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Piperacillin/Tazobactam

An Updated Review of its Use in the Treatment of Bacterial Infections

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Data Selection

Sources: Medical literature published in any language since 1966 on piperacillin/tazobactam, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'tazobactam.piperacillin', and 'bacterial-infections'. Medline and EMBASE search terms were 'tazobactam', 'piperacillin', 'piperacillin adj tazobactam', 'piperacillin plus tazobactam' and 'tazobactam adj piperacillin'. Searches were last updated 16 Apr 1999.

Selection: Studies in patients with bacterial infection who received piperacillin/tazobactam. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Piperacillin, tazobactam, piperacillin/tazobactam, tazobactam/piperacillin, pharmacokinetics, pharmacodynamics, pharmacoeconomics, therapeutic use, drug interactions, dosage and administration.

Contents

Summary

Abstract

Piperacillin/tazobactam is a β-lactam/β-lactamase inhibitor combination with a broad spectrum of antibacterial activity encompassing most Gram-positive and Gram-negative aerobic bacteria and anaerobic bacteria, including many pathogens producing β-lactamases.

Evidence from clinical trials in adults has shown that piperacillin/tazobactam, administered in an 8 : 1 ratio, is an effective treatment for patients with lower respiratory tract, intra-abdominal, urinary tract, gynaecological and skin/soft tissue infections, and for fever in patients with neutropenia. Combination regimens of piperacillin/tazobactam plus an aminoglycoside are used to treat patients with severe nosocomial (hospital-acquired) infections.

In clinical trials, piperacillin/tazobactam was significantly more effective than ticarcillin/clavulanic acid in terms of clinical and microbiological outcome in patients with community-acquired pneumonia. In patients with intra-abdominal infections, clinical and bacteriological response rates were significantly higher with piperacillin/tazobactam than with imipenem/cilastatin (administered at a dosage lower than is recommended in countries outside Scandinavia).

Piperacillin/tazobactam in combination with amikacin was at least as effective as ceftazidime plus amikacin in the treatment of ventilator-associated pneumonia and was significantly more effective than ceftazidime plus amikacin in the empirical treatment of febrile episodes in patients with neutropenia or granulocytopenia. In other trials, the efficacy of piperacillin/tazobactam was similar to that of standard aminoglycoside-containing and other treatment regimens in patients with intra-abdominal, skin/soft tissue or gynaecological infections.

Piperacillin/tazobactam is generally well tolerated. The most frequent adverse

events are gastrointestinal symptoms (most commonly diarrhoea) and skin reactions. The incidence of adverse events with piperacillin/tazobactam is higher when the combination is given in combination with an aminoglycoside than when given as monotherapy.

Conclusion: Because of the broad spectrum of antibacterial activity provided by piperacillin/tazobactam, it is useful for the treatment of patients with polymicrobial infections caused by aerobic or anaerobic β-lactamase-producing bacteria. Piperacillin/tazobactam appears to have a particularly useful role in the treatment of patients with intra-abdominal infections and, in combination with amikacin, in the treatment of patients with febrile neutropenia, especially given the current prevalence of Gram-positive infections in this group.

Rationale for the Use of Piperacillin in Combination with Tazobactam

Although piperacillin has a broad spectrum of antibacterial activity, the increased prevalence of β-lactamase-producing bacteria over recent years has led to an increase in resistance to this agent, and has compromised its activity in the clinical setting. When coadministered with piperacillin, tazobactam, a β-lactamase inhibitor, restores and extends the antibacterial cover provided by piperacillin and thus enhances its clinical potential.

Pharmacodynamic Properties

Tazobactam shows good inhibitory activity against plasmid-mediated β-lactamases, staphylococcal penicillinase and chromosomal 2e β-lactamases. However, it is less inhibitory against group 1 β-lactamase subtypes and against group 3 metallo-β-lactamases. Tazobactam has a minimal ability to induce chromosomally mediated class I β-lactamases, whereas clavulanic acid is a moderate to strong inducer of these enzymes and thus has the potential to compromise the antibacterial activity of coadministered β-lactam agents.

Piperacillin/tazobactam has good *in vitro* activity against methicillin-sensitive *Staphylococcus aureus* and coagulase-negative staphylococci. Piperacillin/tazobactam is also active against *Streptococcus pyogenes* and penicillin-sensitive strains of *S. pneumoniae*. Most strains of *Enterococcus faecalis* are also susceptible to the combination. Methicillin-resistant strains of *S. aureus* and many methicillin-resistant coagulase-negative staphylococci are resistant to piperacillin/tazobactam. Strains of *E. faecium* were resistant to piperacillin/tazobactam in 2 *in vitro* studies.

Many Enterobacteriaceae, including *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp. are susceptible to piperacillin/tazobactam. The combination exhibits excellent activity against *Haemophilus influenzae* and *Moraxella catarrhalis* and is active against *Pseudomonas aeruginosa*. Although there has been a change in susceptibility patterns of *P. aeruginosa* over recent years, with a general trend towards an increase in resistance to various antibacterial agents, piperacillin/tazobactam has maintained its activity against this pathogen: results of several recent surveys showed that 91 to 95% of isolates of *P. aeruginosa* were susceptible to piperacillin/tazobactam. *Stenotrophomonas (Xanthomonas) maltophilia* strains are resistant to the combination.

Piperacillin/tazobactam is highly active against anaerobes, including *Bacteroides* spp., notably *B. fragilis*. It is also highly active against *Clostridium* spp. The combination demonstrated good efficacy in murine models of intra-abdominal infection or pneumonia caused by extended spectrum β-lactamase-producing strains of *K. pneumoniae*.

Pharmacokinetic Properties

After single intravenous 4/0.5g doses of piperacillin/tazobactam, mean maximum plasma concentrations (C_{max}) of piperacillin and tazobactam were 264.4 to 368 and 29.1 to 39 mg/L, respectively, in healthy adult volunteers. There was no evidence of accumulation of either agent after multiple doses in healthy adult volunteers or in adult patients with infection. The ratio of piperacillin C_{max} to tazobactam C_{max} was about 8 : 1 in healthy volunteers or in patients with intra-abdominal infections after multiple doses of 4/0.5g 6- or 8-hourly. However, mean piperacillin area under the plasma concentration-time curve (AUC) values were >2-fold higher in patients with burns than in healthy volunteers or in patients with intra-abdominal infections.

At steady-state, the volume of distribution of piperacillin ranged from 15 to 21L in healthy volunteers and patients with infection; the corresponding range for tazobactam was 18 to 34.6L. Both agents are rapidly and widely distributed in various body tissues and fluids.

About 50 to 60% of an administered dose of piperacillin/tazobactam is excreted via the renal route; biliary excretion accounts for the elimination of <2% of the dose. In healthy volunteers or patients with intra-abdominal infection, piperacillin and tazobactam each have a plasma elimination half-life of 0.8 to 1 hour. Dosage reduction is required for patients with moderate renal impairment [creatinine clearance <1.2 L/h (<20 ml/min)]. As haemodialysis removes up to 50% of piperacillin/tazobactam over 4 hours, an additional 2/0.25g dose should be given after each dialysis session. The pharmacokinetics of piperacillin/tazobactam are not markedly affected in patients with hepatic impairment. In children with infection, mean C_{max} and AUC values of piperacillin and tazobactam increase in a dose-dependent manner.

The pharmacokinetics of piperacillin and tazobactam are not markedly altered when it is coadministered with vancomycin, tobramycin, ondansetron or ranitidine.

Therapeutic Efficacy

Clinical cure or improvement was achieved in 85 to 94% of patients with community-acquired lower respiratory tract infections treated with various dosages of piperacillin/tazobactam. At a dosage of 3/0.375g 6-hourly, piperacillin/tazobactam was significantly more effective than ticarcillin/clavulanic acid 3/0.1g 4 times daily in patients with community-acquired pneumonia. Evaluations at the trial end-point (generally 10 to 14 days after discontinuation of treatment) showed favourable clinical responses in 84 and 64% of piperacillin/tazobactam and ticarcillin/clavulanic acid recipients, respectively ($p < 0.01$). Piperacillin/tazobactam also achieved a significantly higher rate of bacterial eradication than ticarcillin/clavulanic acid at the end of treatment (91 *vs* 68%; $p < 0.01$) and 10 to 14 days later (91 *vs* 83%; $p = 0.02$).

In patients with nosocomial pneumonia associated with mechanical ventilation in the intensive care unit, piperacillin/tazobactam 4/0.5g 4 times daily plus amikacin 7.5 mg/kg twice daily was at least as effective as ceftazidime 1g 4 times daily plus amikacin 7.5 mg/kg twice daily, with successful clinical and bacteriological outcomes documented in 51 and 36% of piperacillin/tazobactam- and ceftazidime-treated patients 6 to 8 days after the end of treatment. The efficacy of piperacillin/tazobactam was similar to that of imipenem/cilastatin in patients with nosocomial pneumonia. In patients with hospital-acquired acute purulent bronchitis or acute bacterial pneumonia, piperacillin/tazobactam 3/0.375g every 4 hours (plus tobramycin or amikacin) was significantly more effective than

ceftazidime 2g every 8 hours (plus tobramycin or amikacin); clinical responses at the study end-point were achieved in 75 and 50% of patients ($p < 0.01$).

Rates of bacterial eradication ranged from 76 to 100% in patients with intra-abdominal infections treated with piperacillin/tazobactam. The clinical efficacy of piperacillin/tazobactam was similar to that of clindamycin plus gentamicin and in 1 study was significantly better than that of imipenem/cilastatin 0.5g 8-hourly (a dosage lower than is recommended in countries outside Scandinavia). Piperacillin/tazobactam (80/10 mg/kg 8-hourly) was also beneficial in the treatment of children with appendicitis or peritonitis, with 91% of patients experiencing cure or improvement.

Clinical success rates of 41 to 83% were reported in patients with febrile neutropenia or granulocytopenia who received empirical treatment with piperacillin/tazobactam 12-16/1.5-2 g/day (in divided doses) in combination with an aminoglycoside. 72 hours after the initiation of treatment, clinical response rates were significantly higher in patients treated with piperacillin/tazobactam plus amikacin than in ceftazidime plus amikacin-treated patients (61% *vs* 45 or 54%; $p \leq 0.05$). In similar patients, piperacillin/tazobactam in combination with gentamicin was significantly more effective than piperacillin/gentamicin; clinical response rates of 83 and 48% ($p < 0.001$) were reported at 72 hours.

The efficacy of piperacillin/tazobactam monotherapy was similar to that of ceftazidime plus amikacin in patients with febrile neutropenia with 81 and 83% of febrile episodes resolved in patients treated with piperacillin/tazobactam and ceftazidime plus amikacin; median times to fever defervescence were also similar in the 2 treatment groups (3.3 *vs* 2.9 days).

The piperacillin/tazobactam combination also showed good clinical and bacteriological efficacy in patients with bacteraemia and in patients with skin and soft tissue, gynaecological or bone and joint infections. Piperacillin/tazobactam is also an effective treatment for patients with complicated urinary tract infections, achieving cure or improvement in 88 and 90.4% of patients 5 to 9 days after the end of treatment and in ≥80% of patients after 4 to 6 weeks of follow-up. Bacterial eradication rates after the same period of follow-up were 79.6 and 73%; *E. coli*, *K. pneumoniae* and *P. aeruginosa* were identified as common persistent pathogens.

Pharmacoeconomic Considerations

In a US economic evaluation, piperacillin/tazobactam was estimated to be less costly than comparator therapies in patients with community-acquired lower respiratory tract or intra-abdominal infection. Direct costs of therapy with piperacillin/tazobactam 3/0.375g 6-hourly were $US2981 per patient lower than with ticarcillin/clavulanic acid 3/0.1g 6-hourly in patients with community-acquired pneumonia. In patients with intra-abdominal infections, direct costs of piperacillin/tazobactam treatment were $US284 per patient lower than costs of treatment with clindamycin plus gentamicin.

A UK study showed that direct costs of treatment of patients with intra-abdominal infections were lower for piperacillin/tazobactam than for ceftazidime plus metronidazole alone or in combination with either gentamicin or netilmicin. Costs of acquisition, preparation, administration and waste disposal were included in this analysis.

However, although the acquisition cost of piperacillin/tazobactam is lower than that of imipenem/cilastatin, a comparative cost analysis showed a cost advantage

for the latter combination when the number of days spent in hospital was included in the economic model.

Results of a Canadian study that included patients with various serious infections showed that direct per patient costs of piperacillin/tazobactam and imipenem/cilastatin were broadly similar ($Can696 *vs* $Can762).

A pharmacoeconomic study, based on data from a trial conducted in patients with febrile neutropenia, showed that piperacillin/tazobactam plus amikacin was more cost effective than ceftazidime plus amikacin: estimated costs per successfully treated patient were DM16 616 and DM20 828 for piperacillin/tazobactam plus amikacin and ceftazidime plus amikacin, respectively. Both direct and indirect costs of treatment were incorporated in this model.

Tolerability

Pooled data from numerous clinical trials indicate that piperacillin/tazobactam, given in dosages of up to 4/0.5g 6-hourly, is generally well tolerated in patients with mild, moderate or severe infections. The most frequently reported adverse events are gastrointestinal symptoms (most commonly diarrhoea) and skin reactions. Adverse events are typically mild or moderate in severity and rarely necessitate the discontinuation of treatment. Incidences of these types of events increase markedly in patients receiving piperacillin/tazobactam in combination with an aminoglycoside.

Other adverse events reported in patients receiving piperacillin/tazobactam include minor changes in laboratory test values (e.g. increases in alanine aminotransferase and in total bilirubin).

Pseudomembranous colitis, bleeding manifestations and anaphylactic reactions have been reported in patients receiving penicillins, including piperacillin.

Dosage and Administration

Piperacillin/tazobactam is given intravenously as a bolus injection over 3 to 5 minutes or by infusion over 20 to 30 minutes. Recommended dosages range from 2/0.25g every 6 to 12 hours (for the treatment of patients with relatively mild infections) to 4/0.5g every 6 or 8 hours for the treatment of more severe infections.

1. Rationale for the Use of Piperacillin in Combination with Tazobactam

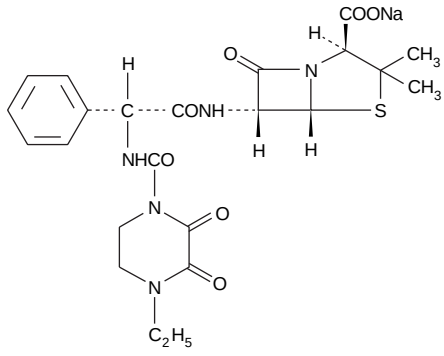
Piperacillin (fig. 1) is a semisynthetic ureidopenicillin with antibacterial activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria.[1] The clinical role of piperacillin has, however, been compromised over recent years, as a result of an increased prevalence of β-lactamase-producing bacteria which exhibit resistance to the drug.

Tazobactam (fig. 1), a triazolymethyl penicillanic acid sulfone derivative, is a β-lactamase inhibitor which protects piperacillin from destruction by β-lactamase enzymes. When combined with piperacillin, tazobactam broadens the spectrum of the latter agent to include many β-lactamase-producing organisms, including staphylococci, many Enterobacteriaceae, *Haemophilus influenzae* and *Bacteroides* spp.

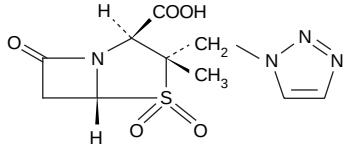
The antibacterial activity, pharmacokinetic properties and therapeutic potential of piperacillin/tazobactam have been reviewed previously in *Drugs*.[1] This review updates information in the previous article and includes new data that further clarify the role of piperacillin/tazobactam in the treatment of patients with mild, moderate or severe infections.

2. Pharmacodynamic Properties

Like other β-lactam antibacterial agents, piperacillin exerts its bactericidal effects by binding with penicillin-binding proteins (PBPs) in the bacterial cell wall. This leads to the inhibition of bacterial septum and cell wall synthesis and to eventual cell lysis (reviewed by Marra and Jewesson[2]).



Piperacillin



Tazobactam

Fig. 1. Chemical structures of piperacillin and tazobactam.

Tazobactam irreversibly inhibits many β-lactamases produced by clinically important Gram-negative or Gram-positive aerobic or anaerobic bacteria by covalently binding with these enzymes. In particular, tazobactam has strong affinity for plasmid-mediated β-lactamases (section 2.1), which are a common cause of resistance to penicillins and cephalosporins. Tazobactam has a low affinity for PBPs and thus shows little intrinsic antibacterial activity.[1,3,4]

2.1 *In Vitro* Activity of Tazobactam

Tazobactam is a substrate for β-lactamase, forming a stable acyl-enzyme intermediate thus rendering the enzyme permanently inactive.[1,3] As reviewed previously,[1] tazobactam has good affinity for plasmid-mediated groups 2b, 2br and 2c Bush-Jacoby-Medeiros β-lactamases (table I), including TEM and SHV β-lactamases and many of their extended-spectrum derivatives.[5,6] It also has affinity for staphylococcal penicillinase and chromosomal 2e β-lactamases.[1,6]

Against these enzymes, concentrations of tazobactam required to reduce the initial hydrolysis rate of nitrocefin or cefalothin by 50% [(IC_{50}) a measure of enzyme inhibitory activity] ranged from ≤0.05 to ≤0.5 mg/L (table I). Tazobactam showed less affinity for group 1 β-lactamase subtypes produced by *Pseudomonas aeruginosa*, *Citrobacter* spp., *Serratia* spp. and *Enterobacter* spp. (IC_{50} values >0.5 to ≤5 mg/L) and for group 3 metallo-β-lactamases (IC_{50} values 3 to >400 μmol/L), common in isolates of *Stenotrophomonas (Xanthomonas) maltophilia*.[1,8,9]

In comparative studies, tazobactam and clavulanic acid generally had greater affinity for plasmid-mediated β-lactamases, including TEM-1 and SHV-1 enzymes, than did sulbactam, whereas tazobactam and sulbactam had greater affinity for chromosomally mediated β-lactamases than clavulanic acid (reviewed by Bryson & Brogden[1] and Sanders & Sanders[10]). Interestingly, the affinity of tazobactam for inhibitor-resistant TEM-30 and TEM-31 enzymes (Bush-Jacoby-Medeiros group 2br[6]) produced by transconjugate strains of *E. coli*. was 10- to 25-fold greater (K_i values 2.1 and 23.5 μmol/L for TEM-30 and 31, respectively) than that of either clavulanic acid (K_i values 28 and

Table I. Summary of *in vitro* inhibitory activity of tazobactam (TAZ) against β-lactamases produced by selected bacteria[1,7]

Enzyme class[a] susceptible to TAZ at IC_{50} of ≤0.05 to ≤0.5 mg/L (β-lactamase-producing organism)	Enzyme class[a] susceptible to TAZ at IC_{50} of >0.5 to ≤5 mg/L (β-lactamase-producing organism)
2e (*Bacteroides fragilis*, *Proteus vulgaris*)	1 (*Enterobacter cloacae*)
2c (*Proteus mirabilis*)	1 (*Escherichia coli*)
2b (*Escherichia coli* TEM-1, *E. coli* SHV-1)	1 (*Pseudomonas aeruginosa*)
2be (*Klebsiella pneumoniae*, *Klebsiella oxytoca*)	
2c (*E. coli* OXA-1, *E. coli* PSE-1)	
Staphylococcal penicillinase (*Staphylococcus aureus*)	

a Enzyme class based on the Bush-Jacoby-Medeiros group classification.[6]

IC_{50} = drug concentration required to reduce the initial rate of hydrolysis of nitrocefin by 50%.

625 μmol/L) or sulbactam (K_i values 185 and 3745 μmol/L).[11] Tazobactam had affinity similar to that of clavulanic acid against the MET_{69}Ile mutant of OHIO-1 β-lactamase (K_i values 18.0 and 15.1 μmol/L for tazobactam and clavulanic acid).[11]

Whereas clavulanic acid is a moderate to strong inducer of chromosomally mediated class 1 β-lactamases, potentially compromising the antibacterial activity of coadministered β-lactam agents, tazobactam has a minimal ability to induce these enzymes.[1]

2.2 *In Vitro* Activity of Piperacillin/Tazobactam

Ranges of mean values of 90% of minimum inhibitory concentration (MIC_{90}) for piperacillin reported in *in vitro* investigations of piperacillin/tazobactam (published since 1994) are presented in figures 2 and 3 of this update.

All investigations employed broth or agar dilution techniques and at least 10 strains of clinical isolates. A fixed tazobactam concentration of 4mg was used in these studies.

Throughout the review, breakpoints from the National Committee for Clinical Laboratory Standards (NCCLS)[41] have been used to define bacterial susceptibility and resistance. According to these guidelines, the breakpoint concentrations of piperacillin/tazobactam indicative of susceptibility and resistance to staphylococci are ≤8/4 mg/L and ≥16/4 mg/L, respectively. In the absence of specific breakpoints for piperacillin/tazobactam against streptococci, the breakpoints for penicillin, as for other β-lactam agents, are used instead. Concentrations of piperacillin/tazobactam indicative of susceptibility and resistance to Gram-negative bacteria (excluding *P. aeruginosa* and *Haemophilus* spp.) are ≤16/4 mg/L and ≥128/4 mg/L, respectively. For nonfermentative rods and anaerobes, the breakpoint concentrations indicating susceptibility and resistance are ≤64/4 mg/L and ≥128/4 mg/L, respectively; for *Haemophilus* spp.,

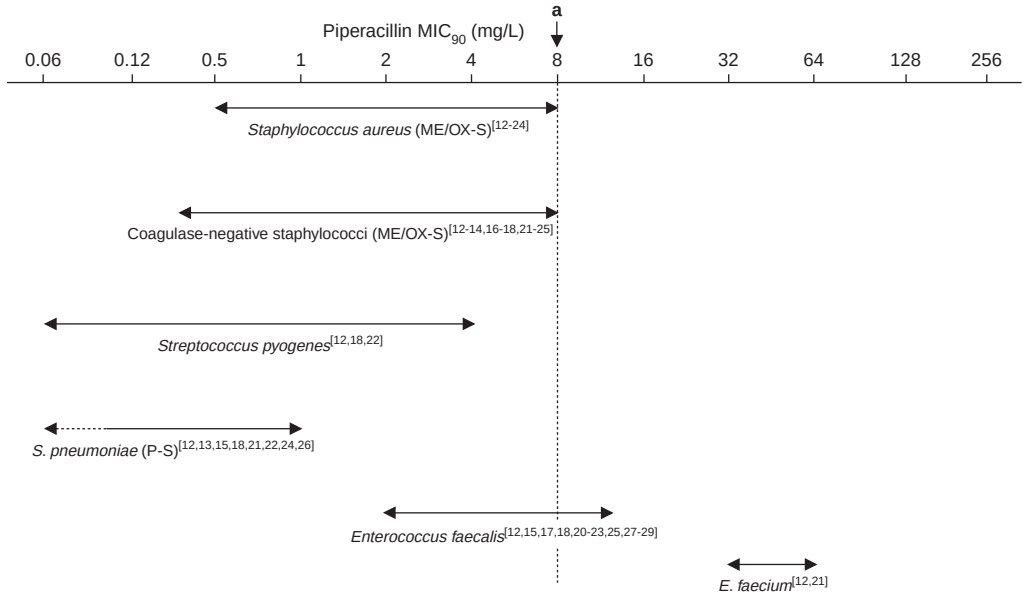


Fig. 2. Summary of the *in vitro* activity of piperacillin/tazobactam against Gram-positive bacteria. Each horizontal arrow shows the range of mean values of 90% of minimum inhibitory concentration (MIC_{90}) for the given bacteria from the cited studies (published between 1994 and 1998). All studies used broth or agar dilution techniques, at least 10 strains of clinical isolates and an inoculum size of 10^4 to 10^6 colony forming units. **ME/OX-S** = methicillin/oxacillin-sensitive; **P-S** = penicillin-sensitive. **a** Susceptibility breakpoint.

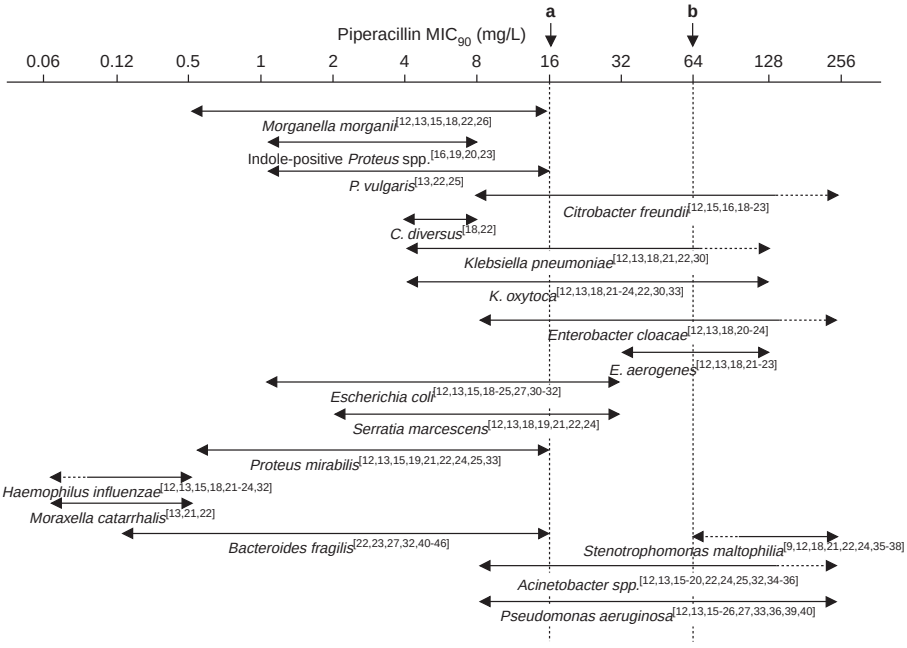


Fig. 3. Summary of the *in vitro* activity of piperacillin/tazobactam against Gram-negative organisms, including Enterobacteriaceae, nonfermentative bacilli and *Bacteroides fragilis*. Each horizontal arrow shows the range of mean values of 90% of minimum inhibitory concentration (MIC_{90}) for the given bacteria (including both β-lactamase- and non-β-lactamase-producing strains) from the cited studies (published between 1994 and 1998). All studies used broth or agar dilution techniques, at least 10 strains of clinical isolates and an inoculum size of 10^4 to 10^6 colony forming units. **a** Susceptibility breakpoint for Gram-negative bacteria (other than nonfermentative bacilli); **b** Susceptibility breakpoint for nonfermentative bacilli and *B. fragilis*.

breakpoint concentrations indicative of susceptibility and resistance are ≤1/4 mg/L and ≥2/4 mg/L.

2.2.1 Gram-Positive Bacteria

Piperacillin/tazobactam shows good *in vitro* activity against the majority of Gram-positive bacteria, including those producing β-lactamases. In comparative studies, the spectrum of *in vitro* antibacterial activity of piperacillin/tazobactam was generally similar to that of ampicillin/sulbactam and broader than that of ticarcillin/clavulanic acid.[10]

Piperacillin/tazobactam demonstrated good *in vitro* activity against methicillin/oxacillin-sensitive strains of *Staphylococcus aureus* and coagulase-negative staphylococci,[42] with mean MIC_{90} values less than the susceptibility breakpoint (≤8 mg/L) [fig. 2]. Like other β-lactam/β-lactamase combinations, piperacillin/tazobactam is inactive against methicillin-resistant *S. aureus* and is generally inactive against other strains of methicillin-resistant staphylococci, including methicillin-resistant coagulase-negative staphylococci.

Penicillin-sensitive *S. pneumoniae* were highly susceptible to piperacillin/tazobactam,[42] with mean MIC_{90} values ranging from <0.06 to 1 mg/L (fig. 2). Piperacillin/tazobactam also showed activity against intermediately penicillin-resistant and penicillin-resistant pneumococci.[26,43] Intermediately penicillin-resistant (n = 70) and penicillin-resistant pneumococci (n = 66) were susceptible to piperacillin/tazobactam (MIC_{90} values ≤0.064 and 2.0 mg/L, respectively), ceftriaxone and ampicillin/sulbactam in 1 investigation. However, the same strains were resistant to ticarcillin/clavulanic acid (MIC_{90} values 64 and 128 mg/L for intermediate and resistant strains, respectively).[26] Moreover,

piperacillin/tazobactam showed greater bacteriostatic and bactericidal activity than ticarcillin/clavulanic acid against penicillin-susceptible, intermediately penicillin-resistant and penicillin-resistant strains of *S. pneumoniae* in a subsequent study.[43] Piperacillin/tazobactam was also active against *S. bovis*, *S. agalactiae* and groups C and G streptococci. The MIC_{90} of piperacillin/tazobactam against viridans streptococci was 1 mg/L and all 40 strains tested were susceptible to the combination.[1,12]

Piperacillin/tazobactam had activity against *Enterococcus faecalis* with MIC_{90} values of ≤8 mg/L reported in the majority of studies (fig. 2).[42,44] In 1 study, 95 gentamicin-resistant strains of *E. faecalis* showed intermediate susceptibility to piperacillin/tazobactam (MIC_{90} 12.5 mg/L).[28] *E. faecium* strains were resistant to piperacillin/tazobactam, with MIC_{90} values of 32 (n = 29) and >64 mg/L (n = 21) reported in each of 2 studies.[12,21] As noted previously,[1] piperacillin/tazobactam and other β-lactam/β-lactamase inhibitor combinations are inactive against *Corynebacterium* Group D2 bacteria.

2.2.2 Gram-Negative Bacteria

Piperacillin/tazobactam is active against a wide range of plasmid-mediated β-lactamase producing (and non-β-lactamase-producing strains) Gram-negative bacteria (fig. 3). Some nonfermentative bacilli are also susceptible to the combination (fig. 3).

Enterobacteriaceae

Strains of *Escherichia coli*, *S. marcescens*, *Proteus mirabilis*, *P. vulgaris*, *Klebsiella pneumoniae*, *K. oxytoca* (and other *Klebsiella* spp.), *Enterobacter aerogenes* and *Citrobacter* spp. were generally susceptible or intermediately susceptible to piperacillin/tazobactam (fig. 3),[45,46] but there was evidence of resistance among some *Citrobacter freundii* and *E. cloacae*.

Strains of *Morganella morganii* were highly susceptible to piperacillin/tazobactam in most studies. Although strains of *Providencia stuartii* were susceptible to piperacillin/tazobactam, *P. rettgeri* strains showed reduced susceptibility to the combination.[22]

Other Gram-Negative Bacteria

Piperacillin/tazobactam showed excellent activity against both β-lactamase- and non-β-lactamase producing strains of *H. influenzae* (but not β-lactamase negative ampicillin-resistant strains[47]) and *Moraxella catarrhalis*, with mean MIC_{90} values markedly lower than the susceptibility breakpoint in all studies (fig. 3).

Nonfermentative Bacilli

Piperacillin/tazobactam is active against piperacillin-susceptible strains of *P. aeruginosa*. In studies published since the previous review,[1] the combination showed variable activity against *P. aeruginosa*, with MIC_{90} values ranging from 8 to 256 mg/L (fig. 3).

Decreases in susceptibility among *P. aeruginosa* to many antibacterial agents,[48] including piperacillin/tazobactam, have been noted in a longitudinal US study,[36] which determined the susceptibility of 8975 nonfermentative bacilli (isolated from patients from 1991 to 1995) to various agents.[36] These findings have been corroborated by more recent studies conducted worldwide. Nevertheless, although MIC_{90} values ranging from 8 to 64 mg/L in some studies,[12,13,17,20-23,25,27,36] and from 128 to >256 mg/L in others[15,16,18,19,24,33] have been reported, >80% of *P. aeruginosa* isolates were susceptible to the combination in the majority of these studies. Moreover, several recent surveys showed that between 91 and 99% of *P. aeruginosa* isolates were susceptible to piperacillin/tazobactam.[12,21,25,40]

Other species of *Pseudomonas*, including *P. acidovorans*, *P. stutzeri*, *P. putida* and *P. fluorescens*, were generally susceptible to piperacillin/tazobactam.[1,22,35,36]

As in earlier studies,[1] *S. maltophilia* (increasingly associated with infections in immunocompromised patients) were resistant to piperacillin/tazobactam (mean MIC_{90} values >64 to ≥256 mg/L), ticarcillin/clavulanic acid and imipenem.[9,24,38]

Piperacillin/tazobactam generally exhibited good activity against *Acinetobacter* spp., including *A. baumannii*, a species frequently isolated from debilitated or immunocompromised patients with

nosocomial infections.[12,20,24,35,36] However, susceptibility rates to piperacillin/tazobactam among species of *Acinetobacter* varied between institutions and countries.[12,20,24,35,36]

2.2.3 Anaerobes

Bacteroides fragilis Group

Piperacillin/tazobactam is highly active against *Bacteroides fragilis* (including cefoxitin- and clindamycin-resistant strains), a common causative pathogen in intra-abdominal infections.[49] The activity of piperacillin/tazobactam against this pathogen is at least as good as that of ticarcillin/clavulanic acid, ampicillin/sulbactam or amoxicillin/clavulanic acid.[1,10,27,50]

Evidence of the good activity of piperacillin/tazobactam against *B. fragilis* has been documented in numerous investigations conducted in Europe and the US, with MIC_{90} values ranging from 0.125 to 16 mg/L (median 8 mg/L).[22,23,27,32,50-57]

β-Lactamase production among the *B. fragilis* group is the main cause of resistance to piperacillin and other β-lactam agents.[53] Analysis of resistance patterns among clinical isolates of *B. fragilis* revealed a decline in the activity of piperacillin over time because of the emergence of resistant strains, whereas piperacillin/tazobactam has shown consistently good activity against β-lactamase-producing strains of *B. fragilis*. Results of 2 US studies conducted in a total of 18 different sites over different 5-year periods (1987 to 1991[53] and 1990 to 1994[57]) showed that piperacillin/tazobactam remained highly active against *B. fragilis* group species over time, whereas there was a trend towards an increase in resistance to piperacillin; annual rates of resistance to piperacillin/tazobactam among *B. fragilis* group species were 0 to 2%,[53,57] compared with 7 to 37% with piperacillin alone.[53,57] Results of the more recent of the 2 studies are shown in figure 4.

Similarly, no decrease in susceptibility of *B. fragilis* to piperacillin/tazobactam occurred over a 6- to 7-year period (from 1987 to 1993/4) in a study conducted in Belgium.[50]

Other members of the *B. fragilis* group that were susceptible to piperacillin/tazobactam included

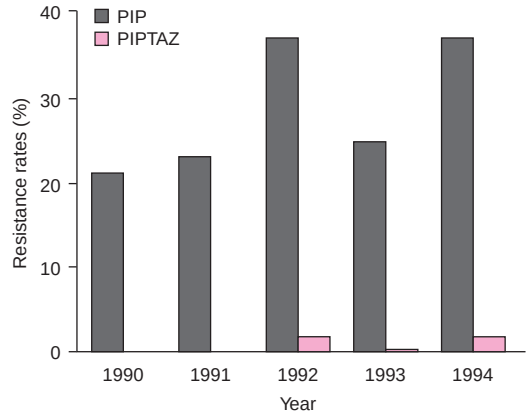


Fig. 4. Resistance to piperacillin/tazobactam (PIPTAZ) or piperacillin (PIP) among *Bacteroides fragilis* group species from 1990 to 1994.[57]

B. thetaiotaomicron, *B. distasonis*, *B. ovatus*, *B. vulgatus*, *B. uniformis* and *B. caccae*.[1,51,52,56,57]

Other Anaerobes

Clostridium spp., *Fusobacterium* spp., *Peptostreptococcus* spp. and *Peptococcus* spp. are also clinically important anaerobes commonly isolated (though less frequently than *B. fragilis*) from patients with intra-abdominal infections.[49] Piperacillin/tazobactam consistently demonstrated excellent activity against both *C. perfringens* (MIC_{90} 0.06 to 0.5 mg/L) and *C. difficile* (MIC_{90} 8 mg/L).[22,52,54]

Piperacillin/tazobactam also showed excellent activity against *Fusobacterium* spp., including *F. nucleatum*, *F. necrophorum* and *F. varium* (MIC_{90} values 2 mg/L).[50,52,54] In addition, peptostreptococci, *Propionibacterium acnes* (MIC_{90} ≤1 mg/L) and miscellaneous nonspore-forming bacilli were highly susceptible to the combination.[1,50,52,54]

2.3 *In Vivo* Activity

Piperacillin/tazobactam demonstrated good efficacy in murine models of intra-abdominal infection[58,59] or pneumonia[60] caused by extended spectrum β-lactamase-producing strains (TEM-26, SHV-7) of *K. pneumoniae*. Such pathogens are now prevalent worldwide and are particularly

widespread in Europe.[61-63] The efficacy of piperacillin/tazobactam was dose-dependent.[58-60]

3. Pharmacokinetic Properties

This overview of the pharmacokinetics of piperacillin and tazobactam is based on information included in the previous review in *Drugs*.[1] The section is supplemented with more recent data derived from investigations conducted in healthy adult volunteers and in adults and children with various types of infection.

As neither piperacillin nor tazobactam is absorbed from the gastrointestinal tract, the combination is administered intravenously as a slow bolus injection or as an infusion (in an 8 : 1 ratio). The 2 agents are particularly suitable for coadministration, as they have broadly similar pharmacokinetic profiles in adults and in children.[64]

The pharmacokinetics of piperacillin and tazobactam in healthy volunteers and in patients with infection are summarised in table II.

In most investigations, piperacillin/tazobactam was given as an intravenous infusion over 30 minutes. The pharmacokinetics of piperacillin and tazobactam have been studied after single doses of 4/0.5g and after multiple doses of 4/0.5g given every 6 or 8 hours.

3.1 Plasma Drug Concentrations

Mean maximum plasma concentrations (C_{max}) of piperacillin and tazobactam were 264.4 to 368 and 29.1 to 39 mg/L, respectively,[1] in healthy adult volunteers after single intravenous 4/0.5g doses of piperacillin/tazobactam (data reviewed previously[1]). There was no evidence of accumulation of either piperacillin or tazobactam after administration of multiple doses of piperacillin/tazobactam to healthy volunteers or to patients with infection (table II). After multiple-dose administration (4/0.5g 6- or 8-hourly), the ratio of piperacillin C_{max} to tazobactam C_{max} was about 8 : 1 in healthy volunteers and patients with intra-abdominal infection.[1,66]

The disposition of piperacillin was altered in patients with burns and signs of infection, because of thermal injury.[65] Mean area under the plasma piperacillin concentration-time curve (AUC) values in these patients were more than twice those in patients with intra-abdominal infections or in healthy volunteers (table II).[1,65,66]

Table II. Summary of pharmacokinetic parameters of piperacillin and tazobactam 4/0.5g after intravenous administration of single doses or multiple doses every 6[1,60] or 8[61,62] hours to healthy volunteers or to patients with infection. Piperacillin/tazobactam was administered as an intravenous infusion over 30 minutes in most investigations

Parameter	Mean value		Reference
	piperacillin	tazobactam	
Plasma drug concentrations			
C_{max} (mg/L)	264.4-277,[a]368[b]	29.1-34,[a] 39[b]	1,67
	322,[c] 368.4[d]	21.9,[c] 18.6[d]	65
	218.7[e]	27.8[e]	66
AUC (mg/L • h)	278,[a] 281[b]	41,[a] 32[b]	1
	640.3,[c] 622.3[d]	42.6,[c] 33.2[d]	65
	288.5[e]	36.3[e]	66
Distribution			
Vd_{ss} (L)	15[a]	18[a]	1
	18.6,[c] 15.8[d]	30.2,[c] 34.6[d]	65
	21.0[e]	22.5[e]	66
In vitro plasma protein binding (%)	21	20-23	1
Elimination			
CL (L/h)	14.5[a]	12.1[a]	1
	8.4,[c] 7.4[d]	15,[c] 18.6[d]	65
	14.75[e]	14.8[e]	66
CL_R (L/h)	8.0[a]	5.9[a]	1
	4.5[c]	9.4[c]	65
	5.7[e]	7.85[e]	66
$t_{½\beta}$ (h)	0.75-0.91[a]	0.78-0.8	1,67
	1.8,[c] 1.5[d]	1.7,[c] 1.4[d]	65
	1.07[e]	1.0[e]	66

a After administration of single or multiple doses to healthy volunteers (number not reported).

b Values for healthy volunteers after 6 days of administration.

c Values for 10 patients with burns and signs of infection after the first dose.

d Values for 10 patients with burns and signs of infection after 3 days of administration.

e Values at presumed steady state (defined as >5 estimated half-lives) for 18 patients with intra-abdominal infections.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **CL** = total body clearance; **CL_R** = renal clearance; **$t_{½\beta}$** = plasma elimination half-life; **Vd_{ss}** = volume of distribution at steady state.

3.2 Distribution

The volume of distribution of piperacillin at steady state (Vd_{ss}) ranged from 15 to 21L in healthy volunteers and patients with infection (table II); the corresponding range of Vd_{ss} values for tazobactam was 18 to 34.6L (table II).[1,65,66] Piperacillin and tazobactam are each about 20% plasma protein bound.[1]

Distribution of piperacillin and tazobactam is rapid, occurring within 30 minutes after the end of a 30-minute infusion.[3] As both compounds are hydrophilic, they penetrate well into many types of body tissues and fluids.[1] Concentrations of both agents achieved in various patient groups included in several investigations are shown in table III.

In patients undergoing intra-abdominal surgery, piperacillin concentrations exceeding the MIC_{90} of most bacterial species were achieved in skin, muscle, fatty mucosa and appendix tissue[72] (data reviewed previously[1]). Piperacillin and tazobactam achieved concentrations of >60 and >8 mg/kg, respectively, in various tissues of the gastrointestinal tract (with the exception of the omentum).[72] Maximum concentrations of piperacillin in gastrointestinal tissue, muscle and skin occurred 1 to 2 hours after the start of the infusion.[72]

3.3 Metabolism and Elimination

The β-lactam rings of piperacillin and tazobactam are each cleaved to produce, respectively, *N*-desethyl-piperacillin (a pharmacologically active metabolite) and M_1 (an inactive metabolite).[1,73]

In adults, approximately 50 to 60% of an administered dose of piperacillin/tazobactam is eliminated by renal excretion; biliary excretion accounts for the elimination of <2% of the dose.[74] Mean concentrations of piperacillin in the gallbladder or choledochal bile of 10 patients undergoing cholecystectomy who received a single 4/0.5g dose of piperacillin/tazobactam were >10-fold higher than the plasma piperacillin concentration, suggesting that an active secretion process (e.g. a carrier-mediated transport system) is involved in the elimination of piperacillin in the bile.[70] On the other hand, the lower relative concentrations of tazobactam in the bile suggest that active biliary secretion does not occur with this compound.

Table III. Concentrations of piperacillin and tazobactam in various body tissues and fluids after single- or multiple-dose administration of piperacillin/tazobactam as an intravenous infusion over 30 minutes

Tissue/fluid	Description of study participants (n)	Dosage (g)	Time after administration of piperacillin/tazobactam (h)	Concentration in tissue/fluid (mg/L or mg/kg)	
				piperacillin	tazobactam
Bronchial secretions[68]	Patients with bacterial pneumonia[a] (8)	4/0.5 q6h	0.5[b]	29.3	6.86
			6[b]	20.2	4.25
Lung tissue[69]	Patients undergoing thoracic surgery (16) or bronchoscopy (12)	4/0.5 SD	1	67.1	14.2
			6	1.2	0.74
Bronchial mucosa[69]		4/0.5 SD	1	162.0	23.7
			4	9.7	1.76
Choledochal bile[70]	Patients undergoing cholecystectomy (10)	4/0.5 SD	1.2	630.4	11.8
Gallbladder bile[70]			1.2	342.3	7.7
Gallbladder wall[70]			1.4	49.3	2.9
Bile drainage fluid[70]	Cholecystectomised patients with external bile duct drainage (5)		Over the subsequent 12h period	28.4mg	1.0mg
Cancellous bone[71]	Patient undergoing total hip replacement (8)	4/0.5 SD	1	21.3	2.46
Cortical bone[71]			1	18.7	2.29

a All patients were receiving mechanical ventilation.

b After the 8th dose.

q6h = every 6 hours; **SD** = single dose.

Piperacillin and tazobactam each have a mean plasma elimination half-life ($t_{½\beta}$) of about 0.8 to 1 hours in healthy volunteers and in patients with intra-abdominal infections (table II). Mean $t_{½\beta}$ values for piperacillin and tazobactam in patients with burns are about 2-fold higher than in healthy volunteers or in patients with intra-abdominal infections (table II).

3.4 Pharmacokinetics in Special Patient Populations

3.4.1 Patients with Renal Impairment

As with other β-lactam/β-lactamase inhibitor combinations, plasma concentrations of piperacillin and tazobactam increase markedly and $t_{½\beta}$ values are prolonged in patients with renal impairment (data reviewed previously[1]). Because of this, dosage reduction is recommended for patients with a creatinine clearance of <20 ml/min (<1.2 L/h) [see section 7].[75]

Since 30 to 50% of piperacillin/tazobactam is removed during 4 hours of haemodialysis, an additional 2/0.25g dose should be given after each dialysis period.[1,75] Dosage adjustment is not generally required for patients receiving peritoneal dialysis, as only 6 and 13% of piperacillin and tazobactam, respectively, are dialysed.[74]

3.4.2 Patients with Hepatic Impairment

The pharmacokinetics of piperacillin and tazobactam are not significantly altered in patients with hepatic impairment. Nevertheless, monitoring of serum concentrations of both drugs is advisable for such patients, as minor dosage adjustments may be required for some individuals.[75]

3.4.3 Infants and Children

Mean C_{max} and AUC values for piperacillin and tazobactam increased in a dose-dependent manner in children with infections (ages not reported) who received doses of 25/6.25 mg/kg (n = 3) or 50/12.5 mg/kg (n = 7), administered as an injection or as an infusion over 30 minutes.[76]

No dose-related differences in the pharmacokinetic parameters of piperacillin and tazobactam, other than C_{max} and AUC values, were seen in infants and children with infection (aged 2 months to 12 years) after single doses of 50/6.25 (n = 23) or 100/12.5 mg/kg (n = 24).[64] However, age-related alterations in some parameters were observed: in infants aged <6 months, $t_{½\beta}$ values of both agents were longer and total body clearance was lower than in children aged ≥6 months, suggesting that dosage adjustment may be required for the younger age group. At least 70% of the administered dose of piperacillin and tazobactam was collected over the 6-hour period following administration.[64]

3.5 Pharmacokinetic Drug Interactions

Piperacillin/tazobactam pharmacokinetic parameters were not significantly altered by coadministration with vancomycin, tobramycin,[1] ranitidine,[77] or ondansetron.[78] The pharmacokinetics of gentamicin, given once a day, were not affected by piperacillin/tazobactam.[79] Piperacillin/ tazobactam should not, however, be mixed with other concomitantly administered drugs in infusion solutions.[75]

4. Therapeutic Efficacy

Since the previous review of piperacillin/ tazobactam in *Drugs*,[1] substantially more data have been published on the efficacy of the combination in patients with various infections, including community-acquired and nosocomial infections of the respiratory tract and intra-abdominal, complicated urinary tract, and serious skin/soft tissue infections. Several trials have also evaluated the efficacy of piperacillin/tazobactam in the treatment of febrile episodes in patients with neutropenia (febrile neutropenia). The efficacy of piperacillin/tazobactam has been evaluated in adults and in a small number of children.

In clinical trials, piperacillin/tazobactam was administered intravenously, usually in dosages of either 4/0.5g 8-hourly or 3/0.375g 6-hourly. Higher dosages of 4/0.5g 6-hourly were used to treat patients with serious infections, including febrile neutropenia and nosocomial respiratory tract infections.

The definition of *bacterial eradication* was the complete documented eradication of the causative pathogen(s); superinfections and/or the presence of persistent and/or resistant bacteria were considered bacteriological failures. The definition of *bacterial relapse* was the reappearance of causative pathogens after a period of partial eradication, and *superinfection* was defined as the presence of a new pathogen or pathogens during therapy. Bacteriological responses were generally reported up to 72 hours after the end of treatment; responses were also recorded up to 6 weeks after treatment in several trials.

Clinical efficacy was determined on the basis of the percentage of patients with *clinical cure* (resolution of signs and symptoms of the infection) and/or *clinical improvement* (partial resolution of signs and symptoms of the infection) up to 72 hours after the end of treatment and, in some trials, after a period of up to 6 weeks of follow-up. A *clinical relapse* was defined as cure or improvement at the end of treatment followed by subsequent reappearance of signs and symptoms of infection; *clinical failure* was defined as no change in, or a deterioration of, signs and symptoms of infection. In Japanese trials, clinical efficacy was determined on the basis of the percentage of patients with a 'good' to 'excellent' response.

Most comparative trials of piperacillin/tazobactam were randomised, nonblind and multicentre in design. Both clinical and microbiological outcomes were generally reported in detail, but data on bacteriological failures (e.g. the identification of persistent or reinfecting pathogens) were limited in some investigations.

4.1 Respiratory Tract Infections

Most information on the use of piperacillin/tazobactam in respiratory tract infections relates to its use in patients with mild to severe community-acquired or severe nosocomial lower respiratory tract infections. Summarised data from comparative[80-87] and noncomparative trials[88-90] of the combination in patients with lower respiratory tract infections are presented in table IV.

Piperacillin/tazobactam dosages of 4/0.5g or 3/0.375g 4-, 6- or 8-hourly were investigated in trials conducted in Europe or the US, whereas lower dosages (2/0.5g twice daily) were evaluated in the 2 trials conducted in Japan (table IV).[85,86]

4.1.1 Community-Acquired Pneumonia or Bronchitis

Bacteriological Response

In patients with community-acquired pneumonia or bronchitis, piperacillin/tazobactam produced bacterial eradication rates ranging from 91 to 98% (table IV). Piperacillin/tazobactam was significantly more effective than ticarcillin/clavulanic acid or piperacillin alone in achieving bacterial eradication in patients with pneumonia, lung abscesses or bronchitis (table IV), but eradication rates were similar in patients with chronic lower respiratory tract infections treated with piperacillin/tazobactam or piperacillin (table IV).[86]

In all 3 trials, detailed bacteriological data were reported.[80,85,86] Bacterial eradication rates 48 to 72 hours after the end of treatment with piperacillin/tazobactam or ticarcillin/clavulanic acid were 91 and 68% ($p < 0.01$); at the study end-point (usually 10 to 14 days after the end of treatment) eradication rates were 84 and 64%; $p = 0.02$) [fig. 5].[80]

Assessment of bacteriological efficacy by pathogen at the end-point showed that 24 (86%) of 28 *H. influenzae* isolates were eradicated by piperacillin/tazobactam compared with 18 (78%) of 23 patients treated with ticarcillin/clavulanic acid. Rates of eradication of *S. pneumoniae* (not reported whether these were penicillin-sensitive, intermediately penicillin-resistant or penicillin-resistant) were similar in both groups [31 (89%) of 35 and 20 (87%) of 23 in the piperacillin/tazobactam and ticarcillin/clavulanic acid groups, respectively]. Notably, however, a higher rate of eradication of other isolated pathogens (including *Acinetobacter* spp., *M. catarrhalis*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. pneumoniae*, *S. aureus* and other streptococci) was achieved in the piperacillin/tazobactam group than in the comparator group (84 *vs* 57%; $p = 0.06$), which may account for the better clinical efficacy of the piperacillin/tazobactam regimen.[80]

Table IV. Piperacillin/tazobactam (PIPTAZ) alone or in combination with amikacin (AN) in the treatment of patients with lower respiratory tract infections (LRTIs); summarised data from randomised, multicentre, nonblind, comparative and noncomparative clinical trials (all drugs were administered intravenously)

Reference	Diagnoses	No. of evaluable patients[a]	Treatment regimen (g) [mean duration in days]	Clinical efficacy[b] (% of patients)			Bacteriological efficacy [no. (%) of patients]		Comparative efficacy
				cure	improvement	failure	eradication[c]	failured	
Hospital-acquired infections									
Brun-Buisson et al.[91]	PNE[e]	51	PIPTAZ 4/0.5 qid [med 15] + AN 7.5 mg/kg bid [med 8]	51[f]		49[f]	51[f]	17/51 (33)[g]*	PIPTAZ+AN ≥ CAZ+AN
		64	CAZ 1 qid [med 14] + AN 7.5 mg/kg bid [med 9]	36[f]		62.5[f]	36[f]	33/64 (51)[g]	
Jaccard et al.[82]	PNE	75[h]	PIPTAZ 4/0.5 tid [NR]	87[i]					PIPTAZ ≡ IPM/C
		79[h]	IPM/C 0.5 qid [NR]	71[i]					
Joshi et al.[83,84] [poster; data on file]	PNE, BRO	78	PIPTAZ 3/0.375 q4h + TM 5 mg/kg/d or AN 15 mg/kg/d [10]	63***	12***	19	65	35	PIPTAZ+TM or AN > CAZ+TM or AN
		58	CAZ 2 q8h + TM 5 mg/kg/d or AN 15 mg/kg/d [10]	26	24	45	38	61	
Smith et al.[89]	PNE, BPNE, BRO, LA, acute LRTIs	32	PIPTAZ 4/0.5 q6h [≥5] + AN 7.5 mg/kg bid [≥5]	59.4	12.5	28.1	19/27 (70.4)	(29.6)	
Community-acquired infections									
Oizumi et al.[85]	PNE, LA	85	PIPTAZ 2/0.5 bid [14[j]]	94[k]			40/41 (98)**		PIPTAZ ≥ PIP
		79	PIP 2 bid [14[j]]	89[k]			28/35 (80)		
Oizumi et al.[86]	chronic LRTIs[l]	88	PIPTAZ 2/0.5 bid [14[j]]	86[k]			42/45 (93)		PIPTAZ ≡ PIP
		85	PIP 2 bid [14[j]]	81[k]			36/41 (88)		
Shlaes et al.[80][m]	BRO, PNE	69	PIPTAZ 3/0.375 q6h [7.2]	47	44	9	59/65 (91***)		PIPTAZ > TC/CL
		50	TC/CL 3/0.1 q6h [7.9]	35	41	20	33/48 (68)		
Community- or hospital-acquired infections									
Mouton et al.[90]	PNE, BRO, BPNE	133	PIPTAZ 4/0.5 q8h [9.1]	86	10	3	97/104 (93.2)		
Sifuentes-Osornio et al.[88]	PNE	77	PIPTAZ 4/0.5 tid [9.3]	83.9	10.3	4.6	74/77 (96.1)	3.9	
Speich et al.[87]	PNE	41	PIPTAZ 4/0.5 q8h [10.7]	81	10		56	0	PIPTAZ ≡ COAM+GM or NET
		43	COAM 2/0.2 q8h + GM or NET 3-6 mg/kg SD [10.5]	65	19		52	4	

a For assessments of clinical efficacy up to 72 hours after the end of treatment.

TABLE IV CONTINUED

LANDSCAPE

Clinical Response

Clinical cure or improvement or a good or excellent response was documented in 86 to 94% of patients with community-acquired respiratory tract infections who received piperacillin/tazobactam (table IV). In trials reviewed previously,[1] clinical cure was documented in 85% of patients who received treatment with piperacillin/tazobactam 12/0.5 g/day (in divided doses).

Piperacillin/tazobactam was significantly more effective than ticarcillin/clavulanic acid in producing a favourable clinical response (cure plus improvement) in patients with mild or moderate community-acquired pneumonia or bronchitis in the double-blind trial reported by Shlaes et al.[80] Favourable responses were documented in 91 and 76% of piperacillin/tazobactam and ticarcillin/clavulanic acid recipients, respectively, 48 to 72 hours after the end of treatment (table IV) and were sustained in 84% and 64% of these treatment responders at the trial end-point (generally 10 to 14 days after the discontinuation of treatment) [$p < 0.01$].[80] Intention-to-treat data confirmed the superiority of piperacillin/tazobactam over ticarcillin/clavulanic acid at the study end-point, with cure/improvement rates of 81 and 68% reported for the 2 groups ($p < 0.01$).

The clinical efficacy of piperacillin/tazobactam was similar to that of amoxicillin/clavulanic acid plus an aminoglycoside in patients with severe community-acquired pneumonia (n = 79) or nosocomial pneumonia (n = 10) [table IV].[87]

4.1.2 Hospital-Acquired Pneumonia

Nosocomial respiratory tract infections, for example, ventilator-associated pneumonia, are often polymicrobial and commonly involve Gram-negative bacilli. Notably, *P. aeruginosa* is a particularly important respiratory pathogen in critically ill patients and is associated with a high rate of failure of antibacterial therapy.[92] For this reason, piperacillin/tazobactam is generally given in combination with an aminoglycoside in the treatment of patients with serious hospital-acquired pneumonia.

b In trials that provided details, cure was defined as the absence of signs or symptoms of infection at the end of treatment; improvement was defined as improved signs and symptoms of infection at the end of treatment; relapse was defined as clinical improvement followed by deterioration during or at the end of treatment; failure was defined as the absence of a response to treatment.

c Documented or presumed eradication of baseline pathogen(s).

d Defined as superinfection, reinfection or persistence of the baseline pathogen.

e Associated with mechanical ventilation in the intensive care unit.

f Six to 8 days after the completion of therapy.

g Clinical and bacteriological failures.

h 47% of PIPTAZ and 51% of IPM/C recipients were receiving mechanical ventilation at baseline.

i Percentage of patients who did not experience 'clinical failure'.

j Duration of treatment for most patients.

k Percentage of patients with a 'good' or 'excellent' clinical response.

l Most patients had chronic bronchitis or bronchiectasis with infection.

m Double-blind in design.

bid = twice daily; **BPNE** = bronchopneumonia; **BRO** = bronchitis; **CAZ** = ceftazidime; **COAM** = amoxicillin/clavulanic acid; **GM** = gentamicin; **IPM/C** = imipenem/cilastatin; **LA** = lung abscesses; **med** = median; **NET** = netilmicin; **NR** = not reported; **PIP** = piperacillin; **PNE** = pneumonia; **qid** = 4 times daily; **q4h** = every 4 hours; **q6h** = every 6 hours; **q8h** = every 8 hours; **SD** = single dose; **TC/CL** = ticarcillin/clavulanic acid; **tid** = 3 times daily; **TM** = tobramycin; ≡ indicates equivalent efficacy; ≥ indicates as least as effective as; **>** indicates significantly more effective than; * p = 0.05 *vs* CAZ+AN; ** p < 0.05 *vs* PIP; *** p < 0.01 *vs* TC/CL or CAZ+TM or AN.

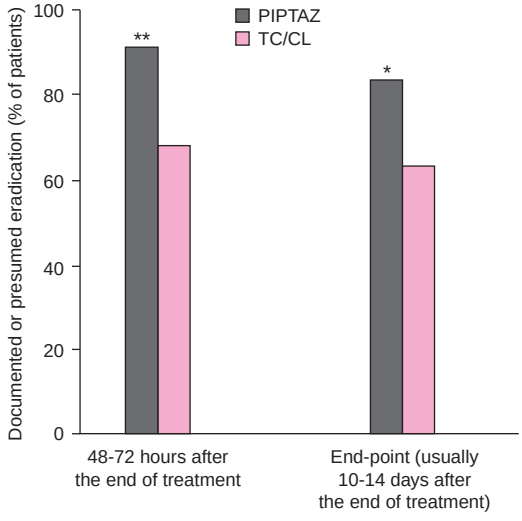


Fig. 5. Bacteriological eradication rates in patients with community-acquired pneumonia after treatment with intravenous piperacillin/tazobactam (PIPTAZ) or ticarcillin/clavulanic acid (TC/CL). Patients received either piperacillin/tazobactam 3/0.375g 6-hourly for 7.2 days (n = 69) or ticarcillin/clavulanic acid 3/0.1g 6-hourly for 7.9 days (n = 50).[80] * **p** = 0.02; ** **p** < 0.01 *vs* TC/CL.

Bacteriological Response

Rates of bacterial eradication ranged from 51 to 70.4% in patients with hospital-acquired pneumonia receiving treatment with piperacillin/tazobactam plus amikacin or tobramycin.[83,84,89,91] The rate of bacteriological failure was significantly lower in patients treated with piperacillin/tazobactam plus amikacin than in recipients of ceftazidime plus amikacin (33 *vs* 51%; p = 0.05) [table IV].[91] The poorer bacteriological outcome in the recipients of ceftazidime plus amikacin was partly attributed to a >2-fold greater incidence of lower respiratory tract superinfections in these patients than in the piperacillin/tazobactam recipients (21 *vs* 9%). Importantly though, 7 superinfections in the ceftazidime plus amikacin-treated patients were caused by methicillin-resistant *S. aureus*, whereas there were no superinfections with this organism in the piperacillin/tazobactam group.

The rate of persistent bacteria or of relapse in patients treated with ceftazidime plus amikacin was more than twice that in the piperacillin/tazobactam plus amikacin group (21 *vs* 9%).[91] Rates of eradication of *P. aeruginosa* were similar in the piperacillin/tazobactam plus amikacin and ceftazidime plus amikacin groups (40 *vs* 39%).[91] 91.7% of causative pathogens (including 7 of 9 isolates of *P. aeruginosa*) were eradicated at the end of treatment and 2 to 4 weeks after the discontinuation of treatment in an earlier noncomparative trial.[89]

At the study end-point, documented or presumed eradication was reported in 51 (65%) of 78 and 22 (38%) of 58 patients treated with piperacillin/tazobactam 3/0.375g every 4 hours (plus tobramycin or amikacin) or ceftazidime 2g every 8 hours (plus tobramycin or amikacin) in the trial reported by Joshi et al.[83,84] Analysis of bacterial outcome by diagnosis at enrolment showed favourable bacterial responses in 45 (64%) of 70 patients with pneumonia treated with piperacillin/tazobactam compared with 17 (40%) of 42 recipients of ceftazidime; 6 (75%) of 8 patients with bronchitis treated with piperacillin/tazobactam and 5 (31%) of 16 recipients of ceftazidime also experienced favourable bacterial responses.[83,84] Rates of eradication of *H. influenzae*, *S. aureus* and *P. aeruginosa* at the study end-point in the piperacillin/tazobactam group were 100, 69 and 67%; corresponding eradication rates in the ceftazidime group were 50, 33 and 30% ($p \leq 0.01$). Eradication of *H. influenzae* at the study end-point was achieved in a significantly larger proportion of piperacillin/tazobactam than ceftazidime recipients (100 *vs* 50%; $p \leq 0.01$).[83,84]

21 recipients of piperacillin/tazobactam and 24 recipients of imipenem/cilastatin in the trial reported by Jaccard et al.[82] had infections caused by *P. aeruginosa*. Of these patients, the incidence of clinical failure was significantly lower in the piperacillin/tazobactam group than in the comparator group (10 *vs* 50%; p = 0.004). Bacterial resistance was the cause of treatment failure in 1 patient treated with piperacillin/tazobactam and in 12 recipients of imipenem/cilastatin.[82]

Clinical Response

In trials conducted in patients with hospital-acquired respiratory tract infections, clinical cure or clinical success was achieved in 51 to 75% of patients treated with piperacillin/tazobactam plus amikacin or piperacillin/tazobactam alone (table IV).[82,83,91] Piperacillin/tazobactam plus amikacin (or tobramycin[83,84]) was at least as effective as ceftazidime plus amikacin in patients with ventilator-associated pneumonia[91] (table IV) and was significantly more effective than ceftazidime plus tobramycin or amikacin in patients with acute purulent bronchitis or acute bacterial pneumonia (table IV).[83,84] In the latter study,[83,84] clinical responses (cure or improvement) were documented in 75 and 50% of patients in the piperacillin/tazobactam and ceftazidime treatment groups, respectively ($p < 0.01$) at the study end-point (defined as the final outcome evaluation, regardless of whether the full protocol had been completed). Piperacillin/tazobactam alone was as effective as imipenem/cilastatin in the treatment of patients with nosocomial pneumonia with clinical failure documented in 17 and 29% of piperacillin/tazobactam and imipenem/cilastatin recipients, respectively.[82] In trials reviewed previously,[1] favourable responses occurred in 74% of patients with hospital-acquired lower respiratory tract infections treated with piperacillin/ tazobactam 16/2 g/day (in divided doses) in combination with amikacin 15 mg/kg/day.

In the trial conducted in patients with ventilator-associated pneumonia,[91] successful clinical and bacterial outcomes were documented in 51 and 36% of patients in the piperacillin/tazobactam plus amikacin and ceftazidime plus amikacin groups, respectively (difference between groups not statistically significant) 6 to 8 days after the completion of therapy. Rates of mortality 28 days after treatment initiation were similar in the piperacillin/tazobactam plus amikacin and ceftazidime plus amikacin groups (16 *vs* 20%; not statistically significant).[91]

The results of this trial confirm and extend those of an earlier study which evaluated at least 5 days' treatment with piperacillin/tazobactam 4/0.5g 6-hourly in combination with amikacin 7.5 mg/kg twice daily in 71 patients with community-acquired (28%) or nosocomial severe pulmonary infections (most commonly pneumonia) [table IV].[89] Clinical cure was achieved in 59.4% of patients 24 to 72 hours after the discontinuation of treatment (table IV) and in 61.8% of patients at follow-up 2 to 4 weeks later.[89]

4.2 Intra-Abdominal Infections

Intra-abdominal infections occur because of microbial contamination of the peritoneal cavity and/or associated organs. Such contamination may be the result of surgery, injury, or intrinsic disease (for example, peptic ulcer disease, Crohn's disease, appendicitis or pancreatitis).[49,93-95] Irrespective of the origin, intra-abdominal infection is usually polymicrobial averaging 2 to 5 bacterial species per infection site.[49]

Standard management of patients with intra-abdominal infections involves rehydration and surgery. Prompt initiation of adjunctive broad spectrum antibacterial therapy is also essential in order to eradicate causative aerobic and anaerobic pathogens, to prevent infections at the operative site and to accelerate recovery.[94] Antibacterial therapy is often initiated on an empirical basis (before the results of bacteriology are known) to avoid the development of potentially serious sequelae.

Members of the Enterobacteriaceae family, including *Proteus* and *Klebsiella* spp., are among the more common aerobic bacteria causing intra-abdominal infections.[49] Frequently isolated anaerobes include *Bacteroides* spp., *Clostridium* spp. and *Fusobacterium* spp.[49] Of the aerobic and anaerobic bacteria isolated in purulent peritoneal fluid, there is a clear predominance of *B. fragilis* and *E. coli*.[49] These pathogens have a synergistic relationship and commonly cause bacteraemia in patients with intra-abdominal infections. As a large proportion of bacteria causing intra-abdominal infection are producers of β-lactamase, a broad spectrum of antibacterial activity encompassing these

Table V. Piperacillin/tazobactam (PIPTAZ) as an adjunct to surgery in adults with moderate or severe intra-abdominal infections; summarised data from comparative and noncomparative nonblind, multicentre trials (all drugs were administered intravenously, unless otherwise indicated)

Reference	Most common diagnoses	No. of evaluable patients[a]	Treatment regimen (g) [mean duration in days]	Clinical efficacy[b] (% of patients)		Bacteriological efficacy [no. (%) of patients]		Comparative efficacy
				cure	improvement	eradication[c]	failure[d]	
Randomised, comparative trials								
Barie et al.[96]	Appendicitis, peritonitis, acute cholecystitis, intra-abdominal abscesses	104	PIPTAZ 3/0.375 q6h [≥2]	83	5	90/104 (86)	14/104 (14)	PIPTAZ ≡ CM+GM
Polk et al.[98]		43	CM 0.6 q6h + GM 0.8-1.6 mg/kg q8h [≥2]	72	5	32/43 (75)	11/43 (25)	
Brismar et al.[99]	Appendicitis, peritonitis, intra-abdominal abscesses	55	PIPTAZ 4/0.5 q8h [5.5]	90.9*	2	38/41 (92.7)*	3/41 (7.3)	PIPTAZ > IPM/C
		58	IPM/C 0.5/0.5 q8h [5.9]	69		37/49 (75.5)	12/49 (24.5)	
Cohn et al.[101] [abstract]	Appendicitis, intra-abdominal abscesses	116	PIPTAZ 3/0.375 q6h	63; 70 (IV+oral)				PIPTAZ < CIP+MET
		134	CIP 400 q12h + MET 500 q6h	74**; 85*** (IV+oral)				
Dupont et al.[100] [abstract]	Severe generalised peritonitis	99 (ITT)	PIPTAZ 4/0.5g q6h [8.2]	44				PIPTAZ ≡ PIPTAZ+AN
		105 (ITT)	PIPTAZ 4/0.5g q6h [8.6] + AN 7.5 mg/kg bid [6]	48				
Eklund et al.[97]	Appendicitis, peritonitis, intra-abdominal abscesses	50	PIPTAZ 4/0.5 q8h [5.5]	90.9*	2	38/41 (92.7)*	3/41 (7.3)	PIPTAZ > IPM/C
		40	IPM/C 0.5/0.5 q8h [5.9]	69		37/49 (75.5)	12/49 (24.5)	
Jaccard et al.[82]	Acute peritonitis	76	PIPTAZ 4/0.5 tid [NR]	95				PIPTAZ ≡ IPM/C
		83	IPM/C 0.5 qid [NR]	93				
Niinikoski et al.[102]	Appendicitis, peritonitis, intra-abdominal abscesses	29	PIPTAZ 4/0.5 q8h [5.9]	87		(100)		PIPTAZ ≡ IPM/C
		26	IPM/C 1/0.5 q8h [6.4]	77		(89)	(11)	
Shyr et al.[103]	Appendicitis, cholecystitis	46	PIPTAZ 4/0.5 q8h [4.3]	93.5	4.3	96.7		PIPTAZ ≡ CM+GM
		25	CM 0.6g q6h + GM 2.5-5 mg/kg/d in divided doses [4.6]	93.3	3.3	95.0		
Noncomparative trials								
Arguedas et al.[107]	Appendicitis, peritonitis	43[e]	PIPTAZ 80/10 mg/kg q8h [6.9]	91[f]		40/43 (93)	3/40 (7)	
Legrand et al.[104]	Appendicitis, peritonitis, intra-abdominal abscesses	23	PIPTAZ 4/0.5 q8h [9.3]	78	9	20/23 (87)	3/23 (13)	
Vestweber & Grundel[105]	Appendicitis, intra-abdominal abscesses, peritonitis, cholecystitis or cholangitis, diverticulitis	106	PIPTAZ 4/0.5 q8h [5-10]	84	3	74/82 (90)	8/82 (10)	

a For assessments of clinical efficacy at the end of treatment.

b In trials that provided details, cure was defined as the absence of signs or symptoms of infection at the end of treatment; improvement was defined as improved signs and symptoms of infection at the end of treatment.

c Documented or presumed eradication of the baseline pathogen(s).

d Defined as superinfection, reinfection or persistence of the baseline pathogen(s).

e Children.

f Cure or improvement.

AN = amikacin; **bid** = twice daily; **CIP** = ciprofloxacin; **CM** = clindamycin; **GM** = gentamicin; **IPM/C** = imipenem/cilastatin; **ITT** = intention-to-treat population; **MET** = metronidazole; **NR** = not reported; **qid** = 4 times a day; **q6h** = every 6 hours; **q8h** = every 8 hours; **q12h** = every 12 hours; **tid** = 3 times a day; ≡ indicates equivalent efficacy; **>** indicates more effective than; **<** indicates less effective than; *** p** < 0.05 *vs* IPM/C; ****p** = 0.03 *vs* PIPTAZ; *****p** = 0.03 *vs* PIPTAZ.

bacteria is a prerequisite for any agent(s) selected to treat infected patients.[49,93,94]

Piperacillin/tazobactam has been evaluated as an adjunct to intra-abdominal surgery in several clinical trials, which included adults[82,96-106] or children[107] with moderate or severe intra-abdominal infection caused by, for example, bowel rupture. Appendicitis, peritonitis and intra-abdominal abscesses were the most common diagnoses (table V).

4.2.1 Bacteriological Response

Rates of bacterial eradication in patients with intra-abdominal infections treated with piperacillin/tazobactam ranged from 76 to 100% in the trials shown in table V and in those reviewed previously.[1,96-98,102-105,107] Piperacillin/tazobactam produced bacterial eradication rates that were significantly higher than with imipenem/cilastatin[97,99] (similar eradication rates were produced in 1 study[102]) and similar to those obtained with clindamycin plus gentamicin.[96,98,103]

A comparison of the efficacy of piperacillin/tazobactam with that of clindamycin plus gentamicin[96,98] showed a nonsignificant trend towards a higher rate of eradication of all pathogens (isolated from the operative site at baseline) with piperacillin/tazobactam than with the comparator regimen. Rates of eradication of strains of *B. fragilis* and of *E. coli* were also higher (statistical significance not reported) with piperacillin/tazobactam than with clindamycin plus gentamicin (fig. 6). Evaluable patients received either piperacillin/tazobactam 3/0.375 6-hourly for ≥2 days (n = 104) or clindamycin 0.6g 6-hourly plus gentamicin 0.8-1.6 mg/kg 8-hourly (n = 43) for ≥2 days. The trial was randomised and nonblind in design. Eradication of piperacillin-resistant β-lactamase–producing bacteria was achieved in 10 (91%) of 11 patients in the piperacillin/tazobactam group.[96]

In trials comparing piperacillin/tazobactam with imipenem/cilastatin (at a dosage lower than that recommended in countries outside Scandinavia for the treatment of intra-abdominal infections[1])[97,99] bacterial eradication was documented in 38 of 41 evaluable patients treated with piperacillin/tazobactam and in 37 of 49 imipenem/cilastatin recipients ($p < 0.05$). Persistent organisms were identified in 3 and 9 patients in the piperacillin/tazobactam and imipenem/cilastatin treatment groups, respectively. In addition, in the imipenem/cilastatin group, 2 patients developed a superinfection and 1 patient experienced a reinfection.[97,99]

In children, pathogens were eradicated in 40 (93%) of 43 evaluable patients with intra-abdominal infections treated with piperacillin/tazobactam. Two of the 3 treatment failures had superinfections caused by 4 pathogens [*K. pneumoniae* (1 strain), *S. aureus* (2), *S. pyogenes* (1)]; the remaining patient had a presumed persistent infection.[107]

4.2.2 Clinical Response

Piperacillin/tazobactam 12/1.5 g/day showed clinical efficacy similar to that of clindamycin 0.6g 6-hourly plus gentamicin 2.4 to 5 mg/kg/day, or metronidazole 0.5g 8-hourly plus gentamicin 6 mg/kg/day plus amoxicillin 1g 8-hourly or ampicillin 0.5g 8-hourly in randomised, comparative trials.[1,96,98] Piperacillin/tazobactam 4/0.5g 8-hourly was as effective as imipenem/cilastatin 0.5 or 1g 8-hourly and achieved a significantly higher clinical cure rate than imipenem/cilastatin administered

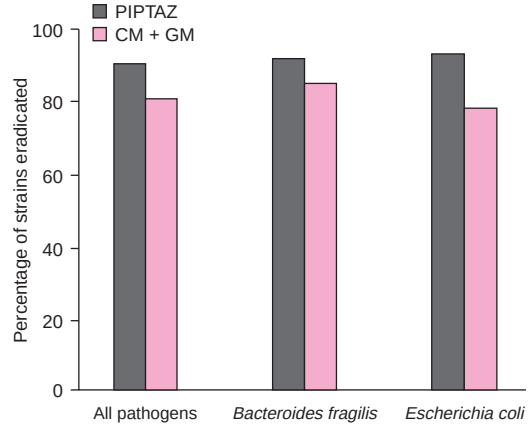


Fig. 6. Bacterial eradication in patients with intra-abdominal infections after treatment with intravenous piperacillin/tazobactam (PIPTAZ) or clindamycin plus gentamicin (CM+GM).[96]

at a dosage of 0.5g 8-hourly (90.9 *vs* 69%; $p < 0.05$).[1,97]

Preliminary results of a trial conducted in patients with severe generalised peritonitis showed that the efficacy of piperacillin/tazobactam 4/0.5g every 6 hours was similar to that of a combination regimen of piperacillin/tazobactam plus amikacin, with clinical responses documented in 44 and 48% of patients, respectively.[100] Rates of mortality were also similar in the 2 treatment groups (19 *vs* 21%).

Piperacillin/tazobactam was also beneficial in children with intra-abdominal infections.[107] Favourable clinical responses were achieved in 39 (91%) of 43 evaluable children (age range 0.8 to 9 years) with appendicitis or peritonitis treated with piperacillin/tazobactam 80/10 mg/kg 8-hourly.[107] Analysis of intention-to-treat data also showed a high rate of clinical response [53 (88%) of 60 children].

4.3 Fever in Patients with Neutropenia

Patients with haematological malignancies who develop neutropenia as a result of myelosuppressive therapy are at high risk of developing serious life-threatening infections. As the inflammatory response is suppressed in these individuals, fever is often the first sign of an infection.[108]

The prompt initiation of broad spectrum empirical antibacterial therapy at the onset of fever and before identification of the causative pathogen(s) is standard practice in the management of immunocompromised patients with febrile neutropenia.[108] This treatment approach has been shown to reduce the incidence of severe infection-related complications that arise as a result of neutropenia[108-110] and has led to a marked increase in survival.[111]

Although Gram-negative bacteria, including *P. aeruginosa* and *E. coli*, were historically the most common pathogens causing infection in patients with febrile neutropenia, there has been a trend over the last decade towards an increase in prevalence of infections caused by Gram-positive bacteria, particularly streptococci, including viridans group streptococci and coagulase-negative staphylococci.[111-113] This change in spectrum of causative organisms has been attributed, in part, to selective intestinal decontamination and to the use of indwelling intravenous catheters.[10]

A wide range of antibacterial treatment regimens are used to treat patients with febrile neutropenia and the choice of regimen is often dictated by the antibacterial policy and local resistance patterns of a particular institution. Options for treatment include an antipseudomonal β-lactam antibacterial agent plus an aminoglycoside, 2 β-lactam drugs or monotherapy with, for example, ceftazidime or imipenem/cilastatin.[108,114-117]

Piperacillin/tazobactam in combination with an aminoglycoside has been compared with various other combinations of antibacterials, including ceftazidime plus an aminoglycoside and piperacillin plus netilmicin or gentamicin (table VI). The efficacy of piperacillin/tazobactam has also been evaluated in numerous noncomparative studies that included adults and children with febrile neutropenia.[108,110,118-122]

The efficacy of piperacillin/tazobactam alone has also been studied (table VI).[131] Although most trials enrolled adult patients, children aged ≥1 year were also included in 1 investigation.[112] Criteria for enrolment in trials included fever, neutropenia or granulocytopenia and a presumed infection.

Notably, at present there is no consensus on which clinical end-point(s) best demonstrates the efficacy of antibacterial therapy in patients with febrile neutropenia. Thus, various criteria have been used in the different trials to evaluate responses to treatment. A number of factors, including the type of cancer, the duration of neutropenia, the type of chemotherapy and the use of antibacterial prophylaxis, are known to influence the efficacy of antibacterial therapy in affected patients.[132]

In trials reviewed previously, resolution of clinical symptoms of febrile neutropenia occurred in 51 to 61% of patients treated with piperacillin/tazobactam 12-16/1.5-2 g/day in divided doses

Table VI. Piperacillin/tazobactam (PIPTAZ) alone or in combination with other antibacterial agents as initial empirical treatment of fever in patients with neutropenia; summarised data from comparative nonblind clinical trials (all drugs were administered intravenously)

Reference	No. of evaluable patients[a] (febrile episodes)	Treatment regimen (g) [duration in days]	Clinical efficacy[b] (% of patients, unless otherwise indicated)	Bacteriological eradication [no. (%) of patients or episodes]	Comparative efficacy
PIPTAZ + amikacin (AN) or tobramycin (TM) versus ceftazidime (CAZ) or ceftriaxone (CTR) + AN or TM					
Cometta et al.[112]	(342)	PIPTAZ 4/0.5 q6h (adults) or 80/10 mg/kg q8h (children) [1-31 (med 7)] + AN ≤20 mg/kg/d [1-31]	210/342 (61);[c]* 49/93 (53)[d]	40/80 (50)*	PIPTAZ + AN > CAZ + AN
	(364)	CAZ 2 q8h (adults) or 35mg/kg q8h (children) [1-30 (med 7)] + AN ≤20 mg/kg/d [1-31]	196/364 (54);[c] 43/112 (38)[d]	35/101 (35)	
Marie et al.[123]	94	PIPTAZ 4/0.5 q8h[e] [mean 10.5] + AN 15 mg/kg/d[f] [mean 10 or 10.5]	57/94 (60.6)**	84[g]	PIPTAZ + AN > CAZ + AN
	94	CAZ 1g q8h[h] + AN 15 mg/kg/day[f] [mean 10 or 10.5]	42/94 (44.7)	72[g]	
Marie et al.[124]	(114)	PIPTAZ 4/0.5 tid + TM 3 mg/kg/d [NR]	62/114 (54.4)[c†]		PIPTAZ + TM > CAZ + TM
	(133)	CAZ 1g tid + TM 3 mg/kg/d [NR]	50/133 (37.6)[c]		
Rossini et al.[125] [abstract]	(37)	PIPTAZ 8 g/m^2/d + AN 20 mg/kg/d [NR]	27/37 (72.9)[c]		PIPTAZ + AN ≡ CTR + AN
	(37)	CTR 30 mg/kg/d + AN 20 mg/kg/d [NR]	26/37 (70.3)		
PIPTAZ + gentamicin (GM) or netilmicin (NET) versus piperacillin (PIP) + GM or NET					
Kern et al.[116]	61	PIPTAZ 4/0.5 q8h [≥5] + NET 0.45 q24h [≥5]	29/61 (48)	45;[i] 100[j]	PIPTAZ + NET ≡ PIP + NET
	160[k]	PIP 4 q8h [≥5] + NET 0.45 q24h [≥5]	64/160 (40)	33;[i] 70[j]	
Lee et al.[126]	(52)	PIPTAZ 4/0.5 tid + GM 5 mg/kg/d [NR]	(83)[c***]		PIPTAZ + GM > PIP + GM
	(50)	PIP 4 tid + GM 5 mg/kg/d [NR]	(48)[c]		
PIPTAZ + AN versus PIP + AN + TEC					
Micozzi et al.[117]	(58)	PIPTAZ 4/0.5 q6h + AN 15 mg/kg/d every 12h	(41)[c]		PIPTAZ + AN ≡ PIP + AN + TEC
	(56)	PIP 300 mg/kg/d (in 4 divided doses) + AN 15 mg/kg/d q12h + TEC 7 mg/kg q12h for 3 doses then daily	(60)[c]		
PIPTAZ monotherapy versus PIPTAZ + NET, AN or TM, imipenem/cilastatin (IPM/C) + TM, cefepime (CEP) or CAZ + AN					
Bischoff et al.[127] [abstract]	80 overall	PIPTAZ 4/0.5 tid [mean 11]	72.5		PIPTAZ ≡ PIPTAZ + NET
		PIPTAZ 4/0.5 tid + NET 2 mg/kg/d [mean 10]	65		
Böhme et al.[128] [abstract]	(51)	PIPTAZ (dosage NR)	22/51 (43)[c]		PIPTAZ ≡ CEP
	(49)	CEP (dosage NR)	19/49 (39)[c]		
Esteve et al.[129] [abstract]	(39)	PIPTAZ 4/0.5g q6h (1-15)	41[c]		PIPTAZ ≡ PIPTAZ + AN
	(46)	PIPTAZ 4/0.5g q6h + AN 15 mg/kg/d (1-15)	44[c]		

Continued on next page

Table VI. Contd

Reference	No. of evaluable patients[a] (febrile episodes)	Treatment regimen (g) [duration in days]	Clinical efficacy[b] (% of patients, unless otherwise indicated)	Bacteriological eradication [no. (%) of patients or episodes]	Comparative efficacy
Hazel et al.[130] [abstract]	(50)	PIPTAZ + TM [dosages NR]	92.3		PIPTAZ + TM ≡ IPM/C + TM
	(49)	IPM/C + TM [dosages NR]	96.6		
Hess et al.[131]	48	PIPTAZ 4/0.5 q8h [med 7.2]	39/48 (81); 11/17 (65)[l]		PIPTAZ ≡ CAZ + AN
	48	CAZ 2 q8h + AN 15 mg/kg/d [med 7.4]	40/48 (83); 16/23 (70)[l]		

a For assessments of clinical efficacy at 72 hours.

b Defined as disappearance of fever and other signs of infection without modification of the antibacterial regimen.

c Number (%) of responsive febrile episodes (all episodes).

d Number (%) of responsive microbiologically documented episodes.

e For patients weighing >80kg, the dosage of PIP was increased to 5g q8h.

f In 2 divided doses.

g Percentage of pathogens susceptible to study medication.

h For patients weighing >80kg, the dosage of CAZ was increased to 1.5g q8h.

i Percentage of Gram-positive pathogens eradicated.

j Percentage of Gram-negative pathogens eradicated.

k Historical controls from the same centre.

l Infections with bacteraemia.

med = median; **NR** = not reported; **q6h** = every 6 hours; **q8h** = every 8 hours; **q24h** = every 24 hours; **TEC** = teicoplanin; **tid** = 3 times daily; > indicates more effective than; ≡ indicates equivalent efficacy; * p = 0.05 *vs* CAZ+AN; ** p = 0.028 *vs* CAZ+AN; *** p < 0.001 *vs* PIP+GM; † p = 0.008 *vs* CAZ+TM.

(0.32/0.04 g/kg/day in children) plus an aminoglycoside 72 hours after the initiation of treatment.[1]

4.3.1 Bacteriological Response

Piperacillin/Tazobactam Plus Amikacin Versus Ceftazidime Plus Amikacin

Piperacillin/tazobactam plus amikacin was significantly more effective than ceftazidime plus amikacin in achieving resolution of bacteraemic infections in adults and children with febrile neutropenia.[112] Bacterial eradication was achieved in 50% of bacteraemic episodes in the piperacillin/tazobactam plus amikacin group, compared with 35% of episodes in the ceftazidime plus amikacin group (p = 0.05) [table VI].[112] However, there were no significant between-group differences in rates of bacteriological eradication of subgroups of bacteraemias or of specific organisms. Results of bacteriology showed a higher incidence of bacteria resistant to ceftazidime than to piperacillin/tazobactam [35 *vs* 25% of microbiologically-documented episodes (not statistically significant]; moreover, there was a trend towards a better clinical response in noncoagulase-negative Gram-positive infections in the piperacillin/tazobactam group than in the ceftazidime group.[112] These factors may have contributed to differences in efficacy between the 2 treatment regimens.

The better outcome of patients treated with piperacillin/tazobactam plus amikacin compared with ceftazidime plus amikacin-treated patients in the trial reported by Marie et al.[123] was attributed to the broader spectrum of activity of the piperacillin/ tazobactam combination, as confirmed by the results of susceptibility testing.[123] Notably, whereas piperacillin/tazobactam plus amikacin and ceftazidime plus amikacin showed equally good efficacy against Gram-negative bacteria (eradication rates 98 and 100%, respectively), the piperacillin/tazobactam regimen achieved a higher rate of eradication of Gram-positive bacteria than the comparator regimen (eradication rates 75 and 52%, respectively).[123]

Bacteriological failure with both treatment regimens was largely attributed to documented or presumed fungal infections and to bacterial infections with Gram-positive organisms, such as methicillin-resistant strains of *S. aureus* or coagulase-negative staphylococci which were identified in about one-third of patients in the 2 trials.[112,123] After excluding the methicillin-resistant staphylococci in the trial reported by Marie et al.[123], *in vitro* susceptibility testing showed that 1 organism only (*P. mirabilis*) was resistant to piperacillin/ tazobactam; this pathogen was sensitive to ceftazidime. In contrast, 14 organisms (9 staphylococci, 4 streptococci and 1 enterococcus) were resistant to ceftazidime, but sensitive to piperacillin/ tazobactam. *In vitro*, 52, 28 and 79% of coagulase-negative staphylococcici were susceptible to piperacillin/ tazobactam, ceftazidime and amikacin; corresponding values for viridans group streptococci were 93, 93 and 66%.

The proportion of febrile episodes requiring the addition of vancomycin or teicoplanin was significantly higher in the patients who received ceftazidime plus amikacin than in the piperacillin/ tazobactam plus amikacin recipients [128 (35%) of 364 *vs* 83 (24%) of 342 episodes; p = 0.002].[112]

Piperacillin/Tazobactam Versus Ceftazidime Plus Amikacin

Resistant pathogens were identified in 3 febrile episodes in the piperacillin/tazobactam treatment group and in 2 episodes in the ceftazidime plus amikacin group.[131] Pathogens showing primary resistance to piperacillin/tazobactam included *Propionebacterium acnes* and coagulase-negative staphylococci. No strains of MRSA were isolated from any patient, but 11 of 16 coagulase-negative staphylococci responsible for bacteraemias were methicillin-resistant.

4.3.2 Clinical Response

Clinical success rates of 41 to 83% were reported in patients with febrile neutropenia or granulocytopenia who received empirical treatment with piperacillin/tazobactam 12-16/1.5-2 g/day (in divided doses) in combination with an aminoglycoside (table VI).

Piperacillin/Tazobactam Plus Amikacin Versus Ceftazidime Plus Amikacin

Piperacillin/tazobactam plus amikacin was significantly more effective than ceftazidime plus amikacin in achieving resolution of febrile episodes in patients with neutropenia or granulocytopenia in 2 large trials at 72 hours.[112,123] In the trial reported by Cometta et al.,[112] significantly more febrile episodes were responsive to piperacillin/ tazobactam plus amikacin treatment than to ceftazidime plus amikacin (p = 0.05) [table VI]. Moreover, compared with the ceftazidime plus amikacin group, recipients of piperacillin/tazobactam plus amikacin experienced a significantly shorter time to defervescence ($p \leq 0.01$) and a significantly longer time to treatment failure ($p \leq 0.02$).[112]

Apyrexia 72 hours after initiation of treatment was documented in 60.6% piperacillin/tazobactam plus amikacin recipients and in 44.7% of ceftazidime plus amikacin recipients (p = 0.028) [table VI] in the other trial.[123] Analysis of responses in patients who had not received vancomycin during the first 72 hours of the trial also showed that patients in the piperacillin/tazobactam group had a significantly better outcome than those in the comparator group (47.9 *vs* 31.9%; p = 0.02).[123] The duration of fever was shorter in the piperacillin/ tazobactam plus amikacin than in the ceftazidime plus amikacin group (6.8 *vs* 9.1 days; p = 0.02). Septicaemia occurred in a smaller proportion of patients treated with piperacillin/tazobactam plus amikacin than in the other treatment group (23 *vs* 41%; p < 0.0008).[123]

Piperacillin/Tazobactam Plus Tobramycin Versus Ceftazidime Plus Tobramycin

Combination therapy with piperacillin/tazobactam plus tobramycin was significantly more effective than ceftazidime plus tobramycin in a trial reported by Marie et al.[124] with 54.4 and 37.4% of febrile episodes successfully treated in the 2 treatment groups (p = 0.008). In addition, recipients of piperacillin/tazobactam plus tobramycin experienced fewer major infections than the comparator group (2.6 *vs* 11.3%; p = 0.02) despite fewer patients in the piperacillin/tazobactam plus tobramycin

group receiving additional vancomycin therapy than in the latter group (54.4 *vs* 77.4%).

Piperacillin/Tazobactam Plus an Aminoglycoside Versus Piperacillin Plus an Aminoglycoside

Piperacillin/tazobactam plus gentamicin was significantly more effective than piperacillin plus gentamicin in a recent investigation reported as an abstract (table VI);[126] complete and partial response rates (defined as total or partial resolution of all signs and symptoms of infection) 72 hours after the initiation of treatment were significantly higher in patients treated with piperacillin/tazobactam plus gentamicin than in recipients of piperacillin plus gentamicin (83 *vs* 48%; $p < 0.001$). Complete or partial response rates in patients with documented coagulase-negative staphylococcal infections were significantly higher in patients who received piperacillin/tazobactam plus gentamicin than in the comparator group (90 *vs* 42%; $p < 0.0001$).[126]

In another study, however, piperacillin/tazobactam in combination with netilmicin showed clinical efficacy similar to that of piperacillin plus netilmicin (in an historical control group).[116] Clinical success (defined as the disappearance of fever and other signs of infection without treatment modification) was documented in 48 and 40% of patients in the piperacillin/tazobactam and piperacillin combination therapy groups, respectively (not statistically significant). Although the median duration of fever was slightly shorter in the piperacillin/tazobactam plus netilmicin group than in the comparator group (4.5 *vs* 5 days), this did not attain statistical significance.

Piperacillin/Tazobactam Versus Ceftazidime Plus Amikacin

Piperacillin/tazobactam alone showed efficacy similar to that of ceftazidime plus amikacin in neutropenic patients with cancer, with resolution of fever and clinical signs of infection documented in 81% of evaluable febrile episodes treated with piperacillin/tazobactam and in 83% of episodes in the comparator group.[131] In addition, there were no significant between-group differences in terms of median times to fever defervescence (3.3 *vs* 2.9 days for piperacillin/tazobactam and ceftazidime plus amikacin), the median duration of antibacterial therapy (7.2 *vs* 7.4 days) and the proportion of patients requiring additional vancomycin therapy (42 *vs* 38%).[131]

4.4 Other Infections

As discussed in other reviews,[1,133] piperacillin/tazobactam was also an effective treatment for hospitalised patients with skin and soft tissue infections, most of which were caused by *S. aureus* and Enterobacteriaceae. Results of comparative and noncomparative trials showed that clinical cure was achieved in 61 to 74% of patients treated with piperacillin/tazobactam 4/0.5g 8-hourly. Rates of bacterial eradication ranged from 76 to 85%.[134-136] Piperacillin/tazobactam showed clinical and bacteriological efficacy similar to that of ticarcillin/clavulanic acid 3/0.1g 6-hourly.[135]

Piperacillin/tazobactam achieved a bacteriological eradication rate of 91% in patients with bacteraemia or bone and joint infections (studies reviewed previously[1]). In women with gynaecological infections, bacterial eradication was reported in 67 (78%) of 86 patients treated with piperacillin/tazobactam 3/0.375g 6-hourly, compared with 23 (82%) of 28 recipients of clindamycin 0.9g 6-hourly plus gentamicin 2.5 to 5 mg/kg/day (in 3 divided doses).[137]

The efficacy of piperacillin/tazobactam (4/0.5g 3 times daily for ≥5 days) in the treatment of patients with complicated urinary tract infections (most commonly pyelonephritis) has been demonstrated in 2 noncomparative multicentre trials (n = 195 evaluable patients).[138,139]

Favourable clinical responses (cure or improvement) were documented in 88[138] and 90.4%[139] of patients 5 to 9 days after the discontinuation of treatment; at long term follow-up (4 to 6 weeks after the discontinuation of treatment), clinical responses were sustained in 80[139] and 86%[138] of patients. Bacterial eradication was achieved in 85.3% of patients 5 to 9 days after therapy,[139] and was sustained in 79.6[139] and 73%[138] of patients 4 to 6 weeks after the end of treatment. Strains of

E. coli were identified as the most common persistent pathogens in both trials.[138,139] *K. pneumoniae* and *P. aeruginosa* were also persistent bacteria.[138] Superinfections, generally associated with the presence of foreign bodies (such as catheters or ureteral stents), were documented in 5[138] and 8%[139] of patients and were caused by *K. pneumoniae*, *E. coli* and *Candida* spp.[139]

Numerous small noncomparative trials (enrolling <30 patients) conducted in Japan[140-146] have also shown that piperacillin/tazobactam is a beneficial treatment for patients with complicated urinary tract infections.

5. Pharmacoeconomic Considerations

Pharmacoeconomic evaluations of antibacterial agents provide information that is valuable in aiding treatment selection and formulary decisions. Importantly, in addition to the acquisition cost of an antibacterial, the total cost of a given treatment comprises 'hidden costs', including those of administration (e.g. administration supplies, nursing time, pharmacy preparation time), plasma drug monitoring (particularly for aminoglycosides) and costs of adverse events.[147]

Several pharmacoeconomic studies (cost analyses and cost-effectiveness evaluations) of piperacillin/tazobactam in patients with various types of infection have been conducted from the perspective of the healthcare payer. It is, however, difficult to compare the results of these investigations because of differences in methodology, clinical setting and country of the evaluation.

5.1 Cost Analyses

Direct costs of piperacillin/tazobactam treatment for community-acquired lower respiratory tract infection or intra-abdominal infection were lower than those of comparator therapies in a cost analysis conducted from the perspective of a US hospital (table VII).[148]

The total (hospitalisation) cost of treatment of patients with community-acquired respiratory tract infections with piperacillin/tazobactam 3/0.375g 6-hourly was $US2981 per patient lower than with ticarcillin/clavulanic acid 3/0.1g 6-hourly (table VII). The lower cost of piperacillin/tazobactam therapy was attributed to lower healthcare resource use [i.e. fewer doses of other parenteral antibacterial agents (7.1 *vs* 15.8), fewer days spent in hospital (11.1 *vs* 13.4) and fewer days spent in the intensive care unit (2.1 *vs* 3.5)] than in the comparator group.

Treatment of patients with intra-abdominal infections with piperacillin/tazobactam led to a net saving in total hospitalisation cost of $US284 per patient compared with clindamycin plus gentamicin (table VII).[148] Although the cost per patient of piperacillin/tazobactam was higher than that of clindamycin plus gentamicin ($US284 *vs* $US113) this was partly offset by other treatment-related costs in the comparator group:[148] costs of serum gentamicin monitoring and more frequent use of additional antibacterial agents were among these extra costs, which offset all but $US49 of the cost of piperacillin/tazobactam therapy. Patients treated with piperacillin/tazobactam spent 1.4 fewer days in hospital than the recipients of clindamycin plus gentamicin.

An economic model that used data from an unpublished study (demonstrating that piperacillin/tazobactam was superior to ceftazidime in patients with nosocomial lower respiratory tract infections) showed that the clinical efficacy advantage of piperacillin/tazobactam was obtained at a net hospitaisation cost of $US702 per patient compared with ceftazidime.[148]

Total direct costs of treatment with piperacillin/tazobactam (n = 42), were significantly lower than costs of imipenem/cilastatin 500mg (n = 46) [$US385.33 *vs* $US538.83 per patient; p = 0.0001] in a US study conducted in patients with intra-abdominal infections.[150] The difference in direct treatment costs was attributed largely to the lower acquisition and administration costs of piperacillin/tazobactam than of imipenem/cilastatin. However, the use of piperacillin/tazobactam led to higher hospitalisation costs than did imipenem/cilastatin ($US18 340 *vs* $US16 150 per patient; p = 0.05), as a result of a higher rate of clinical failure (22 *vs* 11%)

Table VII. Cost analyses comparing piperacillin/tazobactam (PIPTAZ) with other antibacterial agents in the treatment of various infections

Reference	Perspective (country)	Patient diagnosis (clinical trial reference)	Treatment regimen (g)	Direct costs included in the model	Source of resource use data (currency year)	Overall costs
Dietrich et al.[149] [abstract]	Hospital (US)	Febrile neutropenia	PIPTAZ (dosage NR) CAZ + AN (dosage NR)	Drug acquisition costs, adverse events, laboratory monitoring, consumable supplies, working time	Hospital administration, prospective data collection, expert opinion ($US 1998)	Net cost saving of $US538 per patient treated with PIPTAZ compared with CAZ+AN
Jhee et al.[150]	Hospital (US)	IA infection (Jhee et al.[150])	PIPTAZ 4/0.5 q8h IPM/C 0.5 q6h	Drug acquisition costs, drug reconstitution by pharmacy staff, nursing time, laboratory tests, adverse events	Average wholesale drug price list, hospital pharmacy, staff nurse salary ($US 1994)	Net cost of $US2190 per patient treated with PIPTAZ compared with IPM/C
Huse et al.[148]	Hospital (US)	Community-acquired LRTI (Shlaes et al.[80])	PIPTAZ 3/0.375 q6h TC/CL 3/0.1 q6h	Drug acquisition costs, hospitalisation costs, including costs of additional antibacterial agents	US Veterans Administration hospitals, general acute-care hospitals or trauma centres ($US 1994)	Net cost saving of $US2981 per patient treated with PIPTAZ compared with TC/CL
Huse et al.[148]	Hospital (US)	IA infection (Polk et al.[98])	PIPTAZ 3/0.375 q6h	Drug acquisition costs, hospitalisation costs, including costs of additional antibacterial agents	US Veterans Administration hospitals, general acute-care hospitals or trauma centres ($US 1994)	Net cost saving of $US284 per patient treated with PIPTAZ compared with CM+GM
			CM 0.6 q6h + GM 0.8-1.6 mg/kg q8h	Drug acquisition costs, hospitalisation costs, including costs of additional antibacterial agents and costs of gentamicin monitoring		
Huse et al.[148]	Hospital (US)	Nosocomial LRTI (Huse et al.[148])	PIPTAZ 3/0.375 q4h CAZ 2 q8h	Drug acquisition costs, hospitalisation costs, including costs of additional antibacterial agents	US Veterans Administration hospitals, general acute-care hospitals or trauma centres ($US 1994)	Net cost of $US702 per patient treated with PIPTAZ compared with CAZ
Marie et al.[123]	Hospital (France)	Febrile neutropenia (Marie at al.[123])	PIPTAZ 4/0.5 q8h + AN 15 mg/kg/day CAZ 1g q8h + AN 15 mg/kg/day	Drug acquisition costs	Costs to the hospital pharmacy (FF 1993)	Net cost saving of FF1100 per patient treated with PIPTAZ compared with CAZ
Marra et al.[151]	Hospital (Canada)	Various serious infections, including febrile neutropenia, pneumonia, skin/soft tissue infections and IA infections[151]	PIPTAZ 4/0.5 q6h IPM/C 0.5 q6h	Drug acquisition costs, costs of additional antibacterial agents, preparation and delivery costs	Costs to the hospital pharmacy ($Can 1996)	Net cost saving of $Can66 per patient treated with PIPTAZ compared with IPM/C

AN = amikacin**; CAZ** = ceftazidime; **CM** = clindamycin; **FF** = French Francs **GM** = gentamicin; **IA** = intra-abdominal; **IPM/C** = imipenem/cilastatin; **LRTI** = lower respiratory tract infection; **NR** = not reported; **q4h** = every 4 hours; **q6h** = every 6 hours; **q8h** = every 8 hours; **TC/CL** = ticarcillin/clavulanic acid.

and a longer duration of hospital stay (mean 7.8 *vs* 7.1 days) in the piperacillin/tazobactam group.[150] Sensitivity analysis showed that these results were robust even when acquisition costs of both treatments were the same.

The direct cost of treatment of patients with febrile neutropenia with piperacillin/tazobactam plus amikacin was lower than that of ceftazidime plus amikacin (FF11 400 *vs* FF12 500; 1993 costs) in a comparative trial conducted in France.[123] Preliminary results of a more recent evaluation of treatment costs for patients with febrile neutropenia showed that direct costs of piperacillin/ tazobactam (including costs of study drugs, adverse events, laboratory monitoring, consumable supplies) were about 20% lower than costs of ceftazidime plus amikacin (mean cost per patient: $US2364 *vs* $US2902).[149] However, when indirect costs were included in the model, the cost of piperacillin/ tazobactam treatment was higher than that of ceftazidime plus amikacin ($US4952 *vs* $US4873).

A cost-minimisation study that assessed the feasibility of replacing imipenem/cilastatin with piperacillin/tazobactam in a Canadian hospital formulary[151] showed that mean direct per patient costs of treatment (including drug acquisition, preparation and delivery costs) were broadly similar for both agents ($Can696 *vs* $Can762 for piperacillin/tazobactam and imipenem/cilastatin, respectively); mean costs of other antibacterial agents received by patients in the piperacillin/ tazobactam and imipenem/cilastatin groups were $Can629 and $Can518, respectively (table VII).[151]

The total direct costs of 7 days' treatment with piperacillin/tazobactam 4/0.5g 8-hourly were lower (£350 for bolus injection and £403 for intravenous infusion) than total costs of ceftazidime 2g 8-hourly plus metronidazole infusion 500mg 8-hourly (£428) or ceftazidime, metronidazole plus either gentamicin 120mg 8-hourly (£556) or netilmicin 150mg 12-hourly (£552) in a cost-minimisation analysis conducted in the UK.[152] In addition to drug acquisition costs, the model included costs of preparation and administration, and costs of consumables and waste disposal. Costs of assays were also considered in the aminoglycoside-containing regimens.[152]

5.2 Cost-Effectiveness Analyses

A decision model based on data from 2 clinical trials (results not reported) [n = 991] showed that piperacillin/tazobactam was a more cost-effective treatment than ceftazidime (each given with amikacin) for patients with febrile neutropenia. Direct costs, including the costs of drug acquisition, preparation and administration, and adverse events were among resource use costs included in the model. Costs per unit of effectiveness (not defined) for piperacillin/tazobactam and ceftazidime were $US5250 and $US5850, respectively. Piperacillin/ tazobactam treatment was estimated to represent a $US635 reduction in the cost per unit of treatment success compared with ceftazidime.[153] Sensitivity analyses showed that the results were robust to changes in drug costs and the percentage of patients with a successful treatment outcome.

Data from a trial (conducted in Germany) comparing piperacillin/tazobactam plus amikacin with ceftazidime plus amikacin in the treatment of febrile episodes in patients with neutropenia provided the basis for another cost-effectiveness evaluation.[154] Unlike other pharmacoeconomic models of piperacillin/tazobactam which included direct costs only, this analysis also incorporated the indirect costs of lost workplace productivity. Pharmacoeconomic assessments revealed that costs of piperacillin/tazobactam plus amikacin treatment per successfully treated patient were lower than ceftazidime plus amikacin costs (DM16 616 *vs* DM20 828).

6. Tolerability

Data on the tolerability of the piperacillin/tazobactam combination have been derived largely from phase I trials that included both healthy adult volunteers and patients with infections, and from non-comparative and comparative clinical trials conducted in >1500 adults with various infections. Detailed information on specific adverse events reported in these trials is, however, limited. The

overview of tolerability data from phase I and phase III trials of piperacillin/tazobactam (administered alone or with an aminoglycoside) reported by Kuye et al.[155] (reviewed previously[1]) remains the largest published source of adverse event data on piperacillin/tazobactam.

Results of this analysis showed that piperacillin/tazobactam 4/0.5g 6- or 8-hourly (alone or in combination with an aminoglycoside) was usually well tolerated in hospitalised adults with moderate to severe lower respiratory tract infections, intra-abdominal infections, complicated urinary tract infections or skin and soft tissue infections.[155]

6.1 General Profile

6.1.1 Piperacillin/Tazobactam Alone

Piperacillin/tazobactam is usually well tolerated by patients with various types of infection. Adverse events are generally mild or moderate in severity and seldom necessitate discontinuation of treatment.[155]

Gastrointestinal symptoms (most commonly diarrhoea) and reactions of the skin and appendages were the most common events documented in patients treated with piperacillin/tazobactam either alone (n = 944) or in combination with an aminoglycoside (n = 167) in the pooled data analysis.[155] The tolerability profile of piperacillin was not adversely affected by coadministration with tazobactam,[1] with gastrointestinal events reported in 3.6 to 4.0% of patients treated with piperacillin alone,[1] compared with 4.6% of piperacillin/tazobactam recipients.[155] Incidences of moderate or severe events (involving the gastrointestinal tract or the skin and appendages) with piperacillin/ tazobactam, piperacillin/tazobactam plus an aminoglycoside or with imipenem/cilastatin are shown in figure 7.

In more recent clinical trials, gastrointestinal and skin events (e.g. allergic rashes) were also the most common events recorded during treatment with piperacillin/tazobactam.[80,96,137]

Changes in liver function test values (e.g. increases in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and in total bilirubin) were also documented in patients receiving treatment with piperacillin/tazobactam,[137,155] but appeared to be of minor clinical significance.[155] Elevations in eosinophil and platelet counts and positive Coombs' test results have also been reported during treatment with piperacillin/tazobactam.[75,155]

The tolerability profile of piperacillin/tazobactam was broadly similar to that of imipenem/cilastatin (0.5 to 1g 8-hourly) in the comparative trials re-

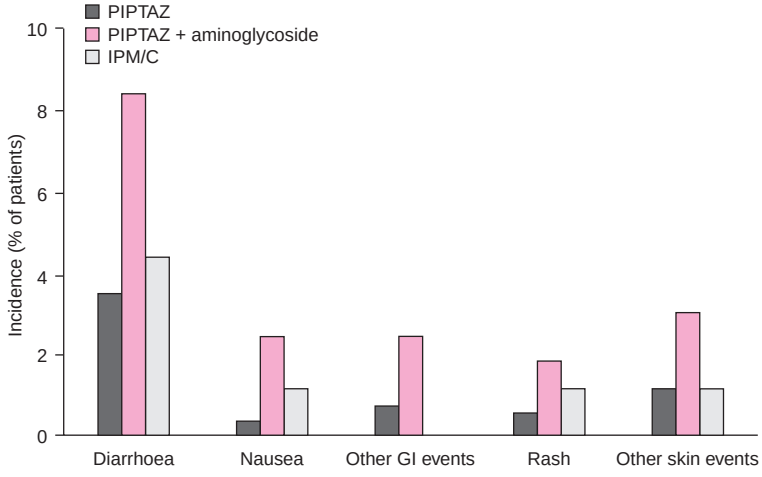


Fig. 7. Moderate or severe adverse events with piperacillin/tazobactam (PIPTAZ) [in dosages of 4/0.5g 6- or 8-hourly] administered alone or in combination with an aminoglycoside] or with imipenem/cilastatin (IPM/C) 0.5 to 1g 8-hourly.[155]

viewed by Kuye et al. (fig. 7).[155] In more recent comparative trials, incidences of adverse events with piperacillin/tazobactam did not differ significantly from those recorded for piperacillin[85,86] or imipenem/cilastatin[82,97] in patients with chronic lower respiratory tract or intra-abdominal infections. Gastrointestinal adverse events occurred more frequently in patients with lower respiratory tract infections treated with piperacillin/tazobactam (3/0.375g 6-hourly) than in a comparator group who received ticarcillin/clavulanic acid 3/0.1g 6-hourly (31.6 *vs* 20.5%; p = 0.02).[80]

Skin rashes were noted in significantly fewer women with pelvic infections treated with piperacillin/tazobactam than in recipients of clindamycin plus gentamicin (0.5 *vs* 3.9%; p = 0.03). Similarly, in patients with intra-abdominal infections, skin reactions (including rashes) were documented in more clindamycin plus gentamicin than piperacillin/tazobactam recipients (10 *vs* 5%) [statistical analysis not performed].[96] However, the incidence of gastrointestinal adverse events,[96] including diarrhoea[137] was higher with piperacillin/tazobactam than with clindamycin plus gentamicin [9.7 *vs* 2.9%; p = 0.04[137]; 20 *vs* 12% (statistical analysis not performed).[96] Overall, the rate of treatment discontinuation was lower in patients treated with piperacillin/tazobactam than in recipients of clindamycin plus gentamicin (1 *vs* 4%).[96]

Pseudomembranous colitis, ranging in severity from mild to life-threatening, has been observed in patients receiving piperacillin/tazobactam.[47] In addition, platelet-mediated bleeding and other bleeding manifestations occur occasionally in patients receiving β-lactam antibacterial agents, including piperacillin.[47,156] Serious and occasionally fatal anaphylactic reactions have been reported in patients receiving treatment with the penicillins.[47]

6.1.2 Piperacillin/Tazobactam in Combination with an Aminoglycoside

As might be expected, the addition of an aminoglycoside to piperacillin/tazobactam led to a higher incidence of gastrointestinal and skin-related adverse events in patients with severe infections [22 (13.2%) of 167 patients] than in recipients of piperacillin/tazobactam alone [43 (4.6%) of 944 patients].[155] Indeed, the respective incidences of moderate or severe diarrhoea and nausea were >2-fold and 8-fold higher with piperacillin/tazobactam plus an aminoglycoside than with piperacillin/tazobactam alone (fig. 7). Similarly, skin rashes and other skin events were recorded in more than twice as many patients treated with piperacillin/tazobactam plus an aminoglycoside than in recipients of piperacillin/tazobactam alone.[155] Incidences of moderate to severe adverse events in patients who received piperacillin/tazobactam in combination with an aminoglycoside were also higher (statistical significance not reported) than in recipients of imipenem/cilastatin (fig. 7).[155]

In more recent clinical trials, the frequency and distribution of adverse events was similar among patients with nosocomial pneumonia treated with either piperacillin/tazobactam plus amikacin or ceftazidime plus amikacin.[91] Similarly, overall incidences of adverse events were comparable in patients treated with either piperacillin/tazobactam plus amikacin or ceftazidime plus amikacin in 2 trials conducted in patients with febrile neutropenia or granulocytopenia.[112,123] However, although one of these investigations showed no significant between-group difference in the incidence of skin reactions,[123] patients treated with piperacillin/tazobactam plus amikacin experienced a significantly higher incidence of rash or urticaria than ceftazidime plus amikacin recipients in the other trial (12 of 421 episodes *vs* 3 of 433 episodes; p = 0.02).[112]

7. Dosage and Administration

Piperacillin/tazobactam is recommended for the treatment of adults or adolescents with moderate to severe infections (including lower respiratory tract, intra-abdominal, urinary tract and skin/soft tissue infections and febrile neutropenia) in which susceptible pathogens have been identified or are suspected. Recommended intravenous dosages range from 2/0.25g given every 6 to 12 hours (for the treatment of patients with milder infections) to

4/0.5g every 6 or 8 hours for the treatment of more severe infections. In patients with nosocomial pneumonia, piperacillin/tazobactam (3/0.375g every 4 hours) should be given in combination with an aminoglycoside to ensure adequate coverage of *P. aeruginosa*.

The combination may be administered as either a slow bolus injection (over 3 to 5 minutes) or as an intravenous infusion (over 20 to 30 minutes). Patients should receive treatment until 48 hours have elapsed after resolution of clinical symptoms, including fever.[1,75]

As renal excretion is a major route of elimination for both piperacillin and tazobactam (see section 3.3), dosage adjustment is required for patients with renal impairment (see section 3.4.1). The dosage recommended for patients with a creatinine clearance of <20 ml/min (<1.2 L/h) is 4/0.5g every 12 hours (table VIII).

Therapeutic drug concentration monitoring is advised by the manufacturer as an additional means of ensuring that plasma concentrations of piperacillin and tazobactam are within the therapeutic range.

The maximum dose of piperacillin/tazobactam recommended for the treatment of patients undergoing haemodialysis (see section 3.4.1) is 8/1g over each 24-hour treatment period; after each period of dialysis, a further dose of 2/0.25g is recommended.

Piperacillin/tazobactam is contraindicated in patients with a history of allergy to any penicillins and/or cephalosporins and/or β-lactamase inhibitors.[75]

8. Place of Piperacillin/Tazobactam in the Management of Bacterial Infections

The widespread use of β-lactam antibacterial agents has led to an increase in resistance to these agents among both Gram-positive and Gram-negative bacteria worldwide.[157-160] As expected, infections caused by resistant pathogens are associated with higher rates of morbidity and mortality than infections caused by bacteria susceptible to antibacterial treatment.[157] β-Lactamase production (either plasmid- or chromosomally mediated) is the most important cause of resistance among Gram-positive and Gram-negative bacteria[161] and has led to a decrease in the spectrum of antibacterial activity of piperacillin and other penicillins, compromising the clinical efficacy of these agents over time.

Data from numerous *in vitro* studies indicate that tazobactam inactivates a wide range of β-lactamases, including Bush-Jacoby-Medeiros group 2b, 2br and 2c enzymes. Thus, when given in combination with piperacillin, it restores and extends the antibacterial activity of the β-lactam agent to include many Gram-negative and Gram-positive aerobic and anaerobic organisms, most notably β-lactamase–producing staphylococci, *Bacteroides* spp. and some Enterobacteriaceae. This wide spectrum of antimicrobial activity, coupled with the ability of piperacillin and tazobactam to achieve therapeutic concentrations in a wide range of body tissues and fluids, has led to the extensive evaluation of the combination in the clinical setting. Limitations in its activity, in common with other β-lactam agents, include its lack of activity against methicillin-resistant staphylococci and *E. faecium*. Piperacillin/tazobactam is generally active against streptococci, many enterococci and *P. aeruginosa*.

Clinical evidence from numerous trials has confirmed the efficacy of piperacillin/tazobactam in the treatment of community-acquired or nosocomial lower respiratory tract infections (including pneumonia), febrile neutropenia, intra-abdominal, urinary tract, skin and soft tissue and gynaecological infections. Most infections were polymicrobial and were often caused by aerobic and/or anaerobic β-lactamase-producing bacteria.

Piperacillin/tazobactam was at least as effective as standard comparators in the treatment of patients with a wide range of moderate to severe infections.

Table VIII. Recommended dosages of intravenous piperacillin/tazobactam for the treatment of adults and children (aged >12 years) with various degrees of renal impairment[75]

Creatinine clearance (ml/min)[a]	Dose (g)	Dosage interval (h)
20-80	4/0.5	8
<20	4/0.5	12

a Conversion factor for L/h = × 0.06.

Of note, piperacillin/tazobactam was significantly more effective, in terms of both clinical and microbiological outcomes, than ticarcillin/ clavulanic acid in patients with community-acquired pneumonia. In keeping with *in vitro* data, there was some evidence to suggest that piperacillin/tazobactam provided better coverage of Gram-negative bacteria than ticarcillin/clavulanic acid. Thus, piperacillin/tazobactam may be considered preferable to the latter agent for inclusion in hospital formularies.

Clinical data also confirm a valuable role for piperacillin/tazobactam as an adjunct to surgery in patients with moderate to severe intra-abdominal infections. Indeed, in clinical trials, the combination showed similar efficacy to clindamycin plus gentamicin and significantly better efficacy than imipenem/cilastatin (administered at a dosage lower than is recommended in countries outside Scandinavia). A possible advantage afforded by piperacillin/tazobactam over clindamycin plus gentamicin in this indication is that, in contrast to the aminoglycoside-containing regimen, its use is not associated with adverse changes in blood urea and serum creatinine levels.

Nosocomial infections, especially those caused by chromosomally mediated β-lactamase–producing pathogens (such as *Pseudomonas* spp.)[10] are a particular challenge to the physician as they are notoriously difficult to treat. Because of this, infections of this type were generally treated with higher dosages of piperacillin/tazobactam (4/0.5g 6-hourly) in combination with an aminoglycoside. In patients with serious nosocomial pneumonia, piperacillin/tazobactam should be given (at a dosage of 3/0.375g every 4 hours) in combination with an aminoglycoside, to provide optimal coverage against *P. aeruginosa* (US prescribing information).[47] In clinical trials, in keeping with the broad spectrum of antibacterial activity provided by piperacillin/tazobactam plus an aminoglycoside, this combination regimen was at least as effective as ceftazidime plus amikacin or tobramycin in patients with nosocomial pneumonia or bronchitis or ventilator-associated pneumonia, validating the use of this treatment approach in such patients. Of note, piperacillin/tazobactam plus tobramycin showed better efficacy than ceftazidime plus tobramycin in eradicating *H. influenzae*, *S. aureus* and *P. aeruginosa* in a large group of patients with nosocomial pneumonia or bronchitis.

Clinical experience has also shown that piperacillin/tazobactam in combination with an aminoglycoside is beneficial as first-line therapy for patients with febrile neutropenia.[162] The efficacy of such therapy has been shown to be significantly better than that of standard treatment with ceftazidime plus amikacin. This appears to be due in part to its broader spectrum of antibacterial activity, particularly against Gram positive pathogens, including staphylococci (particularly coagulase-negative staphylococci) and viridans streptococci. Moreover, the use of piperacillin/tazobactam plus amikacin was associated with a reduced need for vancomycin or teicoplanin treatment compared with ceftazidime plus amikacin.[112] Piperacillin/tazobactam plus amikacin was also a less costly and more cost-effective treatment than ceftazidime plus amikacin in the treatment of febrile neutropenia. Piperacillin/tazobactam alone is also effective in the empirical treatment of patients with febrile neutropenia demonstrating efficacy similar to that of both cefepime monotherapy and ceftazidime plus amikacin combination therapy.

Emerging resistance among nosocomial pathogens has been well documented over recent years. Notably, third generation cephalosporin use in the hospital setting has been associated with the development of resistance in Gram-negative pathogens producing extended-spectrum β-lactamases.[163-165] However, with the restriction of cephalosporins and the use of piperacillin/tazobactam, outbreaks of resistant pathogens were controlled in some US hospitals.[163,165]

The addition of β-lactam/β-lactamase inhibitors (in place of third-generation cephalosporins) to US hospital formularies led to a decrease in the use of vancomycin and a decrease in the emergence of vancomycin-resistant enterococci as a result of reduced cephalosporin usage.[166,167]

Pooled data from a large number of clinical trials indicate that piperacillin/tazobactam is generally well tolerated in adults with various types of infection. Gastrointestinal symptoms (particularly diarrhoea) are the most frequently reported events with piperacillin/tazobactam, occurring at an incidence similar to that in recipients of piperacillin monotherapy. As with other β-lactam antibacterials, allergic reactions, including skin rashes, may also occur during treatment with piperacillin/tazobactam and patients with a known history of allergic reactions to other β-lactam agents should not receive treatment with the combination.

In conclusion, piperacillin/tazobactam is a well tolerated β-lactam/β-lactamase inhibitor combination with a broad spectrum of antimicrobial activity that includes Gram-positive and Gram-negative aerobic and anaerobic bacteria. As with other antibacterial agents, its selection in the clinical setting is likely to depend ultimately on hospital formulary decisions based on local susceptibility and resistance patterns, changes in the frequency of causative pathogens and the overall cost of treatment. Piperacillin/tazobactam appears to be of particular value in the treatment of moderate to severe polymicrobial infections, especially in an environment where β-lactamase–producing bacteria are increasingly common. Piperacillin/tazobactam appears to have a particularly useful role as an adjunct to surgery in patients with intra-abdominal infections and, in combination with an aminoglycoside, as first-line empirical therapy for patients with febrile neutropenia, especially given the current prevalence of Gram-positive infections in this group.

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