REVIEW

# Multiresistant *Acinetobacter* infections: a role for sulbactam combinations in overcoming an emerging worldwide problem

*A. S. Levin*

Division of Infectious Diseases, São Paulo University Hospital, Brazil

Recent studies have highlighted the emergence of infections involving multiresistant *Acinetobacter* clinical isolates. Sulbactam offers direct antimicrobial activity against *Acinetobacter* species. Accordingly, co-administration of sulbactam with ampicillin or cefoperazone offers the potential of effective empirical therapy against *Acinetobacter* and other bacteria such as Enterobacteriaceae in institutions in which they are susceptible. Many in vitro studies have indicated that *Acinetobacter* remains fully susceptible to ampicillin–sulbactam or cefoperazone–sulbactam. Furthermore, ampicillin–sulbactam has proven clinically effective and well tolerated in the treatment of severe acinetobacter infections, including bacteremia. Therefore, ampicillin–sulbactam is a sensible option for the treatment of life-threatening acinetobacter infections.

**Keywords** *Acinetobacter*, ampicillin, cefoperazone, sulbactam

**Accepted** 29 November 2001

*Clin Microbiol Infect* 2002; 8: 144–153

## INTRODUCTION

With the development of modern infection-monitoring programs, the clinical importance of *Acinetobacter* species, particularly *Acinetobacter baumannii*, has been determined. These species are now known to be responsible for a wide range of nosocomial infections, including bacteremia, secondary meningitis and urinary tract infections, and to play an important role as infective agents in late-onset nosocomial pneumonia among intensive care unit (ICU) patients. *Acinetobacter* species are ubiquitous opportunistic pathogens that colonize the skin of up to 25% of healthy adults [1], and are among the most common Gram-negative organisms isolated from the skin of hospital personnel [2]. They are also frequently grown from sputum, urine and feces [3].

In the USA, an audit of infections among adult and pediatric ICU patients during the period 1987–1996 [4], performed by the National Nosocomial Infections Surveillance System, reported 3447 nosocomial acinetobacter infections during 5 596 156 patient-days, the average rates of infection being significantly higher during the summer than in the winter. Elsewhere, other studies have confirmed the association of *Acinetobacter* species with nosocomial infections [1,5–7], and have highlighted sudden increases in the regional incidence of colonization and infection [8].

Acinetobacter infections are most frequently associated with the use of a ventilator or other invasive device [9], and risk factors include neurosurgery, acute respiratory distress syndrome, and head trauma [10]. Given the increasing availability of intensive care facilities and more sophisticated invasive clinical procedures, the prevalence of acinetobacter infections is likely to increase.

Accordingly, it is appropriate to re-evaluate the clinical role of established antibiotics in treating these infections. This review considers the in vitro activity and clinical efficacy and safety of two sulbactam-based $\beta$-lactam/$\beta$-lactamase inihibitor combinations, ampicillin–sulbactam and cefoperazone–sulbactam.

Corresponding author and reprint requests: A. S. Levin, Division of Infectious Diseases, São Paulo University Hospital, Rua Harmonia, 564/52, São Paulo SP 05435-000, Brazil
Tel: +55 11 30696444
Fax: +55 11 30887095
E-mail: gcih@hcnet.usp.br

## EXTENT OF RESISTANCE IN *ACINETOBACTER*

The increasing, and sometimes inappropriate, administration of antibacterial agents [11],

together with the growing use of invasive diagnostic and therapeutic procedures, has contributed to the development of resistant bacterial species among hospitalized patients, especially those at high risk (i.e. ICU patients).

An important feature of *Acinetobacter* species, and *A. baumannii* in particular, is their intrinsic resistance to multiple antibiotics. Recently reported surveillance surveys have demonstrated high rates of resistance to aminoglycosides, cephalosporins, quinolones, penicillins, monobactams, and imipenem, often in excess of 50%, among clinical isolates of *Acinetobacter* [7,12–14]. For example, of 85 strains of *Acinetobacter* species collected at one hospital in Thailand in 1996–1997, $\geq$50% were resistant to cefoperazone, tetracycline and co-trimoxazole, 20–50% to piperacillin, ciprofloxacin, ceftazidime, cefotaxime, doxycycline, amikacin and ofloxacin, and 10–20% to piperacillin–tazobactam, levofloxacin, cefepime, sparfloxacin and minocycline [14]. Other studies have reported imipenem resistance among *Acinetobacter* strains [5,6,15].

Infection due to highly resistant *Acinetobacter* strains can lead to treatment failure, and is associated with an increased risk of death [16]. Even if death is avoided by prescribing alternative medication, an extended stay within the ICU is required, and the total length of stay in hospital will be longer. Thus, infection by highly resistant *Acinetobacter* can lead to a dramatic increase in the overall cost of care [17].

## MECHANISMS OF ANTIBIOTIC RESISTANCE IN *ACINETOBACTER*

The full extent of the mechanisms of resistance of *Acinetobacter* species to $\beta$-lactams remains unclear [18]. One study isolated the $\beta$-lactamase TEM 1 from 16% of 54 clinical isolates of *A. baumannii*, and cephalosporinase from 98% of the strains [19]. Other resistance mechanisms that were detected included three classes of aminoglycoside-modifying enzymes, isolated from up to 28% of strains. However, the presence of TEM 1 and cephalosporinase cannot explain the resistance of *Acinetobacter* strains to either extended-spectrum cephalosporins or carbapenems.

The isolation of a carbapenase from *Acinetobacter* strains that lack any alteration in the outer membrane probably explains the resistance of *Acinetobacter* to imipenem [15]. Another study suggests that the antibiotic resistance of *Acinetobacter* strains is attributable to the expression of altered penicillin-binding proteins (PBPs) [20]. The outer-membrane permeability of *Acinetobacter* species to $\beta$-lactams has been studied and shown to be 1–3% of that of *Escherichia coli*. This decreased permeability is probably due to the presence of the small number of low-molecular-mass porins [21].

Regardless of the mechanisms involved, the high incidence of reduced antibiotic sensitivity among *Acinetobacter* strains isolated from ICU patients demonstrates that more effective strategies are needed to control the selection and spread of resistant organisms, and that alternative safe therapeutic agents are required.

## ROLE OF SULBACTAM IN OVERCOMING RESISTANCE

Co-administration of a $\beta$-lactamase inhibitor with the $\beta$-lactam antiobiotic has proven successful in overcoming $\beta$-lactamase-mediated resistance [22]. $\beta$-Lactamase inhibitors possess a $\beta$-lactam structure but only limited antimicrobial activity [23]. Their major value is in blocking the catalytic activity of $\beta$-lactamases against $\beta$-lactam antibiotics by binding irreversibly to the active sites of enzymes produced by the bacteria. The anti-$\beta$-lactamase spectrum of these inhibitors includes plasmid-mediated transferable enzymes and various extended-spectrum enzymes [23]. There are three $\beta$-lactamase inhibitors in clinical use: sulbactam, tazobactam, and clavulanic acid [22].

Sulbactam is a synthetic $\beta$-lactam molecule, with structural, chemical and pharmacokinetic properties similar to those of aminopenicillins. A feature that distinguishes sulbactam from other available $\beta$-lactamase inhibitors is its direct antimicrobial activity against *Bacteroides fragilis* and *Acinetobacter* species, organisms against which most cephalosporins display little or no activity [23]. Binding of sulbactam to PBP 2 of these organisms imparts intrinsic antibacterial activity [24].

## MICROBIOLOGICAL ACTIVITY OF AMPICILLIN–SULBACTAM AND CEFOPERAZONE–SULBACTAM

There are two sulbactam combinations in clinical use: ampicillin–sulbactam and cefoperazone–sulbactam. The combination of ampicillin and sulbactam is available as both parenteral (intravenous

or intramuscular) and oral formulations (as the mutual prodrug sultamicillin). By contrast, cefoperazone–sulbactam is available as a parenteral (intravenous or intramuscular) formulation only [22].

The findings of studies that have investigated the in vitro susceptibility of *Acinetobacter* species to ampicillin–sulbactam and cefoperazone–sulbactam reveal that the susceptibility rates vary widely geographically (nationally and regionally) and with time. One explanation for this is variation in the methods of susceptibility testing and in the breakpoints used to determine sensitivity. Larger, multicenter, international studies tend to standardize the methods used and provide more valuable information on the true resistance profile of *Acinetobacter* species. Nonetheless, smaller regional studies remain important for identifying the emergence of localized acinetobacter multidrug resistance. The in vitro activity data on combinations with sulbactam probably result from the fact that in most countries sulbactam is not available alone. It would appear, however, that acinetobacter susceptibility is due mainly to sulbactam.

## Ampicillin–sulbactam

In vitro susceptibility studies in North America, South America, Europe, and Asia, involving clinical isolates collected during 1988–1999, have reported a wide variety of susceptibility rates for ampicillin–sulbactam as well as other antibiotics (Table 1). Most studies use National Committee for Clinical Laboratory Standards (NCCLS) criteria, in which a rate of 2:1 for ampicillin–sulbactam is used for agar dilution or a disk with

**Table 1** In vitro susceptibility of *Acinetobacter* species to ampicillin–sulbactam

| Study | Country | Collection date (no. of isolates) | Ampicillin–sulbactam | Comparators (% strains) |
|---|---|---|---|---|
| North America | | | | |
| Marques et al. 1997 [57] | USA | 1994 ($n = 14$) | $MIC_{50}$: 8/4; $MIC_{90}$: 16/8 | MDR isolates:<br>imipenem, 100%;<br>amikacin, 21%;<br>piperacillin/tazobactam, 14%;<br>others, 0.1% |
| Urban et al. 1993 [32] | USA | 1988–1989 ($n = 20$) | $MIC_{90}$: $\leq$8/4 | $MIC_{90}$:<br>ciprofloxacin, >4;<br>co-trimoxazole, >8/152;<br>gentamicin, >8;<br>imipenem, 16;<br>amikacin, >16;<br>cefotaxime, >16;<br>amoxicillin–clavulanic acid, >16/8;<br>piperacillin–tazobactam, 64/8;<br>ticarcillin–clavulanic acid, >64 |
| Murray et al. 1994 [29] | USA | NS ($n = 784$) | 81.4%[a]<br>$MIC_{50}$: 4/2; $MIC_{90}$: 32/16 | Imipenem, 96.4%;<br>ticarcillin–clavulanic acid, 74.4%;<br>piperacillin–tazobactam, 66.8%;<br>ceftazidine, 64.7%;<br>ciprofloxacin, 63.4%;<br>piperacillin, 54.2%;<br>ceftriaxone, 49.4% |
| Murray et al. 1993 [28] | USA | NS ($n = 25$) | 100%[a]<br>$MIC_{50}$: 1/1; $MIC_{90}$: 2/2 | Imipenem, 100%;<br>ceftazidime, 100%;<br>ceftizoxime, 100%;<br>ticarcillin–clavulanic acid, 96%;<br>cefotaxime, 84%;<br>ceftriaxone, 76%;<br>cefoperazone, 32%;<br>cefotetan 12% |

**Table 1** continued

| Study | Country | Collection date (no. of isolates) | Ampicillin–sulbactam | Comparators (% strains) |
|---|---|---|---|---|
| South America | | | | |
| Mendes et al. 1998 [26] | Brazil | 1994 ($n = 9$) | 92%[a]<br>$MIC_{90}$: 8/4 | Co-trimoxazole, 52%;<br>ampicillin, 25%;<br>cephalothin, 15–20% |
| Europe | | | | |
| Tascini et al. 1998 [27] | Italy | NS ($n = 5$) | 100%[a]<br>$MIC_{90}$: 8/4 | Polymixin B, 100%;<br>rifampicin, 0% |
| Garcia-Arata et al. 1996 [30] | Spain | 1990–1994 ($n = 177$) | 97%[a]<br>$MIC_{50}$: 4/2; $MIC_{90}$: 8/4 | Carbapenems, 99%;<br>amikacin, 94%;<br>piperacillin–tazobactam, 60%;<br>ceftazidime, 25%;<br>ticarcillin, 24%;<br>piperacillin, 18.1% |
| Douboyas et al. 1994 [31] | Greece | 1992–1993 ($n = 219$) | 82%[a]<br>$MIC_{50}$: 8/4; $MIC_{90} > 32/16$ | Amikacin, 21%;<br>ciprofloxacin, 16%;<br>ceftazidime, 10%;<br>piperacillin, 10% |
| Asia | | | | |
| Shi et al. 1996 [58] | Taiwan | NS ($n = 248$) | 66.5%[a]<br>$MIC_{50}$: 2/1; $MIC_{90}$: 32/16 | Imipenem, 98.7%;<br>meropenem, 98.7%;<br>ciprofloxacin, 96.8%;<br>amikacin, 72.2%;<br>cefipime, 67.7%;<br>ceftazidime, 58.5%;<br>piperacillin–tazobactam, 55.6%;<br>amoxicillin–clavulanic acid, 30.2%;<br>piperacillin, 28.6% |
| Cheng et al. 1993 [59] | Hong Kong | 1986–1990 ($n = 48$) | $MIC_{50}$: 1/1<br>$MIC_{90}$: 16/16 | $MIC_{90}$:<br>amikacin, 2;<br>amoxicillin–clavulanic acid, 16;<br>ceftazidime, 16;<br>cefpirome, 32;<br>gentamicin, 32;<br>cefuroxime, >128 |

NS, not specified; MDR, multiresistant (resistant to two or more aminoglycosides and two or more extended-spectrum penicillins); MIC, minimal inhibitory concentration, in mg/L; $MIC_{50}$, MIC for 50% of isolates tested; $MIC_{90}$, MIC for 90% of isolates tested. [a]MIC determination and interpretation based on National Committee for Clinical Laboratory Standards (NCCLS) criteria (susceptible if MIC $\leq$ 8/4 mg/L).

10 μg/10 μg [25]. However, some studies do not even mention the susceptibility criteria used. Table 1 includes only studies in which susceptibility criteria were well defined and minimal inhibitory concentrations for sulbactam were obtained. Most strains of *Acinetobacter* species remain fully susceptible to ampicillin–sulbactam. In particular, recent studies in Brazil and Italy have confirmed high rates of susceptibility of *Acinetobacter* species to ampicillin–sulbactam [26,27]. Among the larger, multicenter studies, reported susceptibility rates are in the range 81–100% [26,28,29]. Currently available susceptibility data reveal no clear geographic trend in the global susceptibility of *Acinetobacter* species to ampicillin–sulbactam (Table 1). A few studies have compared temporal changes in susceptibility rates within regions. For example, Garcia-Arata et al. [30] in Spain traced the emergence of resistance among *Acinetobacter* species over a 5-year period (1990–1994), and detected

an increase in resistance to ticarcillin, piperacillin–tazobactam, ceftazidime, amikacin, and ofloxacin, but not ampicillin–sulbactam. A study showed that *Acinetobacter* species remain more susceptible to ampicillin–sulbactam than to other β-lactam/β-lactamase inhibitor combinations [29], but another study demonstrated superior activity for ticarcillin–clavulanic acid [28]. Imipenem and meropenem generally remain more active than ampicillin–sulbactam [28,29], although some studies have shown ampicillin–sulbactam to be superior [31,32]. Ampicillin–sulbactam has consistently been shown to be more active in vitro than a wide variety of other, non-combination β-lactam agents, including many cephalosporins [28,29,31–33]. Furthermore, ampicillin–sulbactam has been demonstrated to be more effective in vitro than ciprofloxacin and ofloxacin [31,33] and gentamicin [32,33].

*Acinetobacter* is not a homogeneous genus, and different genospecies may present different susceptibility patterns [34]. In one study, *A. baumannii* was more resistant to ampicillin–sulbactam, with an $MIC_{50}$ and $MIC_{90}$ of 4/2 and 32/16 mg/L, respectively, compared with 2/1 and 4/2 for other genospecies [35].

### Cefoperazone–sulbactam

Studies in North America, South America, Europe and Asia have also investigated the in vitro activity of cefoperazone–sulbactam, and have shown it to be superior to that of cefoperazone alone against clinical isolates of many Gram-negative bacilli, but particularly against *Acinetobacter* species in which activity is due to sulbactam alone [32,36–39] (Table 2). One of the most important problems with many studies comprises the criteria used to define susceptibility. For the combination cefoperazone–sulbactam, there is no NCCLS standard for sulbactam concentration for agar dilution or disk diffusion tests, and interpretations usually take into account MICs of cefoperazone (Table 2). Some studies use ratios of 2 : 1, but others do not even mention the sulbactam concentration used. Table 2 includes only the studies in which the criteria of interpretation of susceptibility were defined and MICs for sulbactam were obtained.

Few studies have evaluated trends in the resistance of Gram-negative bacilli, including *Acinetobacter* species, to cefoperazone–sulbactam. In Japan, comparison of 1999 susceptibility data with those of 1998 demonstrated continued in vitro activity of broad-spectrum β-lactams, including cefoperazone–sulbactam [40], and the rapid emergence of new or novel resistance was not observed. The greatest changes observed were in the rates of resistance to cefepime (from 7.0% to 10.0%) and cefpirome (from 12.1% to 16.5%).

In vitro studies have shown that cefoperazone–sulbactam is more active than a variety of individual β-lactam agents against *Acinetobacter* species [41], and only imipenem has demonstrated in vitro activity superior to that of cefoperazone–sulbactam [42].

## CLINICAL EFFICACY AND TOLERABILITY OF AMPICILLIN–SULBACTAM

### Efficacy

There have not been any randomized clinical trials published to date, and all the data are based on uncontrolled studies. An experimental study of *A. baumannii* endocarditis in rabbits and pneumonia in mice suggested that the activity of sulbactam is time dependent and similar to that of imipenem against susceptible strains [43]. Clinical studies have demonstrated the efficacy of ampicillin–sulbactam in the treatment of severe multiresistant *A. baumannii* infections [44,45], including meningitis [33] and bacteremia [46], and infections due to imipenem-resistant *A. calcoaceticus* [32].

Several studies have evaluated the clinical efficacy of ampicillin–sulbactam specifically against acinetobacter infections. In 1996–1997, our group investigated the efficacy of ampicillin–sulbactam in treating nosocomial infections due to multiresistant *A. baumannii* (MRAB; resistant to antipseudomonal penicillins and cephalosporins, imipenem, quinolones and aminoglycosides) [44]. In all, 23 patients (aged 8–79 years) were treated with intravenous ampicillin–sulbactam 3–18 g/day. All patients had underlying medical conditions and APACHE II scores in the range 3–28 (mean 16.4). The infections included pneumonia (35%), bacteremia (26%), surgical site infections (13%), meningitis (9%), peritonitis (9%), urinary tract infections (4%), and sinusitis (4%). Cure or marked improvement was observed in 13 of 23 (56.5%) patients. Six clinical failures included two cases of meningitis. The remaining patients were non-evaluable.

**Table 2** In vitro susceptibility of *Acinetobacter* species to cefoperazone–sulbactam

| Study | Country | Collection date (no. of isolates) | Cefoperazone/ sulbactam | Comparators (% strains) |
|---|---|---|---|---|
| North America | | | | |
| Jones et al. 1985 [37] | USA | NS ($n = 15$) | $MIC_{50}$: 1 and $MIC_{90}$: 2 for sulbactam alone | $MIC_{50}$ cefoperazone alone: 64 |
| Eliopoulos et al. 1989 [38] | USA | 1987–1988 ($n = 84$) | $MIC_{50}$: 8 and $MIC_{90}$: 16 for sulbactam alone | $MIC_{50}$ cefoperazone alone: 64<br>$MIC_{90}$ cefoperazone alone >128 |
| Knapp et al. 1989 [39] | USA | NS ($n = 21$) | $MIC_{50}$: 1/0.5; $MIC_{90}$: 2/1 | $MIC_{50}$ cefoperazone alone: 16<br>$MIC_{90}$ cefoperazone alone: 32 |
| South America | | | | |
| Jones et al. 1997 [42] | Colombia | NS ($n = 72$) | 83.3%[a]<br>$MIC_{50}$: 2/1; $MIC_{90}$: 48/24 | Imipenem, 95.8%;<br>cefepime, 86.1%;<br>ceftazidime, 70.8%;<br>cefotaxime, 40.3%;<br>aztreonam, 29.6% |
| Europe | | | | |
| Pfaller et al. 1999 [60] | Turkey | 1997 ($n = 80$) | 73.8%[a]<br>$MIC_{50}$: 6/3; $MIC_{90}$: 64/32 | Imipenem, 85.0%;<br>cefepime, 43.8%;<br>ticarcillin–clavulanic acid, 29.3%;<br>ceftazidime, 23.8%;<br>cefotaxime, 18.8%;<br>aztreonam, 17.2% |
| Asia | | | | |
| Lim and Cheong 1995 [36] | Malaysia | 1994 ($n = 21$) | 21 cefoperazone-resistant strains (MIC > 32 mg/L), $MIC_{50}$: 8 and $MIC_{90}$: 32 for sulbactam | |
| Yamaguchi et al. 1999 [41] | Japan | 1997 ($n = 199$) | 99.5%[a]<br>$MIC_{50}$: 2/1; $MIC_{90}$: 4/2 | Imipenem, 97.0%;<br>cefepime, 89.4%;<br>ceftazidime, 84.4%;<br>cefpirome, 83.4%;<br>piperacillin, 28.0% |

NS, not specified; MIC, minimal inhibitory concentration, in mg/L; $MIC_{50}$, MIC for 50% of isolates tested; $MIC_{90}$, MIC for 90% of isolates tested. [a]MIC determination and interpretation based on National Committee for Clinical Laboratory Standards (NCCLS) criteria for cefoperazone (susceptible if MIC $\leq$ 16 mg/L) [25].

At around the same time, Corbella et al. [45] evaluated ampicillin–sulbactam (2 g/1 g three times daily) compared with sulbactam alone (1 g three times daily) in the treatment of non-life-threatening MRAB. Cure or marked improvement within 72 h of the start of therapy was seen in 22 of 23 (95.6%) evaluable ampicillin–sulbactam-treated patients and 17 of 18 (94.4%) evaluable sulbactam-treated patients. These data illustrate that the clinical activity of the ampicillin–sulbactam combination is attributable to the antimicrobial activity of the sulbactam component, and that sulbactam alone may be clinically effective against MRAB infections. In some European countries, such as Spain, France and Germany, sulbactam is available not in combination.

A study by Jiménez-Mejias et al. [33] confirmed the clinical effectiveness of ampicillin–sulbactam in treating *A. baumannii* meningitis. Eight patients yielded isolates resistant to cephalosporins, ciprofloxacin and gentamicin, and nearly all (7/8) isolates were resistant to imipenem. All patients received intravenous ampicillin–sulbactam 2 g/1 g three or four times daily. Cure was observed in six of eight (75%) cases. The blood–brain barrier permeability to sulbactam is poor in the absence of inflammation [47], and may lead to treatment failures.

In the case of *A. baumannii* bacteremia, Cisneros et al. [46] treated eight patients with ampicillin–sulbactam and 42 with imipenem, and observed response rates of 83.0% and 87.5%, respectively. Another study, by Urban et al. [32], recorded improvement in nine of 10 (90%) patients with imipenem-resistant *A. calcoaceticus* infections treated with ampicillin–sulbactam. Similarly, an eradication rate of 80% was recorded in nine patients with urinary tract infections due to *A. calcoaceticus* treated with ampicillin–sulbactam [48]. Most studies used intravenous treatment, as the infections treated were severe, with daily doses ranging from 1 to 6 g of sulbactam. The oral form may be useful as subsequent treatment.

### Tolerability

A large body of clinical evidence has shown that ampicillin and cefoperazone offer favorable tolerability profiles in the clinical setting. Clinical studies have also shown that ampicillin–sulbactam [33,44,45,49] presents virtually no side-effects, that cefoperazone–sulbactam [50–52] is well tolerated, and that the addition of sulbactam does not compromise the safety of the $\beta$-lactam agents.

## WEIGHING UP THE EVIDENCE

Prior use of broad-spectrum antibiotics, the use of a urinary tract catheter, prior surgery and mechanical ventilation are significant risk factors for nosocomial sepsis caused by *A. baumannii*. Furthermore, as a focus of infection, multiresistant *A. baumannii* contributes to increased mortality, intensifying the need for appropriate management of patients, and the careful selection of antibacterial therapy [44].

An in vitro microbial activity spectrum that includes *Acinetobacter* species, proven clinical efficacy when given intravenously or intramuscularly to patients with moderate-to-severe infections, and a favorable tolerability profile, together suggest that ampicillin–sulbactam is a sensible option for the treatment of acinetobacter infections, and sulbactam alone may be used where available. Several studies have demonstrated clinical efficacy against *Acinetobacter* strains resistant to other commonly used antibiotics, including imipenem.

In recent years, the only other antibacterial agent that has consistently been shown to be active against *Acinetobacter* is colistin [53,54]. Colistin can therefore be considered a useful option against multiresistant infections, despite its potential toxicity (kidney damage, neurotoxicity, and neuromuscular blockade) [55]. The orally administered mutual prodrug sultamicillin possesses a pharmacokinetic/pharmacodynamic profile similar to that of parenteral ampicillin–sulbactam, and this allows the subsequent treatment of patients with an oral formulation of already proven efficacy and tolerability, and avoids the potentially adverse clinical and financial impacts of prolonged parenteral therapy [56].

In the case of cefoperazone–sulbactam, in vitro studies have demonstrated antimicrobial activity against most strains of *Acinetobacter* species, with only imipenem offering superior activity. Further studies are required to confirm the efficacy of cefoperazone–sulbactam against *Acinetobacter* in the clinical setting. Nonetheless, several clinical studies with sulbactam alone or in combination have provided evidence of eradication of clinical *Acinetobacter* isolates and good clinical response rates among patients with acinetobacter infections.

## ACKNOWLEDGMENTS

The writing of this article was supported by an unrestricted educational grant from Pfizer Pharmaceuticals Group, Pfizer Inc.

## REFERENCES

1. Villers D, Espaze E, Coste-Burel M *et al*. Nosocomial *Acinetobacter baumannii* infections: microbiological and clinical epidemiology. *Ann Intern Med* 1998; 129: 182–9.
2. Larson EL. Persistent carriage of Gram-negative bacteria on hands. *Am J Infect Control* 1981; 9: 112–19.
3. Bergogne-Berezin E. The increasing significance of outbreaks of *Acinetobacter* spp.: the need for control and new agents. *J Hosp Infect* 1995; 30 (suppl): 441–52.
4. Mcdonald LC, Banerjee SN, Jarvis WR. Seasonal variation of Acinetobacter infections: 1987–1996. Nosocomial Infections Surveillance System. *Clin Infect Dis* 1999; 29: 1133–7.
5. Afzal-Shah M, Livermore DM. Worldwide emergence of carbapenem-resistant *Acinetobacter* spp. *J Antimicrob Chemother* 1998; 41: 576–7.
6. Levin AS, Mendes CM, Sinto SI *et al*. An outbreak of multiresistant *Acinetobacter baumannii* in a university hospital in Sao Paulo. *Brazil Infect Control Hosp Epidemiol* 1996; 17: 366–8.

7. Sader HS, Jones RN, Gales AC *et al*. Antimicrobial susceptibility patterns for pathogens isolated from patients in Latin American medical centers with a diagnosis of pneumonia: analysis of results from the SENTRY Antimicrobial Surveillance Program (1997). SENTRY Latin America Study Group. *Diagn Microbiol Infect Dis* 1998; 32: 289–301.
8. Marcos MA, Abdalla S, Pedraza F *et al*. Epidemiological markers of *Acinetobacter baumannii* clinical isolates from a spinal cord injury unit. *J Hosp Infect* 1994; 28: 39–48.
9. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med* 1999; 27: 887–92.
10. Baraibar J, Correa H, Mariscal D, Gallego M, Valles J, Rello J. Risk factors for infection by *Acinetobacter baumannii* in intubated patients with nosocomial pneumonia. *Chest* 1997; 112: 1050–4.
11. Cristino JM. Correlation between consumption of antimicrobials in humans and development of resistance in bacteria. *Int J Antimicrob Agents* 1999; 12: 199–202.
12. Hanberger H, Garcia-Rodriguez JA, Gobernado M, Goossens H, Nilsson LE, Struelens MJ. Antibiotic susceptibility among aerobic Gram-negative bacilli in intensive care units in 5 European countries. *JAMA* 1999; 281: 67–71.
13. Bello H, Gonzalez G, Dominguez M, Zemelman R, Garcia A, Mella S. Activity of selected beta-lactams, ciprofloxacin, and amikacin against different *Acinetobacter baumannii* biotypes from Chilean hospitals. *Diagn Microbiol Infect Dis* 1997; 28: 183–6.
14. Aswapokee N, Tiengrim S, Charoensook B, Sangsiriwut K. Antimicrobial resistant pattern of *Acinetobacter* spp. *J Infect Dis Antimicrob Agents* 1998; 15: 43–8.
15. Costa SF, Woodcock J, Gill M *et al*. Outer-membrane protein pattern and detection of beta-lactamases in clinical isolates of imipenem-resistant *Acinetobacter baumannii* from Brazil. *Int J Antimicrob Agents* 2000; 13: 175–82.
16. Garcia-Garmendia JL, Ortiz-Leyba C, Garnacho-Montero J, Jimenez-Jimenez FJ, Monterrubio-Villar J, Gili-Miner M. Mortality and the increase in length of stay attributable to the acquisition of *Acinetobacter* in critically ill patients. *Crit Care Med* 1999; 27: 1794–9.
17. Girou E, Stephan F, Novara A, Safar M, Fagon JY. Risk factors and outcome of nosocomial infections: results of a matched case–control study of ICU patients. *Am J Respir Crit Care Med* 1998; 157: 1151–8.
18. Livermore DM. Are all $\beta$-lactams created equal? *Scand J Infect Dis Suppl* 1996; 101: 33–43.
19. Vila J, Marcos A, Marco F *et al*. In vitro antimicrobial production of beta-lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferase by and susceptibility of clinical isolates of *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 1993; 37: 138–41.
20. Gehrlein M, Leying H, Cullman W, Wendt S, Opferkuch W. Imipenem resistance in *Acinetobacter baumanii* is due to altered penicillin-binding proteins. *Chemotherapy* 1991; 37: 405–12.
21. Sato K, Nakae T. Outer membrane permeability of *Acinetobacter calcoaceticus* and its implication in antibiotic resistance. *J Antimicrob Chemother* 1991; 28: 35–45.
22. Williams JD. Beta-lactamases and beta-lactamase inhibitors. *Int J Antimicrob Agents* 1999; 12: S3–7.
23. Williams JD. Beta-lactamase inhibition and in vitro activity of sulbactam and sulbactam/cefoperazone. *Clin Infect Dis* 1997; 24: 494–7.
24. Noguchi JK, Gill MA. Sulbactam: a beta-lactamase inhibitor. *Clin Pharm* 1988; 7: 37–51.
25. National Committee for Clinical Laboratory Standards. *Performance for antimicrobial susceptibility testing*. Tables M100-S10 (M7). Wayne, Pa: NCCLS, 2000.
26. Mendes CMF, Francisco W, Levy CE. Brazilian multicenter study to evaluate the activity of ampicillin/sulbactam and other antibiotics against 2,000 hospital and community strains. *Rev Bras Med* 1998; 55: 735–41.
27. Tascini C, Menichetti F, Bozza S, Del Favero A, Bistoni F. Evaluation of the activities of two-drug combinations of rifampicin, polymyxin B and ampicillin/sulbactam against *Acinetobacter baumannii*. *J Antimicrob Chemother* 1998; 42: 270–1.
28. Murray PR, Jones RN, Allen SD, Erwin ME, Fuchs PC, Gerlach EH. Multilaboratory evaluation of the in vitro activity of 13 beta-lactam antibiotics against 1474 clinical isolates of aerobic and anaerobic bacteria. *Diagn Microbiol Infect Dis* 1993; 16: 191–203.
29. Murray PR, Cantrell HF, Lankford RB. Multicenter evaluation of the in vitro activity of piperacillin–tazobactam compared with eleven selected beta-lactam antibiotics and ciprofloxacin against more than 42,000 aerobic gram-positive and gram-negative bacteria. *Diagn Microbiol Infect Dis* 1994; 19: 111–20.
30. Garcia-Arata MI, Alarcon T, Lopez-Brea M. Emergence of resistant isolates of *Acinetobacter calcoaceticus–A. baumannii* complex in a Spanish hospital over a five-year period. *Eur J Clin Microbiol Infect Dis* 1996; 15: 512–15.
31. Douboyas J, Tzouvelekis LS, Tsakris A. In-vitro activity of ampicillin/sulbactam against multiresistant *Acinetobacter calcoaceticus* var. *anitratus* clinical isolates. *J Antimicrob Chemother* 1994; 34: 298–300.
32. Urban C, Go E, Mariano N *et al*. Effect of sulbactam on infections caused by imipenem-resistant

*Acinetobacter calcoaceticus* biotype *anitratus*. *J Infect Dis* 1993; 167: 448–51.
33. Jimenez-Mejias ME, Pachon J, Becerril B, Palomino-Nicas J, Rodriguez-Cobacho A, Revuelta M. Treatment of multidrug-resistant *Acinetobacter baumannii* meningitis with ampicillin/sulbactam. *Clin Infect Dis* 1997; 24: 932–5.
34. Traub WH, Spohr M. Antimicrobial drug susceptibility of clinical isolates of *Acinetobacter* species (*A. baumannii*, *A. haemolyticus*, genospecies 3, and genospecies 6. *Antimicrob Agents Chemother* 1997; 33: 1617–19.
35. Visalli MA, Jacobs MR, Moore TD, Renzi FA, Appelbaum PC. Activities of beta-lactams against *Acinetobacter* genospecies as determined by agar dilution and E-test MIC methods. *Antimicrob Agents Chemother* 1997; 41: 767–70.
36. Lim VK, Cheong YM. In vitro activity of cefoperazone–sulbactam combination against cefoperazone resistant clinical isolates in a Malaysian general hospital. *Malays J Pathol* 1995; 17: 73–6.
37. Jones RN, Wilson HW, Thornsberry C, Barry AL. In vitro antimicrobial activity of cefoperazone–sulbactam combinations against 554 clinical isolates including a review and beta-lactamase studies. *Diagn Microbiol Infect Dis* 1985; 3: 489–99.
38. Eliopoulos GM, Klimm K, Ferraro MJ, Moellering RCJ. In vitro activity of cefoperazone–sulbactam combinations against cefoperazone-resistant clinical bacterial isolates. *Eur J Clin Microbiol Infect Dis* 1989; 8: 624–6.
39. Knapp CC, Sierra-Madero J, Washington JA. Comparative in vitro activity of cefoperazone and various combinations of cefoperazone/sulbactam. *Diagn Microbiol Infect Dis* 1989; 13: 45–9.
40. Lewis MT, Yamaguchi K, Biedenbach DJ *et al.* In vitro evaluation of cefepime and other broad-spectrum beta-lactams in 22 medical centers in Japan: a phase II trial comparing two annual organism samples. *Diagn Microbiol Infect Dis* 1999; 35: 307–15.
41. Yamaguchi K, Mathai D, Biedenbach DJ, Lewis MT, Gales AC, Jones RN. Evaluation of the in vitro activity of six broad-spectrum beta-lactam antimicrobial agents tested against over 2,000 clinical isolates from 22 medical centers in Japan. *Diagn Microbiol Infect Dis* 1999; 34: 123–34.
42. Jones RN, Salazar JC, Pfaller MA, Doern GV. Multicenter evaluation of antimicrobial resistance to six broad-spectrum beta-lactams in Colombia using the Etest method. *Diagn Microbiol Infect Dis* 1997; 29: 265–72.
43. Rodriguez-Hernandez MJ, Cuberos L, Pichardo C *et al.* Sulbactam efficacy in experimental models caused by susceptible and intermediate *Acinetobacter baumannii* strains. *J Antimicrob Chemother* 2001; 47: 479–82.
44. Levin AS, Manrique AEI, Medeiros EAS *et al.* Treatment of severe infection by multiresistant *Acinetobacter baumannii* (MRAB) with ampicillin/sulbactam—preliminary report [abstract LM-19]. In: *37th Interscience conference on antimicrobial agents and chemotherapy, Toronto, Canada*. Washington DC: American Society for Microbiology, 1997: 367.
45. Corbella X, Ariza J, Ardanuy C *et al.* Efficacy of sulbactam alone and in combination with ampicillin in nosocomial infections caused by multiresistant *Acinetobacter baumannii*. *J Antimicrob Chemother* 1998; 42: 793–802.
46. Cisneros JM, Reyes MJ, Pachon J *et al.* Bacteremia due to *Acinetobacter baumannii*: epidemiology, clinical findings, and prognostic features. *Clin Infect Dis* 1996; 22: 1026–32.
47. Foulds G. Pharmacokinetics of sulbactam/ampicillin in humans: a review. *Rev Infect Dis* 1986; 8(suppl 5): S503–11.
48. Telenti Asensio M, Moreno Torrico A, Ruiz Palomar J, Bernaldo de Quiros JF. The efficacy of sulbactam–ampicillin in a urinary infection due to *Acinetobacter calcoaceticus* var. *anitratus*. *Med Clin (Barc)* 1995; 105: 438–9.
49. Zervos MJ, Skupien D, Dmuchowski CF. Meta-analysis of the efficacy and safety of ampicillin/sulbactam in the treatment of patients with bacterial infections of the lower respiratory tract. *Infect Dis Clin Pract* 1997; 6: 473–81.
50. Greenberg RN, Cayavec P, Danko LS *et al.* Comparison of cefoperazone plus sulbactam with clindamycin plus gentamicin as treatment for intra-abdominal infections. *J Antimicrob Chemother* 1994; 34: 391–401.
51. Winston DJ, Bartoni K, Bruckner DA, Schiller GJ, Territo MC. Randomized comparison of sulbactam/cefoperazone with imipenem as empirical monotherapy for febrile granulocytopenic patients. *Clin Infect Dis* 1998; 26: 576–83.
52. Li JT, Lu Y, Hou J *et al.* Sulbactam/cefoperazone versus cefotaxime for the treatment of moderate-to-severe bacterial infections: results of a randomized, controlled clinical trial. *Clin Infect Dis* 1997; 24: 498–505.
53. Catchpole CR, Andrews JM, Brenwald N, Wise R. A reassessment of the in-vitro activity of colistin sulphomethate sodium. *J Antimicrob Chemother* 1997; 39: 255–60.
54. Levin AS, Barone A, Penco J *et al.* Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin Infect Dis* 1999; 28: 1008–11.
55. Wolinsky E, Hines JD. Neurotoxic and nephrotoxic effects of colistin in patients with renal disease. *N Engl J Med* 1962; 266: 759–62.

56. Friedel HA, Campoli-Richards DM, Goa KL. Sultamicillin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1989; 37: 491–522.
57. Marques MB, Brookings ES, Moser SA, Sonke PB, Waites KB. Comparative in vitro antimicrobial susceptibilities of nosocomial isolates of *Acinetobacter baumannii* and synergistic activities of nine antimicrobial combinations. *Antimicrob Agents Chemother* 1997; 41: 881–5.
58. Shi Z, Liu PY, Lau Y, Lin Y, Hu BS, Shir J-M. Antimicrobial susceptibility of clinical isolates of *Acinetobacter baumannii*. *Diagn Microbiol Infect Dis* 1996; 24: 81–5.
59. Cheng AF, Ling TK, Lam AW, Fung KS, Wise R. The antimicrobial activity and beta-lactamase stability of cefpirome, a new fourth-generation cephalosporin in comparison with other agents. *J Antimicrob Chemother* 1993; 31: 699–709.
60. Pfaller MA, Korten V, Jones RN, Doern GV. Multicenter evaluation of the antimicrobial activity for seven broad-spectrum beta-lactams in Turkey using the Etest method. *Diagn Microbiol Infect Dis* 1999; 35: 65–73.