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Ampicillin/Sulbactam

Current Status in Severe Bacterial Infections

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Abstract

Ampicillin/sulbactam is a β-lactam/β-lactamase inhibitor combination with a broad spectrum of antibacterial activity against Gram-positive, Gram-negative and anaerobic bacteria. Data from comparative studies justify the use of ampicillin/sulbactam in a 2 **:** 1 ratio in various severe bacterial infections. In comparative clinical trials, ampicillin/sulbactam has proved to be a significant drug in the therapeutic armamentarium for lower respiratory tract infections and aspiration pneumonia, gynaecological/obstetrical infections, intra-abdominal infections, paediatric infections such as acute epiglottitis and periorbital cellulitis, diabetic foot infections, and skin and soft tissue infections. Of particular interest during this era of increasing antimicrobial resistance in various settings and populations is the effectiveness of sulbactam against a considerable proportion of infections due to *Acinetobacter baumannii*.

Ampicillin/sulbactam is a β-lactam/β-lactamase inhibitor combination that was first developed and marketed in the US in 1987. Since then, several clinical studies have been conducted to examine its effectiveness in various types of infections. Moreover, in the era of emerging resistance, there has been an effort to evaluate ampicillin/sulbactam as a drug against multidrug-resistant (MDR) *Acinetobacter* spp. This review updates information concerning the use of ampicillin/sulbactam in severe infections.

A literature search was performed in order to retrieve comparative studies concerning the clinical effectiveness of ampicillin/sulbactam. Studies were identified in the Scopus and PubMed databases. Key words used were 'ampicillin/sulbactam AND severe infection' as well as combinations of ampicillin/sulbactam with specific infections or pathogens (lower respiratory tract, pneumonia, gynaecological infections, obstetrical infections, pelvic inflammatory disease, endometritis, salpingitis, intra-abdominal infections, appendicitis, sepsis, diabetic foot infections, skin or soft tissue infections, *Acinetobacter*). Key terms used to retrieve studies concerning ampicillin/sulbactam spectrum were 'ampicillin/sulbactam AND Gram-negative OR anaerobes' or specific pathogens (pneumococcus, *Staphylococcus, Haemophilus influenzae,* Enterobacteriaceae, *Escherichia coli, Bacteroides fragilis*).

1. Overview of Antibacterial Activity

β-Lactamase production is of critical importance for the emergence of resistant bacterial mutants. Combinations of β-lactams with β-lactamase inhibitors, such as ampicillin/sulbactam, extend the spectrum of β-lactams by preventing the hydrolysis by β-lactamases. Additionally, the fact that β-lactam/β-lactamase inhibitor combinations are less potent β-lactamase inducers than cephalosporins make them a useful weapon in controlling resistance.[1] The cumulating data about the intrinsic antimicrobial activity of sulbactam against *Acinetobacter* species and the synergistic effect it may exhibit in combination with other antimicrobial agents (see section 1.1), make ampicillin/sulbactam an alternative therapeutic option for this nosocomial pathogen.

1.1 Mechanism of Action

Ampicillin inhibits bacterial cell wall synthesis by binding to penicillin binding proteins (PBPs), which are the enzymes responsible for the formation of the cell wall structure. Ampicillin, like all penicillins, acts as a structural analogue of acyl-D-alanyl-D alanine and acylates the transpeptidase enzyme responsible for the final stage of the formation of the peptidoglycan, which is the main component of the cell wall.[2] Sulbactam, a β-lactamase inhibitor obtained by oxidation of the thiazolidine sulfur of penicillanic acid, lacks significant antibacterial activity (except for *Neisseria* and *Acinetobacter* spp.)[3-7] but increases the activity of ampicillin as it protects it from hydrolysis by β-lactamases.[8] The exact mechanism is complicated, but there is general agreement that sulbactam is initially recognised by the β-lactamases as the normal substrate and forms an acyl enzyme by reacting with the active site serine hydroxyl group. This intermediate can then undergo (i) a deacylation and hydrolysis of the enamine liberated, which leads to the formation of smaller products; (ii) a tautomerisation to enamine leading to a transiently inhibited form of the enzyme; and (iii) a transamination reaction or reaction with serine 130 that leads to an irreversibly inhibited enzyme form.[9]

1.2 Spectrum

Table I presents an overview of the antibacterial activity of ampicillin/sulbactam.

Streptococcus pneumoniae, H. influenzae and *Moraxella catarrhalis* are pathogens that exhibit high susceptibility rates to ampicillin/sulbactam according to data obtained from a multicentre study in Germany[16] (331 *S. pneumoniae* isolates, 300 *H. influenzae* isolates and 308 *M. catarrhalis* isolates), and from a study in Argentina[10] (30 *S. pneumoniae* isolates).

Among Enterobacteriaceae, the genera *Morganella, Enterobacter* and *Serratia* have the highest resistance rates to ampicillin/sulbactam. For other

Table I. Susceptibilities of Gram-positive and Gram-negative pathogens, and anaerobes to ampicillin/sulbactam

Pathogen	No. of isolates in the reviewed studies	Susceptibility (%)	Comment
Streptococcus pneumoniae	331[10]	100	Ampicillin/sulbactam has satisfactory activity against Gram-positive pathogens. However, data from large multicentre studies are missing
Haemophilus influenzae	300[10]	100	
Moraxella catarrhalis	30[11]	100	
Escherichia coli	108,[10] 1403,[11] 52,[12] 86 569[13]	21–60	The lowest susceptibility rates were observed in Latin America and Asia/Pacific, and the highest in the US[11]
E. coli (ESBL)	37,[10] 102[11]	5–12	Susceptibility of ESBL strains is lower than non-ESBL strains
Klebsiella pneumoniae	44,[10] 526,[11] 49,[12] 36 456[13]	73–86	The lowest susceptibility rates were observed in Latin America and Asia/Pacific, and the highest in Europe[11]
K. pneumoniae (ESBL)	56,[10] 67,[11] 50[12]	4–7	Susceptibility of ESBL strains is notably lower than non-ESBL strains
Citrobacter spp.	129,[11] 6015[13]	46–54	
Proteus spp.	144,[11] 16 462[13]	81–92	
Morganella spp.	66,[11] 3767[13]	8–31	
Enterobacter spp.	230,[11] 15 587[13]	18–25	
Serratia spp.	39,[11] 51,[12] 9514[13]	2–10	
Acinetobacter baumannii	1248[a]	32–97	The lowest susceptibility rates were observed in Argentina and the highest in Hong Kong
Bacteroides fragilis group	158,[14] 2673[15]	85–98	Non-*Bacteroides fragilis* spp. have higher resistance rates than *B. fragilis*

a Data from relevant studies are presented in detail in table II.

ESBL = extended-spectrum β-lactamase.

members of the Enterobacteriaceae family (*E. coli, Klebsiella pneumoniae, Citrobacter* spp. and *Proteus* spp.), susceptibility rates are higher despite the fact that ampicillin/sulbactam is less active when compared with carbapenems, third or fourth generation cephalosporins, aminoglycosides and piperacillin/tazobactam.[11] It should be noted that ampicillin/sulbactam is not active against *Pseudomonas aeruginosa*[11] and Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBLs).[10-12] The relevant data presented in table I were obtained from a multicentre study conducted in 17 countries (Study for Monitoring Antimicrobial Resistance Trends [SMART]),[11] and from three studies conducted in Argentina, Taiwan and the US.[10,12,13]

Acinetobacter baumannii exhibits variable sensitivity rates to ampicillin/sulbactam according to the sensitivity rates presented in table II. Relevant data were retrieved from the SENTRY Antimicrobial Surveillance Program on three continents[17] and from studies conducted in Esthonia,[18] Germany,[19] Spain,[20] Hong Kong,[20] China,[21] the US,[22] Taiwan,[12] Argentina[10] and Turkey.[23] It should be noted that existing methods to determine *A. baumannii* susceptibilities (disc diffusion and broth microdilution) might not be reliable in predicting susceptibility to sulbactam, which is the active drug against this pathogen. Additionally, there might be discrepancies in minimum inhibitory concentrations (MICs) depending on whether a fixed ratio of ampicillin/sulbactam or a fixed concentration of sulbactam was used.[24]

B. fragilis isolates exhibit high susceptibility rates to ampicillin/sulbactam. The relevant data presented in table I were collected from two multicentre studies conducted in the US.[14,15]

Table II. Susceptibilities of *Acinetobacter baumannii* isolates to ampicillin/sulbactam

Parameter	Estonia 2006 (Loivukene et al.[18])	Germany 2005 (Brauers et al.[19])	Spain 2004–5 (Garcia-Penuela et al.[20])	Hong Kong 2004–5 (Garcia-Penuela et al.[20])	North America, South America, Europe 2004 (Fedler et al.[17])	China 2004 (Huang et al.[21])	USA 2004 (Swenson et al.[22])	Taiwan 2003 (Wang et al.[12])	Argentina 2001–2 (Casellas et al.[10])	Turkey 1994–2000 (Tatman-Otkun et al.[23])
No. of isolates	50	395	74	30	64	132	195	68[a]	60	150
Susceptible (%)	60	92	54	96.6	75	76.5	63.6	76.5	32	73
								30[b]	70	

a Imipenem-sensitive *A. baumannii*.

b Imipenem-resistant *A. baumannii*.

1.3 Resistance

The principal mechanism of resistance against ampicillin involves inactivation by β-lactamases, which are the hydrolytic enzymes responsible for the formation of an acidic derivative of β-lactams deprived of antibacterial activity. Resistance to β-lactams can also arise from a reduced number of porin channels, which are the proteins that regulate the permeability of the outer membrane of Gram-negative bacteria for antibacterials and the interaction with their environment.[2,25] Mutations to genes that encode PBPs is another mechanism of resistance, as alterations in the structure of PBPs may significantly reduce their affinity with β-lactams. There may be more than one resistance mechanism present in a bacterium, i.e. methicillin-resistant *Staphylococcus aureus* (MRSA) exhibits resistance by *mecA* gene expression, which encodes for the altered PBP2, and by increased production of β-lactamases.[26]

The first mechanisms of resistance to the β-lactam/β-lactamase inhibitors described were hyperproduction of wild-type TEM-1 and TEM-2 penicillinases, and alteration of the permeability of the outer membrane due to mutations in the genes encoding porin channels.[27] β-Lactamase hyperproduction is caused by point mutation at position 162 in the promoter region of the bla_{TEM} gene, which encodes β-lactamases.[28] In the 1990s, the first inhibitor-resistant TEM (IRT) β-lactamases were described.[29] These mutated β-lactamases arise from amino acid substitutions, which are different from those responsible for ESBL production, in the genes encoding TEM-1 and TEM-2 β-lactamases, and up to 29 December 2006 there had been 25 IRTs identified.[30] They are found mainly in *E. coli*, *K. pneumoniae* and *K. oxytoca*, *Proteus mirabilis* and *Citrobacter freundii*.[31]

In the era of evolving resistance, the effectiveness of ampicillin/sulbactam against ESBL-producing species would be a matter of great interest. However, existing data suggest that ampicillin/sulbactam should not be used in ESBL-producing bacteria as even when *in vitro* susceptibility is demonstrated, clinical failures may be noticed.[32,33]

Inoculum effect and loss of porin channels are some of the factors contributing to *in vivo* failures. The mainstay of antibacterial treatment for infections due to ESBL-producing strains are the carbapenems.[34]

2. Pharmacodynamics

Sulbactam exhibits a synergistic effect with ampicillin as it inhibits hydrolysis of the latter by β-lactamases.[35] As a result, the antimicrobial activity of ampicillin when combined with sulbactam increases by 4- to 32-fold.[2] Sulbactam is more active against class A β-lactamases (mainly plasma mediated, highly active against penicillins) than class C β-lactamases (mainly chromosomally encoded, highly active against cephalosporins). However, in comparison with clavulanic acid and tazobactam, sulbactam is a less potent inhibitor of class A β-lactamases and a more potent inhibitor than clavulanic for class C β-lactamases. Inhibitory potency of sulbactam against class D enzymes is weaker than against class A β-lactamases.[2] Although sulbactam has the ability to induce β-lactamases, it is a less potent inducer than clavulanic acid and a more potent inducer than tazobactam.[36]

Ampicillin/sulbactam may exhibit the inoculum effect only at high concentrations of bacteria.[37] There are a number of *in vitro* studies that investigate the combination of ampicillin/sulbactam with other antimicrobial agents and their effect on MDR Gram-positive cocci. An *in vitro* synergistic effect of ampicillin/sulbactam has been noticed against MRSA with daptomycin[38] and fosfomycin[39,40] against some strains of vancomycin intermediate *S. aureus* with trovafloxacin,[41] and against *A. baumannii* with tobramycin,[23,42] amikacin,[42] cefepime,[43] meropenem and imipenem.[44,45]

3. Pharmacokinetic Properties

Ampicillin/sulbactam is not well absorbed after oral administration. Sultamicillin, the double ester prodrug of ampicillin/sulbactam, has increased absorption after oral administration that reaches 80%. The pharmacokinetic properties of ampicillin/sulbactam after intravenous administration in adults are presented in table III.[46] Comparative pharmacokinetic data for ampicillin/sulbactam in young and elderly individuals suggest that there is prolongation of ampicillin/sulbactam antimicrobial activity as age increases that is due to the area under the serum concentration-time curve, half-life ($t_{1/2}$), serum maximum concentration and decreased total clearance in older age groups.[46] Given that ampicillin/sulbactam is primarily eliminated by renal excretion, the $t_{1/2}$ and serum concentrations in patients with impaired renal function are increased.[47] Pharmacokinetic properties of ampicillin/sulbactam in children and adults do not differ significantly.[48] However, ampicillin/sulbactam should be administered with caution to infants aged <1 week and to premature neonates as $t_{1/2}$ is significantly increased for both ampicillin and sulbactam because of the underdevelopment of the urinary system in neonates.[48,49] The $t_{1/2}$ of ampicillin/sulbactam is decreased in women during labour, which suggests the appropriateness of a more frequent administration schedule.[49] The protein binding of ampicillin and sulbactam in serum is moderate (38% for sulbactam and 28% for ampicillin). Data on sulbactam penetration into tissues/fluids include: intraperitoneal fluid (60%), sputum (12–14%), cerebrospinal fluid (CSF) [11–34%], intestinal mucosa (0.7–0.8%) and myometrium (64%).[2]

Table III. Pharmacokinetics of ampicillin/sulbactam administered intravenously in healthy middle-aged volunteers.[46]

Parameter	Ampicillin (2g)	Sulbactam (1g)
C_{max} (μg/mL)	82 ± 15	42 ± 7
Vd_{ss} (L/kg)	31 ± 9	30 ± 10
$t_{1/2}$	1 ± 0.2	1 ± 0.2
AUC_{∞} (μg • h/mL)	120 ± 16	72 ± 9
Clearance (mL/min)	281 ± 34	236 ± 27
Renal clearance (mL/min)	144 ± 64	136 ± 58

AUC_{∞} = area under the serum concentration-time curve from zero to infinity; **C_{max}** = serum maximum concentration; **$t_{1/2}$** = elimination half-life; **Vd_{ss}** = volume of distribution at steady state.

4. Adverse Effects

Ampicillin/sulbactam is generally well tolerated. The most prominent adverse reaction is site pain after intramuscular injection and this can be avoided

by diluting the preparation with lidocaine before administration. Other adverse reactions reported are: diarrhoea (1.9%), phlebitis (1.2%) and rash (<2%). Laboratory changes most commonly reported involve elevated hepatic enzymes (AST, ALT, alkaline phosphatase, lactate dehydrogenase). Haematological abnormalities (decreased haematocrit/haemoglobin, leukopenia, lymphopenia, thrombocytopenia or increased lymphocytes, monocytes, basophils, eosinophils and platelets), decreased albumin and total proteins, increased creatinine, and the presence of red blood cells and hyaline casts in the urine are less frequent.[47,50]

5. Therapeutic Effectiveness

5.1 Lower Respiratory Tract Infections (LRTIs) and Aspiration Pneumonia

Pneumonia is the seventh leading cause of death in the US. Causative agents are *S. pneumoniae*, *H. influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila (Chlamydia) pneumoniae*, *S. aureus*, *S. pyogenes*, *M. catarrhalis*, *K. pneumoniae*, *Legionella* spp., and the influenza virus.[51] According to the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) guidelines (2007), ampicillin/sulbactam can be used in intensive care unit (ICU) patients with community-acquired pneumonia who are not at risk for *Pseudomonas* infection, in combination with a macrolide or fluoroquinolone.[51] IDSA/ATS guidelines (2005) for hospital-acquired pneumonia (HAP) suggest that ampicillin/sulbactam may be administered to patients without risk factors for multidrug resistance pathogens and in early-onset HAP.[52]

5.1.1 LRTIs

The eight identified comparable studies[53-60] concern pneumonia, acute exacerbation of chronic bronchitis and bronchitis (table IV). The majority of the studies compare the effectiveness of ampicillin/sulbactam with second- and third-generation cephalosporins (cefuroxime,[53,55,56] cefotaxime,[54] and cefoxitin[58]), except for three studies that used mezlocillin,[57] ticarcillin/clavulanic acid[59] and imipenem/cilastatin[60] as comparators. In all the identified studies, the cure rates achieved with ampicillin/sulbactam were higher than the comparators (though not significantly higher) and ranged from 83% to 100%. An exception to this was noticed in one study,[59] where patients who received ampicillin/sulbactam 3g had lower cure rates than those treated with ticarcillin/clavulanic acid. The authors of this study do not further discuss this finding as it was not statistically significant. Bacteriological eradication rates with ampicillin/sulbactam range from 58% to 100% and are higher than those achieved by the comparators in half of the studies providing relevant data.[53,56,57,60] However, the differences between regimens were not statistically significant.

The efficacy and cost of ampicillin/sulbactam versus ticarcillin/clavulanic acid was compared retrospectively in patients with lower respiratory tract infections (LRTIs) by McKinnon and Neuhauser.[59] Although differences in clinical and bacteriological efficacy between ampicillin/sulbactam and ticarcillin/clavulanic acid were not statistically significant, the length of stay was significantly smaller in patients who received half-dose ampicillin/sulbactam. Additionally, ticarcillin/clavulanic acid was a less expensive treatment option than ampicillin/sulbactam (3g) and more expensive than ampicillin/sulbactam (1.5g). Differences between groups were statistically significant. A meta-analysis[63] of the efficacy and safety of ampicillin/sulbactam versus a set of cephalosporins (cefoxitin, cefotaxime, cefuroxime and cefamandole) showed that rates of clinical cure were higher with ampicillin/sulbactam by 9.56% ($p = 0.055$), whereas rates of clinical cure or improvement were significantly higher with ampicillin/sulbactam ($p = 0.019$). Adverse effects were comparable in both groups.

5.1.2 Aspiration Pneumonia

In the management of aspiration pneumonia, ampicillin/sulbactam has been compared with 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/

Table IV. Summary of the studies examining efficacy of ampicillin/sulbactam in patients with lower respiratory tract infections (LRTIs)

Study (year)	No. of evaluable patients	Infection	Antibacterial (dosage)		Cure and/or improvement			Bacteriological eradication		
			ampicillin/ sulbactam	comparator	ampicillin/ sulbactam (%)	comparator (%)	p-value	ampicillin/ sulbactam (%)	comparator (%)	p-value
Geckler[53] (1994)	37	Pneumonia: 32 AECB: 5	1.5–3g qid	Cefuroxime (750mg–1g q8h)	100	95	0.57	100	94	0.49
Jauregui et al.[54] (1995)	48	LRTI	3g q6h	Cefotaxime (2g q6h)	85.3	81.3	0.82	Total: 55.9 Partial: 20.6	Total: 62.5 Partial: 12.5	0.65
Rossoff et al.[55] (1995)	47	Pneumonia: 41 Bronchitis: 6	3g q6h	Cefuroxime (1.5g q8h)	88	81	0.47	64	68	0.24
Schwigon et al. [56] (1996)	73	Pneumonia: 46 Acute purulent bronchitis: 27	3g tid	Cefuroxime (1.5g tid)	89	80	ND	84	82	ND
Schwigon et al.[57] (1996)	96	Pneumonia: 65 AECB: 31	3g q8h	Mezlocillin (4g q8h)	84	82.6	ND	90.2	88.9	ND
Castellano and Maniatis[58] (1998)	75	Pneumonia AECB	3g q6h	Cefoxitin (2g q6h)	92	87	ND	67	78	ND
McKinnon and Neuhauser[59] (1999)	200	LRTI	G1: 1.5g q6h G2: 3g q6h	G3: ticarcillin/ clavulanic acid (3.1g q6h)	G1: 83 G2: 70	78	0.39	G1: 62 G2: 58	G3: 71	0.42
Allewelt et al.[61] (2004)	70	Aspiration pneumonia	3g tid	Clindamycin (600mg tid)	73	66.7	ND	ND	ND	
Kadowaki et al.[62] (2005)	100 (distributed equally into 4 groups)	Aspiration pneumonia	G1: 1.5g bid G2: 3g bid	G3: clindamycin (600mg bid) G4: imipenem/ cilastatin (0.5g bid)	G1: 76 G2: 84	G3: 76 G4: 88	0.62	ND	ND	
Yanagihara et al.[60] (2006)	67	Community-acquired pneumonia	3g bid	Imipenem/cilastatin (0.5g bid)	91.4	87.5	NS	84	80	ND

AECB = acute exacerbation of chronic bronchitis; **bid** = twice daily; **G** = group; **ND** = no data; **NS** = not significant; **q*x*h** = every *x* hours; **qid** = four times daily; **tid** = three times daily.

improvement rates of ampicillin/sulbactam in clinical trials of LRTIs without aspiration (i.e. 73% and 76%, respectively) in two identified studies (table IV).[61,62] Kadowaki et al.[62] examined the cost effectiveness of ampicillin/sulbactam, clindamycin and imipenem/cilastatin in 100 elderly patients with mild to moderate aspiration pneumonia. Ampicillin/sulbactam was administered in two different dosage protocols: 3g twice daily and 1.5g twice daily. Cure rates in the patients who received ampicillin/sulbactam 3g were higher (84%) than the respective rates in patients treated with the half dose and comparable with those in the imipenem/cilastatin group (88%), which seemed to be the most effective regimen. However, it is noticeable that this study was interrupted early because of the appearance of MRSA in all patient groups except those who received clindamycin. The highest rate of MRSA was noticed in the carbapenem group. Clindamycin was also found to be significantly less expensive than the other three regimens.

5.2 Gynaecological/Obstetrical Infections

Pelvic inflammatory disease (PID) is a broad term that includes endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis. Pathogens commonly responsible for PID are sexually transmitted, such as *N. gonorrhoeae* and *Chlamydia trachomatis*, or they belong to the vaginal flora, i.e. anaerobes, *Gardnerella vaginalis*, *H. influenzae*, Gram-negative bacteria and *S. agalactiae*.[64] First-line treatment options consist of cefotetan or cefoxitin plus doxycycline or clindamycin with gentamicin plus doxycycline (Centers for Disease Control and Prevention 2006).[64] A dosage of ampicillin/sulbactam 3g every 6 hours is recommended as an alternative treatment for PID, with clinical efficacy comparable with the first-line regimens according to existing data.

Eight of 12 identified studies[59,65-71] examine the effectiveness of ampicillin/sulbactam in PID/gynaecological infections in general or focus on tubo-ovarian abscess, endomyometritis, pelvic cellulitis, salpingitis or pelvic peritonitis. The remaining four studies[72-75] examine gynaecological/obstetrical infections, i.e. post-caesarean and post-partum endometritis (table V). In five studies,[67-71] ampicillin/sulbactam is compared with cefoxitin. In four studies,[65,69,74,75] the comparator is clindamycin alone or with gentamicin. In two studies,[66,73] ampicillin/sulbactam is compared with metronidazole ± gentamicin. One study[72] uses cefotetan as a comparator and one study[59] examines ampicillin/sulbactam versus ticarcillin/clavulanic acid. Cure and/or improvement rates ranged from 82% to 100%. Clinical efficacy with ampicillin/sulbactam was higher than[66,68,70] or equal to[67] cefoxitin except in one study,[69] but was inferior than clindamycin plus gentamicin in all relevant studies. Cefotetan and metronidazole plus gentamicin were found to have equal clinical efficacy with ampicillin/sulbactam in two studies.[72,73] However, it should be noted that differences between therapeutic regimens in cure/improvement rates were not statistically significant except in one study conducted by Bruhat et al.,[76] which, in contrast with the studies included in table V, examined the effectiveness of comparative regimens laparoscopically. In this study,[76] ampicillin/sulbactam was compared with cefoxitin in 40 patients with acute salpingitis and achieved 95% cure rates established laparoscopically versus 70% in the cefoxitin arm. Bacteriological eradication was higher in the ampicillin/sulbactam arm in all the studies[59,65,67,70,71,75] providing relevant data (data not available in 6 of 12 studies). In most of the studies, differences in bacteriological efficacy are not significant.[59,65,67,71,75] However, Stiglmayer et al.,[70] who compared ampicillin/sulbactam with cefoxitin in 76 patients with PID, found that despite the fact that cure rates in both regimens were comparable (cure 87%, improvement 10.5% in the ampicillin/sulbactam group vs cure 79%, improvement 10.5% in the cefoxitin group), eradication rates reached 91% in the ampicillin/sulbactam arm versus only 59% in the cefoxitin arm. Thus, the ampicillin/sulbactam regimen was significantly superior to cefoxitin in terms of bacteriological eradication, although not in terms of clinical efficacy.

Table V. Summary of studies examining the efficacy of ampicillin/sulbactam versus comparator in gynaecological and obstetrical infections

Study (year)	No. of evaluable patients	Infection	Antibacterial (dosage)		Cure and/or improvement			Bacteriological eradication		
			ampicillin/ sulbactam	comparator	ampicillin/ sulbactam (%)	comparator (%)	p-value	ampicillin/ sulbactam (%)	comparator (%)	p-value
Gunning[65] (1986)	60	PID	3g q6h	Clindamycin (600mg q6h) + gentamicin (1.5 mg/kg q8h)	85.7	94.4	ND	100	97.1	ND
Crombleholme et al.[66] (1987)	41	Severe PID, tubo-ovarian abscess, endomyometritis, pelvic cellulitis	3g q6h	Metronidazole (15 mg/kg loading, 7.5 mg/kg q6h maintenance) + gentamicin (1.5 mg/kg q8h)	95	86	ND	ND	ND	
Hemsell et al.[67] (1988)	22	Complicated/ uncomplicated PID	3g q6h	Cefoxitin (2g q6h)	100	100	ND	98	94	ND
Scalambrino et al.[72] (1989)	95	gynaecological/ obstetrical infections	3g q6h	Cefotetan (2g q12h)	89	89	ND	ND	ND	
Martens et al.[73] (1989)	67	Postcaesarean endometritis	3g q6h	Metronidazole (500mg q6h) + gentamicin (100–120mg loading, 80mg q8h maintenance)	91	91	ND	ND	ND	
Martens et al.[74] (1990)	68	Postpartum endomyometritis	3g q6h	Clindamycin (900mh q8h)	83	88	ND	ND	ND	
Hemsell et al.[68] (1990)	54	Acute salpingitis	3g q6h	Cefoxitin (2g q6h)	94	89	ND	ND	ND	
McGregor et al.[69] (1994)	304	Endometritis	3g q6h	Clindamycin (900mg q8h) + gentamicin (1.5mg/ kg q8h)	88.7	90.8	0.7	ND	ND	
McGregor et al.[69] (1994)	103	PID	3g q6h	Cefoxitin (2g q6h)	85.5	89.6	0.76	ND	ND	

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Table V. Contd

Study (year)	No. of evaluable patients	Infection	Antibacterial (dosage)		Cure and/or improvement			Bacteriological eradication		
			ampicillin/ sulbactam	comparator	ampicillin/ sulbactam (%)	comparator (%)	p-value	ampicillin/ sulbactam (%)	comparator (%)	p-value
Gall and Koukol[75] (1996)	107	Postpartum endometritis	3g q6h	Clindamycin (900mg q8h) + gentamicin (1.5 mg/kg q8h)	82	84	NS	86	84	NS
Stiglmayer et al.[70] (1996)	76	Endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis	3g q8h	Cefoxitin (2g q8h)	97.5	89.5	ND	91	59	0.03
Jemsek and Harrison,[71] (1997)	93	PID	3g q6h	Cefoxitin (2g q6h)	97	92	0.67	70	56	0.64
McKinnon and Neuhauser[59] (1999)	67	gynaecological infections	G1: 1.5g q6h G2: 3g q6h	G3: ticarcillin/ clavulanic acid (4.1g q6h)	G1: 96 G2: 91	G3: 100	0.68	G1: 80 G 2: 52	G3: 29	ND

G = group; **ND** = no data; **NS** = no significance; **PID** = pelvic inflammatory disease; **qxh** = every *x* hours.

A retrospective pharmacoeconomic study[77] was conducted to assess the cost effectiveness of ampicillin/sulbactam versus cefoxitin in PID. Seventy-six women were treated with ampicillin/sulbactam (3g every 6 hours) and 41 women were treated with cefoxitin (2g every 6 hours). Ampicillin/sulbactam was more effective ($p = 0.05$) and less costly ($p < 0.001$) than cefoxitin. In a prospective trial,[78] 76 patients with postpartum endometritis were treated with ampicillin/sulbactam (1.5g every 6 hours) or clindamycin (900mg intravenously every 8 hours) plus gentamicin (1 mg/kg every 8 hours after a loading dose of 1.5 mg/kg). Failure rates, days of therapy and cost of treatment for ampicillin/sulbactam were 17.6%, 3.3 ± 1.3 and $US139.49, respectively, compared with 9.5%, 3.6 ± 1.8 and $US355.32, respectively, for clindamycin/gentamicin. The authors suggest that ampicillin/sulbactam has comparable cost effectiveness to clindamycin plus gentamicin in early postpartum endometritis. McKinnon and Neuhauser[59] examined ampicillin/sulbactam (1.5g in 24 patients in group 1; 3g in 38 patients in group 2) versus ticarcillin/clavulanic acid (5 patients in group 3) in patients with gynaecological infections. Although clinical and bacteriological efficacy rates were not significantly different among groups, costs for preparation and delivery were significantly lower in the ampicillin/sulbactam group than in the ticarcillin/clavulanic acid group.

5.3 Intra-Abdominal Infections

The mainstay of treatment of intra-abdominal infections is surgical debridement in combination with antimicrobial cover against the anticipated polymicrobial flora. Common aetiological agents of intra-abdominal infections are facultative and aerobic Gram-negative organisms and anaerobes.[79] The IDSA guidelines regarding complicated intra-abdominal infections recommend that ampicillin/sulbactam should be used in mild to moderate community-acquired infections; patients with more severe infections might benefit from regimens with a broader spectrum against facultative and Gram-negative aerobic bacteria. Health care associated with complicated intra-abdominal infections necessitates

the use of multidrug combinations (such as a carbapenem in combination with vancomycin).[79]

In four identified studies[59,80-82] examining patients with intra-abdominal infections (table VI), ampicillin/sulbactam is tested versus clindamycin plus gentamicin, cefoxitin, ampicillin plus clindamycin and ticarcillin/clavulanic acid. The differences between the cure rates achieved with each regimen were comparable except for the ones reported in the study conducted by Yellin et al.[80] (significantly lower for ampicillin/sulbactam vs clindamycin plus gentamicin). Bacteriological eradication rates were comparable in all studies providing relevant data except for one,[59] where the eradication rates achieved with ticarcillin/clavulanic acid were significantly inferior to those achieved by ampicillin/sulbactam.

Many efforts have been made to assess the cost effectiveness of ampicillin/sulbactam versus other treatment regimens for intra-abdominal infections. Chin et al.[83] compared ampicillin/sulbactam (ampicillin 2g/sulbactam 1g four times daily) with clindamycin (900mg three times daily) plus gentamicin (1.5 mg/kg three times daily) administered to patients with perforated appendicitis in a retrospective pharmacoeconomic study. Costs incurring from intravenous supplies, nursing administration, pharmacist and technician preparation, laboratory fees, and pharmacokinetic monitoring were considered. No statistically significant difference in total costs was noticed. McKinnon and Neuhauser[59] examined ampicillin/sulbactam (1.5g every 6 hours in 112 patients in group 1; 3g every 6 hours in 107 patients in group 2) versus ticarcillin/clavulanic acid (38 patients in group 3; 3.1g every 6 hours) in patients with intra-abdominal infections. Although clinical effectiveness was comparable in all groups, bacteriological efficacy rates were significantly higher in patients treated with ampicillin/sulbactam. The low-dose ampicillin/sulbactam regimen was significantly less costly than the full-dose ampicillin/sulbactam and ticarcillin/clavulanic acid regimens. A retrospective analysis[84] was conducted to analyse the length of stay in 2150 patients with intra-abdominal infections who had received one of five first-line antimicrobials (ampicillin/sulbactam, ceftriaxone, ertapenem, levofloxacin or piperacillin/tazobactam). Ampicillin/sulbactam and ertapenem were associated with shorter hospital days, but this finding could be attributed to the fact that surgeons may prefer the previously mentioned regimens for less severe infections. In a retrospective pharmacoeconomic study[85] ampicillin/sulbactam was compared with cefoxitin in the treatment of intra-abdominal infections. Ninety-six patients had received ampicillin/sulbactam and 101 patients had received cefoxitin. Cefoxitin had a 9% higher frequency of failure than ampicillin/sulbactam and when all outcomes of interest were considered (i.e. cure/failure rates, development of new infection, adverse effects), ampicillin/sulbactam was less costly than cefoxitin.

5.4 Diabetic Foot Infections

Diabetic foot infections are a significant cause of morbidity and mortality.[86] A randomised, double-blind study comparing imipenem/cilastatin (0.5g every 6 hours) and ampicillin/sulbactam (3g every 6 hours) in limb-threatening infections in diabetic patients showed comparable outcomes. After 5 days of empirical treatment, improvement was achieved in 94% of the 48 ampicillin/sulbactam-treated infections and in 98% of the 48 imipenem/cilastatin-treated infections. Cure rates were 81% for the ampicillin/sulbactam group versus 85% for the imipenem/cilastatin group, failure rates were 17% for ampicillin/sulbactam versus 13% for imipenem/cilastatin, and bacterial eradication was 67% and 75% for ampicillin/sulbactam and imipenem/cilastatin, respectively. The episodes of treatment failures were associated with resistant pathogens acquisition of nosocomial pathogens.[87] Parenteral treatment with ampicillin/sulbactam (2/1g) has been evaluated against piperacillin/tazobactam (4/0.5g) in a randomised, open-label study comparing efficacy and safety for infected moderate to severe diabetic foot ulcers in 314 patients. Patients with polymicrobial infections including MRSA received additional vancomycin intravenously. Clinical efficacy was comparable (83.1% for ampicillin/sulbactam vs 81% for piperacillin/tazobactam). A higher bacterio-

Table VI. Summary of the studies examining the efficacy of ampicillin/sulbactam versus comparator in intra-abdominal infections

Study (year)	No. of evaluable patients	Infection	Antibacterial (dosage)		Cure and/or improvement			Bacteriological eradication		
			ampicillin/ sulbactam	comparator	ampicillin/ sulbactam (%)	comparator (%)	p-value	ampicillin/ sulbactam (%)	comparator (%)	p-value
Yellin et al.[80] (1985)	105	Perforated or gangrenous appendicitis	3g q6h	Clindamycin (600mg q6h) + gentamicin (1.5 mg/kg q8h)	88	100	0.03	ND	ND	
Walker et al.[81] (1993)	197	Severe intra-abdominal infection	3g q6h	Cefoxitin (2g every q8h)	86	78	ND	85	83	ND
Collins et al.[82] (1998)	114	Intra-abdominal infections (primarily perforated appendicitis)	150–300 mg/kg/d q6h ± gentamicin or tobramycin (6–7.5 mg/kg/d)	Ampicillin (200 mg/kg/d q6h or q8h) + clindamycin (20–40 mg/kg/d q6h or q8h) ± gentamicin or tobramycin (6–7.5 mg/kg/d)	97.3	97.4	ND	89	92	ND
McKinnon and Neuhauser[59] (1999)	257	Appendicitis, cholecystitis, peritonitis, intra-abdominal abscess	G1: ampicillin (1g)/ sulbactam (0.5g) q6h G2: ampicillin (2g)/ sulbactam (1g) q6h	G3: ticarcillin (3g)/ clavulanic acid (0.1g) q6h	G1: 89 G2: 87	G3: 73	ND	G1: 68 G2: 71	G3: 29	0.0011

G = group; **ND =** no data; **qxh** = every *x* hours.

logical success rate was achieved by piperacillin/tazobactam as the most common Gram-negative bacterium in this study was *P. aeruginosa*.[88]

In a pharmacoeconomic study regarding limb-threatening infections in 90 diabetic patients, treatment with ampicillin/sulbactam was $US2924 less than treatment with imipenem/cilastatin.[89] In a non-comparative study, 74 patients with severe diabetic foot infections were treated with parenteral ampicillin/sulbactam (1.5g four times daily). The mean duration (± standard deviation) of treatment in patients with osteomyelitis (n = 49) and soft tissue infections (n = 25) was 41 ± 5 and 14 ± 3 days, respectively. Infected limbs were amputated at various levels in 14 patients (19%). Clinical cure rates were 86% and 100% in patients with osteomyelitis and soft tissue infection, respectively.[90]

In a comparison of ampicillin/sulbactam versus linezolid in a randomised, open-label trial, the comparators were statistically equivalent overall for inpatients and outpatients. Higher cure rates were achieved in the linezolid treatment arm (plus aztreonam in 5% of the 241 patients) than in the ampicillin/sulbactam treatment arm (plus vancomycin in 9.6% of the 120 patients or aztreonam in 3 [2.5%] of the patients) in patients with infected ulcers (81% vs 68%; p = 0.018) and in patients without osteomyelitis (87% vs 72%; p = 0.003).[91]

5.5 Skin and Soft Tissue Infections

In a randomised, double-blind trial, the clinical and bacteriological efficacy of ampicillin/sulbactam (2/1g) and cefoxitin (2g) administered intravenously every 6 hours was compared in patients with or without a history of injection drug abuse who presented with cutaneous or other soft tissue infections. These two agents were equally effective for the empirical treatment of cutaneous or other soft tissue infections in injection drug abusers and patients who did not inject drugs. Cure or improvement occurred in 89.8% of ampicillin/sulbactam-treated patients compared with 93.6% of cefoxitin-treated patients. The median time to resolution of all symptoms was 10.5 days with ampicillin/sulbactam and 15.5 days with cefoxitin. Mixed aerobic-anaerobic infection was encountered frequently in both treatment groups. Patients with a history of injection drug abuse were significantly more likely to have streptococci isolated than those without a history of drug abuse (37% vs 19%, respectively). Bacterial eradication was achieved in 100% of patients receiving ampicillin/sulbactam, whereas the eradication rate with cefoxitin was 97.9%.[92]

A randomised, double-blind study in 58 hospitalised patients compared intravenous administration of ampicillin/sulbactam (1g/0.5g every 6 hours) with cefazolin 0.5g (every 6 hours) in the treatment of cellulitis and with cefoxitin 1g (every 6 hours) in other skin and skin-structure infections; no statistically significant differences in efficacy or safety were detected. More specifically, in patients with cellulitis, ampicillin/sulbactam and cefazolin produced a clinical cure or improvement in 100% and 91.7% of patients, respectively, and duration of hospitalisation was 7.7 and 7.2 days, respectively. In other skin and skin-structure infections, results for ampicillin/sulbactam and cefoxitin, respectively, were clinical cure or improvement 80% and 64.7%; treatment failures 0% and 11.8%; bacterial eradication 40% and 53%; and duration of hospitalisation 7.7 and 9.4 days.[93]

Similar results were shown in a study of 76 hospitalised patients with complicated skin and soft tissue infections in a randomised, prospective, third-party blinded, comparative study of the effectiveness and safety of intravenous or intramuscular administration of ampicillin/sulbactam (1.0–2.0g/0.5–1.0g every 6 hours) and cefoxitin (1.0–2.0g every 6 hours). Twenty-five of the 36 patients who received ampicillin/sulbactam and 33 of 39 patients who received cefoxitin were evaluable. Neither clinical and bacteriological effectiveness nor duration of hospitalisation differed significantly between the two treatment groups. Twenty-one (84%) patients receiving ampicillin/sulbactam were cured, two (8%) improved and treatment failed in two (8%). Twenty-eight (85%) patients receiving cefoxitin were cured, four (12%) improved and treatment failed in one (3%). All primary pathogens were eradicated in six (24%) and partial eradication oc-

curred in nine (36%) ampicillin/sulbactam recipients, while eradication occurred in 15 (47%) and partial eradication in eight (25%) cefoxitin recipients.[94]

In a randomised, open-label, comparative study, 23 patients with bone, joint or soft tissue infections were treated with ampicillin/sulbactam (2/1g) three times daily or cefotaxime (2g) three times daily as an initial 2-week therapy. Monomicrobial infections due to *S. aureus* were the most common bone or joint infections. Clinical cure or improvement 2 weeks after the end of therapy was observed in all 13 patients treated with ampicillin/sulbactam and in 7 of the 8 patients evaluated for efficacy after treatment with cefotaxime. Treatment failed to eradicate *S. aureus* in one patient from each group. In addition, *S. aureus* infection recurred in two patients in the cefotaxime group within 2 weeks after the end of therapy.[95]

Sixty patients with documented soft tissue infections were prospectively randomised to receive either ampicillin/sulbactam (2/1g; n = 30) every 6 hours or clindamycin (600mg) every 6 hours plus tobramycin (1.5 mg/kg) every 8 hours (n = 30). The age and sex of the patients were similar between groups, as were co-morbidity and bacterial isolates of wounds. A 93% cure or improvement rate was seen with ampicillin/sulbactam compared with 81% in the clindamycin plus tobramycin group. Eradication of organisms was greater in the ampicillin/sulbactam group (67% vs 35%). The antibacterial activity of ampicillin against 223 total bacteriological isolates was significantly augmented by the addition of sulbactam from 38% to 70%.[96]

5.6 Sepsis in the Paediatric Population

Ampicillin/sulbactam has proved effective in various severe paediatric infections, such as periorbital infections, acute epiglottitis, bacterial meningitis and acute fulminant meningococcaemia.[97] In a retrospective cohort study of patients with periorbital infections, two antibacterial combinations, penicillin plus chloramphenicol and ampicillin/sulbactam with or without ornidazole, were administered in 30 (43%) and 39 (57%) of 69 children, respectively. *S. aureus* was isolated from 14 (74%) of 19 cultures. The duration of treatment with these two combination regimens was generally between 7 and 10 days. No statistical difference was found between the two regimens in cure and recurrence rates, but five (17%) patients receiving penicillin plus chloramphenicol, and one (3%) receiving ampicillin/sulbactam with or without ornidazole had recurrent periorbital cellulitis.[98]

Thirty-one infants and children with documented acute epiglottitis received intravenous ampicillin/sulbactam (200/30 mg/kg/day). Of the 31 patients, 26 (84%) had *H. influenzae* type B isolated from blood cultures; seven (27%) of these 26 strains were positive for production of β-lactamases. A high (96%) cure rate was achieved with the use of ampicillin/sulbactam. In view of the decreased use of chloramphenicol, ampicillin/sulbactam is probably now the first choice in cases of acute epiglottitis due to *H. influenzae* type B.[99]

In a randomised comparative study, 41 and 40 children with bacterial meningitis, received intravenous ampicillin/sulbactam or ampicillin plus chloramphenicol, respectively. One of 29 (3.4%) treated with ampicillin/sulbactam and 6 of 34 (18%) treated with ampicillin plus chloramphenicol died. Neurological sequelae were also more common in ampicillin plus chloramphenicol recipients (18% vs 12%).[100] According to MIC and time-kill studies of 45 *H. influenzae* β-lactamase strains, an initial decrease in *H. influenzae* type B CSF isolates was observed with ampicillin/sulbactam treatment, but eventually bacteriological eradication was not achieved.[101] Additionally, although ampicillin/sulbactam penetrates into the CSF, concentrations decrease quickly to only one-sixth of what is achieved in serum.[102]

Ampicillin/sulbactam has also been evaluated in the treatment of skin, soft tissues and skeletal infections in a randomised, prospective study of 125 children (105 with skin and soft tissue infections and 20 with suppurative arthritis or osteomyelitis). A total of 84 children received ampicillin/sulbactam (100–200/15–30 mg/kg/day in four divided doses) and 41 children received ceftriaxone (50–75 mg/kg/

day in two divided doses). Ampicillin/sulbactam and ceftriaxone showed a similar clinical and bacteriological response rate of 100% and 93%, respectively.[103] A randomised, open-label, multicentre study of serious paediatric skin and skin structure infections compared ampicillin/sulbactam (150–300 mg/kg/day in four divided doses) with cefuroxime (50–100 mg/kg/day in three or four divided doses). In the ampicillin/sulbactam treatment arm, 46 of the 59 evaluable patients (78%) were cured and 13 patients (22%) were improved. Thirty patients (76.9%) were cured and nine patients (23.1%) improved in the cefuroxime comparator arm. Bacteriological eradication was achieved in 93.2% and 100%, respectively, in the ampicillin/sulbactam and cefuroxime treatment arms. No statistically significant differences in clinical or bacteriological efficacy were observed between the treatment arms.[104]

5.7 Infections in the Intensive Care Unit Setting Due to *Acinetobacter baumannii*

Ampicillin/sulbactam may be an effective and safely used therapeutic option to treat severe nosocomial infections caused by MDR *A. baumannii*. Corbella et al.[6] showed that the active drug against *A. baumannii* in the ampicillin/sulbactam combination is sulbactam. In a non-comparative study,[105] forty consecutive patients with nosocomial infections caused by MDR *A. baumannii* were treated with intravenous ampicillin/sulbactam. MDR *A. baumannii* were resistant to penicillins, cephalosporins, aminoglycosides, fluoroquinolones, imipenem and aztreonam *in vitro*. The median daily dose of ampicillin/sulbactam was 6/3g and six patients received 12/6g. Of the infections, 72.5% occurred in the ICU setting. The infections were primary bacteraemia (32.5%), pneumonia (30%), urinary tract (15%), peritonitis (7.5%), surgical site (7.5%), meningitis (5%) and sinusitis (2.5%). Most were severe infections with underlying conditions (median Acute Physiologic and Chronic Health Evaluation [APACHE] II score: 14.5). A total of 27 patients (67.5%) were improved/cured, 7 (17.5%) experienced treatment failure and 6 (15%) were considered to have an indeterminate outcome because the patients died within the first 48 hours of treatment. Two patients with meningitis were treated and did not respond. No adverse effects were observed.[105]

Wood et al.[106] conducted a retrospective study to compare the efficacy of ampicillin/sulbactam and imipenem/cilastatin. Fourteen patients received ampicillin/sulbactam and 63 patients were treated with the comparator regimen. Mortality, duration of mechanical ventilation and length of stay in the ICU or the hospital, were comparable between treatment groups. In a retrospective study,[107] forty-eight patients with *A. baumannii* bacteraemia were treated with either ampicillin/sulbactam or imipenem/cilastatin. There were no differences between days of bacteraemia (4 vs 2 days; $p = 0.05$), days to resolution of temperature or white blood cell count, success or failure during or at the end of treatment, or ICU total or antibacterial-related length of stay (13 vs 10 days; $p = 0.05$). However, treatment with ampicillin/sulbactam saved $US1000 dollars per patient treated ($p = 0.004$).[107] In an observational prospective study of 79 adult inpatients with *A. baumannii* bacteraemia, ampicillin/sulbactam and imipenem/cilastatin were the most effective agents. A total of 35 patients (83%) of 42 who received imipenem/cilastatin and 7 (87.5%) of 8 patients who received ampicillin/sulbactam were cured.[108]

In a study of 94 patients with nosocomial *A. baumannii* bloodstream infections, 54% involved MDR strains, 81% of which were genetically related. Of the 51 patients with MDR *A. baumannii*, 65% received ampicillin/sulbactam and 35% received inadequate antibacterial therapy, whereas of 43 patients with non-MDR *A. baumannii*, 86% were treated according to susceptibility and 14% were treated inappropriately with antibacterials to which these organisms were resistant. Crude mortality was comparable in the adequately treated groups. Respective mortalities among patients treated adequately and inadequately were 41.4% and 91.7% ($p < 0.001$), respectively. Among severely ill patients, ampicillin/sulbactam therapy significantly decreased the risk of death ($p = 0.02$; odds ratio = 7.64).[109]

Ampicillin/sulbactam was evaluated in a study of eight patients with nosocomial *A. baumannii* meningitis (seven treated with 2/lg every 6 hours and one with 2/lg every 8 hours). All *A. baumannii* isolates were resistant to cefotaxime, ceftriaxone, ceftazidime, ureidopenicillins, ciprofloxacin and gentamicin. Seven isolates were resistant to imipenem. For all CSF isolates of *A. baumannii*, the MIC of ampicillin/sulbactam was ≤8/4 mg/mL. The MIC values for sulbactam by microdilution in two cases were 4 mg/mL. Six patients were cured and two patients died of meningitis.[6]

However, according to data from a non-comparative study and a comparative study with imipenem-cilastatin, lower doses of ampicillin/sulbactam can be effective against MDR *A. baumannii* as well.[105,107] Betrosian et al.[110] conducted a randomised, non-comparative, prospective trial to assess the efficiency of two high-dose regimens of ampicillin/sulbactam in patients with ventilator associated pneumonia due to MDR *A. baumannii*. Patients received either ampicillin/sulbactam 18/9g daily (group A) or 24/12g daily (group B). Clinical improvement and bacteriological success rates were 64.3% and 84.7% for group A, respectively, whereas equivalent figures for group B were 69.2% and 69.2%, respectively. Therefore, despite the reported *in vitro* resistance, high-dose regimens of ampicillin/sulbactam were both clinically and bacteriologically effective in this patient group.

6. Place of Ampicillin/Sulbactam in the Treatment of Severe Infections

It was approximately two decades ago when the production by bacteria of enzymes (lactamases) destroying β-lactams unfortunately narrowed the spectrum of many of these useful medications. The obvious need to put a halt to this inexorable decline was met by the development of β-lactamase inhibitors. Sulbactam significantly restored the lost part of the spectrum. The ampicillin/sulbactam combination covers a broad array of Gram-positive, Gram-negative and anaerobic pathogens. Ample clinical evidence exists regarding the value of ampicillin/sulbactam in various severe respiratory tract infections, especially aspiration pneumonia, and intra-abdominal, gynaecological, skin and soft tissue, and diabetic foot infections, infections due to MDR *A. baumannii,* and paediatric infections, such as acute epiglottitis and periorbital cellulitis.

Ampicillin/sulbactam is comparable to second- and third-generation cephalosporins in the treatment of LRTIs. The role of ampicillin/sulbactam in the treatment of aspiration pneumonia, when anaerobes are a key component of the infection, has been proved comparable to clindamycin and imipenem/cilastatin. *P. aeruginosa* is not among the pathogens that are effectively targeted by ampicillin/sulbactam. In addition, the intracellular bacteria that commonly are aetiological pathogens necessitate the use of a macrolide, respiratory fluoroquinolone or a tetracycline. Ampicillin/sulbactam 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 fluoroquinolone according to IDSA/ATS guidelines (2007). IDSA/ATS guidelines (2004) suggest that ampicillin/sulbactam may be administered to patients without risk factors for MDR pathogens and in early-onset HAP.

In many comparative trials in patients with intra-abdominal infections, ampicillin/sulbactam has been found to have the same favourable responses as clindamycin plus gentamicin and cefoxitin. According to a recent meta-analysis, β-lactams have higher cure rates than clindamycin-aminoglycoside combinations, although mortality is not different.[111] Ampicillin/sulbactam has also has proved itself valuable in the treatment of gynaecological and obstetrical infections. In a significant number of comparative studies, it shows comparable favourable infection outcome to cefoxitin.

Ampicillin/sulbactam has been shown to be non-inferior in direct comparisons with imipenem/cilastatin as well as piperacillin/tazobactam in the treatment of diabetic foot infections. In a comparative study of ampicillin/sulbactam versus linezolid, there was no statistical difference overall between the two regimens, although linezolid achieved higher cure rates in patients with infected ulcers and in patients

without osteomyelitis.[92] Limitations in the management of diabetic foot infection are posed when the disease is due to *P. aeruginosa*, in which case an antipseudomonal penicillin should probably be employed. It is interesting though that in the comparative study of linezolid and ampicillin/sulbactam, the treatment against *P. aeruginosa* (with aztreonam) did not alter the outcome of the infection when the patient population was examined as a whole. Where MRSA is deemed a culprit, vancomycin, or linezolid or daptomycin, should be added according to the IDSA guidelines. As severe diabetic foot infections are frequently polymicrobial, ampicillin/sulbactam is a valid initial approach to their treatment. The same principles apply in the treatment of skin and soft tissue infections in non-diabetic patients. Many studies in non-diabetic patients with skin and soft tissue infections have shown that ampicillin/sulbactam is as effective as cefoxitin in the treatment of these infections.

MDR *A. baumannii* poses a new challenge for physicians world wide, especially when managing critically ill patients. As resistance to carbapenems is a particular problem in many countries, possible options include polymyxins [colistin], ampicillin/sulbactam and tigecycline. Although experimental data suggest that sulbactam is the key player in the treatment of infections due to MDR *A. baumannii*, clinical data do not support monotherapy with sulbactam in these severe infections.[6] In addition, the majority of the clinical data come from studies examining the ampicillin/sulbactam combination. A higher dose of ampicillin/sulbactam than that used in other infections is usually employed in the treatment of *A. baumannii*.[110] Similar effectiveness between imipenem/cilastatin and ampicillin/sulbactam was also shown also in the treatment of *A. baumannii* bacteraemia in a prospective observational study.[87] Ampicillin/sulbactam has also been successfully employed in the treatment of *A. baumannii* meningitis. The potential limitation concerning meningitis treatment stems from the fact that the CSF concentrations achieved are much lower than serum concentrations. Meningitis due to *A. baumannii* is a challenge to physicians world wide as multidrug resistance is a common characteristic; combined intravenous and intrathecal administration of polymyxins is frequently necessary.[112] Microbiological data show that *A. baumannii* is more susceptible to polymyxins than ampicillin/sulbactam.[113]

The value of the ampicillin/sulbactam combination has also been proved in various severe pediatric infections such as acute epiglottitis and periorbital cellulitis. The impact of immunisation against invasive *H. influenzae* type B infections is beyond any doubt. Nevertheless, in the clinical cases of acute epiglottitis that a physician will encounter, the use of a β-lactam/β-lactamase inhibitor is mandatory because of the high level of resistance of *H. influenzae* to β-lactams. Although ampicillin/sulbactam has been assessed in bacterial meningitis and was found effective, it is not regarded as first-line treatment in the IDSA guidelines. The CSF concentration of the drug falls fast to only one-sixth of serum concentration in a matter of days.[102]

7. Conclusion

Ampicillin/sulbactam remains a valuable and safely used antibacterial in the physician's armamentarium when treating monomicrobial as well as polymicrobial infections in the paediatric and adult patient population. Ampicillin/sulbactam has high success rates and a particular role in severe infections such as respiratory tract infections (especially aspiration pneumonia), gynaecological and obstetrical infections, intra-abdominal infections, paediatric infections such as acute epiglottitis and periorbital cellulitis, diabetic foot infections, skin and soft tissue infections, and infections due to MDR *A. baumannii.*

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