replacement for intermittent administration at this time [103]. Other considerations limiting continuous infusion include drug interactions, number of concomitant medications and limited intravenous access [63]. As previously indicated, other intermittent administration methods have been proposed to optimize piperacillin-tazobactam pharmacodynamics [58,63].

A few clinical trials have examined the costs associated with piperacillin-tazobactam with comparators for treatment of various infections. When piperacillin-tazobactam was compared with ceftazidime, direct and indirect costs of treatment were the same for both regimens [80]. In patients receiving ceftriaxone and gentamicin, the cost of antibiotic treatment was 2.5-times higher than those receiving piperacillin-tazobactam due to the lower use of second- and third-line antibiotics as well as fewer febrile treatment days in the latter group [104]. Dietrich and colleagues using a cost-efficacy analysis of 19 published clinical trials comparing piperacillin-tazobactam with imipenem-cilastatin found piperacillin-tazobactam to be more cost effective as patients had fewer relapses and lower daily costs [105].

Conclusion

Piperacillin-tazobactam is a β -lactam/ β -lactamase inhibitor combination that offers broad spectrum of coverage against Gram-positive and -negative aerobic and anaerobic bacteria, including *P. aeruginosa*. The addition of tazobactam to piperacillin has enhanced its stability against a wide range of β -lactamase enzymes. Resistance challenges remain with ESBL-producing bacteria such as *Klebsiella* spp. and *E. coli*. Piperacillin-tazobactam is not recommended for the treatment of infections caused by ESBL-producing *Klebsiella* spp. and *E. coli*. Although piperacillin-tazobactam has been used clinically for some time, limited resistance has developed to this agent. Piperacillin-tazobactam has recently been reformulated to include EDTA and sodium citrate; this new formulation has been shown to be compatible *in vitro* with gentamicin and amikacin, allowing for simultaneous Y-site infusion, but not

with tobramycin. Clinical trials have demonstrated the effectiveness of piperacillin-tazobactam for the treatment of patients with intra-abdominal infections, gynecological infections, nosocomial pneumonia, complicated skin and skin structure infections and febrile neutropenic patients. Clinical trials have shown piperacillin-tazobactam to be equivalent to relevant comparator antibiotics for the treatment of intra-abdominal, complicated skin and skin structure and gynecological infections. Piperacillin has an excellent safety and tolerability profile with the most common adverse effects being mild-to-moderate gastrointestinal symptoms. Piperacillin-tazobactam remains a reliable choice for the empiric treatment of moderate-to-severe infections, including potentially polymicrobial infections and febrile neutropenic patients. The advantages of the new formulation of piperacillin-tazobactam will make it the new standard.

Expert commentary & five-year view

While the addition of tazobactam to piperacillin has increased its stability towards certain β -lactamase enzymes (e.g., TEM-1), some isolates of ESBL-producing *Klebsiella* spp. and *E. coli* are resistant *in vitro*, as are all Gram-negative bacilli expressing AmpC. Piperacillin-tazobactam has recently been reformulated with EDTA allowing for greater convenience of administration with the aminoglycosides amikacin and gentamicin, which were previously incompatible for coadministration. The use of continuous-infusion administration of piperacillin-tazobactam is of interest from both pharmacodynamic and pharmacoeconomic perspectives. Clinical trials have demonstrated the benefit of administering piperacillin-tazobactam by continuous infusion over a 24-h period as this allows for optimization of β -lactam pharmacodynamic properties (maximum $T_{>MIC}$). With regards to pharmacoeconomics, the use of continuous infusion has shown cost-effectiveness compared with intermittent infusion administration due to a decrease in both drug acquisition costs as well as other related drug administration costs. Further pharmacoeconomic studies will provide more information on the applicability of this type of administration to individual institutional settings.

Some questions regarding piperacillin-tazobactam remain to be answered in the years to come and include:

- Will we see increased use of continuous infusion, prolonged intermittent infusion or high-dose administration to optimize cost efficiency and pharmacodynamics over traditional intermittent administration?
- Will the new reformulated piperacillin-tazobactam with EDTA contribute to enhancement and further flexibility of administration with aminoglycosides allowing for greater convenience in combination therapy?
- Will the use of piperacillin-tazobactam increase over that of cefotaxime in the elderly population as an increase in *C. difficile* rates has not been observed with piperacillin-tazobactam use in this population?
- Will we observe greater levels of AmpC and ESBL-producing organisms leading to elevated resistance rates for piperacillin-tazobactam as well as other antibiotics?

Key issues

- Piperacillin–tazobactam has broad-spectrum antimicrobial activity including Gram-positive and -negative aerobic and anaerobic bacteria; piperacillin–tazobactam's spectrum of activity includes *Pseudomonas aeruginosa*, however, its inconsistent activity against extended-spectrum β -lactamase-producing Gram-negative bacilli and AmpC-producing bacteria is an issue.
- Piperacillin–tazobactam has been reformulated with ethylenediaminetetraacetic acid to allow for Y-site administration with the aminoglycosides amikacin and gentamicin.
- Piperacillin–tazobactam maintains an important role in the treatment of moderate-to-severe polymicrobial infections and is a safe and well-tolerated antibiotic.

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