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Clinical Pharmacology of Ampicillin in Infants and Children

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Abstract

Ampicillin is an aminopenicillin and is more active than penicillin G. Ampicillin is destroyed by β-lactamase and is co-formulated with sulbactam an inhibitor of β-lactamase. Ampicillin is bactericidal and it is active against meningococci, Listeria monocytogenes, enterococci, and the co-administration with sulbactam markedly expands the spectrum of activity against Haemophilus influenzae, Escherichia coli, Proteus, and Bacillus fragilis. Ampicillin may be administered intravenously and orally and the intravenous dose is 50 mg twice-daily and thrice-daily in preterm and term infants, respectively. The oral dose in children ranges from 125 to 500 mg 4 times-daily and increases with the chid age. Ampicillin has been found efficacy and safe in infants and children but may cause adverse-effects. In infants, the ampicillin elimination half-life ranges between 2.4 to 5.0 hours and decreases with infant maturation and in children it is about 0.8 hours. Ampicillin interacts with drugs, the treatment and the trials with ampicillin have been extensively studied in infants and children. This antibiotic freely crosses the human placenta but poorly migrates into the breast-milk. Ampicillin penetrates into the cerebrospinal fluid in significant amounts and treated meningitis caused by different pathogens generally co-administered with other antibiotics, particularly with chloramphenicol, but cefotaxime or cefuroxime sterilized the cerebrospinal fluid more rapidly. The aim of this study is to review the ampicillin dosing, efficacy and safety, effects, adverse-effects, tissue concentration, pharmacokinetics, interaction with drugs, treatment, trials, placental transfer, migration into breast-milk, penetration into the cerebrospinal fluid, and treatment of bacterial meningitis in infants and children.

INTRODUCTION

Ampicillin is an aminopenicillin and expands the spectrum of activity of penicillin G in a different direction from the penicillinase-resistant penicillins they allow for useful activity against some gram-negative organisms. Ampicillin is destroyed by β-lactamases (from both gram-positive and gram-negative bacteria); thus further expansion of its activity is enhanced through co-formulation with β-lactamase inhibitors: clavulanate, sulbactam, or tazobactam [1].

Antimicrobial activity of ampicillin

Ampicillin is generally bactericidal for sensitive gram-positive and gram-negative bacteria. The meningococci and Listeria monocytogenes are sensitive to ampicillin. Many pneumococcal isolates have varying levels of resistance to ampicillin, and penicillin-resistant strains should be considered ampicillin-resistant. Haemophilus influenzae and the viridians group of streptococci exhibit varying degrees of resistance. Enterococci are about twice as sensitive to ampicillin as they are to penicillin G. From 30 to 50% of Escherichia coli, significant number of Proteus mirabilis and practically all species of Klebsiella are resistant. Most strains of Shigella, Pseudomonas, Serratia, Acinetobacter, Bacillus fragilis, and indole-positive Proteus also are resistant to ampicillin. Resistant strains of Salmonella are recovered with increasing frequency. Concurred administration of a β-lactamase inhibitor such as clavulanate or sulbactam markedly expands the ampicillin spectrum of activity, particularly against Haemophilus influenzae, Escherichia coli, Klebsiella, Proteus, and Bacillus fragilis [1].

Absorption, distribution, metabolism and elimination of ampicillin

Ampicillin is stable in acid and is well absorbed after oral administration. An oral dose of 500 mg produces peak concentration in plasma of about 3 μg/ml at 2 hours. Intake of food prior to ingestion of ampicillin diminishes absorption. Intramuscular injection of 500 to 1,000 mg sodium ampicillin yields peak plasma concentrations of about 7 to 10 μg/ml, respectively, at 1 hour. Plasma concentrations decline with a half-life of about 80 min in adults. Severe renal impairment markedly prolongs the half-life. Peritoneal dialysis is ineffective in removing the drug from the blood, but haemodialysis removes approximately 40% of the body store in about 7 hours. Adjustment of the dose of ampicillin is required in the presence of renal dysfunction. Ampicillin appears in the bile, undergoes enterohepatic circulations, and is excreted in the faeces [1].

The literature search was performed electronically using PubMed database as search engine and the following key words

were used: "ampicillin dosing infants, children", ampicillin efficacy, safety infants, children", "ampicillin effects infants, children", "ampicillin adverse-effects infants, children", "ampicillin tissue concentration", "ampicillin pharmacokinetics infants, children", "ampicillin drug interactions", "ampicillin therapeutic use infants, children" "ampicillin treatment infants, children", "ampicillin trials infants, children", "ampicillin placental transfer", "ampicillin migration into the breast-milk", "ampicillin penetration into the cerebrospinal fluid", and "ampicillin treatment of meningitis in infants, children". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] were consulted.

RESULTS

Administration schedules of ampicillin to infants and children

Administration to infants [2]: **Infants with a postmenstrual aged ≤ 34 weeks and a postnatal age ≤ 7 days.** Give: 50 mg twice-daily.

Infants with a postmenstrual age ≤ 34 weeks and a postnatal age > 7days and ≤ 28 days. Give: 75 mg twice-daily.

Infants with a postmenstrual age > 34 weeks and a postnatal age ≤ 28 days. Give: 50 mg thrice-daily.

Very large dose of ampicillin may result in central nervous system excitation or seizure activity. Moderate prolongation of blending times (by approximately 60 seconds) may occur after repeated doses. Hypersensitivity reactions (maculopapular rash, urticaria, or fever) are rare in infants. Ampicillin is incompatible with: amikacin, amiodarone, dopamine, epinephrine, erythromycin, lactobionate, fluconazole, gentamicin, hydralazine, metoclopramide, midazolam, nicardipine, sodium bicarbonate, and tobramycin [3].

Administration to children [4]: **3.1.2.1. Oral treatment for susceptible infections including: (1) bronchitis, (2) urinary-tract infections, (3) otitis media, (4) sinusitis, (5) uncomplicated community-acquired-pneumonia, and (6) salmonellosis.**

Children aged 1 to 11 months. Give: 125 mg 4 times-daily; increase the dose if necessary to 30 mg/kg 4 times-daily.

Children aged 1 to 4 years. Give: 250 mg 4 times-daily; increase the dose if necessary up to 30 mg/kg 4 times-daily.

Children aged 5 to 11 years. Give: 500 mg 4 times-daily; increase the dose if necessary up to 30 mg/kg 4 times-daily (maximum per dose = 1 gram 4 times-daily).

Children aged 12 to 17 years. Give: 500 mg 4 times-daily; increase the dose if necessary to 1 gram 4 times-daily, use increased dose in severe infection.

Intravenous infusion for treating: (1) group B streptococcal infection and (2) enterococcal endocarditis in combination with another antimicrobial: Children. Give: 50 mg/kg thrice-daily 4 to 6 times-daily (maximum per dose = 2 grams 6 times-daily).

Intravenous treatment of Listerial meningitis in infants and children [4]: **Infants aged up to 7 days.** Give: 100 mg/kg twice-daily.

Infants aged 7 to 20 days. Give: 100 mg/kg thrice-daily.

Infants aged 21 to 28 days. Give: 100 mg/kg 4 times-daily.

Children. Give: 50 mg/kg 4 to 6 times-daily.

Efficacy and safety of ampicillin in Infants and children

Infants, aged 2 to 24 months, were hospitalized for urinary-tract infections and were treated with ampicillin/sulbactam or cephalosporins. Ampicillin/sulbactam could be an effective alternative to cephalosporins for the treatment of the first-episode of the urinary-tract infections in these infants [5]. Extremely low-birthweight infants at risk of early onset sepsis received ampicillin (N = 36) or penicillin G (N = 39). Ampicillin was efficacy and safe in treating the sepsis and was associated with a lower mortality-rate [6]. The empirical use of ampicillin to cover febrile infants caused by Listeria monocytogenes and enterococcal infections is most justifiable in the first month of life [7]. Children, aged 3 to 59 months, were hospitalized for severe pneumonia and received penicillin G or ampicillin. Both treatments were efficacy and safe and are efficacious options to treat children with pneumonia due to pneumococcal strains having penicillin G MIC up to 4 μg/ml [8]. Children with infections in the lower respiratory-tract, urinary-tract, skin, bone and soft-tissue infections were treated with ampicillin/sulbactam and sultamicillin and this treatment was found efficacy and safe and should be considered to be the first-choice options for the management of a variety of paediatric infections [9]. Either ampicillin/sulbactam or cefuroxime provide safe and effective parenteral antibiotic therapy in paediatric patients with serious skin and skin-structure infections [10]. Twenty-three children, aged 2 months to 11 years, suffering from pus-forming cervical adenitis, and lobar pneumonia caused by Escherichia coli (N = 10), Staphylococcus aureus (N = 7), and Klebsiella pneumoniae (N = 6) were treated with ampicillin/sulbactam or penicillin/

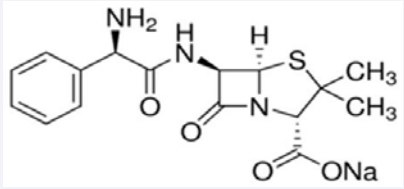

Figure 1 Ampicillin molecular structure (molecular weight = 349.41).

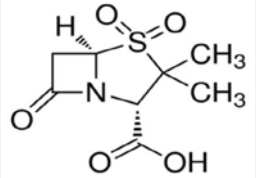

Figure 2 Sulbactam molecular structure (molecular weight = 233.24).

sulbactam. Ampicillin/sulbactam proved to be safe and effective treatment of non-life-threatening paediatric infections [11]. Ampicillin/sulbactam is an effective and well tolerated treatment for children with pneumonia [12].

Effects of ampicillin in infants and children

Ampicillin is effective in treating upper and lower respiratory-tract infections caused by Streptococcus pneumoniae, β-haemolytic streptococci, and non β-lactamase-producing strains of Haemophilus influenzae. It is also effective in the treatment of meningitis caused by group B streptococci and Listeria monocytogenes [13]. Ampicillin administered at a daily dose of 50 to 70 mg/kg to children is effective in treating otitis media caused by Diplococcus pneumoniae and Haemophilus influenzae. Ampicillin showed a relapse-rate in excess of 20% during two months of follow-up and the adverse-effects occurred in 26% of treated children [14]. One-hundred-forty-nine children were diagnosed as bronchopneumonia and acute bronchial obstructive syndrome. Ampicillin is as effective as cefazolin or ceftriaxone for the treatment of community-acquired-pneumonia in children [15]. Ampicillin is active against Salmonella Typhimurium, Salmonella Newport, Salmonella bovis morbificans, Salmonella postsdam, Salmonella saint paul, Salmonella oranienburg, Salmonella Adelaide, Salmonella enteritidis, Shigella sonnei, Shigella flexneri, and Escherichia coli [16].

Adverse-effects caused by ampicillin in children

One-hundred-two children received ampicillin/sulbactam for 10 days and diarrhoea occurred in 70% of children [17]. Two-thousand-five-hundred-one children received ampicillin and the adverse-effects were diarrhoea and skin rash [18]. Twenty-three children received ampicillin orally and the treatment caused diarrhoea in 60% of children [19]. In children, the dose of ampicillin ranged from 50 to 200 mg/kg daily and mild, moderate, and severe diarrhoea occurred in 18 to 30%, 2 to 11% and 1%, of children, respectively [20]. A study of 200 consecutive children receiving ampicillin for various reasons revealed that bowel habits changed in 16% and diarrhoea occurred in 4.5% of children [21].

Tissue concentrations of ampicillin sulbactam in children

Sixteen children undergoing colorectal surgery received 2 grams of ampicillin and 1 gram of sulbactam by intravenous infusion. Serum trough concentrations of sulbactam and ampicillin were 33±22 and 72±55 μg/ml, respectively, and the corresponding concentration in the abdominal tissue ranged from 2.7 to 3.8 μg/ml and from 5.6 and 6.8 μg/ml. In fat tissue, ampicillin concentration ranged from 1.7 to 4.0 μg/ml, and in the colonic wall ampicillin concentration was 7.0±2.8 μg/ml. In most children, the concentrations of ampicillin/sulbactam were greater the MIC_{50} for Bacteroides fragilis in the fatty tissue. In the colonic wall the ampicillin/sulbactam concentrations were higher the MIC_{90} for Bacteroides fragilis [22]. Nine children undergoing orchiectomy for testicular cancer were treated with 3 grams of ampicillin and 1.5 grams of sulbactam preoperatively and the concentrations of both drugs were measured in the epididymis 30 to 65 min after the end of infusion. Ampicillin and sulbactam concentrations were 38.9±15.9 and 19.8±5.2 μg/gram, respectively. These concentrations exceed the MIC of many organisms including Staphylococcus pneumoniae [23]. Twenty-four children undergoing surgery in the ENT region were treated with 2 grams of ampicillin and 1 gram of sulbactam. The respective mean concentrations in serum were 59.2 and 31.6 μg/ml, respectively. About 1 hour after the end of infusion, the mean concentrations of ampicillin and sulbactam in tissue were 33.5 and 19.5 μg/ml. Ampicillin and sulbactam diffuses into different tissues and the serum to tissue concentration ratio is about 2 [24].

Pharmacokinetics of ampicillin in infants

Tremoulet et al. [25] studied the pharmacokinetics of ampicillin in 73 infants who were clustered into 4 groups. Group A consisted in 21 infants with gestational and postnatal ages of 30.3±3.4 weeks and 2.6±2.3 days, respectively. Infants of group B (N = 7) had a gestational and postnatal ages of 36.9±2.5 weeks and 15.4±4.0 days, respectively. Group C consisted in 27 infants with gestational and postnatal ages of 38.2±2.0 weeks and 2.9±2.6 days, respectively. Infants of group D (N = 18) had a gestational and postnatal ages of 34.8±6.4 weeks and 6.6±6.4 days, respectively. Table 1 shows the dosing-regimens of ampicillin in the 4 group of infants. (Table 1) (Table 2)

This table shows that ampicillin total body clearance increases with the postnatal age, ampicillin elimination half-life and ampicillin serum concentrations decrease with the postnatal age. Ampicillin distribution volume is lower than the water volume and it is independent by the postnatal age.

Colding et al. [26] investigated the pharmacokinetics of ampicillin in 88 newborn infants who received intravenous parenteral nutrition and ampicillin. The median gestational age was 34 weeks (range, 27 to 42) and the median body-weight was 1,975 grams (range, 805 to 4,850). Ampicillin was intravenously infused at a dose of 200 mg/kg and the median treatment duration was 5 days (range, 2 to 20). (Table 3)

This table shows that the ampicillin serum concentration decreases with increasing the infant body-weight and the gestational age.

Pharmacokinetics of ampicillin and sulbactam in children

Nahata et al. [27] described the pharmacokinetics of ampicillin and sulbactam in 28 children (19 males and 9 females) who were aged 1 to 6 years (N = 10), 6.1 to 10 years (N = 9) and 10.1 to 12 years (N = 9). Ampicillin and sulbactam (2:1) was intravenously infused at a dose ranging from 40 to 80 mg/kg 4 times-daily for 2 to 6 days. (Table 4) summarizes the pharmacokinetics of ampicillin and sulbactam in these children.This table shows that the pharmacokinetic parameters of ampicillin and sulbactam do not vary with the child age. The pharmacokinetic parameters of ampicillin and sulbactam are not significantly different. The elimination half-life of ampicillin and the distribution volume of ampicillin are similar among these children. The elimination half-life of ampicillin is longer in infants than in children and the distribution volume is similar in infants and children. For

Table 1: Ampicillin as prescribed by primary physicians.

Group	N	Ampicillin daily dose (mg/kg daily)	Ampicillin dose (mg/kg)	Dosing interval	Typical dose
A	21	200 (162 – 303)	100 (81 – 109)	19% thrice-daily, 81% twice-daily	100 mg/kg twice-daily
B	7	185 (113 – 194)	93 (57 – 97)	100% twice-daily	100 mg twice-daily
C	27	218 (100 – 307)	100 (43 – 102)	59% thrice-daily 41% twice-daily	75 mg/kg thrice-daily
D	18	282 (184 – 350)	92 (46 – 100)	11% 4 times-daily 28% thrice-daily 28% twice-daily	100 mg/kg thrice-daily
Overall	73	200 (100 – 350)	98 (43 – 109)	11% 4 times-daily 34% thrice-daily 55% twice-daily	100 mg/kg twice-daily

Table 2: Pharmacokinetic parameters of ampicillin according to the 4 groups of infants.

					Steady stathe concentration (µg/ml)	
Group	**N**	**TBC (L/h/kg)**	**DV (L/kg)**	***Half-life (h)**	**Minimum**	**Maximum**
A	21	0.055 (0.03 – 0.07)	0.40 (0.40 – 0.40)	5.0 (3.9 – 9.4)	77 (36 – 320)	318 (244 – 563)
B	7	0.070 (0.03 – 0.07)	0.40 (0.40 – 0.41)	4.0 (3.8 – 8.3)	33 (21 – 145)	266 (159 – 368)
C	27	0.086 (0.04 – 0.139	0.40 (0.40 – 0.40)	3.2 (2.2 – 6.2)	48 (5 – 173)	274 (127 – 413)
D	18	0.11 (0.06 – 0.13)	0.40 (0.40 – 0.41)	2.4 (2.1 – 4.7)	28 (5 – 173)	246 (138 – 203)
Overall	73	0.072 (0.03 – 0.13)	0.40 (0.40 – 0.41)	3.3 (2.1 – 9.4)	47 (5 – 320)	281 (127 – 563)

TBC = total body clearance. DV = distribution volume. *Elimination half-life.

Table 3: Demographic characteristics of newborns, number of treatments, ampicillin dose, and ampicillin serum concentration.

	Number of treatments						
Gestational age (weeks)	**Days**	**Courses**	**Body-weight**	**Postnatal age (days)**	**Dosage (mg/kg daily)**	**Number of measurements**	**Ampicillin Serum conc. (µg/ml)**
≤ 32	274	42	1,217	20	161	205	45
33 – 36	153	23	1,677	8	159	124	43
≥ 37	332	43	2,730	15	164	265	33*
Body-weight (grams)							
≤ 1,000	88	13	---	16	147	72	47
1,001 – 1,500	220	32	---	17	164	171	41
1,501 – 2,000	150	23	---	12	163	111	45
2,001 – 2,500	104	15	---	11	150	80	35
2.501 – 3,000	116	13	---	16	182	92	33
≥ 3,001	98	14	---	19	162	82	30*
Postnatal age (days)							
≤ 7	242	67	1,862	--	166	149	48
8 – 14	278	77	2,058	---	155	260	38
15 – 21	95	24	1,950	---	150	72	41
≥ 22	161	26	2,026	---	178	128	31**
Mean	---	---	1,977	15	162	---	39§
%Mean	---	---	3.4	20	45	---	82

*P-value < 0.001. **P-value < 0.005, by 2-way analysis of variance. §Geometric main.

comparison of pharmacokinetic parameters of infants see the table 2. Ampicillin total body clearance is difficult to compare in children and infant because it has been expressed in different units in children and infants.

Interactions of ampicillin with drugs in infants and children

Ampicillin inhibits the transport of other drugs [28]. Two-hundred-eight-one newborn infants were recovered in the intensive care unit who received 1,114 potential drug interaction and incompatible drug interactions occurred in 25.0% of infants and those caused by ampicillin were 408 [29]. Quinine reduced the bioavailability and the antimicrobial activity of ampicillin-cloxacillin which may have therapeutic implications, and caution is required with the co-administration of these drugs [30]. Drug rashes were observed among 22.4% of 67 hospitalized children receiving allopurinol and ampicillin concomitantly, whereas the rashes occurred in only 7.5% of 1,257 children who received ampicillin only. Potentiation rashes caused by ampicillin co-administered with allopurinol (or hyperuricemia) seems a likely explanation, since rashes occurred in only 2.1% of 283 children who received allopurinol without ampicillin [31]. A drug–drug interaction between N-acetyl-p-benzoquinone-imine derived from the anodic oxidation of acetaminophen when it was administered with β-lactam antibiotics. The homogeneous rate constants (K_{obs}) of the reaction of N-acetyl-p-benzoquinone-imine were observed with the co-administration of β-lactam antibiotics. The K_{obs} for the reaction between N-acetyl-p-benzoquinone-imine and β-lactam antibiotics was found to vary in the following order: K_{obs} amoxicillin = K_{obs} ampicillin > K_{obs} penicillin at biological pH [32]. The most commonly prescribed multiple antibiotic were ampicillin plus gentamicin (N = 113, 27.1%) followed by intravenous chloramphenicol plus cloxacillin (N = 60, 14.4%). There was a significant interaction between ampicillin and gentamicin in hospitalized children [33]. Chloroquine reduces the urinary excretion of ampicillin when it is co-administered with cloxacillin [34].

Therapeutic use of ampicillin/sulbactam in children

Ampicillin/sulbactam was used for the treatment of lower respiratory-tract infections, aspiration pneumonia, gynaecological/obstetric, intraabdominal and paediatric infections such as acute epiglottitis, and periorbital cellulitis, diabetic foot, skin and soft-tissue infections [35]. Ampicillin/sulbactam is active against organisms that produce β-lactamase including Bacteroides fragilis and Neisseria gonorrhoea. Ampicillin/sulbactam improves the therapeutic and prophylactic efficacy in a wide range of microorganisms [36]. Ampicillin/sulbactam is a sensible option for the treatment of life-threatening acinetobacter infections [37]. Ampicillin/sulbactam

Table 4: Pharmacokinetic parameters of ampicillin and sulbactam which were obtained in 28 children.

	Age group						
	1 to 6 years		6.1 to 10 years		10.1 to 12 years		*P-value
Ampicillin							
	N	Mean±SD	N	Mean±SD	N	Mean±SD	
Dose (mg/kg)	10	69.5±10.2	9	63.7±13.2	9	65.9±11.2	0.9888
Peak conc. (µg/ml)	10	200±118	9	183±36.5	9	177±31.9	0.7066
$AUC_{0\text{-}6\ hours}$	9	179±79.2	8	159±42.6	9	175±45.5	0.7066
TBC (ml/min/kg)	9	5.11±2.36	8	4.88±1.49	9	4.31±0.92	0.8082
§Half-life (h)	9	0.74±0.07	8	0.72±0.11	9	0.85±0.18	0.7903
DVss (L/kg)		0.34±0.17	8	0.30±0.08	9	0.32±0.07	0.7903
Sulbactam							
Peak conc. (µg/ml)	10	102±64.2	9	85.8±21.2	9	81.9±20.7	0.7066
$AUC_{0\text{-}6\ hours}$	9	90.5±42.8	8	76.8±25.2	9	81.8±15.7	0.7903
TBC (ml/min/kg)	9	5.10±2.24	8	5.17±1.73	9	4.60±1.09	0.9041
§Half-life (h)	9	0.77±0.08	8	0.76±0.10	9	0.89±0.13	0.7903
DVss (L/kg)	9	0.34±0.16	8	0.34±0.10	9	0.35±0.10	0.9888

Difference between pharmacokinetics of ampicillin and sulbactam (**P-value)				
Peak concentration	$AUC_{0\text{-}6\ hours}$	TBC	Elimination half-life	DVss
Age group 1 to 6 years				
0.5066	0.8248	0.8248	0.8248	1.0000
Age group 6.1 to 10 years				
0.8248	0.8248	0.8248	0.8248	0.8248
Age group 10.1 to 12 years				
0.8248	0.8248	0.5066	0.8248	0.8248

TBC = total body clearance. §Elimination half-life. DVss = distribution volume at steady-state. *Kruskal-Wallis test. ** Mann Whitney test.

Table 5: Concentration of ampicillin in the cerebrospinal fluid (CSF) and serum of healthy volunteers.

	Cerebrospinal fluid			Serum			
Time after dosing (min)	Number of specimens	Range (µg/ml)	Mean (µg/ml)	Number of specimens	Range (µg/ml)	Mean (µg/ml)	CSF to serum ratio
30	0	0.00 – 0.00	0.00	6	22 – 165	116	---
60	3	0.35 – 0.70	0.46	6	33 – 56	42	0.011
120	3	0.34 – 0.54	0.41	6	8.6 – 15.7	12.7	0.032
240	3	0.70	0.70	6	0.7 – 3.2	1.8	0.39

is used in the treatment of the upper and lower respiratory-tract infections, urinary-tract, skin, bone, soft-tissue infections and meningitis and it is effective for the prophylaxis of infections which occurred after surgery [38]. Ampicillin/sulbactam has proved efficacy against Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae b, Moraxella catarrhalis, and gram-negative rods [39].

Treatment with ampicillin or with ampicillin/sulbactam in infants and children

An infant had an infection caused by Enterococcus faecalis which was resistant to ampicillin plus vancomycin but the infection was eradicated with ampicillin plus cefotaxime [40]. Seventy-five extremely low-body-weight infants had a sepsis caused by Klebsiella pneumoniae, 36 infants received ampicillin and 39 infants were treated with penicillin. The eradication-rate of the infective organism was more rapid with ampicillin than with penicillin [41]. Parenteral penicillin or ampicillin for treatment of non-complicated community-acquired-pneumonia in hospitalized children is as effective as cefuroxime, and should remain the recommended first-line therapy [42]. The parenteral ampicillin/sulbactam is indicated for the treatment of mild-to-moderate severe infections such as intra-abdominal or gynaecological infections. Moreover, it represents the alternative of choice for the treatment of Acinetobacter baumannii infections which are carbapenem-resistant strains. Thus, ampicillin-sulbactam remains a valuable agent in the physician's armamentarium for the management of adult and paediatric infections [43]. Twenty-five children with otitis media were treated with amoxicillin (25 mg/kg daily in three divided doses) or with ampicillin (50 mg/kg daily in three divided doses). Results were considered good in 87.7% and in 88.0% of children who received amoxicillin or ampicillin, respectively [44]. Thirty-one infants and children, with mean age of 3.6 years, had documented acute epiglottitis and received parenteral sulbactam sodium (30 mg/kg daily) in combination with ampicillin (200 mg/kg daily). Of 31 subjects, 26 (84.0%) had Haemophilus influenzae type b isolated from the blood and seven of the 26 subjects (26.9%) were infected by Haemophilus influenzae type b who was β-lactamase-positive. Twenty-five children (96.1%) with Haemophilus influenzae type b epiglottitis responded rapidly to the treatment. The ampicillin/sulbactam appeared to be an effective and safe alternative to chloramphenicol/ampicillin therapy for acute epiglottitis in infants and children [45]. Ampicillin/sulbactam was given by intravenous bolus at a dosage range of 75 to 450 mg/kg daily in four divided doses for variable periods of time depending on the type and severity of the infection. Of a total of 83 episodes of infections, 80 (96.4%) children were either cured or improved. Bacteriologic eradication also occurred in 46 (93.9%) of 49 infections. Side effects were diarrhoea in two patients, acute haemolytic anaemia in one patient, and transient elevations in SGOT and leukopenia in one patient. Side effects disappeared upon completion of treatment. Sulbactam/ampicillin is a safe and effective antibiotic for the treatment of common paediatric infections [46]. Ampicillin/sulbactam has proved to be clinically and bacteriologically effective against a variety of frequently encountered paediatric infections, including mild-to-moderate upper respiratory-tract infections (acute otitis media, sinusitis, pharyngitis, and tonsillitis), severe post-operative, intra-abdominal and periorbital infections, acute epiglottitis, bacterial meningitis, and brain abscess. Ampicillin/sulbactam has also proved to be effective in the prevention of post-operative surgical infections in paediatric patients. The clinical efficacy profile of ampicillin/sulbactam and sultamicillin, combined had excellent tolerability profile and make these agents attractive options for the management of many life-threatening infections in paediatric patients [47]. Ampicillin/sulbactam is clinically effective in children with infections in the respiratory-tract, ears, nose, throat, urinary-tract, skin and soft-issues, obstetric and gynaecological infections, and in the treatment of gonorrhoea, streptococcal pharyngitis, and acute otitis media in children. Ampicillin associated with cefaclor was effective in the treatment of acute otitis media in adults. Ampicillin associated with bacampicillin, cloxacillin and flucloxacillin is effective in the treatment of children with skin and soft-tissue. Ampicillin/sulbactam is superior in efficacy to bacampicillin in the treatment of chronic respiratory-tract infections, superior to cefaclor in the treatment of acute otitis media, and superior to cefadroxil in the treatment of patients with complicated urinary-tract infections in children [48]. In children with severe shigellosis, treatment with ceftriaxone for 5 days is effective and better than ampicillin in clinical cure and in the eradication of Shigella organisms from the stool [49].

Trials with ampicillin in infants and children

A randomized, controlled, open-label, non-inferiority trial was conducted in children, aged 2 to 59 months, who received either intravenous ampicillin or intravenous amoxicillin, plus intravenous gentamicin in both study arms. The monitoring of the patients was carried out according to the WHO protocol for the treatment of severe pneumonia. This trial demonstrated that both treatments were effective in curing infections caused be susceptible organisms [50]. A multicentre randomized trial was conducted in children, aged 2 to 59 months, testing the efficacy of chloramphenicol and ampicillin plus gentamicin for the treatment of infections caused by Staphylococcus aureus and Streptococcus

pneumoniae. Intravenous ampicillin plus gentamicin is superior to intravenous chloramphenicol for the treatment of community-acquired very severe pneumonia in these children [51]. A prospective, randomized, double-blind trial compared the efficacy, safety and cost-effectiveness of ampicillin, gentamicin and clindamycin or cefotaxime and clindamycin for the treatment of children with complicated appendicitis. Forty-seven children were assigned to the ampicillin, gentamicin and clindamycin regimen and 50 children received cefotaxime and clindamycin. Forty-two children (87.4%) in the ampicillin, gentamicin and clindamycin groups had an appropriate therapeutic outcome and 48 of 50 children (96.0%) who received cefotaxime and clindamycin completed the trial successfully. There were no differences between the groups with respect to the duration of antibiotic administration, fever, leucocytosis or length of hospitalization. Complications of therapy were uncommon and neither regimen demonstrated a significant advantage from an economic standpoint. Children with complicated appendicitis can be treated with cefotaxime and clindamycin or with ampicillin, gentamicin and clindamycin and both treatments had equal efficacy [52]. Sixteen children, aged 1 to 10 years, suffering from urinary-tract infection, were randomly divided into two groups. Ten children (62.5%) were treated with ampicillin paediatric suspension at a dose of 100 mg/kg daily divided in 4 doses and 6 children (37.5%) were treated with pivampicillin base paediatric suspension at a dose of 64.8 mg/kg daily divided in 4 doses. The treatment period was 14 days and all infections were cured with both treatments [53].

Transfer of ampicillin across the human placenta

Cord blood ampicillin concentration was assayed in 23 newborn infants whose mothers received the antibiotic by the obstetrical service and the ampicillin concentration ranged from 2.9 to 36.2 μg/ml. Nineteen of 23 infants (82.6%) had a serum ampicillin level in excess of 5 μg/ml at delivery, which is significantly greater than the MIC to inhibit ampicillin-sensitive Enterobacteriaceae and far exceeds the MIC for group B β-haemolytic streptococci. Antenatal ampicillin therapy results in significant ampicillin concentration in the neonate that may obscure cultures obtained after delivery [54]. Ampicillin was administered to 30 healthy pregnant women during labour by continuous intravenous infusion of 1 gram or by intravenous injection of 2 grams twice-daily. Following infusion, the maternal serum concentration of ampicillin ranged from 25 to 30 μg/ml and the peak concentration ranged from 52 to 73 μg/ml after intravenous injection. Ampicillin concentration in the amniotic fluid was 5 μg/ml 2 to 3 hours and 25 μg/ml after 6 to 7 hours. Both cord serum and amniotic fluid concentrations of ampicillin were higher after the repeated injections. Following the repeated intravenous injections, ampicillin concentration was sufficient to kill gram-negative pathogens causing intrauterine infections [55]. Ampicillin was administered intravenously to 25 pregnant women undergoing therapeutic abortion in the middle trimester of pregnancy. The concentrations ampicillin became equal between maternal and foetal plasma 90 min after administration and the foetal to maternal ratio of plasma ampicillin concentration steadily increased at least for 200 min following dosing. Thus the placenta is not a barrier for ampicillin [56]. Placental transfer of ampicillin was studied in 103 pregnant women. A rapid transfer of ampicillin rapidly occurs between the mothers to foetus. Ampicillin appeared in the amniotic fluid 90 min after dosing and the amniotic fluid compartment forms a depot for the sequestration of ampicillin. Varying rates of transfer, out the amniotic fluid, occur in different stages of pregnancy [57].

Migration of ampicillin into the breast-milk

Low concentrations of ampicillin were found in colostrum/breast milk from 6 mothers treated with pivampicillin at doses of 1.0 to 2.1 grams daily during the first to eighth day postpartum in the maternity ward. It was calculated that the breast-fed infant could theoretically receive 0.05 to 0.37% of the dose per kg given to the mother. The exposure of the breast-fed infant suckling from a mother under treatment with ampicillin or pivampicillin seems to be minimal [58]. The concentration of ampicillin was determined in the breast-milk and in the plasma of 14 lactating mothers receiving pivampicillin for puerperal infections and in plasma of their suckling infants. Ampicillin could not be detected in plasma of the infants, i.e. all levels were < 0.03 μg/ml the assay limit. Maximum ampicillin concentration occurs in plasma 60 to 120 min and in milk 180 to 240 min after dosing. Milk to plasma ratio varied between 0.01 and 0.58. The highest level of ampicillin in breast-milk was 1.02 μg/ml in a woman receiving pivampicillin tablets 700 mg thrice-daily. An infant can at the most ingest 0.5 mg of ampicillin daily and this dose is too small to cause any symptoms in the suckling infant [59].

Penetration of ampicillin into the cerebrospinal fluid (CSF)

Thirty-five infants with suspected septicaemia were randomized to receive tobramycin or ceftazidime, both in combination with ampicillin. Ampicillin concentration in the CSF ranged from 1 to 80 μg/ml which should be sufficient for treatment of meningitis caused by enterococci and Listeria monocytogenes, the most important neonatal pathogens not covered by ceftazidime [60]. Five patients with Listerial meningitis received ampicillin at a dose of 50 to 60 mg/kg. Ampicillin concentration ranged from 5 to 8 μg/ml which means a CST to serum ratio of 3 to 5% in four patients. In the fifth patient, the ampicillin concentration in the CSF ranged from 60 to 130 μg/ml indicating a CSF to serum ratio of 40 to 87% [61]. The penetration of ampicillin into the CSF was studied in 12 subjects who had not the meninges inflamed. Ampicillin was administered at a dose of 33 mg/kg. The CSF specimens were sampled at 1, 2, and 4 h after the beginning of the infusion. Blood samples were obtained at the end of the infusion and at 45, 60, 90, 120, 180, and 240 min after the beginning of the infusion. (Table 5) shows ampicillin concentration in the CSF and in the serum of these subjects.

This table shows that ampicillin penetrates into the CSF in significant amounts and the penetration-rate increases with the time after dosing [62].

Twenty-eight patients with bacterial meningitis received ampicillin by the intramuscular route and 16 patients received it by the intravenous route. The mean ampicillin concentration in the CSF was similar in the two groups 1 h after the first or second day of treatment. Ampicillin concentration was higher in the

intramuscular group on both days of treatment 4 h after the dose. CSF to serum ratios were similar in both groups but considerably higher at 4 hours than at 1 hour following the dose [63].

Treatment of meningitis with ampicillin/sulbactam or with ampicillin combined with antibiotics in infants and children

Eighty-one infants and children, aged one month to 14 years, with meningitis were randomized to receive either ampicillin/sulbactam at a dose of 400/50 mg/kg (N = 41) or ampicillin/chloramphenicol at a dose of 400/50 mg/kg (N = 40). Pathogens were isolated from the cerebrospinal fluid in 65 subjects (77.3%). In the ampicillin/sulbactam group, there were 18 Haemophilus influenzae isolates (one resistant to ampicillin), 5 Streptococcus pneumoniae, 5 Neisseria meningitides, one Klebsiella pneumoniae, one Pseudomonas aeruginosa, and one Listeria meningitides. In the chloramphenicol/ampicillin group, there were 19 Haemophilus influenzae, 10 Streptococcus pneumoniae, 3 Neisseria meningitides, one Haemophilus parainfluenzae, and one Citrobacter isolates. Sulbactam/ampicillin was as effective as chloramphenicol/ampicillin in the eradication the pathogens and thus in curing meningitis [64]. One-hundred-seven children with bacterial meningitis were initially given cefuroxime or ampicillin plus chloramphenicol for 7 days or 10 day. Organisms isolated in the cerebrospinal fluid included Haemophilus influenzae type b (of which 25% were β-lactamase positive), Streptococcus pneumoniae, and Neisseria meningitides. Clinical cure rates were similar (95%) in both treatments thus the two treatments are equivalent in eradication-rate of pathogens [65]. A prospective study was performed comparing high ampicillin dose of 400 mg/kg daily and low dose of 150 mg/kg daily in the treatment of 172 children with bacterial meningitis. Response to both regimens was equivalent in terms of average hospital stay, duration of ampicillin therapy, microbiological response, and death. Children with Haemophilus influenzae infections treated with low-dosage regimens had slightly prolonged febrile courses. These results suggest that high-dosage regimen of ampicillin offers no benefit over low-dosage regimen in the treatment of bacterial meningitis in children [66]. Two-hundred children, aged > 3 months, were randomised to receive chloramphenicol, ampicillin (initially with chloramphenicol), cefotaxime, or ceftriaxone. The drugs were given in 4 equal daily doses for 7 days, except for ceftriaxone which was given only once-daily. The causative organisms were Haemophilus influenzae type b (N = 146), meningococci (N = 32), pneumococci (N = 13), and others (N = 9). In children with Haemophilus influenzae type b meningitis, the sterilisation of the cerebrospinal fluid occurred more rapidly with ceftriaxone. Ampicillin is a good and cheap alternative, but may induce resistance [67]. Fifty children with bacterial meningitis were prospectively randomized to receive cefotaxime (50 mg/kg 4 times-daily) or ampicillin and chloramphenicol in standard doses. Twenty-three children received cefotaxime and 27 children received ampicillin and chloramphenicol. Bacterial isolates included Haemophilus influenzae (N = 29), Streptococcus pneumoniae (N = 8), Neisseria meningitides (N = 8), group B streptococci (N = 3), and Salmonella enteritidis (N = 2). Ten of Haemophilus influenzae isolates were resistant to ampicillin of which nine were on the basis of β-lactamase production. All strains were susceptible to cefotaxime. Clinical cure-rates and survival-rate were similar with the two treatments and no adverse adverse-effects were noted in either group. Cefotaxime was found to be as safe and effective as ampicillin plus chloramphenicol for the treatment of bacterial meningitis in children [68]. Ceftriaxone was compared in a randomized fashion with ampicillin and chloramphenicol in the treatment of 19 children with Haemophilus influenzae type b meningitis. Ninety per cent of the isolates of Haemophilus influenzae type b were inhibited by 0.0625 μg/ml, 1 μg/ml and 1 μg/ml of ceftriaxone, ampicillin and chloramphenicol, respectively. One child with pneumococcal meningitis and two children with meningococcal meningitis recovered rapidly during ceftriaxone therapy. Three children, with gram-negative meningitis caused by multiply-drug resistant organisms, were bacteriologically cured within 5 days after the onset of therapy. Ceftriaxone, as a single agent, was comparable in efficacy to ampicillin and chloramphenicol in children with meningitis [69]. Seventy-eight children with bacterial meningitis were evaluated in a prospective, randomised study comparing twice-daily ceftriaxone as single-drug therapy and with ampicillin and chloramphenicol given 4 times-daily. The pathogens were Haemophilus influenzae type b (N = 54), streptococci (N = 9), meningococci (N = 9), and unknown organisms (N = 6). In 40 specimens of cerebrospinal fluid, obtained 4 to 12 hours after initiation of therapy, the cultures were negative in 57% of children treated with ceftriaxone and in 42% of children who received ampicillin plus chloramphenicol. The mean bactericidal activity in the cerebrospinal fluid was significantly greater in the ceftriaxone than in the ampicillin and chloramphenicol group at the beginning and at the end of therapy but there were no significant differences in clinical responses or in frequency of complications [70]. Sixty-two children with Haemophilus influenzae meningitis were treated with ampicillin sodium at a dose of 200 mg/kg daily for 10 days. Thirty-one children received the drug intravenously for 10 days and the other 31 children received ampicillin intravenously for 5 days followed by intramuscular ampicillin during the last for 5 days of treatment. Ampicillin concentrations in cerebrospinal fluid were higher one hour after intravenous administration, but at 2 and 4 hours, the concentrations were greater after intramuscular doses. Responses to therapy and rates of complications were similar in the two groups. All organisms were ampicillin-susceptible and all cerebrospinal fluid cultures were negative by 48 hours. The schedule of 5 days of intravenous treatment followed by 5 days of intramuscular therapy is pharmacologically and clinically as effective as 10 days of intravenous therapy and has practical advantages [71].

DISCUSSION

Ampicillin is an aminopenicillin and expands the spectrum of activity of penicillin G in a different direction from the penicillinase-resistant penicillins they allow for useful activity against some gram-negative organisms. Ampicillin is destroyed by β-lactamases (from both gram-positive and gram-negative bacteria); thus further expansion of its activity is enhanced through co-formulation with sulbactam a β-lactamase inhibitor. Ampicillin is bactericidal for susceptible gram-positive and gram-negative bacteria. Ampicillin is active against meningococci, Listeria monocytogenes, enterococci and concurred

administration of a β-lactamase inhibitor such as sulbactam markedly expands the ampicillin spectrum of activity against Haemophilus influenzae, Escherichia coli, Klebsiella, Proteus, and Bacillus fragilis. Ampicillin is absorbed after oral administration; the intake of food diminishes its absorption and undergoes enterohepatic circulation [1]. Ampicillin may be administered intravenously and orally; the intravenous dose is 50 mg twice-daily and thrice-daily in preterm and term infants, respectively [2]. In children, the oral dose ranges from 125 to 500 mg 4 times-daily and increases with the child age [4]. Listerial meningitis is treated with ampicillin intravenously at a dose of 100 mg/kg twice-daily, thrice-daily, and 4 times daily to infants aged up to 7 days, 7 to 20 days and 21 to 28 days, respectively, and the intravenous dose is 50 mg/kg given 4 to 6 times-daily to children [4]. Ampicillin/sulbactam or ampicillin has been found efficacy and safe in infants and children [5-12]. Ampicillin/sulbactam is efficacy in the treatment of urinary-tract infections in infants [5], ampicillin if efficacy and safe in treating the sepsis cussed by Listeria monocytogenes and enterococci in infants [6], ampicillin is effective in the treatment of fever and caused lower mortality-rate than penicillin G in infants [7], and in the treatment of severe pneumococcal pneumonia in children [8]. Ampicillin/sulbactam is effective and safe in the treatment of lower respiratory-tract, urinary-tract, skin, bone and soft-tissue infections [9] in the treatment of serious skin and skin-structure infections in children [10], in the treatment of pneumonia caused by Escherichia coli, Staphylococcus aureus and Klebsiella pneumoniae in children [11] and in the treatment of severe pneumonia in children [12]. Ampicillin causes different effects [13-16]. Ampicillin cures the upper and lower respiratory-tract infections caused by Streptococcus pneumoniae, β-haemolytic streptococci, group B streptococci, and Listeria monocytogenes in infants [13], ampicillin cures the otitis media caused by Diplococcus pneumoniae and Haemophilus influenzae in children [14], bronchopneumonia and acute bronchial obstructive syndrome in children [15], and ampicillin is effective against various salmonella species [16]. Ampicillin may induce adverse-effects [17-21]. The adverse-effects are: diarrhoea [17-21] and changes of bowel habits [21]. Ampicillin and sulbactam diffuse in tissues but reaches lower concentration in the abdominal tissue, in fat tissue and in the colonic wall [22], in the epididymis [23], and in various body-tissues [24] than in serum. The pharmacokinetics of ampicillin have been studied in infants [25-26]. The elimination half-life ranges from 2.4 to 5.0 hours and decreases with infant gestational and the postnatal ages [25] and ampicillin serum concentration decreases with the gestational age and body-weight [26]. The total body clearance ranges from 0.055 to 0.11 L/h/kg in infants and increases with the gestational age [25]. These pharmacokinetic modifications may be explained by the increase of renal function which increases with the infant maturation. The distribution volume of ampicillin is 0.40 L/kg, thus it is lower than the water volume, and it is not modified by infant maturation [25]. In children, the elimination half-life, the total body clearance and the distribution volume are about 0.8 hours, 5 ml/min/kg, and 0.3 L/kg, respectively [27]. Thus the ampicillin elimination half-life is shorter in children than in infants whereas the distribution volume is similar in children and infants. The comparison of the total body clearance in children and infants is difficult because different units have been used in children and infants. Ampicillin interacts with drugs [28-34]. Ampicillin inhibits the transport of drugs [28], incompatible drug interactions occurred in 25% of infants receiving ampicillin and other drugs [29], quinine reduces the bioavailability and the antimicrobial activity of ampicillin-cloxacillin [30], the co-administration of allopurinol and ampicillin induces rashes [31]. A drug interaction was observed following the co-administration of ampicillin with N-acetyl-p-benzoquinone-imine [32], following the co-administration of ampicillin and gentamicin [33], and chloroquine reduces the urinary excretion of ampicillin when it is co-administered with cloxacillin [34]. The therapeutic use of ampicillin/sulbactam has been reported in children [35-39]. Ampicillin/sulbactam has been used in the treatment of respiratory-tract, gynaecological/obstetric, intraabdominal, acute epiglottitis, periorbital cellulitis, diabetic food, skin, and soft-tissue infections [35]. This drug combination is found efficacy against organisms that produce β-lactamase including Bacteroides fragilis and Neisseria gonorrhoea and has therapeutic and prophylactic efficacy for a wide range of microorganisms [36], ampicillin/sulbactam is efficacy for the treatment of life-threating infections caused by Acinetobacter [37], for the treatment of upper and lower respiratory-tract, urinary-tract, skin, bone, soft-tissue infections and for the prophylaxis of infections which occurred during surgery [38], and for the treatment of infections caused by Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and gram-negative rods [39]. The treatment with ampicillin or with ampicillin/sulbactam has been performed in infants and children [40-49]. Ampicillin plus cefotaxime eradicated the infection caused by Enterococcus faecalis in an infant [40] and the sepsis caused by Klebsiella pneumoniae in infants [41], and ampicillin treated non-complicated community-acquired-pneumonia in children [42]. Ampicillin/sulbactam successfully treated mild-to-moderate intraabdominal and gynaecological infections caused by Acinetobacter baumannii, which were carbapenem-resistant in children [43], otitis media [44], and epiglottitis caused by Haemophilus influenzae type b in children [45]. Ampicillin/sulbactam eradicated bacteriological infections [46], cured otitis media infections, sinusitis, pharyngitis, tonsillitis, intraabdominal, periorbital infections, acute epiglottitis, bacterial meningitis, brain abscess and in many life-threatening infections in paediatric patients [47]. Ampicillin/sulbactam has clinical efficacy in the treatment of respiratory-tract, ears, nose, throat, urinary-tract, skin, soft-tissue, obstetric, and gynaecological infections [48] and ampicillin eradicated Shigella organism from the stool [49] in children. The trials with ampicillin have been conducted in infants and children [50-53]. Ampicillin plus gentamicin cured the pneumonia caused by susceptible organisms [50]. Ampicillin plus gentamicin was efficacy as chloramphenicol in the treatment of pneumonia caused by Staphylococcus aureus and Streptococcus pneumoniae in children [51]. Trials with chloramphenicol and ampicillin plus gentamicin resulted efficacy in curing complicated appendicitis and this treatment is equivalent to cefotaxime and clindamycin in children [52]. Ampicillin cured the urinary-tract infections in children [53]. Ampicillin freely crosses the human placenta [54-57] and the foetal and maternal plasma concentrations of ampicillin became equal 90 min following ampicillin administration [56]. Ampicillin poorly migrates into the breast-

milk [58, 59]. The exposure to ampicillin of the breast-fed infant suckling from a mother treated with ampicillin is minimal [58]. Ampicillin penetrates into the cerebrospinal fluid in significant amounts [60-63]. Following ampicillin administration, ampicillin concentration in the cerebrospinal fluid is sufficient for the treatment of meningitis caused be enterococci and Listeria monocytogenes in infants [60]. The cerebrospinal fluid to serum ratio of ampicillin ranges in a wide interval [61] and this ratio increases with the time after ampicillin administration [62, 63]. The meningitis caused by different pathogens was treated with ampicillin/sulbactam or with ampicillin combined with various antibiotics in infants and children [64-71]. Ampicillin/sulbactam or ampicillin/chloramphenicol eradicated Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitides, Klebsiella pneumoniae, Pseudomonas aeruginosa and Listeria meningitides from the cerebrospinal fluid and cured the meningitis caused by these pathogens in infants [64]. Haemophilus influenzae type b, Streptococcus pneumoniae, and Neisseria meningitides were isolated from the cerebrospinal fluid of children and ampicillin plus chloramphenicol eradicated these microorganisms and this treatment was equivalent to the treatment with cefuroxime [65]. Low dose of ampicillin (150 mg/kg) was sufficient as high dose (400 mg/kg) to cure the meningitis caused by Haemophilus influenzae in children [66]. Ampicillin, chloramphenicol, and cefotaxime eradicated Haemophilus influenzae type b, meningococci, pneumococci and other pathogens from the cerebrospinal fluid of children but the treatment with ceftriaxone sterilized the cerebrospinal fluid more rapidly [67]. Ampicillin plus chloramphenicol cured the meningitis of children caused by Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitides, group B streptococci and salmonella enteritidis and this treatment was equivalent to the treatment with cefotaxime [68]. Ampicillin plus chloramphenicol cured the meningitis by organism multi-drug resistant but the children recovered more rapidly following ceftriaxone [69]. The meningitis caused by Haemophilus influenzae type b, streptococci, meningococci, and other organisms in children was cured by ampicillin plus chloramphenicol but the sterilization of the cerebrospinal fluid occurred more rapidly with ceftriaxone [70]. The efficacy of intravenous ampicillin given for 10 days was compared to intravenous ampicillin give for 5 days followed by intramuscular ampicillin administered for 5 days and the two treatments are comparable [71].

In conclusion, Ampicillin is an aminopenicillin and kills gram-positive and gram-negative organisms. This drug is rapidly absorbed following oral administration but the intake of food diminishes its absorption. Ampicillin may be administered intravenously and orally and the intravenous dose is 50 mg twice-daily and thrice-daily in preterm and term infants, respectively. The oral dose in children ranged from 125 to 400 mg 4 times-daily and increase with the child age. Ampicillin has been found efficacy and safe in infants and children but may induce adverse-effects. This ampicillin and sulbactam diffuse in tissues but their concentrations are lower in different tissues than that in serum. Ampicillin elimination half-life ranges from 2.4 to 5.0 hours in infants and decreases with infant maturation and it is about 0.8 hours in children. The ampicillin total body clearance is lower in infants that children because ampicillin is mainly eliminated by renal route and the renal function increases with infant maturation and child development. Ampicillin interacts with drugs and the treatment and trials with ampicillin have been extensively investigated in infants and children. Ampicillin crosses the placenta freely but poorly migrates into the breast-milk. Ampicillin penetrates into the cerebrospinal fluid in significant amounts. Ampicillin/sulbactam or ampicillin co-administered with other antibiotics, particularly with chloramphenicol, treated the meningitis caused by different pathogens. The aim of this study is to review the clinical pharmacology of ampicillin in infants and children.

CONFLICT OF INTERESTS

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

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