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REVIEW

Ampicillin/Sulbactam in Combination: A Review of its Use in the Treatment of Severe Bacterial Infections

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Abstract: Ampicillin/Sulbactam is a combination of antibiotics made up of ampicillin, a betalactam and Sulbactam, a betalactamase inhibitor introduced in the eighties. The most frequent used combination is Ampicillin/Sulbactam (ratio 2:1) although the two agents are not synergetic. Ampicillin/Sulbactam has a wide range of antibacterial activity that includes Gram-positive and Gram-negative aerobic and anaerobic bacteria. However, the drug is not active against *Pseudomonas aeruginosa* and pathogens producing extended-spectrum β-lactamases. The combination could be considered particularly active against *Acinetobacter baumannii* infections due to the intrinsic activity of Sulbactam. In clinical trials, sultamicillin has proved clinically and bacteriologically effective against a severe bacterial infections, including mild upper and lower respiratory tract infections, meningitis, intra-abdominal, diabetic foot and skin and soft tissue infections, etc. Furthermore, adverse effects rarely occur with the diarrhoea to represent the most commonly reported. Moreover, it seems to represent the alternative of choice for the treatment of *A. baumannii* infections for carbapenem-resistant strains in the nosocomial setting. This review focuses on the efficacy of the β-lactam ampicillin co-administered with the β-lactamase inhibitor sulbactam, parenterally (Ampicillin/Sulbactam), for the treatment of bacterial infections.

Keywords: ampicillin/sulbactam, acinetobacter baumannii, respiratory tract infections, meningitis

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Introduction

Ampicillin/Sulbactam is a combination of the common penicillin-derived antibiotic ampicillin and sulbactam, an inhibitor of bacterial β-lactamase developed in the eighties.[1,2] Ampicillin/Sulbactam combination is the most frequently used although both agents are not synergetic. Studies have been conducted to examine its effectiveness in several types of infection.[3–6] From the past decade, conducted clinical findings confirm the results of numerous older studies and together provide good evidence to support the frequent use of Ampicillin/Sulbactam in hospital-and community-acquired infections in both, adults and children.

On the another hand, the multidrug-resistant microorganism appearance, especially multidrug-resistant *Acinetobacter spp*, makes the treatment of nosocomial infections more difficult being imperative a new agent search and old drugs use as optimal treatment of these multidrug-resistant organisms.

Ampicillin/Sulbactam may represent the alternative choice for the treatment of *A. baumannii* infections for carbapenem-resistant strains in the nosocomial setting. This paper focuses on the efficacy of the β-lactam ampicillin co-administered with the β-lactamase inhibitor sulbactam, parenterally (Ampicillin/Sulbactam), for severe bacterial infection with specially attention in multidrug resistant infections treatment.

Mechanism of Action and Antimicrobial Spectrum

Ampicillin inhibits bacterial cell wall synthesis by binding Penicillin Binding Proteins (PBPs) which are the enzymes responsible for the cell wall structure formation. It acts as a structural analogue of acyl-D-alanyl-D alanine and acylates the transpeptidase enzyme responsible for the final stage in the peptidoglycan formation, the main component of the cell wall.[7]

Sulbactam is a potent, highly specific inhibitor of β-lactamases (most plasma-mediated and some chromosomal β-lactamases) obtained by the oxidation of thiazolidine sulfur of penicillanic acid.[8] Sulbactam doesn't enhance bactericidal activity of Ampicillin but prevents it from being destroyed by β-lactamase producing bacteria as it inhibits hydrolysis of the latter by β-lactamases. As a result, the antimicrobial activity of ampicillin, when combined with sulbactam increases by 4–32 folds and its spectrum is extended to include β-lactamase-producing strains of many common pathogens[6] because it protects ampicillin from hydrolysis by β-lactamases.[9] Sulbactam joins with the β-lactamases forming an acyl enzyme for reaction with the active site serine hydroxyl group. This intermediate can undergo (a) deacylation and hydrolysis of the enamine liberated, which leads to the formation of smaller products; (b) a tautomerisation to enamine leading to a transiently inhibited form of the enzyme and; (c) a transamination reaction or reaction with serine 130 that leads to an irreversibly inhibited enzyme form.[3,10]

Sulbactam distinguishes from other available β-lactamase inhibitors due to the high level of antimicrobial activity against *Neisseria spp*, *Bacteroides fragilis* and *Acinetobacter species*, organisms against which most cephalosporins display little or no activity. In addition, the antimicrobial spectrum of Ampicillin/Sulbactam included gram positive coccus and rods aerobic gram negative and some anaerobes like *Peptococcus* and *Peptostreptococcus spp*, *Group B Streptococcus*, *E. faecalis*, *Streptococcus pneumoniae, Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus aureus*, *coagulase-negative Staphylococci, C. diphtheriae*, *Listeria monocytogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *E. coli* (over 50% of the strains may be resistant), *K. pneumoniae* (30% of strains may be resistant), *P. mirabilis*, *Salmonella spp* (*S. typhimurium* may be 30% to 40% resistant), *Shigella flexneri*, *Fusobacterium spp*, *Bacteroides spp*, and *Clostridium spp*. However for most of these target organisms, the minimum bactericidal concentration of Ampicillin/Sulbactam is only one dilution greater than its minimum inhibitory concentration (MIC).[6]

The susceptibility rates showed to *E. coli*, *Klebsiella pneumoniae*, *Citrobacter spp* and *Proteus spp* are less active that carbapenems, 3rd and 4th generation cephalosporins, aminoglycosides or piperacillin/tazobactam[3] and the resistance in gram negative bacilli as *E. coli* increased in the last time. In a study analysing about 3,004 gram-negative bacilli collected from intraabdominal infections in the Asia Pacific region during 2007 a decline in ampicillin sulbactam susceptibility was noted with only 34.5% of all *Enterobacteriaceae* inhibited.[11] In another study[12] on the antimicrobial resistance of *E. coli* bloodstream isolated from tertiary care centres, the Ampicillin/Sulbactam resistance rates

increased from 23% to 45%. Another gram negative bacillis like *Morganella spp*, *Enterobacter spp* and *Serratia spp*, have higher resistance rates against Ampicillin/Sulbactam.[13] It has no activity against *Pseudomonas aeruginosa* and extended-spectrum β-lactamases *Enterobacters*. The Ampicillin/Sulbactam resistance rates against imipenem-susceptible and -resistant *Acinetobacter baumannii* were 23.5 and 30%, respectively.[14]

Ampicillin/Sulbactam Pharmacokinetics and Pharmacodynamics

Intravenous or oral sulbactam has a similar pharmacokinetic profile than i.v. or oral ampicillin, which favours their combination into a single formulation.[3,5,15,16] The ampicillin and sulbactam pharmacokinetics are linear up to at least 1000 mg and the profile of i.v. ampicillin is unaffected co-administered with sulbactam. On the other hand, sulbactam profile remains unchanged after co-administration of ampicillin. Both drugs have a half life of 1 hour, and >75% is excreted unchanged in the urine in both cases.[3,5]

Ampicillin is partially (40%) absorbed after oral administration, and Sulbactam oral absorption is very poor. Ampicillin/Sulbactam is not well absorbed after oral administration. This problem was overcome with the combination of ampicillin and sulbactam in one oral prodrug, sultamicillin. This double ester is well absorbed in the intestine (80% bioavailability) and rapidly hydrolysed during absorption from the gastrointestinal tract to provide high levels (in equimolar quantities) of ampicillin and sulbactam and increases the bioavailability of ampicillin when administered as sultamicillin than when administered alone.[3,5,6] Comparative data suggest that there is a prolongation of Ampicillin/Sulbactam antimicrobial activity as age increases due to the area under the serum concentration-time curve half life, serum maximum concentration and decreased total clearance in older age groups.[17] The pharmacokinetic profiles of ampicillin and sulbactam in children are the same as those in adults. In children, age appeared to have no effect on the pharmacokinetics of Ampicillin or Sulbactam and the results were also independent of dose and gender.[6]

Although the elimination half-lives of both ampicillin and sulbactam take 1 h, sultamicillin has the advantage that it can be given twice or three times a day. This leads to high serum and tissue concentrations sustained above MICs of many common pathogens.[15,16]

The protein binding of ampicillin and sulbactam in serum is moderate (38% for sulbactam and 28% for ampicillin). Both ampicillin and sulbactam are arranged extensively to a variety of tissues and body fluids (e.g. intestinal mucosa, prostatic and appendiceal tissue, sputum, peritoneal fluid, peritonsillar abscess pus, and cerebrospinal fluid in the presence of inflamed meninges).[6,18] Data on sulbactam penetration into tissues/fluids include: intraperitoneal fluid (60%), sputum (12%–14%), cerebrospinal fluid (11%–34%), intenstinal mucosa (0.7%–0.8%) and myometrium (64%).[15,16]

Approximately 75 to 85% of both ampicillin and sulbactam are primarily eliminated by renal excretion and the half-life and serum concentrations in patients with impaired renal function are increased. Accordingly, the frequency of dosing is reduced routinely (from three or four times daily to twice or once daily) in patients with renal impairment.[3] It should be administered with caution to infants aged <1 week and to premature neonates as half-time is significantly increased for both because of the immature renal function in neonates and newborn.[19]

Clinical Trials and Efficacy

Classical indications of Ampicillin/Sulbactam are upper (e.g. sinusitis, otitis media, tonsillitis) and lower (e.g. bacterial pneumonias, bronchitis) respiratory tract infections (RTIs), urinary tract infections (UTIs) and pyelonephritis, skin and soft-tissue infections (SSTIs), gonococcal infections, intra-abdominal infections such as peritonitis, cholecystitis, endometritis and pelvic cellulitis, and bacterial septicaemia. It may also be used preoperatively for prophylaxis in abdominal or pelvic surgery. The usual dosage of i.v./intramuscular (i.m.) Ampicillin/Sulbactam is 1.5–12 gr. per day in adults and 150 mg/kg/day i.v./i.m. in children, infants and neonates, given in three or four doses per day in a 2:1 ampicillin: sulbactam ratio. The focus of this review is to make an overview of the clinical usefulness of Ampicillin/Sulbactam for the treatment of severe bacterial infections.

Lower respiratory tract infections and aspiration pneumonia

Bacterial respiratory tract infections continue to represent a major source of morbidity and mortality,

despite continuing improvements in diagnosis and the development of new kinds of antibiotic. Unfortunately, the emergence of β-lactamase-mediated bacterial resistance among many common pathogens has threatened the usefulness of β-lactam agents.[6,20,21]

In the case of IV Ampicillin/Sulbactam, many clinical trials have shown its effectiveness in the treatment in adults with serious non-specific lower respiratory tract infections (LRTIs) (Table 1).

Ampicillin/sulbactam (2–12 gr./day), followed by oral sultamicillin in some cases, has been compared with imipenem/cilastatin, second and third generation cephalosporins, ticarcillin/clavulanic, clindamycin (with or without cephalosporin), or moxifloxacin for the treatment of community- or hospital-acquired lower respiratory tract infections without significantly differences.[22–36] In the review made by Lode[6] in 2001 on the role of Ampicillin/Sulbactam in the treatment of bacterial respiratory tract infections in adult patients, based on 20 researches comparatives and two meta-analyses published in the 1980s and 1990s, the clinical success rates were in the range of 84%–100% and bacteriological eradication rates ranged from 44% to 100%. In recent studies (mainly comparative, prospective and randomised) the clinical efficacy (cure or improvement) rates are ranged from 62% to 100% and bacteriological efficacy rates from 58%–100%.[27–29] These response rates are generally compared with the clinical and bacteriological response rates for the comparators, cefuroxime (41%–95% and 50%–93%),[32,34,36] cefotaxime (81 and 48%),[33] cefoxitin (81 and 76%)[25] and mezlocillin (83 and 89%),[35] imipenem (83%),[30] clindamycin (67%)[27] or moxifloxacin (66.7%)[26] (Table 1). In an open-label, comparative study Ampicillin/Sulbactam and cefuroxime yielded similar clinical responses (98 and 95%, respectively) but the eradication rate for Ampicillin/Sulbactam was significantly superior (95 versus 50%, *P*-0.001).[22] However, only the metaanalysis carried out by Zervos et al on the efficacy and safety of Ampicillin/Sulbactam (2/1 or 1/0.5 g IV four times daily) versus second- or third-generation cephalosporins (cefoxitin, cefotaxime, cefuroxime, or cefamandole) showed that the observed rate of clinical cure or improvement was greater for Ampicillin/Sulbactam than for comparators (93.3 versus 86.6%, $P = 0.019$), being the rate of clinical cure 60.3 versus 54.6%, $P = 0.055$. The bacteriological eradication rate was similar for Ampicillin/Sulbactam (85.3%) and comparators (83.5%).

Regarding the efficacy of Ampicillin/Sulbactam compared to another β-lactam/β-lactamase inhibitor combination, a clinical trial of Ampicillin/Sulbactam versus ticarcillin/clavulanic acid recorded a satisfactory clinical response in 83 and 78% of patients with respiratory tract infections, respectively. The corresponding rates of bacteriological efficacy were 62 and 71%.[31] These data suggest that Ampicillin/Sulbactam is as effective as another β-lactam/β-lactamase inhibitor combination in the treatment of lower respiratory tract infection.

Aspiration pneumonia and primary lung abscess are diseases following aspiration of infectious material from the oropharynx or stomach. An antibiotic therapy, also covering anaerobic pathogens, is the chosen treatment. Ampicillin/Sulbactam has been compared to antimicrobials with antianaerobic activity such as clindamycin and imipenem/cilastatin. Cure rates with Ampicillin/Sulbactam in aspiration pneumonia were relatively low in comparison with the cure improvement rates of Ampicillin/Sulbactam in clinical trials of lower respiratory tract infections without aspiration (i.e. 66.7% in two studies.[26,27] In the prospective, open-label, randomized, multicenter trial of Ott et al[26] the efficacy of Ampicillin/Sulbactam vs. moxifloxacin in these entities were compared. 139 patients were studied, 96 of them were evaluable for efficacy, 48 patients in each treatment group. The overall clinical response rates in both groups were numerically similar (66.7%). Both treatments seem to be clinically effective and safe; however, moxifloxacin shows the additional benefit of a more convenient (400 mg qd) treatment.

With respect to the treatment doses, some authors have used higher doses of Ampicillin/Sulbactam in aspiration pneumonia. Kadowaki et al[28] administred Ampicillin/Sulbactam in two different dosages protocols: 3 gr. twice a day and 1.5 gr. twice a day and compared them with clindamycin and imipem cilastatin in 100 elderly patients with aspiration pneumonia. Cure rates in patients receiving Ampicillin/Sulbactam 3 gr. were higher (84%) than the rates in patients treated with half dose and comparable with those in the imipem group (88%) which seemed to be the most effective regimen.

The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS)

Table 1. Role of Ampicillin/Sulbactam in lower respiratory tract infections (LRTIs).

Reference	Design	Patients	Treatments		Cure rate (%)		
			Treatment/dosing	Comparator	Treatment	Comparator	*P*-value
Ozbay et al[22]	Prospective Randomized	98 infections	Ampicillin/Sulbactam 1 gr i.v/12 hours; n = 56	Cefuroxime 750 mg/12 h i.v; n = 42	27%	24%	NS
Yanahigara et al[23]	Prospective Randomized	67 CAP	Ampicillin/Sulbactam 3 gr i.v/twice day; n = 35	Imipenem 500 mg/12 h i.v; n = 32	91%	87.5%	NS
Castellano et al[25]	Prospective Randomized	75 Pneumonia	52 Ampicillin/Sulbactam 3 gr i.v/6 h; n = 52	Cefoxitin 2 gr/6 h i.v; n = 23	92%	87%	NS
Allewelt et al[27]	Prospective Randomized	70 Aspiration pneumonia	37 Ampicillin/Sulbactam 3 gr i.v every/8 hours	Clindamycin 600 mg/8 h i.v; n = 33	73%	66.7%	NS
Kadowaki et al[28]	Prospective Randomizes	100 Aspiration pneumonia	Ampicillin/Sulbactam 1.5 gr/12 hours i.v; n = 25 Ampicillin/Sulbactam 3 gr/12 h i.v; n = 25	Clindamycin 600 mg/12 h i.v Imipenem 500 mg/12 h i.v	1,5 gr 76% 3 gr 84%	76% 88%	NS
Betrosian et al[29]	Prospective Randomized	27 MDR *A. baumannii* VAP	Ampicillin/Sulbactam 27 gr i.v/day (in three doses) 36 gr i.v/day (in three dosis)		64.3%	69.2%	NS
Wood et al[30]	Retrospective	75 *A. baumannii* VAP	14 Ampicillin/Sulbactam Not reported	Imipenem. Dose not reported n = 63	93%	83%	NS
McKinnon et al[31]	Retrospective	200 LRTIs	Ampicillin/Sulbactam 82 patients 1.5 gr/6 hours i.v Ampicillin/Sulbactam 49 patients 3 gr/6 hours i.v	Ticarcillin/clavulanic acid 3.1 gr/6 h i.v; n = 69	83% 70%	78%	NS
Geckler et al[32]	Retrospective	32 Pneumonia 5 AECB	Ampicillin/Sulbactam 1.5–3 gr/6 hours i.v	Cefuroxime 750 mg^{-1} gq 8 h	100%	95%	NS
Jauregui et al[33]	Randomized	53 LRTIs	Ampicillin/Sulbactam 3 gr/6 hours i.v; n = 36	Cefotaxime 2 g/6 h i.v; n = 17	85.3%	81.3%	NS
Rossoff et al[34]	Randomized	Pneumonia 41 Bronchitis 6	Ampicillin/Sulbactam 3 gr i.v/6 hours i.v; n = 25	Cefuroxime 1.5 g/8 h i.v; n = 22	88%	81%	NS
Schwigon et al[36]	Randomized Prospective	Pneumonia 46 Acute purulent bronchitis 27	Ampicillin/Sulbactam 3 gr i.v/8 hours i.v; n = 36	Cefuroxime 1.5 g/8 h i.v; n = 37	89%	80%	NS
Schwigon et al[35]	Comparative	Pneumonia 65 AECB 31	Ampicillin/Sulbactam 3 gr/8 hours i.v	Mezlocillin 4 g/8 h i.v	84%	82.6%	NS
Ott et al[26]	Prospective Randomized	139 patients Aspiration pneumonia and primary lung abscess	Ampicillin/Sulbactam 2 gr/8 h i.v	Mxifloxacin 400 mg/24 i.v	66.7%	66.7%	NS
Okimoto N et al[24]		83 CAP	Ampicillin/Sulbactam dose not reported.		Mild 86% Moderate 67.5%		

Abbreviations: CAP, Community-acquired pneumonia; NS, not significative; MDR, multidrug-resistant; VAP, ventilator-associated pneumonia; AECB, acute exacerbation of chronic bronchitis.

guidelines said that Ampicillin/Sulbactam can be used in patients with community-acquired pneumonia who are not at risk for pseudomonas infections, in combination with a macrolide or fluorquinolone. IDSA/ATS guidelines (2005) for hospital-acquired pneumonia suggest that Ampicillin/Sulbactam may be administered to patients without risk factors for multidrug resistance pathogens and in early hospital-acquired pneumonia.[38,39]

Intra-abdominal infections

The first treatment of intra-abdominal infections is the combination of surgical debridement and antimicrobial treatment against polymicrobial flora. Antibiotics used for empiric treatment of community-acquired intra-abdominal infection should be active against gram-negative aerobic enteric facultative bacilli and gram-positive enteric *Streptococci*.[40]

Ampicillin/Sulbactam has been compared in patients with intra-abdominal infections versus clindamycin plus gentamicin, cefoxitin, and ampicillin plus clindamycin (Table 2). The differences between the cure rates achieved with each treatment were comparable except in the study conducted by Yellin et al that showed significantly lower results for Ampicillin/Sulbactam vs. clindamycin plus gentamicin.[41–43] Another study[44] assessed the efficacy and cost of Ampicillin/Sulbactam versus cefoxitin or clindamycin plus gentamicin in patients with various bacterial infections. The study conduced by Messick CR et al[44] compared Ampicillin/Sulbactam (96 patients) and cefoxitin (101) in the treatment of intraabdominal infections and find approximately 9% of greater frequency of failure with cefoxitin relative to Ampicillin/Sulbactam.

A review[3,6,45] of randomised controlled trials of various antibiotics in IAIs and/or peritonitis included two studies of Ampicillin/Sulbactam published in the 1980s/1990s.[41,42] The clinical success rate (87%) was similar to the most widely studied antibiotics: gentamicin/clindamycin 80%; tobramycin/clindamycin 83%; meropenem 89%; imipenem 85%; aztreonam/clindamycin 89%; cefoxitin 88%; cefotetan 92%; moxalactam 83%; cefotaxime/metronidazole 87%; and piperacillin/tazobactam 90%.

A Cochrane systematic review[46] of antibiotics for the treatment of secondary peritonitis of gastrointestinal origin showed that there were no differences between treatments in comparison with gentamicin/clindamycin[47] and cefoxitin;[42] however whilst Ampicillin/Sulbactam and gentamicin/clindamycin were equally effective for anaerobe infections, gentamicin/clindamycin was more effective for *Pseudomonas* infections.[41] The Cochrane review[46] concluded that no specific recommendation could be made in favour of one antibiotic for the first-line treatment of secondary peritonitis.

However, the current Infectious Diseases Society of America (IDSA) guidelines[41] did not recommend the use of Ampicillin/Sulbactam in intra-abdominal infections because of high rates of resistance to this agent among community- acquired *E. coli* (B-II).[48]

Gynaecological/obstetrical infections

Pelvic inflammatory disease includes endometritis, salpingitis, tuboovarian abscess and pelvic peritonitis.

Table 2. Principal studies about Ampicillin/Sulbactam in intra-abdominal infections.

Reference	Infections	Treatments		Cure rate (%)		
		Treatment/dosing	Comparator	Cure	Comparator	*P*-value
Yellin et al[41]	105 Perforated or gangrenous apendicitis	Ampicillin/Sulbactam 3 gr i.v/6 hours	Clindamycin (600 mg/6 h i.v) +gentamicin (1.5 m/Kg/8 h)	88%	100%	0.03
Walker et al[42]	197 Severe intra-abdominal infections	Ampicillin/Sulbactam 3 gr i.v/6 h	Cefoxitin 2 gr/8 h i.v	86%	78%	ND
Collins et al[43]	114 Intra-abdominal infections	Ampicillin/Sulbactam 150–300 mg/Kg/day/6 h ±gentamicin or tobramycin (6–7.5 mg/Kg/d)	Ampicillin (200 mg/Kg/day every 6–8 h) + clindamycin (20–40 mg/Kg/d every 6–8 h) ±gentamicin or tobramycin (6–7.5 mg/Kg/d)	97.3%	97.4%	ND

Pathogens commonly responsible for pelvic inflammatory disease are sexually transmitted, such as *N. gonorrhoeae* and *C. trachomatis* or belong to the vaginal flora i.e. anaerobes, *Gardnerella vaginalis*, *H. influenzae*, or gram-negative bacteria.[3,5]

Ampicillin/Sulbactam has been compared with cefoxitin in various studies[49–53] with clinical efficacy rates between 85%–90% in the group of Ampicillin/Sulbactam without significantly differences with the group of cefoxitin (clinical cure rates 85%–95%). In another study clindamycin alone or with gentamicin, cefotetan or cefoxitin and metronidazole with or without gentamicin were compared[54–59] (Table 3). Cure and/or improvement rates ranged from 82% to 100%. Clinical efficacy with Ampicillin/Sulbactam was higher than or equal to cefoxitin, but was inferior to clindamycin plus gentamicin in all relevant studies. Cefotetan and metronidazol plus gentamicin were found to have the same clinical efficacy as ampoicillin/sulbactam in two studies.[55,56] However, the differences between therapeutic treatments in cure/improvement rates were not statistically significant.

Ampicillin/Sulbactam is an effective therapy for the treatment of post-operative infections, pelvic inflammatory disease and post-Caesarean and postpartum endometritis, with equivalent clinical efficacy to other agents, including metronidazole/gentamicin, cefoxitin, cefoxitin/doxycycline, gentamicin/clindamycin and clindamycin.

Diabetic foot infections

Serious lower-limb infections treatment in diabetics can be difficult. Factors such as the presence of polymicrobial infection, underlying or contigous

Table 3. Principal studies about Ampicillin/Sulbactam in gynaecological and obstetric infections.

Reference	Infections	Treatments		Cure rate (%)		
	Design	Treatment/doping	Comparator	Cure	Comparator	*P*-value
Gunning et al[54]	60 PID	Ampicillin/Sulbactam 3 gr i.v/6 h	Clindamycin (600 mg/6 h) +gentamicin (1.5 m/Kg/8 h)	85.7%	94.4%	ND
Crombleholme et al[59]	41 Severe PID, tuboovarian absceso, endomyometritis	Ampicillin/Sulbactam 3 gr i.v/6 h	Metronidazole (7.5 mg/Kg/6 h) +gentamicin (1.5 m/Kg/8 h)	95%	86%	ND
Hamsell et al[49]	22 Complicated/ Uncomplicated PID	Ampicillin/Sulbactam 3 gr i.v/6 h	Cefoxitin 2 gr/6 h	100%	100%	ND
Scalambrino et al[55]	95 Gynaecological/ Obstetrical infections	Ampicillin/Sulbactam 3 gr i.v/6 h	Cefotetan 2 gr/12 h	89%	89%	ND
Martens et al[56]	65 Postcaesarean endometritis	Ampicillin/Sulbactam 3 gr i.v/6 h	Metronidazole (500 mg/6 h) +gentamicin 80 mg/8 h	91%	91%	ND
Martens et al[57]	68 Postpartum endomyometritis	Ampicillin/Sulbactam 3 gr i.v/6 h	Clindamycin (900 mg/8 h)	83%	88%	ND
Hemsell et al[50]	54 Acute salpingitis	Ampicillin/Sulbactam 3 gr i.v/6 h	Cefoxitin 2 gr/6 h	94%	89%	ND
McGregor et al[51]	103 PID	Ampicillin/Sulbactam 3 gr i.v/6 h	Cefoxitin 2 gr/6 h	85.5%	89.6%	ND
Gall et al[58]	107 Postpartum endometritis	Ampicillin/Sulbactam 3 gr i.v/6 h	Clindamycin (900 mg/8 h) +gentamicin (1.5 m/Kg/8 h)	82%	84%	NS
Stiglmayer et al[52]	76 Endometritis, salpingitis, tubo-ovarian absceso	Ampicillin/Sulbactam 3 gr i.v/8 h	Cefoxitin 2 gr/8 h	97.5%	89.5%	ND
Jemsek et al[53]	93 PID	Ampicillin/Sulbactam 3 gr i.v/6 h	Cefoxitin 2 gr/6 h	97%	92%	0.67

Abbreviation: PID, pelvic inflamatory disease.

osteomyelitis, hyperglycemia and diabetic sequelae commonly influence their medical and surgical management.[60]

Akova et al[61] studied seventy-four patients with diabetic foot infections treated with parenteral Ampicillin/Sulbactam (1.5 g, q.i.d.). The result were clinical cure rates of 86% and 100% in patients with osteomyelitis and with soft tissue infection, respectively which indicates that Ampicillin/Sulbactam is safe and effective in the treatment of diabetic foot infections.

A randomized double-blind study compared imipenem 0.5 gr./6 hours and Ampicillin/Sulbactam (3 gr./6 hours) in limb-threatening infections in diabetic patients showed comparable outcomes. Cure rates were 81% for the Ampicillin/Sulbactam group versus 85% for the imipenem group, failure rates were 17% for Ampicillin/Sulbactam versus 13% for imipenem and bacterial eradication was 67% and 75% for Ampicillin/Sulbactam and imipenem respectively.[3,60]

Ampicillin/Sulbactam has been compared with piperacillin/tazobactam, clyndamicin, cefoxitin and linezolid. In the case of piperacillin/tazobactam the clinical efficacy was comparable (83.1% for Ampicillin/Sulbactam vs. 81% for piperacillin/tazobactam). A higher bacteriological success rate was achieved by piperacillin/tazobactam as the most common gram-negative bacterium in this study was *P. aeruginosa*.[62] Cindamycin compared to cefoxitin showed similar results.[63,64]

Ampicillin/Sulbactam has been compared with linezolid in a randomised, open-label trial, without significantly statistically differences. Higher cure rates were achieved in the linezolid treatment arm than in the Ampicillin/Sulbactam treatment arm in patients with infected ulcers (81% vs. 68% $P = 0.018$) and in patients without osteomyelitis (87% vs. 72%, $P = 0.003$).[65]

Skin and soft tissue infections

Ampicillin/Sulbactam has been compared with cefoxitin,[66] cefazolin[67] or clindamycin. Parenteral Ampicillin/Sulbactam was effective in treating various skin and soft tissue infections (Table 4).

Ampicillin/Sulbactam and cefoxitin were compared in a randomised, double-blind trial in patients with or without history of injection drug abuse who presented skin or another soft tissue infections. These two agents were equally effective for the empirical treatment of skin or another soft tissue infections in both patients. Cure occurred in 89.8% of Ampicillin/Sulbactam treated patients compared with 93.6% of cefoxitin treated patients.[66]

A randomized double blind study in 58 hospitalized patients compared intravenous Ampicillin/Sulbactam (1 gr/6 hours) with cefazolin 500 mg/6 hours in the treatment of cellulitis and with cefoxitin (1 gr/6 hours). In other skin infections, no statistically significant differences in efficacy or safety were detected. In patients with cellulitis, Ampicillin/Sulbactam and cefazolin produced a clinical cure or improvement in 100% and 91.7% of patients respectively.[67] In other infections the result for Ampicillin/Sulbactam and cefoxitin were 80 and 64.7% respectively.

Table 4. Principal studies about Ampicillin/Sulbactam in skin and soft-tissue infections.

Reference	Design	Patients	Treatments	Comparator	Cure rate (%)		
			Treatment/doping		Cure	Comparator	*P*-value
Talan et al[66]	Prospective Randomized	96 soft tissue infections	49 Ampicillin/Sulbactam 3 gr i.v/6 h	Cefoxitin 2 gr/6 h	89.8	93.6	NS
Harkless et al[62]	Prospective Randomized	289 diabetic foot infection	150 Ampicillin/Sulbactam 3 gr i.v/6 h	Piperacillin/ Tazobactam	83%	81%	NS
Stridde et al[63]	Prospective Randomized	36 diabetic foot infection	17 Ampicillin/Sulbactam 3 gr i.v/8 h	Clindamycin	82%	83%	NS
Erstad et al[64]	Prospective Randomized	36 diabetic foot infection	18 Ampicillin/Sulbactam 3 gr i.v/6 h		83%		
Lipsky et al[65]	Prospective Randomized	88 diabetic foot infection	41 Ampicillin/Sulbactam 1.5–3 gr/iv every 6 h	Linezolid 600 mg/12 h	83%		
Grayson et al[60]	Randomized Double mind	Diabetic foot Infection	Ampicillin/Sulbactam 3 gr i.v/6 h	Imipenem 500 mg i.v/6 h	81%	85%	NS

Abbreviation: NS, not significative.

In the case of clindamycin, sixty patients with soft tissue infections received Ampicillin/Sulbactam (2 gr/6 h, n = 30) or clindamycin (600 mg/6 h) plus tobramycin (1.5 mg/Kg/8 h, n = 30). A 93% cure or improvement rate was shown with Ampicillin/Sulbactam compared with 81% in the clindamycin group.[68]

Infections due to *A. baumannii*

Ampicillin/Sulbactam may be an effective and safely used therapeutic option to treat severe nosocomial infections caused by multidrug-resistant (MDR) *A. baumannii* given Sulbactam *in-vitro* activity against the organism including some carbapenems-resistant strains.[69] Its mechanism of antimicrobial activity against *A. baumannii* strains is related to its intrinsic affinity for essential penicillin-binding proteins (PBPs) of these organisms and to alter the permeability of the outer membrane of gram-negative bacilli resulting in the leakage of β-lactamases and thus better penetration by other antibacterial agents.[3]

Ampicillin/Sulbactam has been used in meningitis, bacteraemia, ventilator-associated pneumonia with different results (Table 5). Levin et al[4] studied 40 patients with nosocomial infections caused by MDR *A. baumannii* treated with intravenous Ampicillin/Sulbactam. The average daily dose of Ampicillin/Sulbactam was 6 gr and 3 gr respectively and six patients received 12 g and 6 g respectively. The infections were primary bacteraemia (32.5%), pneumonia (30%), urinary tract infection (15%), peritonitis (7.5%) surgical site (7.5%), meningitis (5%) and sinusitis (2.5%). In this case, 67.5% of patients were improved/cured and 17.5% experienced treatment failure. The patients with meningitis did not respond to the treatment.

The intravenous Sulbactam penetrates about 1% through the blood brain barrier, which will increase to 32% in the meningeal inflammation.[2,18] Ampicillin/Sulbactam combination has been used to treat MDR *A. baumannii* meningitis by some authors in doses of 2 gr/6–8 hours with a mortality of 20%–25%.[4,18,70,71] In our experience of 4 cases treated with 3 gr/8 hour, mortality was 33% without lower evidence than in other treatments except intrathecal colistin intravenously.[18] Within the eight cases published by Jimenez Mejias et al[70] doses of 1 gr/6–8 hours were used producing the death of patients receiving treatment every 8 hours. Nowadays the dose of 2 gr/6 hours is considered to be more suitable for the treatment of meningitis.[71]

The efficacy and safety of Ampicillin/Sulbactam for MDR *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) has been assessed in several researches with clinical improvement of 67%.[72–74] and

Table 5. Main clinical studies on *A. baumannii infections*.

Reference	Design	Patients	Treatment	Cure rate (%)
Levin et al[4]	Prospective nonrandomized	2 CNS infections Bloodstream 13 Pneumonia 5 Urinary tract 6 Surgical site 3 Peritonitis 3 Sinusitis 1	Ampicillin/Sulbactam 6 gr/day in 3 doses Six patients 12 gr/day in 3 doses.	67.5% cure None meningitis
Jimenez-Mejias et a[70]	Retrospective	8 postsurgical meningitis	Ampicillin/Sulbactam 2 gr i.v/6–8 hours	75% cure
Cawley et al[71]	Case report	Meningitis	Ampicillin/Sulbactam 2 gr i.v every 3 hours	Cure
Rodriguez-Guardado et al[18]	Retrospective	51 postsurgical meningitis	Ampicillin/Sulbactam 3 gr/8 hours (7 cases)	57%
Jellison et al[76]	Retrospecive observacional	48 bacteremias	Group 1: Ampicillin Sulbactam 1–2 gr/6 h, n = 30 Group 2:Imipenem 0.5–1/6–8 h, n = 18	Group 1, 97% Group 2, 100%
Smolyajov et al[78]	Retrospective analysis	94 bacteremias	Ampicillin/Sulbactam	65% AMS reduced mortality *P* = 0.02, R = 7.64

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high-dose Ampicillin/Sulbactam were comparably safe and effective treatments respect to colistin for critically ill patients with MDR *A. baumannii* VAP.[74] The safety and efficacy of Ampicillin/Sulbactam was compared with colistin in the treatment of MDR *A. baumannii* ventilator-associated pneumonia (VAP).[75] The patients received doses of Ampicillin/Sulbactam 9 gr/8 hours (n = 13) or colistin 3 MIU/8 hours intravenously (n = 15). Resolution of symptoms and signs occurred in 60% of the colistin group and 61.5% of the Ampicillin/Sulbactam group without any significant difference. Additionally, no significant differences in the mortality rates and in the side effects were shown.

In the Oliveira et al[73] research, 82 patients were treated with polymyxins and 85 with Ampicillin/Sulbactam. Multiple logistic regression analysis revealed that independent predictors of mortality during treatment were the treatment with polymyxins. In this research, Ampicillin/Sulbactam appears to be more effective than polymyxins, which was an independent factor associated with mortality during treatment.

Data evaluating the safety of high dose or non-traditional dosage of Ampicillin/Sulbactam are limited.[71,74,75] Betrosian et al[74] conducted a randomised non-comparative, prospective trial to assess the efficiency of two high-dose treatments of Ampicillin/Sulbactam in patients with ventilator associated pneumonia due to MDR *A. baumannii.* Group A of patients received Ampicillin/Sulbactam 18/9 gr/day and group B received 24/12 gr/day. Clinical improvement and bacteriological success rates were 64.3% and 84.7% in group A and B respectively and 69.2 and 69.2 in group B respectively without side effects reported.

Ampicillin/Sulbactam has been assessed in the bacteraemia due to *A. baumannii.* It was compared with imipenem in various studies without any significant difference.[76–78]

Side Effects

The adverse event profile of Ampicillin/Sulbactam is similar to the favourable profile of Ampicillin alone.[79] The most frequent adverse reaction is site pain after intramuscular injection. Another adverse reactions reported are: diarrhoea (3%), phlebitis (1.2%), and rash (<2%). Laboratory changes most commonly reported are high hepatic enzymes (serum aspartate aminotransferase, 6.2%; serum alanine aminotransferase,6.9%).[80] Haematologic abnormalities (decreased haematocrit/haemoglobin, leukopenia, lymphopenia, thrombocytopenia or increases lymphocytes, monocytes, basophils, eosinophils and platelets) decreases albumin and total proteins, increased creatinine, and the presence of red blood cells and hyaline casts in the urine are less frequent.[3,5]

Clostridium difficile-associated disease is a significant nosocomial infection and is common in hospitalised patients receiving broad-spectrum antibiotics.[81] It has been reported after almost all antibiotic agents, including Ampicillin/Sulbactam, and clinicians should be aware of the possibility of *C. difficile* in patients presenting diarrhoea after antibiotic use.

Place of Ampicillin/Sulbactam in the Treatment of Severe Infections

Ampicillin/Sulbactam is comparable to second and third-generation cephalosporins in the treatment of lower respiratory infections. However, it is not effective against *Ps. aeruginosa* or intracellular bacteria that are common pathogens and must be accompanied by a macrolide or quinolone. Ampicillin/sulbactan can be used in ICU patients with community-acquired pneumonia who are not at risk for *Pseudomonas* infection, in combination with a macrolide or a fluorquinolone according to IDSA/ATS guidelines (2007).[38,39]

The recent guidelines about intra-abdominal do not recommend the use of Ampicillin/Sulbactam as empiric treatment due the emergence of resistant strains of *E. coli*.[40]

Ampicillin/Sulbactam has been shown not to be inferior to imipenem as well as piperacillin/tazobactam in the treatment of diabetic foot infections.[60–62] In a comparative research of Ampicillin/Sulbactam vs. linezolid there was not statistically difference between both treatments although linezolid achieved higher cure rates in patients with infected ulcers and in patients without osteomyelitis.[65] However there are important limitations in the management of diabetic foot infection when the disease is due to *Pseudomonas aeruginosa* or Methicillin-resistant *Staphylococcus aureus*.

Ampicillin/Sulbactam may be an effective and safely used therapeutic option to treat severe nosocomial infections caused by multidrug-resistant (MDR)

bacteria, lthough probably it needs higher doses than normally used.

Conclusions

Ampicillin/Sulbactam has a wide range of antibacterial activity that includes Gram-positive and Gram-negative aerobic and anaerobic bacteria. However, the drug is not active against Pseudomonas aeruginosa and pathogens producing extended-spectrum β-lactamases. The combination could be considered particularly active against *Acinetobacter baumannii* infections due to the intrinsic activity of Sulbactam. In clinical trials, sultamicillin has proved to be clinically and bacteriologically effective in adults with severe bacterial infections, bacterial infection of the lower respiratory tract, meningitis, urinary tract infections, intra-abdominal infections, diabetic foot and skin and soft tissue infections. Furthermore, side effects rarely occur being the diarrhoea the most commonly reported. Moreover, it seems to represent the alternative choice for the treatment of *A. baumannii* infections for carbapenem-resistant strains in the nosocomial setting.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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