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Clinical Efficacy of Hybrid of Ampicillin and Sultamicillin: A Review

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ABSTRACT

Emergence of lactamase-mediated resistance to β-lactam antibiotics among respiratory infections threatens the utilisation of clinically effective and well-tolerated lactam medicines. This article reassesses the clinical utility of ampicillin in conjunction with the β- lactamase inhibitor sulbactam in treating upper and lower respiratory tract infections. Clinical trials and meta-analyses show that ampicillin/sulbactam and sultamicillin are efficacious and well-tolerated in adults and children.

Keywords- ampicillin/sulbactam, Combine therapy, treatments, Clinical trials.

I. INTRODUCTION

The use of lactam/ lactamase inhibitor combinations, especially ampicillin/ sulbactam, as empiric therapy or prophylaxis for a range of paediatric diseases is well documented and was reviewed in 1998. 1-4 Resistance has been observed not only among nosocomial pathogens like Staphylococcus aureus, coagulase-negative staphylococci, Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa1,6 but also among community-acquired respiratory pathogens like Moraxella catarrhalis and Haemophilus influenzae. 7 Antimicrobial activity of ampicillin/sulbactam has been proven in vitro against a wide range of Gram-positive, Gram-negative organisms, and anaerobes1,8. It provides an efficient solution to lactamase-mediated resistance to -lactam drugs among prevalent paediatric infections. 3 Infections in children, including those caused by -lactamase-producing organisms, respond well to ampicillin/sulbactam. 1,2 Other -lactam/-lactamase inhibitor combos include clavulanic acid and tazobactam. These combinations aren't covered. Ampicillin/function sulbactam's in treating paediatric infections should be reevaluated. Antibiotic therapy for children has changed over time, but many criteria persist. Lactam resistance has been linked to improper antibiotic dosage, limited bacterial eradication, and inability to complete therapy. Physicians and parents can be educated to only prescribe antibiotics when required. For parents, it can promote commitment to complete therapy even after clinical improvement. Antibiotics that are effective against all infections are another crucial weapon in the fight against treatment failure and antibiotic resistance (including -lactamase-producing strains). Ampicillin/therapeutic sulbactam's efficacy should be investigated. To ensure patient adherence, consider formulation characteristics including oral and intramuscular dosing frequency. Ampicillin/continuous sulbactam's intravenous and oral formulations have allowed clinicians to examine novel paediatric indications, enhance the database of ampicillin/sulbactam tolerance, and investigate the advantages of two-day oral dose.

Due to -lactam resistance, new antibiotics are being developed faster. Recent studies compared ampicillin/efficacy sulbactam's and tolerance to those of newer antibiotics for paediatricpatients. In vitro susceptibility, pharmacokinetics, and clinical research are used to reevaluate ampicillin/sulbactam. Examine ampicillin/current sulbactam's treatment needs.

II. AMPICILLIN/SULBACTAM

Ampicillin/sulbactam (UNASYN®, Pfizer Inc.) was developed over a decade ago. Pathogenic bacterial -lactamase. Sulbactam is a -lactam with potent -lactamase inhibitory activity.9 It is active against transferable, plasmid-mediated -lactamases, which are responsible for the spread of -lactam resistance.9 Unlike other -lactamase inhibitors, sulbactam also has direct antimicrobial activity. Many nations offer paediatric intravenous, intramuscular, and oral ampicillin/sulbactam. Oral formulations include uncoated tablets, film-coated tablets, and a powder for oral suspension; all contain sultamicillin, a mutual prodrug of ampicillin and sulbactam.11 The availability of a range of formulations makes ampicillin/ sulbactam suitable for use in the community as well as in the hospital, allowing for continuity of treatment as patients are discharged.

III. ANTIMICROBIAL ACTIVITY

In vitro investigations suggest ampicillin/sulbactam is efficient against a wide spectrum of Gram-positive and Gram-negative bacteria, including

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clinically relevant anaerobes. 12 A US multicenter investigation of antibiotic susceptibility among 42,000 aerobic bacteria, using National Committee for Clinical Laboratory Standards breakpoints, found high in vitro susceptibility for a wide range of aerobic pathogens (Table 1). 13 Both Gram-positive and Gram-negative isolates were sensitive. Ampicillin/sulbactam is comparable to ampicillin alone in its action against lactam-resistant bacteria without lactamase generation (such as altered penicillin- binding sites in penicillin-resistant pneumococci). Serratia is the only significant Gram-negative isolate.

Table 1: Susceptibility of Gram-positive and Gram-negative aerobic and anaerobic bacteria to ampicillin/sulbactam

	No. of strains (if reported)	Susceptibility [a] (% strains)
Gram-positive aerobes		
Enterococcus faecalis	**2624**	**97**
Staphylococcus aureus	**4454**	**98**
***Streptococcus*, GroupB**	**505**	**100**
Streptococcu spneumoniae	**701**	**100**
Gram-negative aerobes		
***Acinetobacter* species**	**784**	**81**
Enterobacter aerogenes	**978**	**44**
Enterobacter cloacae	**1789**	**20**
Escherichia coli	**10942**	**65**
Haemophilus influenzae	**774**	**91**
Klebsiella pneumoniae	**4405**	**75**
Moraxella catarrhalis	**298**	**100**
Gram-positive anaerobes		
Anaerobic cocci	**–**	**100**
Clostridium ramosum	**–**	**85–95**
Other Clostridium species	**–**	**100**
Gram-negativeanaerobes ***Bacteroides fragilis***	**–**	**100**
***Bacteroides fragilis*group**	**–**	**100**
***Fusobacterium* species**	**–**	**100**
Gram-negative rods	**–**	**100**

Pharmacokinetics

The pharmacokinetic characteristics of ampicillin and sulbactam in children are similar to those in adults16,17, favouring parenteral or oral coadministration. Studies reveal that co-administering ampicillin and sulbactam has no effect on pharmacokinetics. In early research in paediatric patients, intravenous infusion of sulbactam 12.5 mg/kg or 25 mg/kg to 17 patients resulted in an elimination half-life of 1.75 h, compared with 1 h in adults16 and peak blood concentrations of 71 g/ml and 163 g/ml, respectively, 5 min after dosage. 18 A multiple-dosing research with intravenous ampicillin/sulbactam in paediatric patients (age 1 – 12 years) with intra-abdominal infections (IAIs) or skin and soft- tissue infections (SSTIs) explored a dose regimen of 40 – 80 mg/kg four times daily for 2 – 6 days. 19 Mean maximal serum concentrations of ampicillin and sulbactam were 177–200 g/ml. Mean ampicillin and sulbactam half-lives were 0.77 and 0.81 hours. Both ampicillin and sulbactam were dose- and gender-neutral. ampicillin and sulbactam pharmacokinetics in neonates. In a study with 16 infants, twice-daily ampicillin/sulbactam (50/50 mg/kg) bolus injections were adequate to generate microbiologically effective serum concentrations of ampicillin (87 g/ml) and sulbactam (110 g/ml) 3 h after dose. 20 The newborn's undeveloped renal function results in extended half-lives (ampicillin 9.4 h, sulbactam 7.9 h). Few research has tested ampicillin and sulbactam intramuscularly. Intramuscular or intravenous dose of ampicillin 12.5 mg/kg or 25 mg/kg led to therapeutic serum concentrations, with intramuscular administration producing a longer elimination half-life. 21

Community paediatric infections are best treated orally. As a mutual prodrug, ampicillin and sulbactam have good oral bioavailability and serum concentrations (Table 2). 22,23 Once the prodrug is absorbed and cleaved, ampicillin and sulbactam have independent pharmacokinetics, as with intravenous delivery. Studies show that ampicillin/sulbactam

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penetrates paediatric tissues well. Nahata et al.19 showed steady-state volumes of distribution of 0.32 l/kg for ampicillin and 0.34 l/kg for sulbactam.

Table 2: Pharmacokinetic parameters for sultamicillin infants and young children

	Ampicillin	**Sulbactam**
$C_{max(\mu g/ml)}$	11.3	8.1
$T_{max(h)}$	1.3	1.3
AUC ($\mu g.h/ml$)	19.6	13.4
$T_{1/2(h)}$	1.1	1.2

Clinical efficacy of ampicillin /sulbactamin pediatric infections

Most paediatric research have tested the oral formulation of ampicillin/sulbactam. An worldwide paediatric clinical trial involving 14 investigators from North, Central, South America, Asia, and Europe has shown the efficacy of twice-daily sultamicillin to treat a range of infections. 8 408 clinically evaluable children who took sultamicillin 25 mg/kg twice daily were bacteriologically evaluable. Tonsillitis/pharyngitis (41%), acute otitis media (26%), SSTIs (13%), and LRTIs were the most prevalent diagnosis (LRTIs; 12 percent). 94% of patients were cured and 4% improved (Table 3). 95% of diagnosis were cured or improved. 153/155 (99%) baseline pathogens were eradicated bacteriologically, including.

Table 3: Clinical efficacy of oral sultamicillin in pediatric patients8

		Clinical response (%)	
Diagnosis (no. of patients)	**Cure**	**Improvement**	**Failure**
Skin/ soft tissue infections (54)	54(100)	0(0)	0(0)
Acute otitis media(105)	92(88)	7(7)	6(6)
Tonsillitis/pharyngitis (169)	165 (98)	2(1)	
Sinusitis(23)	19(83)	3(13)	
Lower respiratory tract infections(49)	46(94)	1(2)	
Other infections(8)	6(75)	2(25)	
Total(408)	382 (94)	15(4)	

A recent study by Lopez and Rivas26 in Argentina involved 467 children (ages 5 to 16) with mild to moderate illnesses. Oral sultamicillin 25-50 mg/kg twice day for 7-14 days (only patients treated for at least 5 days were clinically evaluable). 306 of 466 patients had URTI (AOM 172, sinusitis 69, pharyngitis 65) and 59 LRTI. 416/466 (89%) evaluable patients were cured, and 37 (8%) improved, for a clinical response rate of 453/466. (97 percent). In 94/95 (99%) evaluable cases, bacteriologic eradication was observed, except for a P. aeruginosa UTI. Streptococcus pyogenes, E. coli, S. aureus, and S. pneumoniae were most prevalent at baseline. Smaller trials confirm oral sultamicillin's therapeutic efficacy in treating paediatric infections. 30-27

Two studies have evaluated parenteral ampicillin/sulbactam in paediatric infections. Alpuche-Aranda et al.31 compared intravenous ampicillin/sulbactam 100/50 mg/kg per day, administered four times daily, to cefuroxime 100 – 200 mg/kg per day, three times daily, in 50 children with significant illnesses. Pneumonia (58%), SSTI (15%), septic arthritis (11%) and UTI were the most frequent infections (5 percent). Ampicillin/sulbactam and cefuroxime had 93% and 96% clinical cure rates after 7 days, with 92% and 93% bacteriologic eradication rates.

Kanra et al.32 studied intravenous or intramuscular ampicillin/sulbactam 200/100 mg/kg per day or 400/200 mg/kg per day in the treatment of skeletal infections, systemic salmonellosis, intrathoracic infections, and soft-tissue infections. Treatment lasted 8-23 days. 67/68 ampicillin/sulbactam-treated patients were cured (99 percent). The effectiveness of intravenous ampicillin/sulbactam then oral sultamicillin has also been evaluated. In one trial, 41 children with respiratory infections (n = 27), urinary tract infections (UTIs; n = 2), SSTIs (n = 7) or gastrointestinal infections (n = 2) received ampicillin/sulbactam 100/50 mg/kg per day for 2.8 days (range 2 – 4 days). 33 This was followed by sultamicillin 50 mg/kg twice day for 13.2 days (range 9-18 days). 34/35 (97%) clinically evaluable patients were successful. Most common were -hemolytic streptococci and S. aureus. 18/22 (82%) patients were eradicated.

Respiratory tract infections

Sultamicillin treats URTIs and LRTIs. CAI AOM. Sultamicillin is as effective as cefaclor34 and amoxicillin/clavulanic acid, according to studies.

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Sultamicillin treats tonsillitis/pharyngitis,8 epiglottitis,37 and sinusitis. 8 Multicenter investigation showed ampicillin/efficacy sulbactam's in treating LRTIs. 8 A new study compared the care of 149 children (1-12 years) with CAPD. 38 Ampicillin/sulbactam 25 mg/kg twice daily and cefuroxime axetil 10 mg/kg twice daily exhibited similar clinical responses: cure, 67/73 (92%); improvement, 3 of 73 (4%); success, 70/73 (96%); cefuroxime axetil: cure, 68/76 (89%); improvement, 5 of 76 (7%); success, 73/76. (96 percent). 25% of each treatment group had failed antibiotics, including unprotected -lactams. Often isolated were M. catarrhalis, H. influenzae, S. aureus, and S. pneumoniae. 30% of ampicillin/sulbactam-treated and cefuroxime axetil-treated patients had -lactamase at baseline.

Urinary tract infections

Lower UTI is a common paediatric infection. High urine concentrations of ampicillin and sulbactam favour eradicating urinary pathogens like E. coli. Two trials support ampicillin/sulbactam for paediatric UTIs. Solbiati et al.39 treated children with ampicillin/sulbactam 100/50 mg/kg per day for 3-8 days (mean 4.8 days). Most patients (84%) received injectable ampicillin/sulbactam. All 25 (100%) patients were cured. Ampicillin/sulbactam eliminated all 25 baseline isolates, including 11 ampicillin-resistant ones. 62% of 276 ampicillin-resistant, Gram-negative bacteria were susceptible to low-dose sultamicillin. 40 18/23 (78%) patients responded to twice-daily sultamicillin 25 mg/kg.

INTRA-Abdominal infections

Gram-positive, Gram-negative, and anaerobes cause intra-abdominal infections. 41 IAI antibiotics must be effective against several microbes. Combining ampicillin/sulbactam with an aminoglycoside helps treat IAIs in children (primarily perforated appendicitis). 42 The experiment compared 150–300 mg/kg/day ampicillin/sulbactam plus an aminoglycoside against 20–40 mg/kg/day ampicillin/clindamycin plus an aminoglycoside. Daily amoxicillin/sulbactam treatment. Researchers choose gentamicin or tobramycin. 3-11-year-olds were hospitalised. Clinical success was 97% in both groups, whereas bacteriologic eradication was 89% with ampicillin/sulbactam plus aminoglycoside and 92% with ampicillin/clindamycin plus aminoglycoside. Intra-abdominal surgery uses antibiotics. Foster et al.43 examined the efficacy of a single perioperative dose of ampicillin/sulbactam 15/7.5 mg/kg or metronidazole 7.5 mg/kg with cefotaxime 25 mg/kg in 100 children having appendectomy. Intravenous doses were provided during anaesthesia induction. After surgery, children with a perforated or gangrenous appendix received ampicillin/sulbactam or metronidazole/cefotaxime IV. 8% of evaluable cases suffered post-surgical infection. ampicillin/sulbactam had 9% infection rates and metro-nidazole + cefotaxime 7%. Four of 28 (14%) patients with a burst or gangrenous appendix in both groups developed an infection. Another trial compared ampicillin and ampicillin/sulbactam for UTM surgery. 44 patients got ampicillin/sulbactam 150 mg/kg/day intravenously 1 h before, 8 h, and 16 h after surgery. Post-operative UTI incidence was 4% for ampicillin/sulbactam and 15% for ampicillin.

Meningitis

Children die from bacterial meningitis. Ampicillin/sulbactam treats meningitis by penetrating CSF. Neisseria meningitidis and S. pneumoniae cause sub-Saharan epidemic meningitis. 45 meningitis patients aged 10–40 received 1 g/0.5 g intramuscularly four times daily for 5–10 days (mean 5.2 days). 14 of 47 N. meningitidis patients developed arthritis, cranial nerve palsy, or uveitis. 93% of patients could drink after 48 hours. Cured S. pneumoniae meningitis. 4-patients died in 6 hours. S. pneumoniae infected one patient. In a research comparing ampicillin/sulbactam 400/50 mg/kg every 4 h versus ampicillin 400 mg/kg every 6 h + chloramphericol 100 mg/kg every 6 h, 65 patients had CSF pathogens at baseline. 46 37 H. influenzae isolates were ampicillin-resistant. 2% of ampicillin/sulbactam failed clinically, and 18% of ampicillin/chloramphenicol. Every ampicillin/chloramphenicol/sulbactam failure died. 12% of ampicillin/sulbactam and 18% of ampicillin/chloramphenicol patients had neurological problems. Researchers found ampicillin/sulbactam effective for meningitis.

In a second retrospective analysis, 57 meningococcemia patients received benzylpenicillin G 300 000 IU/kg six times daily plus chloramphenicol 100 mg/kg four times daily (n = 31) or ampicillin/sulbactam 400/100 mg/kg four times daily (n = 26). Benzylpenicillin / chloramphenicol had 19% mortality, ampicillin / sulbactam 8%. Benzylpenicillin / chloramphenicol and ampicillin/sulbactam were 10.8 4.8 days.

Bone, Skin and soft-Tissue infections

Falls and accidents cause skin and soft tissue infections in children. Skin, tissue, and bone infections can result from punctures. Untreated bone infections in children can cause deformities. Immune deficiency and bacteremia can be fatal. Skin, soft-tissue, and bone infections have been examined using ampicillin/sulbactam. In a prospective research, 105 children with SSTIs were administered intravenous ampicillin/sulbactam 100–200/15–30 mg/kg four times day or ceftriaxone 50–75 mg/kg twice daily. 48 Cellulitis took 2 days, suppurative arthritis 7 days, and osteomyelitis 7-10 days. 100% of ampicillin/sulbactam- and ceftriaxone-treated patients were cured. Sultamicillin and cloxacillin were equally effective in another research. 49 patients took sultamicillin 250–750 mg twice daily or cloxacillin 50 mg/kg per day for 7 days. 16/21 (76%) and 13/21 (62%). Third, ampicillin/sulbactam was evaluated on children with bone and joint infections. 8- to 17-year-olds with osteomyelitis or septic arthritis were given ampicillin/sulbactam 50/12.5 mg/kg IV four times daily, followed by sultamicillin 25 mg/kg IV four times daily.

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All nine patients were clinically and bacterially cured, with no relapse at 4–6 months.

Tolerability profile

Ampicillin/sulbactam has a good tolerability profile, therefore it's a first-line treatment in many paediatric infections. In 1994, Raillard et al.8 reported sultamicillin tolerability results for 431 children. The average daily dose of sultamicillin in the study sample was 26 mg/kg (range: 15–100 mg/kg), twice daily, for 10 days (range: 2–22 days). Sultamicillin was well-tolerated. Only 34 (8%) of 431 children had drug-related or probably drug-related adverse events to ampicillin/sulbactam, despite -lactam resistance. These research have gathered clinical data to support the wider use of sultamicillin to treat paediatric infections and shown clinical equivalency between ampicillin/sulbactam and newer antibiotics. Ampicillin/sulbactam can be used orally twice day, unlike other antibiotics. The oral suspension is tasty and can be taken between meals. This regimen is more convenient than others for treating children since it fits with their everyday routine, which may increase compliance. The strong tolerability profile of sultamicillin, supported by a growing tolerance database, may help paediatric patients, who are less able than adults to tolerate a medicine with a bad side-effect profile. Diarrhea (6%) and rash (3%). (1 percent). Other side effects were 1%. No deaths were reported from adverse drug reactions (gastrointestinal, eight; rash, one). Clinically significant laboratory abnormalities were rare. Pediatric ampicillin/sulbactam experience is minimal. Lees et al.51 found adverse effects in 8 of 66 (12%) children receiving multiple-dose therapy (mean daily dose 1 g, mean duration of treatment 4 days). Injection-site discomfort and skin problems were most common (3 percent). Neonates tolerate ampicillin/sulbactam well. Airede et al.52 studied 27 neonates in a NICU. 11 kids had pneumonia and 12 SSTIs. One child (4%) reported minor loose stools, which did not need therapeutic discontinuation. Laboratory tests showed no clinically meaningful treatment changes. In another trial, 16 infants given ampicillin/sulbactam prophylactically for umbilical, arterial, or venous catheterization had no adverse reactions or hematologic or biochemical disturbances. Ampicillin/sulbactam has a long history of treating paediatric infections. Numerous trials show it's efficient and well-tolerated for URTIs, LRTIs, IAIs, UTIs, and SSTIs. Recent investigations confirm bacteriologic effectiveness.

IV. CONCLUSION

Our sultamicillin cure rate was higher than prior reports. Comparing our study's results to others, we can conclude that low-dose sultamicillin for 10 days should lead to cure rates comparable to amoxicillin-clavulanic acid. Diarrhea is sultamicillin's most prevalent side effect. Previous trials found this side effect at 0% to 50%. Amoxicillin-clavulanic acid seldom causes serious liver damage in elderly people. Comparatively, our study's sample size was big. Further clinical trials with bigger sample numbers are needed to support the general negative finding reported so far, namely the equal frequency of problems with sultamicillin and amoxicillin-clavulanic acid. Low-dose sultamicillin (375 mg twice daily for 10 days) is an efficient and safe treatment for acute bacterial sinusitis.

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