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Expert Opinion

Pharmacokinetic evaluation of piperacillin-tazobactam

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Importance of the field: Piperacillin-tazobactam is a frequently prescribed intravenous antibiotic for moderate to severe infections used in hospital settings because of its broad activity against many pathogenic bacteria including *Pseudomonas aeruginosa.* However, its pharmacokinetics (PK) can be significantly altered in a variety of states.

Areas covered in this review: This article provides a comprehensive and critical review of the PK of piperacillin-tazobactam in different patient populations. The pharmacodynamics (PD) of piperacillin-tazobactam is also discussed.

What the reader will gain: The importance of appropriate antibiotic dosing in the context of the global tendency for reduced susceptibility of bacteria, including *P. aeruginosa* is emphasized. The interrelationship between PK and PD is discussed to provide an understanding of methods for procuring dosing regimens that increase the likelihood of clinical success for individual patients. Alternative dosing regimens, which may include administration by extended or continuous infusion of piperacillin-tazobactam as a mechanism to increase the likelihood of pharmacodynamic target attainment, are described.

Take home message: Where piperacillin-tazobactam is required for treatment, applying knowledge of PK and PD characteristics can facilitate optimal outcomes.

Keywords: β-lactamases, pharmacodynamics, pharmacokinetics, piperacillin-tazobactam, *Pseudomonas aeruginosa*

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1. Introduction

Piperacillin-tazobactam is the intravenous antibiotic presently with the largest volume of sales worldwide [1]. Piperacillin-tazobactam is a penicillin and β-lactamase inhibitor combination product that is preferentially prescribed in the hospital or critical care setting for the treatment of moderate to severe infections including hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), healthcare-associated pneumonia (HCAP) [2], community-acquired pneumonia (CAP) with risk factors for *Pseudomonas aeruginosa* [3], complicated urinary tract infections, catheter-related blood stream infection [4], complicated skin and soft tissue infections including diabetic foot and necrotizing fasciitis [5,6], complicated intra-abdominal infection [7], neutropenic fever [8], and severe sepsis and septic shock [9]. Piperacillin-tazobactam has the broadest spectrum of activity among the penicillin class of β-lactam antibiotics and is generally active against most of the typical human pathogens including aerobic and anaerobic Gram-positive and Gram-negative bacteria.

Knowledge of pharmacokinetics (PK) and pharmacodynamics (PD) are important for the development of dosing regimens that can maximize the effects of antibiotics and conceivably to reduce development of antimicrobial resistance. In fact, the escalation of antimicrobial resistance is becoming increasingly important for the treatment of challenging Gram-negative bacilli such as *P. aeruginosa.* A great concern for clinicians, however, is the lack of effective antibiotics in the

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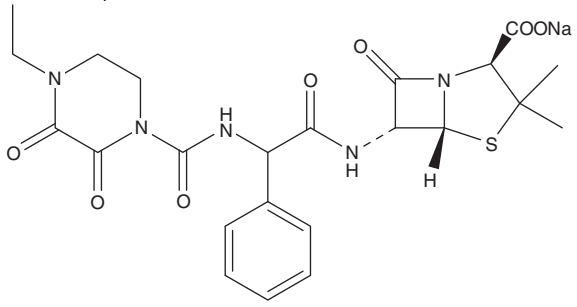
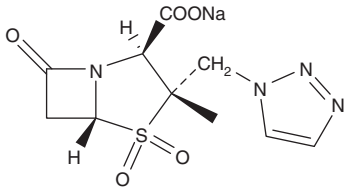
Box 1. Drug summary.

Drug name	Tazobactam-piperacillin
Phase	Launched
Indication	Bacterial infection
Pharmacology description	β-Lactamase inhibitor Cell wall synthesis inhibitor
Route of administration	Parenteral, intravenous
Chemical structure	 Piperacilin sodium  Tazobactam sodium
Pivotal trial(s)	[73,74,78,79,83]

pipeline available to treat such pathogens [10]. Thus, it is significantly important to use currently available antibiotics wisely to maximize their clinical utility. A simple measure that can be undertaken and which should be considered essential is the wider application of PK/PD. The common prescription of piperacillin-tazobactam mandates that PK/PD principles be applied to develop optimal dosing for different patient populations, especially in critically ill patients whose PK is prone to be altered by pathology. Therefore, a better understanding of PK of the drug is essential for successful management of significant infections.

The principal objective of this review is to identify and critically evaluate the literature describing PK of piperacillin-tazobactam. Additionally, we will consider relevant pharmacodynamic and toxicity issues during this review.

2. Physicochemical

Piperacillin is a semisynthetic ureidopenicillin. Piperacillin sodium is derived from D(-)-α-aminobenzylpenicillin, and has a chemical name of sodium (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-piperazine-carboxy-amino)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.1]-heptane-2-carboxylate [11]. As a combination product, one vial of piperacillin 4.0 g and tazobactam 0.5 g contains 0.536 g sodium [12].

Tazobactam is a penicillinate sulfone, a synthetic compound [13]. Tazobactam sodium is derived from triazolymethyl penicillanic-acid sulfone, and has a chemical name of sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1H,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo-[3.2.0]-heptane-2-carboxylate-4,4-dioxide. The triazole ring of tazobactam facilitates its binding to β-lactamases [11].

Piperacillin and tazobactam have acid dissociation constant (pK_a) values of 4.41 and 2.1, respectively, and solubility in water (g/l) of 714 and > 500 (tazobactam sodium), respectively [14]. This level of hydrophilicity enables distribution in line with intra- and extra-vascular water, which typically corresponds with poor penetration of lipid membranes.

The molecular weight of piperacillin ($C_{23}H_{27}N_5O_7S$) and tazobactam ($C_{10}H_{12}N_4O_5S$) is 517.6 and 300.3, respectively, which enables distribution across vascular walls through vessel fenestrations. The chemical structures of both molecules are shown in **Box 1**.

3. Mechanism of action

Piperacillin, as with all other β-lactam antibiotics, interferes with the final stage of peptidoglycan synthesis by inhibiting penicillin-binding proteins (PBPs), which crosslink the peptidoglycan polymers. Peptidoglycan is an essential component of the bacterial cell wall, which protects the organism from osmotic rupture, determines cell shape, and is integral to cell growth and division. Thus inhibition of PBPs causes bacteriolysis. Because of increased affinity to PBP-3, ureidopenicillins such as piperacillin have increased activity

against Gram-negative bacilli as compared with other classes of penicillin [15].

Tazobactam first forms a non-covalent complex with a β-lactamase (acyl-enzyme). Subsequently a covalent acyl-enzyme is produced and the β-lactamase is permanently inactivated [13,16].

4. Microbiology

4.1 Tazobactam inhibition of β-lactamases

In general, class A serine β-lactamases such as TEM-1, TEM-2, SHV-1 and PC1 are inhibited by tazobactam, whereas class B metallo-β-lactamases such as IMP-1 and VIM-1, class C cephalosporinases (e.g., AmpC) and class D serine oxacillinases (e.g., OXA-1) are not inhibited by tazobactam [13]. However among class A serine β-lactamases, KPC-2 is not inhibited by tazobactam [17]. By contrast, OXA-2 and OXA-32 (class D oxacillinases) and CMY (a class C cephalosporinase) are inhibited by tazobactam *in vitro,* although clinical efficacies are unknown [13]. Class A extended spectrum β-lactamases (ESBLs) of SHV-type, TEM-type and CTX-Ms are also inhibited by tazobactam *in vitro.* Hence, minimum inhibitory concentrations (MICs) of piperacillin-tazobactam against class A ESBL-producers are lower than those of piperacillin alone, however, the clinical relevance of this feature is debated [18-20].

4.2 Susceptibility to piperacillin-tazobactam

Piperacillin (alone) generally has broad spectrum activity against many Gram-positive and Gram-negative aerobes and anaerobes including *Pseudomonas aeruginosa, Streptococcus pneumoniae* and *Enterococcus faecalis.* Piperacillin-tazobactam retains the activity of piperacillin and is also active against class A serine β-lactamase producing organisms which can include *Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis,* Enterobacteriaceae and *Bacteroides fragilis* group. Of note, the addition of tazobactam to piperacillin generally does not increase susceptibility in *P. aeruginosa* because resistance to piperacillin in *P. aeruginosa* is not mediated by class A serine β-lactamases. Similarly, piperacillin-tazobactam is not always more effective than piperacillin to AmpC-producing Enterobacteriaceae such as *Enterobacter* spp. and *Citrobacter* spp. because AmpC is resistant to tazobactam inhibition as previously mentioned. There are conflicting reports on the clinical efficacy of piperacillin-tazobactam for the treatment of class A ESBL-producing Enterobacteriaceae. Paradoxical ineffectiveness despite low *in vitro* MIC may be explained by the 'inoculum effect' [20]. Currently, the use of piperacillin-tazobactam for the treatment of ESBL-producers is not generally recommended, especially for severe infections. Piperacillin-tazobactam is generally ineffective to *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* due to multiple mechanisms of resistance including non-class A β-lactamases production. Piperacillin-tazobactam MIC_{50} and MIC_{90} values for a range of pathogens, obtained from nationwide or international surveys are summarized in **Table 1**.

5. Pharmacokinetics

5.1 Basic pharmacokinetics

There is ongoing debate as to whether piperacillin has linear or nonlinear PK. Nonlinear PK has been demonstrated in dose-ranging studies in healthy volunteers and clinical studies in patients with cystic fibrosis [21-25]. However, other studies have only been able to support linear PK models [26-28]. The possible explanation for this discrepancy between studies is that the studies that describe linear PK are for one dose increment only, whereas other dose-ranging pharmacokinetic studies are more likely to detect nonlinear PK.

There is less data available on this issue for tazobactam, although current evidence would suggest that it displays nonlinear PK [29].

5.2 Pharmacokinetics in healthy volunteers

Pharmacokinetic parameters of piperacillin and tazobactam after administration of piperacillin-tazobactam are shown in **Table 2**.

5.2.1 *Bioavailability*

Neither piperacillin nor tazobactam is absorbed from the gastrointestinal tract and therefore parenteral administration is necessary for systemic therapy. The bioavailabilities of intramuscularly administered piperacillin and tazobactam calculated from the area under the concentration–time curve (AUC) values are 71 and 84%, respectively. The maximum concentrations (C_{max}) after intramuscular administration for piperacillin and tazobactam are reached within 45 and 30 min, respectively [14]. However, the poor solubility of the piperacillin and tazobactam co-formulation means that intravenous administration is preferred because of the large volume of fluid required for solubilization (10 – 20 ml water for injection). Administration is recommended by the product information as a slow intravenous injection (3 – 5 min), or a slow intravenous infusion (20 – 30 min) [12].

5.2.2 *Protein binding capacity*

Protein binding capacities of piperacillin and tazobactam are 20 – 30% and 20 – 23%, respectively [14]. Data to support this proportion of protein binding have also been shown in other patient populations, including critically ill patients with sepsis [26].

5.2.3 *Apparent volume of distribution*

Both piperacillin and tazobactam have small apparent volumes of distribution (V_d). Following intravenous infusion of 3.375 g (3 g of piperacillin plus 0.375 g tazobactam) and 4.5 g (4 g of piperacillin plus 0.5 g of tazobactam) of piperacillin-tazobactam over 5 min, the V_d at steady state

Table 1. *In vitro* susceptibility of various organisms to piperacillin-tazobactam.

Organism	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Number of isolates	Region	Year of publication
Gram-positive					
Enterococcus faecalis	2	4	5637	Global	2009 [37]
VR *E. faecalis*	2	16	159	Global	2009 [37]
E. faecium	≥ 32	≥ 32	2008	Global	2009 [37]
VR *E. faecium*	≥ 32	≥ 32	921	Global	2009 [37]
Staphylococcus aureus	1	≥ 32	13,197	Global	2009 [37]
MRSA	16	≥ 32	5875	Global	2009 [37]
Streptococcus pneumoniae	≤ 0.25	2	6456	Global	2009 [37]
β-Hemolytic streptococci	≤ 0.12	0.5	397	Global	2005 [90]
Gram-negative					
Acinetobacter baumannii	32	≥ 256	6292	Global	2009 [37]
Burkholderia cepacia	8	> 64	269	Global	2005 [91]
Citrobacter spp.	4	64	147	EU	2009 [38]
AmpC de-repressed *Citrobacter* spp.	128	> 128	55	US	2008 [39]
Enterobacter cloacae	2	128	8786	Global	2009 [37]
AmpC de-repressed *E. cloacae*	> 128	> 128	103	US	2008 [39]
E. aerogenes	4	32	47	Canada	2008 [92]
Escherichia coli	1	8	13,739	Global	2009 [37]
Non-ESBL *E. coli*	4	8	1742	US	2008 [39]
ESBL *E. coli*	4	32	243	AP	2010 [35]
	4	64	958	Global	2009 [37]
	8	32	194	LA	2008 [40]
Haemophilus influenzae	≤ 0.06	≤ 0.06	6070	Global	2009 [37]
Klebsiella pneumoniae	2	128	10,644	Global	2009 [37]
Non-ESBL *K. pneumoniae*	4	16	1183	US	2008 [39]
ESBL *K. pneumoniae*	32	≥ 256	1495	Global	2009 [37]
	> 128	> 128	44	US	2008 [39]
	64	≥ 256	280	LA	2008 [40]
K. oxytoca	1	128	2486	Global	2009 [37]
Moraxella catarrhalis	≤ 2	≤ 2	78	Canada	2008 [92]
Morganella morganii	0.5	2	119	EU	2009 [38]
Proteus mirabilis	0.5	2	244	EU	2009 [38]
Indole-positive *Proteae*	≤ 1	2	96	US	2007 [93]
Pseudomonas aeruginosa	8	> 64	694	Japan	2010 [34]
	8	> 64	426	AP	2010 [35]
	8	256	548	China	2010 [36]
	4	128	10,825	Global	2009 [37]
	8	> 128	728	EU	2009 [38]
	8	64	419	Canada	2008 [92]
	16	> 128	355	US	2008 [39]
	8	128	715	LA	2008 [40]
Salmonella spp.	4	4	530	Global	2005 [90]
Serratia marcescens	1	16	4857	Global	2009 [37]
Stenotrophomonas maltophilia	> 64	> 64	2076	Global	2005 [91]
Anaerobes					
Bacteroides spp.	0.5	8	522	EU	2010 [94]
B. fragilis group	4	32	824	EU	2010 [95]
Clostridium perfringens	≤ 0.06	0.5	86	EU	2010 [94]
Fusobacterium spp.	0.016	1	30	Belgium	2007 [96]
Peptostreptococcus spp.	≤ 0.06	0.25	101	EU	2010 [94]
Prevotella spp.	≤ 0.06	1	197	EU	2010 [94]

AP: Asia Pacific; EU: Europe; LA: Latin America; US: United States of America.

(V_{ss}) of piperacillin was 14.9 and 15.8 l, respectively, and V_{ss} of tazobactam was 19.0 and 19.2 l, respectively [14]. This V_d corresponds well with the volume of extracellular (intravascular plus interstitial) water (0.2 – 0.3 l/kg) and is similar to data for other β-lactam antibiotics.

5.2.4 Distribution characteristics (into body compartments – clinical data)

The distribution characteristics of piperacillin-tazobactam into different body compartments are described in **Table 3**. Both piperacillin and tazobactam appear to distribute well

Table 2. Pharmacokinetics of piperacillin in healthy volunteers and patients with renal deficiency after administration of piperacillin-tazobactam.

Patient	Dose, infusion time	C_{max} (mg/l)	AUC (mg·h/l)	CL (ml/min)	V_d (l)	$T_{1/2}$ (h)
Piperacillin						
Healthy volunteers [14]	4.5 g, 30 min	277	278	242	12.3	0.88
Healthy volunteers [14]	3.375 g, 5 min	336	230	219	14.9	1.04
CL_{cl}: > 90 ml/min [97]	3.375 g, 30 min	209	228	225	14.9	0.95
CL_{cl}: 60 – 90 ml/min [97]	3.375 g, 30 min	228	323	159	13.0	1.10
CL_{cl}: 40 – 60 ml/min [97]	3.375 g, 30 min	274	417	134	12.5	1.26
CL_{cl}: 20 – 40 ml/min [97]	3.375 g, 30 min	248	462	114	12.4	1.43
CL_{cl}: < 20 ml/min [97]	3.375 g, 30 min	253	665	83	13.1	1.92
Tazobactam						
Healthy volunteers [14]	4.5 g, 30 min	34.4	41.4	202	12.6	0.78
Healthy volunteers [14]	3.375 g, 5 min	28.9	23.8	267	19.0	0.94
CL_{cl}: > 90 ml/min [97]	3.375 g, 30 min	23.6	29.0	219	15.9	0.89
CL_{cl}: 60 – 90 ml/min [97]	3.375 g, 30 min	27.6	44.6	147	14.7	1.21
CL_{cl}: 40 – 60 ml/min [97]	3.375 g, 30 min	30.4	59.1	118	14.4	1.47
CL_{cl}: 20 – 40 ml/min [97]	3.375 g, 30 min	29.4	84.0	78.1	14.0	2.09
CL_{cl}: < 20 ml/min [97]	3.375 g, 30 min	31.6	146	49.5	15.2	3.58

Values shown are mean values.

AUC: Area under the concentration curve; CL: Clearance; C_{max}: The maximum concentration; V_d: Volume of distribution; $T_{1/2}$: Elimination half-life.

into skin and lung tissues in which both have over 90% penetration [14,30]. Penetration decreases in gastrointestinal tissue to ca. 50% [30] with < 30% penetration into fatty tissue [30], muscle [30], cancellous bone [31] and cortical bone [31]. Of note, approximately 5% of piperacillin and 17% of a tazobactam dose will spread into cerebrospinal fluid (CSF) across non-inflamed meninges [32]. There have been no human data to evaluate intraocular penetration of systemically administered piperacillin-tazobactam.

It is likely that for infections involving tissue with < 30% penetration of piperacillin and tazobactam, treatment failure risk will increase for less susceptible organisms (e.g., *P. aeruginosa* and class A β-lactamase-producing Enterobacteriaceae) even if the organisms test susceptible in routine laboratory tests. It needs to be considered that MIC_{50} and MIC_{90} of piperacillin-tazobactam for clinically isolated strains of *P. aeruginosa* are generally 8 and > 64 mg/l, respectively, in most regions worldwide (**Table 1**) [33-40]. For Enterobacteriaceae with typical class A β-lactamases such as TEM-1 tazobactam, concentrations between 1.2 and 8.1 mg/l are required to inhibit the enzyme [16] and these levels may not be attained in tissues in which penetration is low (**Table 3**). Of note, a constant tazobactam concentration of 4 mg/l is employed in the *in vitro* susceptibility testing for piperacillin-tazobactam [41-43]. The strategies available to combat this possibility of failure are to prescribe increased doses, use an extended or continuous infusion as a strategy to increase time above MIC, or to choose an alternative therapeutic agent.

5.2.5 *Clearance mechanisms*

Following intravenous administration of 4.5 g of piperacillin-tazobactam, 49.8 ± 4.7 and 56.8 ± 2.7%, of piperacillin and tazobactam, respectively, were excreted into urine over the subsequent 24 h [44]. Interestingly, the presence of piperacillin results in a 10% decrease in tazobactam urinary excretion, whereas tazobactam does not affect urinary excretion of piperacillin [44]. Following the administration of 4.5 g of piperacillin-tazobactam, the biliary recovery of unchanged piperacillin and tazobactam over 12 h was 0.7 ± 0.4 and 0.2 ± 0.1% of the dose, respectively [45]. The total clearance, renal clearance and biliary clearance were 276.0 ± 128.0, 96.6 ± 52.3 and 1.74 ± 1.33 ml/min for piperacillin, respectively, and 196.0 ± 96.0, 129.0 ± 90.8 and 0.47 ± 0.40 ml/min for tazobactam, respectively [45].

5.2.6 *Metabolism*

Metabolism plays a small role in the clearance of piperacillin and tazobactam. Both molecules undergo cleavage of the β-lactam ring. Degradation of piperacillin results in the formation of a minor inactive metabolite (*N*-desethyl-piperacillin) whereas tazobactam is metabolized to an inactive compound (M_1). Up to 26% of tazobactam is recovered as this inactive metabolite [14].

5.3 Alteration of pharmacokinetics in special conditions

5.3.1 *Renal dysfunction*

PK parameters of piperacillin and tazobactam after administration of piperacillin-tazobactam in patients with various levels of renal function are shown in **Tables 1** and **2**. The elimination half-life of both piperacillin and tazobactam increases with diminishing renal function. Compared with patients with normal renal function, in patients with a creatinine clearance (CL_{Cr}) of 10 – 30 ml/min, only 35% of the administered dose was renally excreted [46]. From an AUC perspective in a patient with a CL_{Cr} of 20 ml/min, piperacillin

Table 3. The distribution characteristics of piperacillin-tazobactam into different body compartments.

Body compartment	Patient group	Author and year	Dose administered	Time of sample collection after initiation	Tissue/plasma concentration ratio of piperacillin	Tissue/plasma concentration ratio of tazobactam	Tissue concentration of piperacillin (mg/l)	Tissue concentration of tazobactam (mg/l)
Skin	Colorectal surgery	Kinzig *et al.*, 1992 [30]	4.5 g, 30 min	91 – 150 min	1.11 ± 0.360	0.933 ± 0.867	61.8 ± 23.8	6.31 ± 3.80
Fatty tissue	Colorectal surgery	Kinzig *et al.*, 1992 [30]	4.5 g, 30 min	91 – 150 min	0.115 ± 0.070	0.128 ± 0.080	6.61 ± 4.01	0.986 ± 0.555
Muscle	Colorectal surgery	Kinzig *et al.*, 1992 [30]	4.5 g, 30 min	91 – 150 min	0.288 ± 0.109	0.295 ± 0.159	16.2 ± 8.32	2.21 ± 1.18
Intestinal mucosa (proximal)	Colorectal surgery	Kinzig *et al.*, 1992 [30]	4.5 g, 30 min	91 – 150 min	0.545 ± 0.298	1.15 ± 0.981	31.4 ± 20.5	10.3 ± 9.63
Intestinal mucosa (distal)	Colorectal surgery	Kinzig *et al.*, 1992 [30]	4.5 g, 30 min	91 – 150 min	0.588 ± 0.163	2.08 ± 1.51	31.2 ± 14.9	14.5 ± 6.89
Appendix	Colorectal surgery	Kinzig *et al.*, 1992 [30]	4.5 g, 30 min	91 – 150 min	0.498 ± 0.157	1.41 ± 0.703	26.5 ± 11.1	9.12 ± 5.90
Lung	Thoracic surgery	Sorgel *et al.*, 1993 [14]	2.5 g, 30 min	60 min	N/A	N/A	40.8 ± 16.6	8.63 ± 3.65
Lung	Thoracic surgery	Sorgel *et al.*, 1993 [14]	2.5 g, 30 min	90 – 150 min	0.92 ± 0.16	N/A	N/A	N/A
Gallbladder	Cholesystectomy	Sorgel *et al.*, 1994 [29]	3.375 g, 30 min	90 – 150 min	N/A	N/A	34.3 ± 19.5	2.11 ± 1.12
Bile	Cholesystectomy	Sorgel *et al.*, 1994 [29]	3.375 g, 30 min	N/A	N/A	N/A	220 – 1045	1.33 – 42.9
Prostate	Prostate resection	Sorgel *et al.*, 1994 [29]	2.5 g, 30 min	< 60 min	N/A	N/A	17.9 ± 10.6	5.50 ± 2.46
Prostatic fluid	Prostate resection	Sorgel *et al.*, 1994 [29]	2.5 g, 30 min	< 60 min	N/A	N/A	7.24	2.93
Cancellous bone	Total hip replacement	Incavo *et al.*, 1994 [31]	3.375 g, 30 min	60 min	0.23 ± 0.12	0.26 ± 0.09	21.3 ± 10.1	2.46 ± 0.96
Cortical bone	Total hip replacement	Incavo *et al.*, 1994 [31]	3.375 g, 30 min	60 min	0.18 ± 0.08[a]	0.22 ± 0.08[a]	18.7 ± 7.8	2.29 ± 0.93
CSF	Hydrocephalus	Nau *et al.*, 1997 [32]	6.5 g, 30 min		0.051 ± 0.035[a]	0.170 ± 0.232[a]		

[a]AUC_{CSF}/AUC_{plasma}.

has 300% larger AUC and tazobactam a 500% higher AUC [29] than a patient with a CL_{Cr} of > 90 ml/min. Dose reduction of piperacillin and tazobactam is required in renal dysfunction although biliary clearance of piperacillin appears to be upregulated in renal dysfunction [47]. As antibiotics with time dependent killing, it is preferable to reduce the dose rather than the frequency of the administration with decreasing dose requirements. However, this must be undertaken with reference to the available formulation. It follows that most commonly the same dose is given less frequently in renal dysfunction. As a guide, we have found locally with our therapeutic drug monitoring program that when CL_{Cr} is 30 – 50 ml/min, 8-hourly dosing is appropriate; 10 – 30 ml/min, 12-hourly dosing is appropriate and < 10 ml/min, 24-hourly dosing is appropriate [48]. Maintaining the same dose and reducing the dosing frequency would also be appropriate if the same $fT_{>MIC}$ could be achieved.

5.3.2 Hepatic dysfunction

There is no data to suggest that dose adjustment for piperacillin or tazobactam is required in patients with mild to severe hepatic dysfunction [49].

5.3.3 Biliary tract dysfunction

At present, there is no data to suggest that dose adjustment for piperacillin or tazobactam is required in patients with mild to severe gastrointestinal tract dysfunction. However, given the contribution of biliary clearance to total body clearance of both piperacillin and tazobactam, research is required to define whether gastrointestinal tract dysfunction may result in diminished dose requirements.

5.3.4 Vascular pathologies

There is little data to suggest whether patients with vascular pathologies and concomitant impaired peripheral tissue perfusion may require altered dosing strategies. A study by Legat *et al.* in patients with inflamed diabetic foot infections used *in vivo* microdialysis to determine tissue penetration of piperacillin and tazobactam [50]. The authors found similar C_{max} and AUC values in plasma and tissue suggesting that standard dosing approaches are appropriate for this indication where the site of infection is inflamed.

5.3.5 Critically ill patients

5.3.5.1 Sepsis

Critically ill patients are well known to undergo pathophysiological changes that can alter PK [51].

A study by Roberts *et al.* investigated the PK of piperacillin-tazobactam at first dose and at steady state in critically ill patients with sepsis [27]. The authors found that the V_d in these patients (25.0 l) was significantly larger than that found in previous studies in healthy volunteers – 10.4 l [52] and 7.4 l [53]. In this study, the authors also found that drug clearance was significantly higher (17.2 l/h) than studies from healthy volunteers – 11.3 l/h [52] and 8.1 l/h [53].

In patients with sepsis due to pneumonia, interstitial lung tissue concentrations of piperacillin and tazobactam were measured using microdialysis. Following the administration of 4.5 g of piperacillin-tazobactam over 20 min, C_{max}, AUC and elimination half-life ($T_{1/2}$) in the plasma were 326 ± 60.6 mg/l, 470 ± 142 mg·h/l and 0.943 ± 0.52 h for piperacillin, and 30.7 ± 5.88 mg/l, 36.2 ± 26.0 mg·h/l and 0.656 ± 0.456 h for tazobactam, respectively [54]. C_{max}, AUC and $T_{1/2}$ in interstitial lung tissue were 176 ± 105 mg/l, 288 ± 167 mg·h/l and 1.47 ± 1.28 h for piperacillin, and 20.5 ±14.5 mg/l, 45.7 ± 44.8 mg·h/l and 1.2 ± 1.53 h for tazobactam, respectively [54]. The ratio of AUC in the lung to AUC in plasma of piperacillin and tazobactam (AUC_{Lung}/AUC_{plasma}) were 0.63 ± 0.29 and 1.93 ± 1.56, respectively [54]. Tissue concentrations in the lung exceeded the MIC threshold for many clinically relevant pathogens for at least 4 – 6 h. However, the concentrations of piperacillin exceeded the MIC of *P. aeruginosa* for a much shorter period. Thus, dosing modification such as administration by extended or continuous infusion might be beneficial for treating *P. aeruginosa* infections that commonly have a higher MIC for piperacillin than other pathogens in order to achieve the 50% $fT_{< MIC}$ associated with maximal activity [54].

In patients with severe nosocomial pneumonia (presumably with sepsis) in ICU receiving 4.5 g of piperacillin-tazobactam over 30 min 8-hourly, plasma concentrations of piperacillin at steady state were 8.5 ± 4.6 mg/l at just before the subsequent dose (8 h after previous infusion), 55.9 ± 13.8 mg/l at 1 h after starting infusion, and 24.0 ± 13.8 mg/l at 5 h, when plasma concentrations of tazobactam were 2.1 ± 1.0, 4.8 ± 2.1 and 2.4 ± 1.2 mg/l, respectively [55]. Concentrations in epithelial lining fluid (ELF) at 5 h were 13.6 ± 9.4 mg/l for piperacillin and 2.1 ± 1.1 mg/l for tazobactam [55]. ELF/plasma concentration ratios at 5 h were 56.8 ± 33.6% for piperacillin and 91.3 ± 27.7% for tazobactam [55]. These data suggested that a regimen of piperacillin-tazobactam 4.5 g 8-hourly might provide insufficient time above MIC in patients with severe nosocomial pneumonia considering MIC_{90} values of typical nosocomial pathogens [55].

An alternative dosing strategy to maximize $fT_{> MIC}$ that has been subject to research recently, is administration by continuous infusion of 18 g/day of piperacillin-tazobactam (16 g of piperacillin plus 2 g of tazobactam) after a loading dose of 4.5 g. The PK of this approach was evaluated in patients with VAP and without renal dysfunction (mean CL_{Cr} 99 ml/min). At steady state, median concentrations of piperacillin were 38.9 mg/l in plasma and 19.1 mg/l in ELF, and median concentration of tazobactam were 5.9 mg/l in serum and 5.0 mg/l in ELF, and median ELF/serum concentration ratio were 0.43 for piperacillin and 0.84 for tazobactam [56]. Maintaining alveolar concentrations of piperacillin above 16 mg/l would be suggested empiric targets for administration by

continuous infusion to cover most of the likely causative Gram-negative pathogens [57]. Although whether a concentration 1× MIC or 4 – 5× MIC is the appropriate target for administration by continuous infusion remains unresolved, although some studies suggest the latter would be more appropriate. A dose of 18 g/day of piperacillin-tazobactam would be likely to consistently achieve this target and would be an appropriate target for treatment of VAP. In the comparator group receiving 13.5 g/day of piperacillin-tazobactam in this study, ELF concentration of piperacillin were suboptimal (12.7 mg/l) [56].

In patients with sepsis and septic shock, subcutis and muscle concentrations of piperacillin-tazobactam have been measured using *in vivo* microdialysis. Joukhadar *et al.* compared piperacillin concentrations in plasma, subcutis and muscle in a single dose study in patients with septic shock and healthy volunteers [58]. The authors found that subcutis interstitial concentrations of piperacillin were never > 11 mg/l and therefore not suitable for treatment of likely pathogens. Muscle concentrations were slightly higher and the authors concluded that piperacillin concentrations in subcutaneous tissue may be subinhibitory, even though effective concentrations are attained in plasma. Similar results were found by Roberts *et al.,* who were also able to show that administration by continuous infusion (13.5 g/day) maintained higher trough concentrations at steady state (5.2 mg/l) than administration by intermittent infusion (4.5 g 6- or 8-hourly) over 20 min (0.8 mg/l) [26].

5.3.5.2 *Continuous renal replacement therapy (CRRT)*

Although commonly prescribed in ICUs, piperacillin-tazobactam has not been studied in continuous renal replacement therapy (CRRT) to any significant extent. The early studies that looked at piperacillin and piperacillin-tazobactam administered 8 hourly in anuric patients on continuous veno-venous hemofiltration (CVVHF), generally demonstrated the accumulation of piperacillin with longer half lives than in normal subjects [59,60]. The tazobactam component has shown greater accumulation relative to piperacillin in anuric patients and this is possibly due to the larger V_d of tazobactam and the greater reliance on renal clearance mechanisms [59,61]. Alternating doses of piperacillin alone with piperacillin-tazobactam has been recommended in order to avoid accumulation of tazobactam in CVVHF particularly as the toxicities of tazobactam are not known [59,60].

A useful study by Valtonen *et al.* examined piperacillin-tazobactam PK during continuous veno-venous hemodiafiltration (CVVHDF) and this study compared dialysate flow rates of 1 l/h with 2 l/h [61]. The authors found that the higher dialysate flow rate (2 l/h) displayed greater removal of the drug [61]. This study also compared CVVHF and CVVHDF with piperacillin-tazobactam and described different half-lives (CVVHF 7.7 ± 2.3 h and CVVHDF 1 l/h 6.7 ± 1.9 h and CVVHDF 2 l/h 6.1 ± 2.0 h) and decreased clearance for CVVHF (3.89 ± 1.23 l/h) compared with CVVHDF (1 l/h, 5.0 ± 1.68 l/h and CVVHDF (2 l/h, 5.48 ± 2.11 l/h). Apart from the difference between dialysis modalities, other factors that have been shown to influence the PK of piperacillin-tazobactam include membrane type and the patients' level of residual renal function. Higher drug removal during CVVHF has been observed with the use of the polysulfone hemofilter membrane compared with the acrylonitrile hemofilter [62]. Patients on CVVHF with a preserved level of residual renal function displayed significantly enhanced elimination of piperacillin-tazobactam compared to patients with moderate and total renal failure [63].

5.3.5.3 *Burns*

PK in patients with burn injuries can differ from those in other patient populations. Larger V_d and clearances are well documented. Limited data exist for piperacillin-tazobactam at this time. A study by Bourget *et al.* in 10 patients with third degree burns (~ 30% total body surface area) administered the antibiotic as a 4.5-g dose 6-hourly [64]. The minimum concentration (C_{min}) was > 20 mg/l on Day 1 and Day 3 for piperacillin and > 1.0 mg/l on both days for tazobactam. The authors found that the proportional increase of V_d to clearance was highly significant resulting in a prolongation of half-life to 1.8 h compared with healthy volunteer data (~ 1.5 h) for piperacillin and tazobactam (1.7 – 1.4 h). The authors concluded that dosing of 4.5 g 6-hourly, which is the currently licensed maximum dosing, is the minimum dose required for this patient population without renal dysfunction.

5.3.6 *Obesity*

The obese body has a higher proportion of adipose tissue and lower proportions of tissue water and lean body mass, which can affect drug distribution and absorption. In a case report of a 39-year-old man with morbid obesity (weight 167 kg, body mass index 50 kg/m^2) treated with 3.375 g of piperacillin-tazobactam 4-hourly for cellulitis – compared with population values – had a reduced average serum steady-state concentration: 39.8 versus 123.6 mg/l, an increased V_d: 54.3 versus 12.7 l, and an increased half life: 1.4 versus 0.6 h [65].

5.3.7 *Cystic fibrosis*

The PK of piperacillin-tazobactam in eight patients with cystic fibrosis was investigated by Vinks *et al.* [24]. The authors found that the observed data were best described using a nonlinear model. The parameter estimates for the best nonlinear model were: the concentration at which the metabolic rate was half of maximum (Km) 58 ± 75 mg/l; the maximum rate of metabolism (Vm) 1.9 ± 1.0 mg/h; and V_d (central compartment) 14.1 ± 3.0 l. This data show that patients with cystic fibrosis have a moderately increased V_d compared with healthy volunteers, but have very high clearance (24.4 l/h) necessitating more aggressive dosing.

5.3.8 Pregnancy

In a study with patients of 25 – 31 weeks of gestation, following the administration of 4.5 g of piperacillin-tazobactam, C_{max}, AUC, V_d at steady state (V_{ss}), and half-life ($T_{1/2}$) were 162.6 ± 11.2 mg/l, 178.8 ± 18.5 mg · h/l, 18.5 ± 1.6 l (0.27 ± 0.02 l/kg), and 0.61 ± 0.05 h for piperacillin, and 17.8 ± 1.2 mg/l, 22.1 ± 1.2 mg·h/l, 21.9 ± 2.9 l (0.31 ± 0.44 l/kg), and 0.69 ± 0.06 h for tazobactam, respectively. Compared with previously obtained data in healthy volunteers, pregnant women had significantly lower C_{max}, smaller AUC, larger V_{ss}, and shorter $T_{1/2}$ of both piperacillin and tazobactam [66].

5.3.9 Pediatric patients

In a study with patients of 2 months to 12 years of age receiving a single dose of either 50 and 6.25 mg/kg (body weight) or 100 and 12.5 mg/kg (body weight) of piperacillin and tazobactam, respectively, C_{max} and AUC values of piperacillin and tazobactam increased in a dose-dependent manner, and no difference in pharmacokinetic parameters other than C_{max} and AUC values of the drugs was observed between the two doses [67]. PK of piperacillin and tazobactam after administration of piperacillin-tazobactam in different age groups are shown in **Table 4**. With increasing age, elimination of both piperacillin and tazobactam increased, whereas V_{ss} remained relatively constant.

6. Pharmacodynamics

β-Lactam antibiotics are generally described as time-dependent antibiotics because bacterial killing is related to the time for which the antibiotic free (or unbound) concentration (T) is maintained above the MIC of the infecting pathogen ($fT_{> MIC}$). An increase in bactericidal activity is noted at concentrations up to four to five times the MIC, with higher concentrations providing no added benefit [68]. Data on the precise $T_{> MIC}$ required for optimal activity for β-lactam antibiotics have been obtained from dynamic *in vitro* and animal *in vivo* models and suggest that $fT_{> MIC}$ 50% is required for Gram-negative bacteria and 40 – 50% for Gram-positive bacteria [69,70]. A shorter $fT_{> MIC}$ is required for Gram-positive organisms because of a post-antibiotic effect that exists against these organisms. The optimal exposure of β-lactams required for the treatment of infections in different patient populations and for minimization of the development of bacterial resistance is yet to be described.

Anti-pseudomonal activity is one of the major advantages of piperacillin-tazobactam over most other β-lactam antibiotics. Of note, in a current standard susceptibility testing for *P. aeruginosa* recommended by Clinical and Laboratory Standards Institute (CLSI), strains with MICs of ≤ 64 mg/l to piperacillin-tazobactam are determined as susceptible [42]. However, it seems to be difficult to maintain adequate $fT_{> MIC}$ for strains with MICs of 64 mg/l and possibly 32 mg/l at target tissues, even by the currently authorized maximum dosing of 4.5 g 6-hourly [71]. The appropriateness of the current susceptibility breakpoint setting of piperacillin-tazobactam for *P. aeruginosa* requires further debate. In fact, inconsistency in this issue is highlighted by European Committee on Antimicrobial Susceptibility Testing (EUCAST) defining strains of *P. aeruginosa* with MICs of > 16 mg/l are resistant to piperacillin-tazobactam (**Table 5**) [43]. Where *P. aeruginosa* with MICs between 32 and 64 mg/l are being treated, piperacillin (if available) can be administered as a single agent as much as 4 g 4-hourly (24 g/day), and may be more appropriate than piperacillin-tazobactam 4.5 g 6-hourly. Where *P. aeruginosa* with MICs between 32 and 64 mg/l are concerned in empirical treatment and other anti-pseudomonal agents are not reliable according to the local antibiogram, continuous infusion of the piperacillin-tazobactam (18 g/day) plus piperacillin (8 g/day) combination may be a possible option despite a lack of experience.

The PD for tazobactam is certainly less clear. At this time, it is assumed that for a β-lactam plus β-lactamase inhibitor combination, the AUC is the important factor [23].

7. Clinical outcome data

There have been a number of randomized controlled trials (RCTs) of piperacillin-tazobactam comparing with other antimicrobial regimes in treatment of a variety of infections. Clinical outcome data of piperacillin-tazobactam versus comparators have been extensively reviewed elsewhere [72] and therefore will not be discussed in detail. Suffice to say, piperacillin-tazobactam has been shown to be as effective and safe as imipenem-cilastatin or doripenem for nosocomial pneumonia [73,74], as imipenem-cilastatin or ertapenem for complicated intra-abdominal infections [75-78], as meropenem, cefepime, ceftazidime, or piperacillin-tazobactam plus amikacin for febrile neutropenia [79-82], as ertapenem or imipenem-cilastatin for diabetic foot infection [83,84], as ertapenem for complicated skin and soft tissue infections [85,86], and as ertapenem for acute pelvic infections [87]. Therefore, piperacillin-tazobactam has been recommended in various clinical guidelines for treatment of a wide range of infections [2-9].

8. Adverse effects

Piperacillin-tazobactam is usually well tolerated. Adverse events are generally mild to moderate and seldom necessitate discontinuation of treatment [49]. The type and incidence of adverse events vary with patient category. In patients with intra-abdominal infections, diarrhea (7.5%) and phlebitis (3.3%) were observed [78]. In patients with nosocomial pneumonia, elevation of γ-glutamyltransferase (1.8%), thrombocythemia (2.3%), diarrhea (2.3%), elevation of alanine aminotransferase (0.9%), phlebitis (0.9%), elevation of asparate aminotransferase (0.5%), and elevation of

Table 4. Pharmacokinetics of piperacillin and tazobactam after administration of piperacillin-tazobactam (56.25 or 112.5 mg/kg) in various age groups [67].

Age	CL (ml/min/kg)	CL_R/CL (%)	V_d (l/kg)	$T_{1/2}$ (h)
Piperacillin				
2 – 5 months	3.3	72	0.37	1.4
6 – 23 months	4.7	46	0.36	0.9
2 – 5 years	5.5	66	0.36	0.7
6 – 12 years	5.9	73	0.36	0.7
Tazobactam				
2 – 5 months	3.3	80	0.43	1.6
6 – 23 months	4.9	65	0.42	1.0
2 – 5 years	5.5	78	0.38	0.8
6 – 12 years	6.2	75	0.40	0.9

Values shown are mean values.
CL: Clearance; CL_R: Renal clearance; V_d: Volume of distribution; $T_{1/2}$: Elimination half-life.

Table 5. Comparison of susceptibility breakpoints of Gram-negative bacilli for piperacillin-tazobactam between CLSI [42] and EUCAST [43].

	CLSI (mg/l)	EUCAST (mg/l)
Enterobacteriaceae	≤ 16	≤ 8
Pseudomonas aeruginosa	≤ 64	≤ 16
Pseudomonas spp. other than *P. aeruginosa*	≤ 16	≤ 16
Acinetobacter spp.	≤ 16	None*

For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/l.
*EUCAST does not recommend the use of piperacillin-tazobactam for the treatment of *Acinetobacter* spp. regardless of MIC values because susceptibility testing of *Acinetobacter* spp. to penicillin class antibiotics is unreliable.

eosinophil count (0.5%) were observed [73]. In patients with diabetic foot infection, diarrhea (14%), nausea (7%), headache (6%), and adverse laboratory events (10%) were observed [83]. In patients with febrile neutropenia, skin rash (29.4%), stomatitis (21.9%), infusion site reaction (21.9%), epistaxis (13.2%), diarrhea (34.3%), abdominal pain (21.9%), nausea (12.5%), vomiting (12.5%), headache (15.1%), and laboratory abnormalities (48.3%) were observed [79]. These data were obtained from recent representative RCTs and these incidences were similar to those of comparators in the studies. As with other β-lactam antibiotics, likely toxicities from excessive dosing include seizures and confusion, interstitial nephritis and elevation of γ-glutamyltransferase. Clinicians need to be aware of these effects if more aggressive dosing is selected for treatment of infections caused by less susceptible organisms (e.g., *P. aeruginosa, A. baumannii*).

9. Conclusion

The information discussed above details the suitability of piperacillin-tazobactam for empiric treatment of various infections. However, use of this broad spectrum antibiotic should be in line with accepted principles for antibiotic prescription with de-escalation to narrower spectrum antibiotics undertaken where possible to minimize antibiotic collateral damage. Where piperacillin-tazobactam is required for treatment, an application of knowledge of PK and PD characteristics can facilitate optimal outcomes.

10. Expert opinion

The altered PK of piperacillin-tazobactam in various patient populations has been relatively well described. It is evident that in patients with increased V_d or clearances (e.g., critically ill patients with sepsis and/or burns without renal dysfunction; cystic fibrosis) more aggressive dosing should be considered. This can be achieved by more frequent administration of the antibiotic, or administration by extended or continuous infusion as a mechanism to elevate the C_{min} in line with the PD characteristics of piperacillin-tazobactam [27,88,89]. In patients with renal dysfunction, or those prescribed with renal replacement therapies, reduced dosing compared with 'normal' patients may be required. The challenge for clinicians is to identify what level of dose adjustment should be correctly undertaken. The disparity between empiric dosing and achievement of therapeutic concentrations has been described in a study by Roberts *et al.* that evaluated the need for therapeutic drug monitoring (TDM) for this antibiotic in critically ill patients [48]. The authors found that up to 70% of patients did not achieve optimal concentrations of piperacillin thereby necessitating dose adjustment. It follows that a need for TDM for piperacillin, as for other β-lactams may be seen as a mechanism to improve treatment with this antibiotic. The patient populations likely to benefit from TDM are critically ill patients, patients with renal dysfunction necessitating renal replacement therapy or patients with difficult-to-predict PK (e.g., cystic fibrosis, burns). Dosing should be monitored as frequently as possible in these patient groups with daily monitoring advisable.

Consideration of pathogen susceptibility is another primary indicator for altered dosing of piperacillin-tazobactam, although this is not well understood. The MIC_{90} of organisms for which piperacillin-tazobactam is selected as treatment can vary from 0.0625 (e.g., *Streptococcus pyogenes*) to 16 mg/l (e.g., *P. aeruginosa*) and therefore the concentrations required to achieve the target $fT_{>MIC}$ can vary up to 250-fold. It is logical therefore, that dosing can be varied according to the MIC of the infecting pathogen, and in many cases this would result in a significant dose reduction and cost saving when treating highly susceptible pathogens. Of course for many of these more

susceptible organisms, de-escalation to a narrower-spectrum agent may be possible.

Administration of piperacillin-tazobactam by extended or continuous infusion is appropriate in environments that are considered to be difficult-to-treat due to limited drug penetration (e.g., osteomyelitis) or high MICs (e.g., *P. aeruginosa* with a MIC of 32 mg/l) [27]. Many centers rarely have such susceptibility problems at present and therefore, use of extended or continuous infusion as the sole administration method is not essential at this time. The other utility of administration by extended or continuous infusion is to increase the tissue distribution of piperacillin-tazobactam in patients with complicated PK such as critically ill patients with sepsis [26]. It follows that standard doses of piperacillin-tazobactam (4.5 g 8-hourly) by intermittent infusion remain appropriate except where a less susceptible organism is suspected, or in patients with an elevated V_d or clearances at which time higher doses by intermittent infusion (4.5 g 6-hourly) or preferably, by extended or continuous infusion are suggested.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Projan SJ. Francis tally and the discovery and development of tigecycline: a personal reminiscence. Clin Infect Dis 2010;50(S1):S24-5
2. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated Pneumonia. Am J Respir Crit Care Med 2005;171(4):388-416
3. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(S2):S27-72
4. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49(1):1-45
5. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39(7):885-10
6. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005;41(10):1373-406
7. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50(2):133-64
8. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34(6):730-51
9. Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36(1):296-327
10. Boucher HW, Talbot GH, Bradley JS, et al. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Clin Infect Dis 2009;48(1):1-12
11. Culver SM, Martens MG. Piperacillin/tazobactam (ZOSYN). Infect Dis Obstet Gynecol 1996;4(5):258-62
12. Wyeth Pharmceticals, Inc. Zosyn product information; 2009
13. Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. Clin Microbiol Rev 2010;23(1):160-201
14. Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. J Antimicrob Chemother 1993;31(Suppl_A):39-60
• **This paper describes in detail the pharmacokinetics and distribution characteristics of piperacillin/tazobactam.**
15. Essack SY. The development of beta-lactam antibiotics in response to the evolution of beta-lactamases. Pharm Res 2001;18(10):1391-9
16. Livermore DM. Determinants of the activity of beta-lactamase inhibitor combinations. J Antimicrob Chemother 1993;31(Suppl A):9-21
17. Papp-Wallace KM, Bethel CR, Distler AM, et al. Inhibitor resistance in the KPC-2 beta-lactamase, a preeminent property of this class A beta-lactamase. Antimicrob Agents Chemother 2010;54(2):890-7
18. Gavin PJ, Suseno MT, Thomson RB Jr, et al. Clinical correlation of the CLSI susceptibility breakpoint for piperacillin-tazobactam against extended-spectrum-beta-lactamase-producing Escherichia coli and Klebsiella Species. Antimicrob Agents Chemother 2006;50(6):2244-7
19. Rodriguez-Bano J, Navarro MD, Romero L, et al. Bacteremia due to extendeded spectrum beta-lactamase-producing Escherichia coli

in the CTX-M era: a new clinical challenge. Clin Infect Dis 2006;43(11):1407-14

20. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008;8(3):159-66
21. Aronoff GR, Sloan RS, Brier ME, et al. The effect of piperacillin dose on elimination kinetics in renal impairment. Eur J Clin Pharmacol 1983;24(4):543-7
22. Bergan T, Williams JD. Dose dependence of piperacillin pharmacokinetics. Chemotherapy 1982;28(3):153-9
23. Kim M-K, Xuan D, Quintiliani R, et al. Pharmacokinetic and pharmacodynamic profile of high dose extended interval piperacillin-tazobactam. J Antimicrob Chemother 2001;48(2):259-67
24. Vinks AA, den Hollander JG, Overbeek SE, et al. Population pharmacokinetic analysis of nonlinear behavior of piperacillin during intermittent or continuous infusion in patients with cystic fibrosis. Antimicrob Agents Chemother 2003;47(2):541-7
25. Tjandramaga TB, Mullie A, Verbesselt R, et al. Piperacillin: human pharmacokinetics after intravenous and intramuscular administration. Antimicrob Agents Chemother 1978;14(6):829-37

• **Early pharmacokinetic study of piperacillin outlining the differential pharmacokinetic parameters observed after different administered doses.**

26. 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):926-33

•• **Detailed pharmacokinetic evaluation of altered distribution characteristics of piperacillin in patients with sepsis.**

27. Roberts JA, Kirkpatrick CM, Roberts MS, et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. Int J Antimicrob Agents 2010;35(2):156-63
28. Li C, Kuti JL, Nightingale CH, et al. Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection. J Antimicrob Chemother 2005;56(2):388-95

•• **Large cohort and population pharmacokinetic analysis identifying covariates that describe causes of altered pharmacokinetics of piperacillin.**

29. Sorgel F, Kinzig M. Pharmacokinetic characteristics of piperacillin/tazobactam. Intensive Care Med 1994;20(Suppl 3):14-20
30. Kinzig M, Sorgel F, Brismar B, et al. Pharmacokinetics and tissue penetration of tazobactam and piperacillin in patients undergoing colorectal surgery. Antimicrob Agents Chemother 1992;36(9):1997-2004
31. Incavo SJ, Ronchetti PJ, Choi JH, et al. Penetration of piperacillin-tazobactam into cancellous and cortical bone tissues. Antimicrob Agents Chemother 1994;38(4):905-7
32. Nau R, Kinzig-Schippers M, Sorgel F, et al. Kinetics of piperacillin and tazobactam in ventricular cerebrospinal fluid of hydrocephalic patients. Antimicrob Agents Chemother 1997;41(5):987-91
33. Jones RN, Stilwell MG, Rhomberg PR, et al. Antipseudomonal activity of piperacillin/tazobactam: more than a decade of experience from the SENTRY Antimicrobial Surveillance Program (1997-2007). Diagn Microbiol Infect Dis 2009;65(3):331-4
34. Fujimura T, Anan N, Sugimori G, et al. Susceptibility of Pseudomonas aeruginosa clinical isolates in Japan to doripenem and other antipseudomonal agents. Int J Antimicrob Agents 2009;34(6):523-8
35. Farrell DJ, Turnidge JD, Bell J, et al. The in vitro evaluation of tigecycline tested against pathogens isolated in eight countries in the Asia-Western Pacific region (2008). J Infect 2010;60(6):440-51
36. Wang H, Chen M, Ni Y, et al. Antimicrobial resistance among clinical isolates from the Chinese Meropenem Surveillance Study (CMSS), 2003-2008. Int J Antimicrob Agents 2010;35(3):227-34
37. Garrison MW, Mutters R, Dowzicky MJ. In vitro activity of tigecycline and comparator agents against a global collection of Gram-negative and Gram-positive organisms: Tigecycline Evaluation and Surveillance Trial 2004 to 2007. Diagn Microbiol Infect Dis 2009;65(3):288-99
38. Turner PJ. MYSTIC Europe 2007: activity of meropenem and other broad-spectrum agents against nosocomial isolates. Diagn Microbiol Infect Dis 2009;63(2):217-22
39. Pillar CM, Torres MK, Brown NP, et al. In vitro activity of doripenem, a carbapenem for the treatment of challenging infections caused by Gram-negative bacteria, against recent clinical isolates from the United States. Antimicrob Agents Chemother 2008;52(12):4388-99
40. Rossi F, Garcia P, Ronzon B, et al. Rates of antimicrobial resistance in Latin America (2004-2007) and in vitro activity of the glycylcycline tigecycline and of other antibiotics. Braz J Infect Dis 2008;12(5):405-15
41. Higgins PG, Wisplinghoff H, Stefanik D, et al. In Vitro Activities of the beta-lactamase inhibitors Clavulanic acid, sulbactam, and tazobactam alone or in combination with beta-lactams against epidemiologically characterized multidrug-resistant Acinetobacter baumannii Strains. Antimicrob Agents Chemother 2004;48(5):1586-92
42. The Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twentieth International Supplement; 2010
43. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters Version 1.0 December 2009
44. Wise R, Logan M, Cooper M, et al. Pharmacokinetics and tissue penetration of tazobactam administered alone and with piperacillin. Antimicrob Agents Chemother 1991;35(6):1081-4

45. Westphal JF, Brogard JM, Caro-Sampara F, et al. Assessment of biliary excretion of piperacillin-tazobactam in humans. Antimicrob Agents Chemother 1997;41(8):1636-40

46. Aronoff GR, Sloan RS, Brier ME, et al. The effect of piperacillin dose on elimination kinetics in renal impairment. Eur J Clin Pharmacol 1983;24(4):543-7

47. Brogard JM, Jehl F, Blickle JF, et al. Biliary pharmacokinetic profile of piperacillin: experimental data and evaluation in man. Int J Clin Pharmacol Ther Toxicol 1990;28(11):462-70

48. Roberts J, Ulldemolins M, Roberts M, et al. Therapetuic drug monitoring of Beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 2010; In press

49. Perry CM, Markham A. Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. Drugs 1999;57(5):805-43

50. Legat FJ, Krause R, Zenahlik P, et al. Penetration of piperacillin and tazobactam into inflamed soft tissue of patients with diabetic foot infection. Antimicrob Agents Chemother 2005;49(10):4368-71

51. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37(3):840-51

52. Bulitta JB, Duffull SB, Kinzig-Schippers M, et al. Systematic comparison of the population pharmacokinetics and pharmacodynamics of piperacillin in cystic fibrosis patients and healthy volunteers. Antimicrob Agents Chemother 2007;51(7):2497-507

53. Landersdorfer C. Modern pharmacokinetic-pharmacodynamic techniques to study physiological mechanisms of pharmacokinetic drug-drug interactions and disposition of antibiotics and to assess clinical relevance Universitat Wurzburg, Fakultat fur Chemie und Pharmazie. Institut fur Pharmazie und Lebensmittelchemie, 2006

54. Florian T, Peter D, Alfred M, et al. Penetration of piperacillin and tazobactam into pneumonic human lung tissue measured by in vivo microdialysis. Br J Clin Pharmacol 2003;55(6):620-4

55. Boselli E, Breilh D, Cannesson M, et al. Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 g/0.5 g administered to critically ill patients with severe nosocomial pneumonia. Intensive Care Med 2004;30(5):976-9

56. Boselli E, Breilh D, Rimmele T, et al. Alveolar concentrations of piperacillin/tazobactam administered in continuous infusion to patients with ventilator-associated pneumonia. Crit Care Med 2008;36(5):1500-6

• **Describes ELF penetration of piperacillin and tazobactam in critically ill patients with VAP.**

57. Blondiaux N, Wallet F, Favory R, et al. Daily serum piperacillin monitoring is advisable in critically ill patients. Int J Antimicrob Agents 2010;35(5):500-3

• **Describes application of therapeutic drug monitoring for piperacillin administered by continuous infusion.**

58. Joukhadar C, Frossard M, Mayer BX, et al. Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. Crit Care Med 2001;29(2):385-91

59. van der Werf TS, Mulder PO, Zijlstra JG, et al. Pharmacokinetics of piperacillin and tazobactam in critically ill patients with renal failure, treated with continuous veno-venous hemofiltration (CVVH). Intensive Care Med 1997;23(8):873-7

60. Capellier G, Cornette C, Boillot A, et al. Removal of piperacillin in critically ill patients undergoing continuous venovenous hemofiltration. Crit Care Med 1998;26(1):88-91

61. Valtonen M, Tiula E, Takkunen O, et al. Elimination of the piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodiafiltration in patients with acute renal failure. J Antimicrob Chemother 2001;48(6):881-5

•• **Describes differential piperacillin/tazobactam pharmacokinetics in three different renal replacement therapy settings.**

62. Arzuaga A, Isla A, Gascon AR, et al. Elimination of piperacillin and tazobactam by renal replacement therapies with AN69 and polysulfone hemofilters: evaluation of the sieving coefficient. Blood Purif 2006;24(4):347-54

63. Arzuaga A, Maynar J, Gascon AR, et al. Influence of renal function on the pharmacokinetics of piperacillin/tazobactam in intensive care unit patients during continuous venovenous hemofiltration. J Clin Pharmacol 2005;45(2):168-76

64. Bourget P, Lesne-Hulin A, Le Reveille R, et al. Clinical pharmacokinetics of piperacillin-tazobactam combination in patients with major burns and signs of infection. Antimicrob Agents Chemother 1996;40(1):139-45

65. Newman D, Scheetz MH, Adeyemi OA, et al. Serum piperacillin/tazobactam pharmacokinetics in a morbidly obese individual. Ann Pharmacother 2007;41(10):1734-9

66. Bourget P, Sertin A, Lesne-Hulin A, et al. Influence of pregnancy on the pharmacokinetic behaviour and the trans-placental transfer of the piperacillin-tazobactam combination. Eur J Obstet Gynecol Reprod Biol 1998;76(1):21-7

67. Reed MD, Goldfarb J, Yamashita TS, et al. Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. Antimicrob Agents Chemother 1994;38(12):2817-26

68. Burgess DS, Waldrep T. Pharmacokinetics and pharmacodynamics of piperacillin/tazobactam when administered by continuous infusion and intermittent dosing. Clin Ther 2002;24(7):1090-104

69. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26(1):1-10

•• **Outstanding overview of pharmacokinetics and pharmacodynamics of antimicrobials.**

70. Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious

Diseases Pharmacists. Pharmacotherapy 2006;26(9):1320-32

71. DeRyke CA, Kuti JL, Nicolau DP. Reevaluation of current susceptibility breakpoints for Gram-negative rods based on pharmacodynamic assessment. Diagn Microbiol Infect Dis 2007;58(3):337-44

72. Gin A, Dilay L, Karlowsky JA, et al. Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. Expert Rev Anti Infect Ther 2007;5(3):365-83

73. Rea-Neto A, Niederman M, Margareth Lobo S, et al. Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. Curr Med Res Opin 2008;24(7):2113-26

74. Schmitt D, Leitner E, Welte T, et al. Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia – a double Blind Prospective Multicentre Study. Infection 2006;34(3):127-34

75. Namias N, Solomkin JS, Jensen EH, et al. Randomized, multicenter, double-blind study of efficacy, safety, and tolerability of intravenous ertapenem versus piperacillin/tazobactam in treatment of complicated intra-abdominal infections in hospitalized adults. Surg Infect 2007;8(1):15-28

76. Dela Pena AS, Asperger W, Kockerling F, et al. Efficacy and safety of ertapenem versus piperacillin-tazobactam for the treatment of intra-abdominal infections requiring surgical intervention. J Gastrointest Surg 2006;10(4):567-74

77. Erasmo AA, Crisostomo AC, Yan LN, et al. Randomized comparison of piperacillin/tazobactam versus imipenem/cilastatin in the treatment of patients with intra-abdominal infection. Asian J Surg 2004;27(3):1015-9584

78. 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):235-45

79. Bow EJ, Rotstein C, Noskin GA, et al. A Randomized, Open-Label, Multicenter Comparative Study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. Clin Infect Dis 2006;43(4):447-59

80. Harter C, Schulze B, Goldschmidt H, et al. Piperacillin//tazobactam vs ceftazidime in the treatment of neutropenic fever in patients with acute leukemia or following autologous peripheral blood stem cell transplantation: a prospective randomized trial. Bone Marrow Transplant 2006;37(4):373-9

81. Gernot R, Oliver AC, Michael S, et al. Empirical antimicrobial monotherapy in patients after high-dose chemotherapy and autologous stem cell transplantation: a randomised, multicentre trial. Br J Haematol 2005;130(2):265-70

82. Del Favero A, Menichetti F, Martino P, et al. A Multicenter, Double-Blind, Placebo-Controlled Trial comparing piperacillin-tazobactam with and without amikacin as empiric therapy for febrile neutropenia. Clin Infect Dis 2001;33(8):1295-301

83. Lipsky BA, Armstrong DG, Citron DM, et al. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet 2005;366(9498):1695-703

84. 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 2009. [Epub ahead of print]. Doi: 10.1111/j.1469-0691.2009.03067.x

85. Gesser RM, McCarroll KA, Woods GL. Evaluation of outpatient treatment with ertapenem in a double blind controlled clinical trial of complicated skin/skin structure infections. J Infection 2004;48(1):32-8

86. Graham DR, Lucasti C, Malafaia O, et al. Ertapenem once daily versus piperacillin-tazobactam 4 times per day for treatment of complicated skin and skin-structure infections in adults: results of a Prospective, Randomized, Double-Blind Multicenter Study. Clin Infect Dis 2002;34(11):1460-8

87. Fau RS, Higareda I, Angel-Muller E, et al. Ertapenem once a day versus piperacillin-tazobactam every 6 hours for treatment of acute pelvic infections: a prospective, multicenter, randomized, double-blind study. Infect Dis Obstet Gynecol 2003;11(1):1064-7449

88. Shea KM, Cheatham SC, Wack MF, et al. Steady-state pharmacokinetics and pharmacodynamics of piperacillin/tazobactam administered by prolonged infusion in hospitalised patients. Int J Antimicrob Agents 2009;34(5):429-33

89. Kim M-K, Capitano B, Mattoes HM, et al. Pharmacokinetic and pharmacodynamic evaluation of two dosing regimens for piperacillin-tazobactam. Pharmacotherapy 2002;22(5):569-77

90. Fritsche TR, Stilwell MG, Jones RN. Antimicrobial activity of doripenem (S-4661): a global surveillance report (2003). Clin Microbiol Infect 2005;11(12):974-84

91. Sader HS, Jones RN. Antimicrobial susceptibility of uncommonly isolated non-enteric Gram-negative bacilli. Int J Antimicrob Agents 2005;25(2):95-109

92. Zhanel GG, DeCorby M, Nichol KA, et al. Antimicrobial susceptibility of 3931 organisms isolated from intensive care units in Canada: Canadian National Intensive Care Unit Study, 2005/2006. Diagn Microbiol Infect Dis 2008;62(1):67-80

93. Rhomberg PR, Jones RN. Contemporary activity of meropenem and comparator broad-spectrum agents: MYSTIC program report from the United States component (2005). Diagn Microbiol Infect Dis 2007;57(2):207-15

94. Nagy E, Dowzicky MJ. In vitro activity of tigecycline and comparators against a European compilation of anaerobes collected as part of the Tigecycline Evaluation and Surveillance Trial (TEST). Scand J Infect Dis 2010;42(1):33-8

95. Elisabeth N, Edit U, Carl Erik N. Antimicrobial susceptibility of Bacteroides fragilis group isolates in

Europe; twenty years' experience. Clin Microbiol Infect 2010: In press

96. Wybo I, Pierard D, Verschraegen I, et al. Third Belgian multicentre survey of antibiotic susceptibility of anaerobic bacteria. J Antimicrob Chemother 2007;59(1):132-9

97. Johnson CA, Halstenson CE, Kelloway JS, et al. Single-dose pharmacokinetics of piperacillin and tazobactam in patients with renal disease. Clin Pharmacol Ther 1992;51(1):32-41

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