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Clinical Pharmacology of Ampicillin in Neonates and Infants: Effects and Pharmacokinetics

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Abstract

Ampicillin is a bactericidal antibiotic, it penetrates into the bacterial wall better than penicillin G and is active against gram-negative bacteria that are resistant to penicillin G. Ampicillin has a broad-spectrum antimicrobial activity and is the most widely used antibiotic for treating infections caused by Listeria, Beta-lactamase-negative Haemophilus, enterococci, Shigella, streptococci, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Neisseria gonorrhea, Neisseria meningitis and many coliform organisms. Ampicillin is excreted unchanged in the urine. In neonates with a gestational and postnatal ages of ≤ 34 weeks and ≤ 7 days, respectively, the half-life, the clearance and the distribution volume of ampicillin are 5.0 hours, 0.055 l/h/kg, and 0.40 l/kg, respectively.

The ampicillin half-life decreases and the clearance of ampicillin increases with the neonatal maturation whereas the distribution volume is not affected by the neonatal maturation. Ampicillin may be administered orally. Ampicillin penetrates into the cerebrospinal fluid, especially when the meninges are inflamed. The recommended dose of ampicillin is 50 mg/kg every 12 hours in the first week of life, every 8 hours in neonates 1-3 weeks old, and every 6 hours in neonates 4 or more weeks old. Bacteremia, caused by group B Streptococcus, is treated with 150 to 200 mg/kg/day ampicillin and meningitis is treated with 300 to 400 mg/kg/day ampicillin in divided doses. Some organisms are resistant to ampicillin and a combination of gentamicin and a third-generation cephalosporin is recommended. The aim of this study is to review the effects and pharmacokinetics of ampicillin in neonates and infants.

Key Words: Ampicillin, Effects, Neonate, Resistance, Susceptibility.

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1-INTRODUCTION

Ampicillin is a bactericidal antibiotic belonging to the family of penicillins. Ampicillin, like all penicillins, kills susceptible bacteria by interfering with the biosynthesis of the bacterial wall, eventually lysing the bacteria by autolysis. Ampicillin penetrates into the bacterial wall better than penicillin G, enabling it to kill many gram-negative bacilli. Ampicillin is unique in that it is active against some gram-negative bacilli that are resistant to penicillin G. Organisms that are susceptible to penicillin G also are susceptible to ampicillin (1). Ampicillin has a broad-spectrum antimicrobial activity and is the most widely used antibiotic for treating infections caused by Listeria, beta (β)-lactamase-negative Haemophilus influenzae, enterococci, Shigella, streptococci, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Neisseria gonorrhea, Neisseria meningitis, and many coliform organisms (2).

Ampicillin has frequently been used prophylactically to reduce the risk of infection after abdominal surgery including caesarean delivery (2). Ampicillin is especially useful in treating acute and uncomplicated urinary tract infections caused by Escherichia coli and/or Proteus species. Haemophilus influenzae meningitis can be treated with ampicillin if the organisms do not produce β-lactamase. Peak concentrations in the cerebrospinal fluid is achieved 2 to 7 hours after a 40 to 70 mg/kg intravenous dose in infants with meningitis. The mean cerebrospinal fluid concentrations at 2 and 6 hours were 13.6 and 15.2 µg/ml, respectively, and represented 11.6% and 15.5% of the corresponding serum concentration. Serious infections caused by Pseudomonas usually require the synergistic effects of ampicillin plus an aminoglycoside (2). The distribution of a drug in the body is affected largely by organ and tissue blood flow, pH, intracellular and extracellular fluid volumes and their ratio, the lipophilic feature of the drug, ionization, protein binding, and membrane permeability (3). Because of the maturation of hepatic and renal functions in the first month of life, pharmacokinetic parameters of drugs are continuously changing, dependent not only on postnatal age, but also on gestational age. The increased Cmax (Maximum Concentration observed), of ampicillin observed in premature infants appears to be primarily due to decreased clearance of this drug. Renal excretion of drugs consists of glomerular filtration, active tubular secretion, and reabsorption from the tubular lumen to tubular cells. Many antibacterial drugs are excreted by the renal route as unchanged compounds such as ampicillin. In neonates, the renal functions: renal blood flow, glomerular filtration rate, concentration ability, acid excretion ability, and maximal glucose reabsorption amount are low. Therefore, the excretion of drugs excreted via the kidneys as an unchanged compound, is delayed. The glomerular filtration rate is 25 ml/min per 1.73 m^2 at 24 hours in normal full-term neonate, which doubles or trebles at the age of 1-13 weeks (4-6).

It increases gradually in 12-24 months, and reaches the level for adults at the age of 3 years. Therefore, the dose and dosing intervals should be considered fully when a drug excreted predominantly via the kidney is administered. Antibacterial drugs, such as ampicillin, are bound to plasma protein, and when the binding sites are saturated, the amount of those unbound will increase. The binding is reversible, and a balance between the bound and free drugs is always kept. Protein-bound drugs are ineffective, and only free drugs are transferred into tissues to exert their antibacterial activities. Ampicillin is stable in acid and is well absorbed after oral administration (7). Peak concentrations of ampicillin after oral administration are

variable, delayed until 4 hours after the dose, and are 2- to 8-fold lower than peak concentrations achieved after equivalent intramuscular dose. Oral ampicillin medication can alter the normal flora of the bowel, causing diarrhea, and the reduction of absorption and bioavailability of ampicillin. The serum half-life of ampicillin in term infants younger than 7 days is approximately 4 hours (8). The penetration of ampicillin in the cerebrospinal fluid is moderately good particularly when the meninges are inflamed (2). Ampicillin is often used to treat meningitis caused by susceptible bacteria. Very large doses of ampicillin may result in central nervous system excitation or seizure activity. Moderate prolongation of bleeding times (by approximately 60 seconds) may occur after repeated doses. Hypersensitivity reactions (maculopapular rash, urticarial rash, or fever) are rare in neonates (8). The following drugs are incompatible with ampicillin therapy: amikacin, amiodarone, dopamine, epinephrine, erythromycin, lactobionate, fluconazole, gentamicin, hydralazine, metoclopramide, midazolam, nicardipine, sodium bicarbonate, and tobramycin (8).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; August 2017 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "ampicillin dosing neonates", "ampicillin effects neonates", "ampicillin meningitis neonates", "ampicillin susceptibility neonates", "ampicillin resistance neonates", and "ampicillin pharmacokinetics neonates" were used. In addition, the books Neonatal Formulary (2) and NEOFAX by Young and Mangum (8) were consulted.

3-RESULTS

3-1. Dose and administration of ampicillin in neonates and infants

Give 50 mg/kg ampicillin every 12 hours in the first of week of life, every 8 hours in infants 1-3 weeks old, every 6 hours in infants 4 or more weeks old. Increase the dosage interval if there is severe renal failure (2). Bacteremia, caused by group B streptococci, is treated with 150 to 200 mg/kg/day of ampicillin, and 300 to 400 mg/kg/day of ampicillin, in divided doses, are used to treat meningitis. Sustain treatment for 10-14 days in proven septicemia, for 3 weeks in infants with meningitis and four weeks in otitis. The addition of an aminoglycoside for initial therapy is also recommended (8). Oral medication can sometimes be used to complete treatment even though absorption is limited and variable (2).

3-2. Antimicrobial effects of ampicillin and other antibiotics in neonates and infants

Septicemia continues to be an important cause of neonatal morbidity and mortality (9). The bacteria most commonly responsible are group-B β-hemolytic streptococci and Escherichia coli, but regional differences exist. Sepsis caused by Staphylococcus epidermis has occurred with increasing frequency in several neonatal intensive care units. Other organisms are less commonly responsible. The choice of antibiotics for suspected sepsis is based on the possible organisms involved and their antibiotic susceptibility patterns, which vary from hospital to hospital and at different times in the same hospital. Currently recommended initial therapy consists of ampicillin and gentamicin. The addition of vancomycin is

indicated when staphylococcal septicemia is suspected. During outbreaks of neonatal sepsis caused by aminoglycoside-resistant gram-negative bacteria, the use of third-generation cephalosporins or acylaminopenicillins may be appropriate, depending on the results of susceptibility tests. Continuing efforts to develop antibiotics for the treatment of neonatal sepsis are warranted. Hornik et al. (10) evaluated the relationship between ampicillin dosing, exposure, and seizures. These authors used the electronic health record data from 348 infants with a gestational age and body weight ranging from 24-41 weeks and 500-5,400 grams, respectively. A total of 131,723 infants receiving 134,041 courses of ampicillin for 653,506 infant-day of exposure was assessed. The median daily dose was 200 mg/kg/day. On multivariable analysis, dosing was not associated with seizures. However, increasing the ampicillin dosage was associated with increased odds of seizures. In these infants, higher ampicillin exposure was associated with seizures as documented in the electronic health record.

On the day of birth, the bleeding time of very-low-birth-weight neonates is generally prolonged, compared with term neonates. However, their bleeding time generally improves (shortens) over the next 7 to 10 days. Ampicillin can prolong the bleeding times of term and late preterm neonates, but its effect on very-low-birth-weight neonates, who already have a somewhat bleeding time initially, is not known. A total of 20 very-low-birth-weight neonates have been studied by Sheffield et al. (11). The neonates ranged from 23 to 30 gestational age and the body weight ranged from 500 to 1,410 grams at birth. Initial bleeding times averaged 166 seconds (95%confidence interval [CI], 138 to 194) and initial platelet function analyzer-100 times averaged 119 seconds (95% CI, 90 to 148). In all, 10 neonates had ampicillin dosing stopped after a shorter course (4 to 7 doses) and 10 neonates continued for a longer course. After stopping the ampicillin following a short course the bleeding times and the platelet function analyzer-100 times were similar to the initial values. However, after a longer course the bleeding times were prolonged by an average of 2 min, to 4.7 min. The number of doses of ampicillin received in the first week correlated with the degree of prolongation in bleeding time ($r = 0.68$). Clark et al. (12) described the antibiotic use during the first 3 days after birth in neonates admitted to the neonatal intensive care unit. There were 128,914 neonates selected as the study cohort; 24,111 were treated concurrently with ampicillin and cefotaxime and 104,803 were treated concurrently with ampicillin and gentamicin. Neonates treated with ampicillin/cefotaxime were more likely to die and were less likely to be discharged home or for faster care than neonates treated with ampicillin/gentamicin.

For neonates receiving ampicillin, the concurred use of cefotaxime during the first 3 days after birth either is a surrogate for an unrecognized factor or is itself associated with an increased risk of death, compared with the concurrent use of gentamicin. Terrone et al. (13) evaluated the relationship between neonatal death caused by sepsis associated with ampicillin-resistant organisms and length of antibiotic exposure. Of the 78 neonatal deaths, 35 met the inclusion criteria. There were 8 cases of sepsis from ampicillin-resistant Escherichia coli and 27 cases caused by other organisms. There was a statistically significant difference between the mean number of doses of ampicillin received by the ampicillin-resistance Escherichia coli group (17.6 ± 5.5) compared with the other organisms group (4.9 ± 3.6) ($p < 0.001$). The administration of gentamicin, at least 1 hour before administration of ampicillin, in neonates has been advocated because of in vitro

inactivation of aminoglycosides by β-lactam antibiotics. Daly et al. (14) studied the effect of varying concentrations of ampicillin (50, 100, 200, and 400 µg/ml) on aminoglycoside antibiotics in vitro with the use of stock solutions diluted in pooled sera obtained from cord blood and incubated samples at degrees 37 degrees C, and 40 degrees C. Daly et al. (14) found inactivation of aminoglycosides to be dependent on time, temperature, and ampicillin concentration, but the degree of inactivation was small and does not support temporal separation of parenteral administration of ampicillin and aminoglycosides to neonate. The impact of ampicillin and cefuroxime on the bacterial flora of neonates was examined in a neonatal intensive care unit (15). For the first period of study (January-September), ampicillin plus gentamicin were used as empirical therapy of infection. During this time, 92.6% of all gram-negative bacilli were resistant to ampicillin and 56.6% to cefuroxime. These percentages decreased significantly ($p< 0.05$) to 60% and 16.2%, respectively, over the next period of study (October 1989-October 1990) when cefuroxime plus gentamicin were used.

A decrease in the number of cases of gram-negative bacilli from bacteremia and meningitis was also significant (from 21.2% to 11.2%). However, the number of enterococcal isolates and cases of enterococcal bacteremia increased. These findings underline the important effect of ampicillin and cefuroxime in modulating the bacterial flora and its antibiotic resistance in neonates in a neonatal intensive care unit. A total of 341 episodes of invasive infections in 338 newborn infants were evaluated (16). Of the 365 pathogens isolates from blood and/or cerebrospinal fluid, 91% were sensitive to either ampicillin or aminoglycosides or both. Ampicillin resistance was mainly found in very-low and low-birth-weight infants with late-onset infections, in which aerobic gram-negative rods were common pathogens. In contrast, aminoglycosides resistance was common in early infections, due to the dominance of group B streptococcal infections. The ampicillin-aminoglycoside combination had been given as initial treatment in 189 cases of septicemia or meningitis. Treatment failed in 36 infections (20%), although all organisms were sensitive to one or both antibiotics. Treatment failed in 6 to 34 (25%) neonates with meningitis but the failure was not related to ampicillin or aminoglycoside resistance. In conclusion, both in vitro and clinical results show that the ampicillin-aminoglycoside combination can be used as initial treatment of invasive infections in neonates.

A total of 147 neonates with bacterial infections were enrolled in the study. Twenty-eight neonates were treated with aztreonam plus ampicillin and 72 neonates received amikacin plus ampicillin (conventional therapy) (17). Treatment groups were comparable in age, clinical status, and type and severity of underlying disease at the time of enrollment. Bronchopneumonia and infections caused by Pseudomonas species occurred significantly more often in amikacin plus ampicillin treated infants compared with patients given aztreonam plus ampicillin group. Sepsis was documented in 83% of neonates in each treatment group and gram-negative enteric bacilli and Pseudomonas species were the principal pathogens. Median peak serum bacterial titers against the etiologic agent were 1:64 for the aztreonam/ampicillin-treated neonates and 1:16 for amikacin/ampicillin-treated neonates. Case fatality rates resulting from the primary infection were 7% and 22% ($p = 0.001$), respectively, superinfections occurred in 39% and 34%, and treatment failure occurred in 7% and 28% ($p= 0.036$) of the aztreonam/ampicillin and

amikacin/ampicillin-treated neonates, respectively. No clinical adverse reactions were observed in the neonates of both groups. Based on these results aztreonam appears to be more effective than amikacin when used initially with ampicillin for empiric treatment of neonatal bacterial infections. Fifty children with bacterial meningitis were prospectively randomized to receive cefotaxime (50 mg/kg/dose every 6 hours) or ampicillin and chloramphenicol in standard doses (18). Twenty-three children received cefotaxime and 27 children received standard therapy. Bacterial isolates included: Haemophilus influenzae (n = 29), Streptococcus pneumoniae (n = 8), Neisseria meningitis (n = 8) group B streptococci (n = 3), and Salmonella enteritis (n = 2). Ten (34%) of the Haemophilus influenzae isolates were resistant to ampicillin, nine on the basis of β-lactamase production. All strains were susceptible to cefotaxime. Clinical cure rates for the cefotaxime (100%) and standard therapy (96%) groups were similar; survival without detectable sequelae was similar, at 78% and 77%, respectively. The duration of therapy, 11.1±2.4 days versus 11.9±3.9 days, and days to efervescence, 4.7±2.6 days versus 5.6±2.9 days, were similar in the cefotaxime and standard therapy groups. No adverse drug reactions or side effects were noted in either group.

Cefotaxime was found to be as safe and effective as standard therapy (ampicillin and chloramphenicol) for the treatment of bacterial meningitis in children. The activity of ampicillin and chloramphenicol in combination was evaluated against 16 gram-negative bacteria isolates from the cerebrospinal fluid of neonates with meningitis (19). The combination of antibiotics was synergistic (fractional inhibitory concentration less than 1.0) against 11 of 16 (69%) isolates by agar dilution technique and 12 of 16 (75%) isolates by microbroth dilution technique. In kinetic studies, ampicillin and chloramphenicol together exhibited an increased rate of killing against 9 of 14 isolates.

3-3. Management of bacterial meningitis with ampicillin and other antibiotics in neonates and infants

Ouchenir et al. (20) studied the effects of ampicillin in 113 neonates with a postnatal age < 90 days. Sixty-three neonates had a proven meningitis and 50 neonates had suspected meningitis. Predominant pathogens were Escherichia coli (33%) and group B Streptococci (31%). Two of 15 neonates presenting meningitis on day 0 to 6 had isolates resistant to both ampicillin and gentamicin (Escherichia coli and Haemophilus influenzae type B). Six of 60 infants presenting a diagnosis of meningitis from home from day 7 to 90 had isolates, for which cefotaxime would be a poor choice (Listeria monocytogenes, Enterobacter cloacae, Enterobacter sakazakii, and Pseudomonas stutzeri). Sequelae were documented in 84 neonates (74%), including 8 deaths (7%). Escherichia coli and group B Streptococci remain the most common causes of bacterial meningitis in the first 90 days of life. For empirical therapy of suspected bacterial meningitis, one should consider a third-generation cephalosporin (plus ampicillin for at least the first month), potentially substituting a carbapenem for the cephalosporin if there is evidence for gram-negative meningitis.

The three major pathogens in developed countries causing meningitis are: Group B streptococci, gram-negative rods and Listeria monocytogenes (21). Positive culture of cerebrospinal fluid may be the only way to diagnose neonatal bacterial meningitis and to identify the pathogen. When neonatal bacterial meningitis is suspected, treatment must be aggressive, as soon as possible. Antibiotics should be administered intravenously, at the highest clinically validated doses. Empiric

antibiotic treatment should include agents active against all main pathogens; currently the recommended empiric treatment of the neonatal bacterial meningitis is ampicillin, plus an aminoglycoside and a third-generation cephalosporin. Therapy should be reassessed after cultures and antibiotic susceptibility is available. Prevention of neonatal sepsis, early recognition of infants at risk, prompt treatment and future adjunctive therapies will improve prognosis. Six neonates had early-onset (< 7 days) meningitis and 47 neonates had late-onset (≥ 7 days) group B streptococcal meningitis. Three infants died. Infants received broad-spectrum antibiotics initially penicillin (68%), ampicillin (28%), or cefotaxime (4%) for a mean of 21 days (range, 15 to 44 days (22).

Among survivors, 11 (22%) were neurologically impaired at hospital discharge with manifestations including persistent seizures (n = 10), hypertonicity (n = 9), and dysphasia (n = 3). The 14 infants who died or had adverse outcomes at hospital discharge were more likely to present with seizures within hours of admission ($p < 0.001$), had coma or semicoma ($p < 0.001$), required pressor support ($p = 0.001$), and had an initial cerebrospinal fluid protein ≥ 300 mg/dl ($p = 0.005$) or glucose < 20 mg/dl ($p = 0.03$) than the 39 infants with normal neurologic examinations. Seizures at admission remained a significant risk factor ($p = 0.024$) by multivariate analysis. Despite advances in intensive care, 26% of term and near-term neonates with group B streptococcal meningitis died or had neurologic impairment at hospital discharge. Additional strategies to prevent group B streptococcal meningitis are needed. Of the 4,467 outborn young infants admitted to a Kenyan rural district hospital, 748 (17%) died (23). Five-hundred-five (11%) had invasive bacterial infections (10% bacteremia and 3% bacterial meningitis), with a case fatality of 33%. The commonest organisms were Klebsiella species, Staphylococcus aureus, Streptococcus pneumoniae, group B streptococcus, Acinetobacter species, Escherichia coli, and group A streptococcus. Notably, some blood culture isolates were seen in outborn neonates in the first week of life but not in inborn neonates. Eighty-one percent of isolates were susceptible to penicillin and/or gentamicin and 84% to ampicillin and/or gentamicin. There was a trend of increasing in vitro antimicrobial resistance to these combinations but without a worse outcome. Invasive bacterial infection is common in outborn young infants admitted to African hospitals with a high mortality rate. Presumptive antimicrobial use is justified for all young infants admitted to the hospital.

Acute bacterial meningitis is one of the most important causes of morbidity and mortality in developing countries (24). The choice of antimicrobial agents depends mainly on the age of the patient and its cerebrospinal fluid penetrability. Neonatal meningitis is commonly caused by gram-negative organisms such Escherichia coli, Klebsiella and Pseudomonas, group B streptococci and Listeria, though other organisms like Staphylococcus species also contribute. The neonatal meningitis is best treated with a combination of ampicillin and a third-generation cephalosporin given for 14 to 21 days. Post-neonatal meningitis usually occurs due to Streptococcus pneumoniae, Neisseria meningitides, and Haemophilus influenzae and is best treated with third-generation cephalosporins used with or without crystalline penicillin or ampicillin depending on the clinical situation. The therapy should be modified, if necessary, on availability of culture sensitivity report. Signs suggestive of meningeal irritation, including stiff neck, bulging fontanelle, convulsions, and opisthotonus, occur only

in a minority of neonates with bacterial meningitis and cannot be relied on solely to identify such patients (25). Ampicillin and either gentamicin or cefotaxime are recommended for initial empiric therapy of neonatal meningitis. When the results of the cerebrospinal fluid culture and susceptibilities are known, therapy can be narrowed to cover the specific pathogen identified. In general, penicillin G or ampicillin for Listerial monocytogenes meningitis, and ampicillin plus either an aminoglycoside or cefotaxime for gram-negative meningitis are suggested. For the very-low-birth-weight neonate who has been in the nursery for a prolonged period of time, organisms such as enterococci and gentamicin-resistant gram-negative enteric bacilli must also be considered. Empiric combinations of antibiotics for such patients would include ampicillin or vancomycin, plus amikacin or cefotaxime. All neonates should undergo repeat cerebrospinal fluid examination and culture at 48 to 72 hours after initiation of therapy. If organisms are observed on gram stain, modification of the therapeutic regimen should be considered, and neuroimaging should be performed.

In general, therapy should be continued for 14 to 21 days for neonatal meningitis caused by group B streptococci or Listeria monocytogenes, and for at least 21 days for disease caused by gram-negative enteric bacilli. All patients with neonatal meningitis should have hearing and development monitored serially. The first audiologic evaluation should occur 4 to 6 weeks after resolution of the meningitis. A total of 85 bacterial meningitis neonates with positive cerebrospinal fluid cultures were tested (26). The ages of these patients ranged from 1 to 28 days. The most common causative agents were group-B β-hemolytic streptococci (31.8%), followed by Escherichia coli (20%), Proteus mirabilis (7.1%), Enterobacter cloacae (5.9%), Chryseobacterium meningosepticum (5.9%), enterococci (4.7%), and Klebsiella pneumoniae (3.5%). Among the 85 neonates treated, 51 (60%) were younger than 7 days old. Among them, dyspnea was the most common clinical manifestation. In contrast, fever and diarrhea were seen more frequently in neonates with late onset of disease (after 7 days of age). Ampicillin and cefotaxime were the most commonly used antibiotics. The most frequently encountered complications were hydrocephalus and seizures, group-B β-hemolytic has overtaken Escherichia coli as the leading cause of neonatal bacterial meningitis. This was accompanied by a fall in the mortality rate, but a sustained high incidence of complications and sequelae were seen. The results of the present study highlight the importance of developing strategies to prevent group B streptococcal infection.

A prospective study of neonatal meningitis was carried out to determine the clinical spectrum and particular characteristics of meningitis in the newborn (27). The 53 cases studied represented an incidence of 1.1 per 1,000 live births. The commonest bacterial pathogens isolated were Klebsiella species (40%) followed by Enterobacter (19%). The mortality rate and the neurological sequelae among surviving neonates were 32% and 39%, respectively, with higher rates among preterm or low-birth-weight and early onset meningitis groups. Of the presenting clinical features, there was a highly positive association between two risk factors and outcome. A bulging anterior fontanelle was the only significant predictor of mortality ($p= 0.009$) and altered sensorial was the only predictive of post-meningitis sequelae ($p= 0.016$). There is a need to recognize that Klebsiella species is an increasingly important pathogen; cefotaxime or ceftazidime plus ampicillin are the most appropriate antibiotics to be used initially, and continuous surveillance thereafter

have been stressed. For initial treatment of presumed bacterial meningitis, the third-generation cephalosporins alone or combined with ampicillin for infants 5 weeks of age is suggested (28). Amoxicillin remains the preferred drug for initial treatment of acute otitis media. The combination of amoxicillin and clavulanic acid is favored in the setting of an increased proportion of β-lactamase-producing bacterial pathogens. The synergy of four combinations of antimicrobial agents potentially useful in the treatment of neonatal meningitis was examined with 19 strains of Escherichia coli K1 (29). The effect on antimicrobial activity of changes in Escherichia coli concentration and pH to values similar to those of cerebrospinal fluid from infected neonates was also assessed. The degree of synergy, assessed by checkerboard agar dilution of the antimicrobial agents in combination with gentamicin, decreased in the following order: trimethoprim, cefamandole, ampicillin, and chloramphenicol. Significant variation in activity against different strains of Escherichia coli was not observed. Bactericidal activities of the β-lactam and trimethoprim combinations were similar. Chloramphenicol antagonized the bactericidal effect of gentamicin and ampicillin plus gentamicin.

3-4. Bacterial susceptibility to ampicillin and other antibiotics in neonates and infants

Sakata (30) measured the minimal inhibitory concentration (MIC_{90}) and the minimal bactericidal concentration (MBC_{90}) of ampicillin against Streptococcus pyogenes isolated from children with invasive infections. The MIC_{90}/MBC_{90} values for ampicillin were 0.03/0.03 µg/ml. All the group B streptococcus isolates (n = 1,166) were fully susceptible to penicillin, ampicillin and cephalexin (31). Disk diffusion results interpreted by the standard interpretative criteria recommended by the National Committee on Clinical Laboratory Standards correlated well with Vitek results as well as the E-test for penicillin. The MIC of penicillin against all isolates ranged between 0.016 and 0.064 µg/ml. Ampicillin and penicillin susceptibility increased significantly during the study period ($p < 0.0001$ for both). Enterococcus faecalis isolates (n = 1,112) were highly susceptible (> 97%) to ampicillin. All group B streptococcus agalactiae isolates were fully susceptible to penicillin and ampicillin (32). Women with group B streptococcus bacteriuria in the current pregnancy and those who previously delivered a group B streptococcus-septic newborn were not screened but automatically received intrapartum antibiotics (33). Intrapartum chemoprophylaxis is selected based on maternal allergy history and susceptibility of group B streptococcus isolates. Intravenous penicillin G is the preferred antibiotic, with ampicillin as an alternative. Newborns who appear septic should have diagnostic work-up including blood culture followed by initiation of ampicillin and gentamicin. Intrapartum prophylaxis of group B streptococcus carriers and selective administration of antibiotics to newborns reduce neonatal group B streptococcus sepsis by as much as 80% to 95%.

According to consensus guidelines, pregnant women at risk receive intrapartum prophylaxis with either ampicillin or penicillin or, in case of allergy, with erythromicin or clindamycin. Ruess et al. (34) investigated the susceptibility patters of 190 group B streptococci strains from neonates and 150 group B streptococci strains from adult women. All isolates were susceptible to penicillin, ampicillin and cefotaxime. The serotypes and the levels of antibiotic resistance of 59 Streptococcus agalactiae isolates from neonates in Casablanca were

studied by Aitmhand et al. (35). Most of the isolates (86.4%) were recovered from early-onset disease. The serotype distribution was as follows: serotype III 39%; serotype Ia 32%; and serotype V 10.2%. All strains were susceptible to penicillin G, cefotaxime and ampicillin. A vaccine should comprise the most prevalent serotypes and also provide protection against serotype V disease. The antibiotic susceptibility patters reported in this study support the recommended treatment and prophylaxis of invasive group B streptococcus disease.

The susceptibility profiles of 119 colonizing and 8 invasive strains of group B streptococcus isolated were studied by Rouse et al. (36). Minimal inhibitory concentration determinations indicate that all colonizing strains were susceptible or moderately susceptible to ampicillin and penicillin G. All the 8 invasive strains were susceptible or moderately susceptible to ampicillin, penicillin G, clindamycin, and all were resistant to gentamicin. The susceptibility of 100 group B streptococci to 16 β-lactam antibiotics was tested by agar dilution (37). Penicillin G and N-formimidoyl thienamycin were the most active agents tested, both having a MIC_{90} of 0.06 µg/ml. Ampicillin, cephalotin, and mezlocillin had a MIC_{90} of 0.25 µg/ml.

3-5. Bacterial resistance to ampicillin and other antibiotics in neonates and infants

Désinor et al. (38) performed a prospective case series in 42 neonates with sepsis or meningitis. Beside the clinical signs, a positive blood culture and/or a positive culture of cerebrospinal fluid was present in each case. Gram-negative bacteria were most commonly found as a cause of early onset sepsis, with Enterobacter aerogenes as the most common agent. There was no such difference between gram-negative and gram-positive in late onset sepsis. Group B streptococcus was associated with neonatal meningitis (44% of cases) which was more related to gram-positive bacteria (66%). Thirty-three percent of the pathogens found, among them Klebsiella pneumoniae, were resistant in vitro to ampicillin and gentamicin. Resistance to gentamicin and ampicillin should be taken into consideration for the treatment of sepsis and meningitis in the neonate. Of the 271 stool samples isolated from 0 to 59 months old children, Vibrio cholera 01 subtype and Ogawa serotype were the most commonly detected pathogens (40.8%), followed by Salmonella species (25.5%), diarrhoegenic Escherichia coli (18%), Shigella species (14.4%), and Campylobacter species (3.5%) (39). The majority of the bacterial pathogens were resistant to two or more drugs tested, with ampicillin and co-trimoxazole being the most ineffective drugs. All diarrhoegenic Escherichia coli isolates were extended spectrum β-lactamase producers. Five different groups of bacteria pathogens were isolated from stool specimens, and the majority of these organisms were multidrug resistant. These data call for urgent revision of the current empiric treatment of diarrhea in children using ampicillin and co-trimoxazole, and emphasizes the need for continuous antimicrobial surveillance as well as implementation of prevention programmers for childhood diarrhea.

Antibiotic resistance is linked to carriage of papC and aerobactrim (iutA) virulence genes and phylogenetic group D background in commensal and Uropathogenic Escherichia coli from infants and young children (40). Escherichia coli from infants and young children is associated with carriage of virulence genes and to phylogenetic group origin and, in the case of fecal strains, to persistence in the gut and fecal population levels. The commensal strains (n = 205) were derived from a birth cohort study, while the urinary isolates (n = 205) were derived from outpatient clinics. Resistance

to ampicillin, tetracycline, and trimethoprim was most prevalent. Multivariate analysis showed that resistance to any antibiotic was significantly associated with carriage of genes encoding P fimbriae (papC) and aerobactrim (iutA), a phylogenetic group D origin. The present study confirms the importance of phylogenetic group D origin for antibiotic resistance in Escherichia coli and identifies the virulence genes papC and iutA as determinants of antibiotic resistance. The incidence of ampicillin (ABPC)-resistant Escherichia coli infection in very-low-birth-weight infants has been increasing. Saida et al. (41) encountered two cases of severe infection due to resistant Escherichia coli and retrospectively studied the prevalence of ABPC- and ABPC/sulbactam - resistant Escherichia coli in regular surveillance cultures obtained from all neonatal intensive care unit patients between 2000 and 2013. The overall prevalence of ABPC-resistant Escherichia coli was 39% (47/120), accounting for 63% of cases (32/51) between 2007 and 2013, compared with 22% (16/69) between 2000 and 2006. The prevalence of ABPC/sulbactam resistance was 17% (20/120), which was similar in both periods (16%, 8/51 versus 17%, 12/69). According to these results, not only ABPC, but also ABPC/sulbactam-resistant Escherichia coli must be considered in the neonatal intensive care unit.

Serotyping, multidrug resistant pattern and phylogenetic typing revealed that Escherichia coli are an emergent and highly virulent neonatal pathogen causing meningitis (42). The isolate was resistant to both ampicillin and gentamicin. The presence of highly-virulent multidrug resistant organisms isolated in neonates underscores the need to implement rapid drug resistance diagnostic methods and should prompt consideration of alternate empiric therapy in neonates with gram-negative meningitis. Kakuta et al. (43) investigated the antimicrobial susceptible profile, mechanisms of ampicillin resistance, and molecular epidemiology of ampicillin resistance in Haemophilus strains causing acute otitis media in infants aged between 0 to 3 years. Of 157 isolates, 108 (68.8%) demonstrated reduced susceptibility to ampicillin, including 95 (60.5%) of β-lactamase-non-producing isolates and 13 (8.3%) of β-lactamase-producing isolates. All β-lactamase-non-producing ampicillin-resistant (MIC of ampicillin ≥ 4 μg/ml) isolates had amino acid substitutions related to ampicillin resistance. Multilocus sequence typing and pulsed-field gel electrophoresis demonstrated genetic diversity although there were 2 clusters of highly resistant isolates with identical STs (sequence types; ST161 and 549). Alterations of penicillin-binding protein 3 (PBP3) represented the most prevalent mechanism of ampicillin resistance among Haemophilus influenzae isolates causing acute otitis media in Japanese children. B-lactamase-non-producing ampicillin-resistant isolates from children with acute otitis media demonstrated genetic diversity.

A total of 71,326 children, of whom 7,056 had positive blood cultures, gram-negative organisms were isolated in 4,710 (66.8%) infants (44). In neonates, Klebsiella pneumoniae median resistance to ampicillin was 94% in Asia and 100% in Africa. Large variations in resistance rates to commonly prescribed antibiotics for Salmonella species were identified. Multidrug resistance (resistance to ampicillin, chloramphenicol, and cotrimoxazole) was present in 30% in Asia and 75% in Africa. There is a need for an international pediatric antimicrobial resistance surveillance system that collects local epidemiological data to improve the evidence base for WHO guidance for childhood gram-negative bacteria. The

main resistance mechanism against aminopenicillin is conferred by β-lactamase production, which can be inhibited by clavulanate or sulbactam. The β-lactamase negative ampicillin resistance has been reported due to mutations in the penicillin-binding protein 3 (PBP3). The prevalence of β-lactamase negative ampicillin resistance varies considerably in different countries. In Germany, Lam et al. (45) analyzed 704 culture positive cases with bacteremia or detection of Haemophilus influenzae in cerebrospinal fluid; 82 isolates (11.6%) were phenotypically resistant to ampicillin. Among these isolates, 65 (79.3%) showed β-lactamase production, and 17 isolates (20.7%) were phenotypic β-lactamase negative ampicillin resistance of Haemophilus influenzae. The proportion of ampicillin resistant isolates remained stable over the observation period. Analysis of the PBP3 sequences of 133 isolates with different susceptibility phenotypes including susceptibility, β-lactamase negative ampicillin resistance, and β-lactamase positive isolates, revealed a high genetic diversity. Previously described PBP3 mutations were associated with elevated MIC values, albeit not exclusively, since few highly susceptible strains were found to be positive for the mutations. Furthermore, since ampicillin susceptible strains with elevated MIC values frequently harbored these mutations, prediction of the resistance phenotype using ftsl sequencing appears to be impossible.

Blood cultures were performed on admitted neonates (age, 0 to 28 days) to rule out sepsis (46). Out of 1,000 screened blood cultures, 87 (8.7%) reported as positive and the gram-positive and gram-negative bacteria for 21 (24.1%) and 66 (75.9%), respectively. The most common gram-positive organisms were Coagulase Negative Staphylococcus Aureus (18.4%) and Staphylococcus Aureus (4.8%), and gram-negative organisms were Acinetobacter (34.4%) Pseudomonas (21.8%) and Klebsiella species (6.9%). The susceptibilities were remarkable low to ampicillin (20%) and cefotaxime (29.6%) for both gram-positive and gram-negative isolates. Gram-negative bacteria showed high level of resistance to ampicillin. Mohammadi et al. (47) determined neonatal bacteremia isolates and their antibiotic resistance pattern in a neonatal intensive care unit in Iran. A total of 355 blood cultures from suspected cases of sepsis were processed, of which 27 (7.6%) were positive for bacterial growth. Of the 27 isolates, 20 (74%) were staphylococcus species as the leading cause of bacteremia. The incidence of gram-negative bacteria was 14.8%. The isolated bacteria were resistant to commonly used antibiotics. Maximum resistance among Staphylococcus species was against penicillin and ampicillin. The spectrum of neonatal bacteremia as seen in the neonatal intensive care confirmed the importance of pathogens such as Staphylococcus species. Penicillin, ampicillin and cotrimoxazole resistance was high in these isolates with high mecA gene carriage.

Ecker et al. (48) investigated if changes have occurred in the causative pathogens/or antibiotic susceptibility profiles in early onset neonatal infections since initiation of group B streptococcus prophylaxis and determined the risk factors for ampicillin and penicillin resistant microorganisms. Data on 220 infants with positive blood, urine, or cerebrospinal fluid cultures for bacteria or fungi at ≤ 7 days of age were examined in three epochs, based on intrapartum antibiotic prophylactic practices. Pathogens and antibiotic resistance were compared among epochs. A significant decrease in the group B streptococcus infections occurred over time, with no change in the incidence of other pathogens

or the emergence of antibiotic resistance, including the very low-birth-weight population. In regression analysis, ampicillin resistance was associated with male gender (odds ratio [OR]: 3.096). No emergence of antibiotic resistant pathogens was found. Changing microorganisms and increasing antibiotic resistance found in prior studies are likely multi-factorial. There were 159 episodes of sepsis (81 urban and 77 rural) affecting 158 neonates (49). Gram-negative bacilli caused 117 infections (68%) and predominated at both centers in both early and late sepsis. Klebsiella pneumoniae was the commonest organism, causing 61 infections (38.3%). In early sepsis (0 to 2 days of age), non-fermenting gram-negative bacilli caused 42.1% of infections at the urban centre and there were no cases of early group B streptococcus sepsis. Late onset sepsis was mainly caused by gram-negative bacilli at both centers. Multi-drug resistance of over 80% of early-onset gram-negative organisms to ampicillin, third generation cephalosporins and gentamicin indicates that these multi-resistant organisms are almost certainly circulating widely in the community. The overall mortality from early sepsis was 27.3% (9 of 33) and from late sepsis was 26.2% (33 of 126). Gram-negative bacilli caused all deaths from early sepsis and 87.5% of deaths from late sepsis. In total, 216 neonatal blood culture samples were processed, of which 100 (46.3%) grew potential pathogens (51).

Gram-negative infection was predominant (58/100 cases) mainly caused by enteric gram-negative bacteria. Klebsiella pneumoniae was the most common gram-negative isolate. The emergence of fungal infection was observed, with 40% of the infection caused by yeast. Gram-negative organisms exhibited 100% resistance to ampicillin. Gastrointestinal symptoms were highly specific for fungal infections. One-third of infants (n = 29), who developed culture-positive sepsis died. The present study attempted to provide data for evidence-based antibiotic therapy given to sick infants in rural units in India. Out of 190 neonates admitted to the neonatal intensive care unit, 60 (31.57%) showed blood culture positive (50). Ninety-five percent cases were due to early onset septicemia. Thirty-one neonates had gram-negative septicemia, 27 neonates had gram-positive septicemia and two had candidal infection. Seventy percent gram-positive isolates were resistant to penicillin and 90% gram-negative were resistant to ampicillin. There is an increasing trend of antibiotic resistance to the commonly used drugs. Continuous surveillance for antibiotic susceptibility should be done to look for resistance pattern.

A total of 106 nosocomial sepsis attacks were found in 100 neonates, 72 neonates were preterm (52). Gram-negative bacteria were isolated at a rate of 70.8%, gram-positive were 22.6%, and Candida species were 6.6%. The most commonly isolated microorganisms were, in order of frequency, Klebsiella species (39.6%), Pseudomonas aeruginosa (11.3%) and Coagulase-negative staphylococci (9.4%). During the study, 12 of 28 term neonates (42.9%) and 26 of the 72 preterm neonates (36.1%) died due to nosocomial sepsis, with a mortality rate of 38%. Resistance to ampicillin was 100% in gram-negative bacteria. Blood culture was done for 997 neonates with suspected clinical sepsis (53). The incidence of culture proven neonatal sepsis among inborn neonates was 14.8 per 1,000 live births. The proportion of culture positive sepsis for outborn infants admitted in neonatal intensive care unit was 8.3%. Gram-negative etiology was predominant (71.6%), with Klebsiella pneumoniae being the most common isolate. The etiology of early onset and late onset sepsis was similar. The resistance to ampicillin was 98.3%. A total of 533 infants were admitted to the new born unit.

Seventy-four (13.9%) had confirmed sepsis from blood culture (54). The case fatality rate was 36.5%. Place and mode of delivery, antenatal clinic attendance and premature rupture of membranes did not increase the rate of sepsis. The common organisms isolated were gram-negative organisms (n= 60) (66.6%), while gram-positive organisms were 30 (33.4%). Antibiotic sensitivity revealed high resistance to ampicillin. One-hundred and eighteen newborns in the neonatal intensive care unit group (n = 38), the neonates the ward group (n = 36), and the control group (n = 44) were enrolled (55). Three or four stool samples were obtained from each infant, 15 days apart. Bacterial growth in Eosin Methylene Blue agar plus 10 µg/ml ampicillin was considered to be ampicillin-resistant bacteria, and antibiotic susceptibility, and extended spectrum β-lactamases production was investigated in those bacteria. Colonization with ampicillin-resistant commensal fecal flora microorganisms was determined in 75.2% of 367 stool samples. Klebsiella species, and Escherichia coli were found in 59% and 41% of the samples, respectively. The lowest rate of ampicillin-resistant bacteria colonization was determined in the neonatal intensive care unit group. Microorganisms producing extended spectrum β-lactamases production were identified in 33.7% of 367 stool samples. Fifty-one and 73 of ampicillin-resistant Escherichia coli and Klebsiella species isolates were determined to produce extended spectrum β-lactamases, respectively. There was no difference with respect to colonization with extended spectrum β-lactamases-production microorganisms between the three groups.

A total of 455 of Haemophilus influenzae strains were isolated from children with meningitis (n = 425) and pneumonia (n = 30), and an additional 68 Haemophilus influenzae type B meningitis cases were detected by latex agglutination testing (56). Overall, 35% of pyrogenic meningitis cases were a result of Haemophilus influenzae, 97.1% of which were Haemophilus influenzae type B. Most (91.4%) cases occurred during the first year of life. Resistance to ampicillin was 32.5%. There was a trend toward increasing resistance for ampicillin. Resistance to ampicillin was associated with increased sequelae compared with the children infected with susceptible strains (31% [23/75] versus 11% [21/183]; $p<0.001$). A total of 212 organisms were isolated. These included Staphylococcus aureus (n = 65), Klebsiella pneumoniae (n =73), Acinetobacter baumanii (n = 23), Escherichia coli (n = 22), Enterobacter cloacae (n = 18), Citrobacter diversus (n = 5), Pseudomonas aeruginosa (n = 4), and group B streptococcus (n = 2) (57). More than 90% gram-negative rods were resistant to ampicillin.

Antibiotic susceptibility of 40 isolates was detected by the standard disk diffusion method according to the National Committee for Clinical Laboratory Standards Guidelines (58). The double-disk synergy method was used to determine the extended-spectrum β-lactamase activity, which is associated with resistance to β-lactam antibiotics, ampicillin was resistant. With the increasing incidence of antimicrobial resistance, which poses a clinically significant risk to vulnerably patients, it is important that clinical microbiology laboratories have accurate and timely information concerning the strains of bacteria present to enable them to predict which antibiotics are likely to be effective in treating the infections they may cause.

3-6. Pharmacokinetics of ampicillin in neonates and infants

Cies et al. (59) described the population pharmacokinetics and pharmacodynamics target attainment of ampicillin in 13 neonates with hypoxic-ischemic encephalopathy undergoing controlled

hypothermia. Ampicillin was administered intravenously at the dosage of 100 mg/kg/dose every 8 hours. Blood (0.5 ml) was collected at 8, 10, and 14 hours. The neonates had a median gestational age of 39 weeks, the mean± standard deviation (SD) birth weight was 3,340±610 mg, and the estimated glomerular filtration rate was 43±12.6 ml/min/1.73 m^2. Ampicillin concentrations were best described by a two-compartment model with gestational age as a covariate with allometric scaling on total body clearance. The mean ± SD total body clearance for the population was 0.43±0.12 ml/min/kg (median 0.36 ml/min/kg). The distribution volume of the central compartment was 0.35±0.46 l/kg, and the calculated population estimate for the total distribution volume was 0.52±0.28 l/kg. Dosing regimens of 25 and 50 mg/kg/dose every 24 hours provided for an appropriate pharmacodynamic target of 50% and 100% fT>MIC. Dosing regimens of ampicillin 25 and 50 mg/kg/day were able achieve optimal probability of target attainment against all susceptible gram-negative and gram-positive bacteria in a population of neonates with hypoxic-ischemic encephalopathy receiving controlled hypothermia.

Table.1 shows the individual ampicillin population pharmacokinetic parameters for 13 neonates, and **Table.2** shows the ampicillin population pharmacokinetic parameter estimates for 13 neonates. The mean ± SD and the median of ampicillin clearance were 0.43±12 and 0.36 ml/min/kg, respectively. The distribution volume of the central comportment was 0.35±0.46 l/kg. The calculated population estimate for the total body distribution volume was 0.52±0.28 l/kg. Tremoulet et al. (60) studied the pharmacokinetics of ampicillin in 73 neonates. The indications for ampicillin treatment were presumed or confirmed infections (n = 38), sepsis (n = 31), necrotizing enterocolitis (n = 2), abdominal procedure (n = 2), meconium ileus with peritonitis (n = 1), and pneumonia (n = 1). The pharmacokinetic parameters of ampicillin are summarized in **Table.3**. Tremoulet et al. (60) conducted an open-label, multicenter, opportunistic, prospective pharmacokinetic study of ampicillin in 73 neonates stratified by gestational age (≤ 34 or > 34 weeks) and postnatal age (≤ 7 or > 7 days). The gestational age ranged from 24 to 41 weeks (median, 36 weeks), and the postnatal age ranged from 0 to 25 days (median, 5 days). The median ampicillin dose ranged from 100 to 300 mg/kg/day (median, 200 mg/kg/day) administered every 6 to 12 hours. The postmenstrual age and serum creatinine concentration were covariates for ampicillin clearance.

A simplified dosing regimen of 50 mg/kg every 12 hours was administered to 73 neonates with a gestational age ≤ 34 weeks and a postnatal age ≤ 7 days, 75 mg/kg every 12 hours were administered to neonates with a gestational of ≤ 34 weeks and a postnatal age ≥ 8 and ≤ 28 days, and 50 mg/kg every 8 hours were administered to neonates with a gestational age > 34 weeks and a postnatal age ≤ 28 days. This ampicillin regimen achieved the surrogate efficacy target in 90% of simulated subjects.

Table.3 summarizes the median and range of ampicillin clearance, distribution volume and half-life in 73 neonates. Ampicillin clearance and half-life were associated with neonatal development. Therefore, the ampicillin clearance increased, and consequently the ampicillin half-life decreased with neonatal maturation. Serum half-life of ampicillin decreased rapidly in the first 2 weeks of life as a result of ampicillin clearance increase. The distribution volume of ampicillin was 0.40 l/kg in all studied subjects and was not influenced by neonatal maturation. Yoshioka et al. (61) administered ampicillin to 3 full-term newborn infants by continuous intravenous

infusion. The demographic data of neonates and the kinetic parameters of ampicillin are shown in **Table.4**. Samples of blood were taken at appropriate intervals by means of heel puncture during and 6 hours after the infusion. The serum ampicillin level initially rose rapidly, then rose more slowly, and reached a plateau at 3 to 6 hours.

Table-1: The Individual ampicillin population pharmacokinetic parameter estimates for 13 neonates, by Cies et al. (59).

Patient No	Gestational age (weeks)	Birth weight (grams)	eGFR (ml/min/1.73 m^2)	Half-life (hours)	Vc (l/kg)	Vd (l/kg)	Cl (ml/min/1.73 m^2)
1	37	2,945	27.4	28.52	0.17	0.92	0.40
2	41	3,737	37.7	19.19	0.03	0.44	0.47
3	39	3,440	28.7	19.54	0.03	0.48	0.50
4	38	2,975	44.2	17.01	0.46	1.03	0.72
5	40	2,415	54.1	14.65	0.03	0.42	0.50
6	40	3,170	46.3	29.76	0.05	0.71	0.38
7	40	4,850	36.2	16.16	0.29	0.64	0.47
8	39	3,218	46.6	13.72	0.02	0.27	0.37
9	36	2,710	41.7	17.11	0.11	0.53	0.41
10	36	3,215	33.0	10.83	0.02	0.18	0.35
11	39	3,760	49.6	10.35	0.02	0.14	0.31
12	38	3,165	38.1	9.42	0.05	0.23	0.37
13	41	3,757	75.7	29.73	0.04	0.60	0.32
Mean $\pm$ SD	38.8$\pm$1.70	3,351$\pm$607	43.0$\pm$12.6	18.1$\pm$7.1	0.10$\pm$0.13	0.50$\pm$0.27	0.43$\pm$0.11

eGFR = estimated glomerular filtration rate; Vc = volume of the central compartment; Vd = total distribution volume; Cl = clearance; SD = standard deviation.

Table-2: The Ampicillin population pharmacokinetic parameter estimates for 13 neonates, by Cies et al. (59).

Statistics	Cl (ml/min/kg)	Vc (l/kg)	Kep ($hours^{-1}$)	Kpc ($hours^{-1}$)
Mean	0.43	0.35	1.1	0.23
SD	0.12	0.46	0.22	0.21
Median	0.36	0.13	1.1	0.13

Cl = clearance; Vc = volume of the central compartment; Kcp = intercompartmental transfer rate constant from the central to peripheral compartment; Kpc = intercompartmental transfer rate constant from the peripheral to central compartment; SD: standard deviation.

Table-3: The Individual empirical Bayesian post hoc parameter estimated in 73 neonates. The figures are medians and range, by Tremoulet et al. (60).

Variables							Steady-state concentration (µg/ml)	
Parameter	Number of cases	Postnatal age (days)	Gestational age (weeks)	Clearance (l/h/kg)	Distribution volume (l/kg)	Half-life (hours)	Minimum	Maximum
Group 1	21	1.0 (0.0-7.0)	32.3 (24.0-34.0)	0.055 (0.03-0.07)	0.40 (0.40-0.40)	5.0 (3.9-9.4)	77 (36-320)	318 (244-563)
Group 2	7	16.0 (9.0-21.0)	26.1 (25.0-32.0)	0.070 (0.03-0.07)	0.40 (0.40-0.41)	4.0 (3.8-8.3)	33 (21-145)	266 (159-368)
Group 3	27	2.0 (0.0-7.0)	38.0 (34.0-41.0)	0.086 (0.04-0.13)	0.40 (0.40-0.40)	3.2 (2.2-6.2)	48 (5-173)	274 (127-413)
Group 4	18	12.5 (8.0-25.0)	38.8 (35.0-41.0)	0.11 (0.06-0.13)	0.40 (0.40-0.41)	2.4 (2.1-4.7)	28 (5-129)	246 (138-203)
Overall	73	5.0 (0.0-25.0)	36.1 (24.0-41.0)	0.072 (0.03-0.13)	0.40 (0.40-0.41)	3.3 (2.1-9.4)	47 (5-320)	281 (127-563)

Table-4: Calculated values for elimination rate constant (K_1), distribution volume (V), and K_1V distribution volume during the continuous intravenous infusion of ampicillin; k2 was the elimination rate constant of ampicillin during the infusion, and the biological half-life ($T_{1/2}$) after the infusion was stopped, by Yoshioka et al. (61).

Variables				During infusion			After infusion	
Infant	BW	PA	IR	K_1 (min^{-1})	V (ml)	Kv (ml)	K_2 (min^{-1})	$T_{1/2}$ (hours)
1	3,020	4	210	0.0113	792	8.9	0.0061	1.90
2	2,770	4	192	0.030	1067	13.9	0.0042	2.75
3	3,120	2	108	0.0171	829	14.1	0.0056	2.07
Average	2,947	3.3	___	0.0138	896	12.3	0.0053	2.24

BW = body weight (grams); PA = postnatal age (days); IR = infusion rate (mg ampicillin/kg per min).

4-DISCUSSION

Septicemia is an important cause of morbidity and mortality. Group-B β-hemolytic streptococci and Escherichia coli are the major causes of septicemia in neonates. Currently recommended initial therapy of septicemia consists of ampicillin and gentamicin. The addition of vancomycin is indicated when septicemia is caused by staphylococcal species. When septicemia is caused by aminoglycoside-resistant gram-negative bacteria, the use of a third-generation cephalosporin is indicated (9). Clark et al. (12) compared the treatment of ampicillin and cefotaxime with the treatment of ampicillin and gentamicin in neonates 3 days old. Neonates treated with ampicillin/cefotaxime were more likely to die and were less likely to be discharged to home or further care than neonates treated with ampicillin/gentamicin. Terrone et al. (13) evaluated the relationship between neonatal death caused by sepsis associated with ampicillin-resistant organisms and length of antibiotic exposure. Of the 78 neonatal deaths, 35 met the inclusion criteria. There were 8 cases of sepsis from ampicillin-resistant Escherichia coli and 27 cases caused by other organisms. There was a statistically significant difference between the mean number of doses of ampicillin received by the ampicillin-resistant Escherichia coli group (17.6+5.5)

compared with the other organisms group (4.9+3.6) ($p < 0.001$). The administration of gentamicin at least 1 hour before administration of ampicillin in neonates has been advocated because of in vitro inactivation of aminoglycosides by beta-lactam antibiotics. This method would cause a delay in ampicillin dosing in the treatment of serious bacterial infections and unnecessarily complicate nursing procedures. Daly et al. (14) studied the effect of varying concentrations of ampicillin (50, 100, 200, and 400 µg/ml) on aminoglycosidic antibiotics in vitro with the use of stock solutions diluted in pooled sera obtained from cord blood and incubated samples at 25 degrees C, 37 degrees C, and 40 degrees C. Daly et al. (14) found inactivation of aminoglycosides to be dependent on time, temperature, and ampicillin concentration, but the degree of inactivation was small and does not support temporal separation of parenteral administration of ampicillin and aminoglycosides to neonates.

The impact of ampicillin and cefuroxime on the bacterial flora of neonates was examined in a neonatal intensive care unit (15). For the first period of study (January-September 1989), ampicillin plus gentamicin were used as empirical therapy of infection. During this time, 92.6% of all gram-negative bacilli were resistant to ampicillin and 56.6% to cefuroxime. These percentages decreased significantly ($p < 0.05$) to 60.0% and 16.2% respectively, over the next period of study (October 1989-October 1990) when cefuroxime plus gentamicin were used. A decrease in the number of cases of gram-negative bacilli from bacteremia and meningitis was also significant (from 21.2% to 11.2%), and this correlated with a decline in the occurrence of Klebsiella pneumoniae. However, the number of enterococcal isolates and cases of enterococcal bacteremia increased. These observations underline the important effect of ampicillin and cefuroxime in modulating the bacterial flora and its antibiotic resistance in patients on a neonatal intensive care unit. Tessin et al. (16) evaluated 365 pathogens isolated from neonatal blood and/or cerebrospinal fluid and 91% were sensitive to either ampicillin or aminoglycosides or both. Ampicillin resistance was mainly found in very-low-birth-weight infants with late-onset infections, in which aerobic gram-negative rods were common pathogens. In early-late infections, the group B streptococci was the predominant cause of infection. The ampicillin-aminoglycoside combination was given to 189 cases of septicemia or meningitis. Treatment failed in 36 infection (20%), although all organisms were sensitive to one or both antibiotics.

Ampicillin-aminoglycoside combination can be used as initial treatment of invasive infections in neonates. Umana et al. (17) compared the treatment of aztreonam plus ampicillin (n = 75 neonates) with amikacin plus ampicillin (n = 72 neonates). Bronchopneumonia and infections caused by Pseudomonas species occurred significantly more in amikacin plus ampicillin treated infants compared with neonates treated with aztreonam plus ampicillin group. Thirty-two neonates had bacteriologically documented infections caused by gram-negative enteric bacilli or Pseudomonas. Case fatality rates resulting from the primary infection were 7 and 22% ($p = 0.011$), superinfections occurred in 39% and 34% and treatment failure occurred in 7% and 28% ($p = 0.036$) of the aztreonam/ampicillin and amikacin/ampicillin-treated neonates, respectively. No clinical adverse reactions were observed in either group. Based on these results, aztreonam appears to be more effective than amikacin when used initially with ampicillin for empiric treatment of neonatal bacterial infections. Fifty children with bacterial meningitis were prospectively randomized to receive

cefotaxime (50 mg/kg/dose every 6 hours) or ampicillin and chloramphenicol in standard doses (18). Twenty-three children received cefotaxime and 27 children received standard therapy. Bacterial isolates included Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitis, group B streptococci, and Salmonella enteritis. Ten (34%) of the Haemophilus influenzae isolates were resistant to ampicillin, nine on the basis of β-lactamase production.

All strains were susceptible to cefotaxime. Clinical cure rates for the cefotaxime (100%) and standard therapy (96%) groups were similar and survival without detectable sequelae was similar, at 78% and 77%, respectively. The duration of therapy, 11.1±2.4 days versus 11.9±3.9 days, respectively. Cefotaxime was found to be as safe and effective as standard therapy (ampicillin and chloramphenicol) for the treatment of bacterial meningitis in children. Kaplan and Mason (19) evaluated the activity of ampicillin and chloramphenicol on 16 gram-negative isolates from the cerebrospinal fluid of neonates with meningitis. The combination of these antibiotics was synergistic (fractional inhibitory concentration less than 1.0) against 11 of 16 (69%) isolates by agar dilution technique and 12 of 16 (75%) isolates by microbroth dilution technique. In kinetic studies, ampicillin and chloramphenicol together exhibited an increased rate of killing against 9 of 14 isolates. Escherichia coli (33%) and group B streptococcus (31%) were the pathogens isolated from 133 neonates (20). Escherichia coli and group B Streptococcus remained the most common causes of bacterial meningitis in the first 90 days of life. For empirical therapy of suspected bacterial meningitis, one should consider a third-generation cephalosporin (plus ampicillin for at least the first month), potentially substituting a carbapenem for the cephalosporin if there is evidence for gram-negative meningitis.

The three major pathogens in developed countries causing meningitis are group B streptococcus, gram-negative rods and Listeria monocytogenes (21). Positive culture of cerebrospinal fluid may be the only way to diagnose neonatal bacterial meningitis and to identify the pathogen. When neonatal bacterial meningitis is suspected, treatment must be aggressive, as soon as possible. The recommended empirical treatment of the neonatal bacterial meningitis is ampicillin, plus an aminoglycoside and a third-generation cephalosporin. Levent et al. (22) enrolled six neonates (< 7 days of life) and 47 neonates (≥ 7 days of life). All these neonates were affected by bacterial meningitis. Infants received initial broad-spectrum antibiotics such as penicillin (68%), ampicillin (28%), or cefotaxime (4%) for a mean of 21 days (range, 15 to 44 days). Fourteen infants died.

Among survivors, 11 (22%) were neurologically impaired at hospital discharge with manifestations including persistent seizures (n = 10), hypertonicity (n = 9) and dysplasia (n = 3). Seizures at admission remained a significant risk factor (p = 0.024) by multiple analysis. Additional strategies to prevent group B meningitis are needed. Talbert et al. (23) admitted 4,467 young infants to a Kenyan rural district hospital, 748 (17%) died. Five-hundred-five (11%) had invasive bacterial infections, (10% had bacteremia) and 3% had bacterial meningitis. The case fatality was 33%. The commonest organisms were Klebsiella species, Staphylococcus aureus, Streptococcus pneumoniae, group B streptococcus, Acinetobacter species, Escherichia coli, and group A streptococcus. Eighty-one percent were susceptible to penicillin and/or gentamicin and 84% to ampicillin and/or gentamicin. Invasive bacterial infection is common in outborn young

infants admitted to African hospitals with a high rate of mortality. Acute bacterial meningitis is one of the most important causes of morbidity and mortality in developing countries (24). Neonatal meningitis is commonly caused by gram-negative organisms such as Escherichia coli, Klebsiella and Pseudomonas, group B streptococci, Listeria, and Staphylococcus. The neonatal bacterial meningitis is best treated with a combination of ampicillin and a third-generation cephalosporin given for 14 to 21 days. Postneonatal meningitis occurs due to Streptococcus pneumoniae, Neisseria meningitis, and Haemophilus. The best therapy is a third-generation cephalosporin and penicillin or ampicillin.

Ampicillin and either gentamicin or cefotaxime are recommended for initial therapy of neonatal bacterial meningitis (25). For the very-low-birth-weight infants who have been in the nursery for a prolonged period of time, organisms such as enterococci and gentamicin-resistant gram-negative enteric bacilli must be considered. Empiric combinations of antibiotics for such neonates would include ampicillin or vancomycin, plus amikacin or cefotaxime. In general, therapy should be continued for 21 days. All neonates should undergo repeat cerebrospinal fluid examination and culture at 48 to 72 hours after initiation of therapy. Chang Chien et al. (26) tested 85 neonates with bacterial meningitis aged from 1 day to 28 days. The most common causative agents were group-B β-hemolytic streptococci, Escherichia coli, Proteus mirabilis, and Enterobacter cloacae. Fifth-one (60%) of infants were younger than 7 days old. Among them, dyspnea was the most common clinical manifestation. In neonates older than 7 days, fever and diarrhea were the most frequently side-effects observed. Ampicillin and cefotaxime were the most commonly used antibiotics. Escherichia coli was the leading cause of bacterial meningitis. This therapy was accompanied by a fall in the mortality rate, but a sustained high incidence of complication and sequelae was seen in survivors. A prospective study of neonatal bacterial meningitis was carried out in 53 infants by Daoud et al. (27). The commonest bacterial isolates were Klebsiella species and Enterobacter. The mortality rate and the neurological sequelae were 32% and 39%, respectively. Cefotaxime or ceftazidime plus ampicillin are the most appropriate antibiotics to be used initially. Klass and Klein (28) suggested that presumed bacterial meningitis in infants 5 weeks of age should be treated with third-generation cephalosporins alone or in combination with ampicillin. Alternatively, ampicillin alone or combined with an aminoglycoside or chloramphenicol may be used. Third generation cephalosporins are also drugs of choice for presumed sepsis combined with ampicillin for infants 5 weeks of age.

The synergy of four combinations of antimicrobial agents potentially useful in the treatment of neonatal meningitis was examined with 19 strains of Escherichia coli K1 (29). The degree of synergy, assessed by checkerboard agar dilution of the antimicrobial agents in combination with gentamicin, decreased in the following order: trimethoprim, cefamandole, ampicillin, and chloramphenicol. Significant variation in activity against different strains of Escherichia coli was not observed. Bactericidal activities of the beta-lactam and trimethoprim combinations were similar. Chloramphenicol antagonized the bactericidal effect of gentamicin and of ampicillin plus gentamicin. Sakata (30) measured the MIC_{90} and the MBC_{90} values of ampicillin against Streptococcus pyogenes isolated from children with invasive infections. Both MIC_{90} and MBC_{90} were 0.03 μg/ml. Brandon and Dowzicky (31) observed that ampicillin

and penicillin susceptibility increased significantly during the study period ($p< 0.0001$ for both). Enterococcus faecalis isolates were highly susceptible (> 97%) to ampicillin. All groups of B streptococcus agalactiae isolates were fully susceptible to ampicillin (32). Based on susceptibility profiles, these data support the use of penicillin or ampicillin for intrapartum chemoprophylaxis to prevent early-onset neonatal group B streptococcus infections (33). Ruess et al. (34) investigated the susceptibility patterns of 190 group B streptococcus strains from neonates and 150 groups B streptococcus from adult women. All isolates were susceptible to ampicillin. Aitmhand et al. (35) studied the levels of antibiotic resistance of 59 Streptococcus agalactiae isolated from neonates in Casablanca. Most of the isolates (86.4%) were recovered from early-onset disease. All strains were susceptible to ampicillin.

Rouse et al. (36) studied the susceptibility profiles of 119 colonizing and 8 invasive strains of group B streptococcus. All colonizing strains and the 8 invasive strains were susceptible or moderately susceptible to ampicillin. Universal susceptible of group B streptococcus to members of the penicillin family supports the continued use of penicillin G or ampicillin for early onset neonatal group B streptococcal disease prevention. The susceptibility of 100 groups B streptococcus to 16 β-lactam antibiotics was tested by agar dilution by Jacobs et al. (37). Penicillin G and N-formimidoyl were the most active agents, both having a MIC_{90} of 0.06 µg/ml, and ampicillin had a MIC_{90} of 0.25 µg/ml. Désinor et al. (38) performed a prospective case series in 42 neonates with sepsis or meningitis. Gram-negative bacteria were most commonly found as a cause of early onset sepsis, with Enterobacter aerogenes as the most common agent. There were no such differences between gram-negative and gram-positive bacteria in late onset sepsis. Group B streptococcus was associated with neonatal meningitis (44% of cases) which was more related to gram-positive bacteria (66%). Thirty-three percent of the pathogens found, among them Klebsiella pneumoniae, were resistant in vitro to ampicillin and gentamicin. Resistance to ampicillin and gentamicin should be taken into consideration for the treatment of sepsis and meningitis in the neonate.

Vibrio cholera 01 subtype and Ogawa serotype were the commonly detected pathogens, followed by Salmonella species, diarrhoegenic Escherichia coli, Shigella species, and Campylobacter species (39). The majority of the bacterial pathogens were resistant to two or more antibiotics tested, with ampicillin being the most ineffective antibiotic. All diarrhoegenic Escherichia coli isolates were extended spectrum β-lactamase producers. Five different bacteria isolated from the stool specimens were multidrug resistant. These data emphasize the need for continuous antimicrobial surveillance as well as implementation of prevention programmers for childhood diarrhea. Karami et al. (40) investigated whether phenotypic resistance to antibiotics in commensal and uropathogenic Escherichia coli from infants and young children is associated with carriage of virulence genes and to phylogenetic group origin and, in the case of fecal strains, to persistence in the gut and fecal population levels. Resistance to ampicillin, tetracycline, and trimethoprim was most prevalent. Multivariate analysis showed that resistance to any antibiotic was significantly associated with carriage of genes encoding P fimbriae (papC) and aerobactin (iutA), and a phylogenetic group D origin. Neither fecal population numbers nor the capacity for long-term persistence in the gut were related to antibiotic resistance among fecal strains. This study confirms the importance of

phylogenetic group D origin for antibiotic resistance in Escherichia coli and identifies the virulence genes papC and iutA as determinants of antibiotic resistance. The incidence of ampicillin (ABPC)-resistant Escherichia coli infection in very low-birth weight infants has been increasing. The rate of ABPC/sulbactam-resistant Escherichia coli in this population, however, is currently unknown. Saida et al. (41) encountered two cases of severe infection due to resistant Escherichia coli and retrospectively studied the prevalence of ABPC- and ABPC/sulbactam-resistant Escherichia coli from all neonates in intensive care unit neonates between 2000 and 2013. The overall prevalence of ABPC-resistant Escherichia coli was 39%, accounting for 63% of cases between 2007 and 2013, compared with 22% between 2000 and 2006. The prevalence of ABPC/sulbactam-resistance was 17%, which was similar in both periods (16% versus 17%). According to these results, not only ABPC, but also ABPC/sulbactam-resistant Escherichia coli must be considered in the neonatal intensive care unit. Neonatal meningitis is a rare but devastating condition (42).

Multi-drug resistant bacteria represent a substantial global health risk. Serotyping multi-drug resistant bacteria pattern and phylogenetic typing revealed that Escherichia coli isolate is an emergent and highly virulent factor of neonatal meningitis. This isolate was resistant to both ampicillin and gentamicin; antibiotics currently used for empiric neonatal sepsis treatment. The presence of highly-virulent organism multi-drug resistant bacteria is isolated in neonates underscores the need to implement rapid drug resistance diagnostic methods and should prompt consideration of alternate empiric therapy in neonates with gram negative meningitis. Ampicillin-resistant Haemophilus influenzae may cause acute otitis media in infants and young children (43). A percentage of 68.8 of isolates obtained from this population demonstrated reduced susceptibility to ampicillin, including 60.5% of β-lactamase-non-producing isolates and 8.3% of β-lactamase-producing isolates. The MIC of ampicillin for β-lactamase-non-producing was ≥ 4 µg/ml and isolates had amino acid substitutions related to ampicillin resistance. Alterations of penicillin-binding protein 3 (PBP3) represented the most prevalent mechanism of ampicillin resistance among Haemophilus influenzae isolates causing acute otitis media in Japanese children. Beta-lactamase-non-producing ampicillin-resistant isolates from children with acute otitis media demonstrated diversity.

Le Doare et al. (44) enrolled 71,326 children of whom 7,056 had positive blood cultures, gram-negative organisms were isolated in 4,710 (66.8%). In neonates, Klebsiella pneumoniae median resistance to ampicillin was 94% in Asia and 100% in Africa, respectively. Large variations in resistance to Salmonella species were identified. Multidrug resistance values for ampicillin were 30% in Asia and 75% in Africa. Epidemiological data to improve the evidence for World Health Organization (WHO) guidance for childhood gram-negative bacteria is needed. The main resistance mechanism again aminopenicillin is conferred by β-lactamase production, which can be inhibited by clavulanate or sulbactam (45). Apart from that, β-lactamase negative ampicillin resistance has been reported due to mutations in the penicillin-binding protein 3 (PBP3). In the cerebrospinal fluid, 11.6% of Haemophilus influenzae were resistant to ampicillin. Among these isolates, 79.3% showed β-lactamase producing and 20.7% were β-lactamase negative ampicillin resistant to Haemophilus influenzae. Since ampicillin susceptible strains with elevated MIC values frequently harbored these

mutations, prediction of the resistance phenotype is needed. A 1,000 blood cultures from neonates, aged between 0 and 28 days, were screened (46). A percentage of 8.7 reported as positive and the gram-positive and the gram-negative bacteria of 24.1% and 75.9%, respectively, were observed. Coagulase Negative Staphylococcus Aureus and Staphylococcus Aureus were the most common gram-positive bacteria found. Acinetobacter, Pseudomonas and Klebsiella species were the most gram-negative found. The susceptibility value to ampicillin was 20%. Gram-negative bacteria showed high level of resistance to ampicillin, ceftazidime and cefotaxime.

Mohammadi et al. (47) determined the commonly used antibiotic resistance in 355 blood cultures from neonates. A percentage of 7.6 cultures were resistant to commonly used antibiotics. Maximum resistance among Staphylococcus species was against ampicillin and penicillin. A significant decrease in the group B Streptococcus infections occurred over time. Ecker et al. (48) determined if changes occurred in the causative pathogens or antibiotic susceptibility profiles in early onset neonatal infections since initiation of group B prophylaxis. A significant decrease in the group B Streptococcus infections occurred over time, with no change in the incidence of other pathogens. In regression analysis ampicillin resistance was associated with male gender (OR = 3.096). No change in the incidence of other pathogens or the emergence of antibiotic resistance was found. There were 159 episodes of sepsis affecting 158 neonates. Gram negative bacilli caused 117 infections (68%) (49). Klebsiella pneumoniae was the commonest organism, causing 61 infections (38.3%). In early sepsis (0-2 days), non-fermenting gram negative bacilli caused 42.1% of infections; there were no cases of early group B streptococcus sepsis. Late onset sepsis was mainly caused by gram negative bacilli at both centers. Multi-drug resistance of over 80% of early-onset gram-negative organisms to ampicillin, third generation cephalosporins and gentamicin indicates that these multi-resistant organisms are almost certainly circulating widely in the community. The overall mortality from early sepsis was 27.3% (9 of 33) and from late sepsis was 26.2% (33 of 126). Gram-negative bacilli caused all deaths from early sepsis and 87.5% of deaths from late sepsis.

Out of 190 neonates admitted to the neonatal intensive care unit, 60 (31.57%) showed blood culture positive (50). Ninety-five percent cases were due to early onset septicemia. Thirty-one neonates had gram-negative, twenty-seven neonates had gram-positive septicemia and two had candidal infection. Seventy percent gram-positive isolates were resistant to penicillin and ninety percent gram-negative were resistant to ampicillin. There is an increasing trend of antibiotic resistance to the commonly used drugs. Ninety-five percent cases of 190 neonates admitted to the neonatal intensive care unit were due to early onset septicemia (51). Seventy percent gram-positive isolates were resistant to penicillin, and 90% of gram-negative neonates were resistant to ampicillin and gentamicin. Continuous surveillance for antibiotic susceptibility should be done to look for resistance pattern. Gram-negative bacteria were isolated at a rate of 70.8%, gram-positive at 22.6%, and Candida species at 6.6% (52). The most commonly isolated microorganisms were, in order of frequency, Klebsiella species, Pseudomonas aeruginosa, and Coagulase-negative staphylococci. During the study, 12 of 28 term neonates (42.9%) and 26 of the 72 preterm neonates (36.1%) died due to nosocomial sepsis, with a mortality rate of 38%. Resistance to ampicillin was 100% in gram-negative bacteria. One-

hundred-eight neonates were enrolled in the study by Viswanathan et al. (53). Gram-negative bacilli (68%) caused infections. Klebsiella pneumoniae caused 38.3% infections. Multidrug resistance of over 80% of early-onset gram-negative organisms was observed for ampicillin, third generation cephalosporins and gentamicin indicates that these multiresistant organisms are almost certainly circulating widely in the community. Simiyu et al. (54) admitted to the newborn unit 533 infants. A percentage of 13.9 had confirmed sepsis from blood culture. The common organisms isolated were gram-negative (66.6%), while gram-positive organisms were 33.4%. Ampicillin had high resistance for both gram-negative and gram-positive isolates. One-hundred-eighteen neonates were enrolled by Duman et al. (55). Three or four stool samples were obtained from each infant, 15 days apart. Bacterial growth in Eosin Methylene Blue agar plus ampicillin was considered to be ampicillin-resistant bacteria. Fifty-one were resistant to ampicillin. Haemophilus influenzae strains were isolated from children with meningitis (n = 425) and pneumoniae (n = 30), and an additional 68 Haemophilus influenzae type B meningitis cases were detected by latex agglutination testing (56). Most (91.4%) cases occurred during the first year of life.

Resistance to ampicillin was 32.5%. Resistance to ampicillin was associated with increased sequelae compared with the patients infected by susceptible strains (31% [23/75] versus 11% [21/183]; p <0.001). Mahmood et al. (57) isolated 212 organisms. The bacteria included in the study were Staphylococcus, Klebsiella pneumoniae, Citrobacter diversus, Pseudomonas aeruginosa, and group B streptococcus. The sensitivity testing revealed that 61.54% of Streptococcus aureus isolates were found to be methicillin resistant. The resistance to ampicillin was 90% in gram-negative rods, whereas the susceptibility to other commonly used antibiotics was higher. Aktas et al. (58) designed a study to determine the antimicrobial resistance and the extended-spectrum beta-lactamase activities of Klebsiella pneumoniae strains isolated from the neonatal intensive care unit of Atatürk University Hospital, Erzurum, Turkey. A percentage of 24 Klebsiella pneumoniae isolates were found to be the most effective antibiotic (100%), and ampicillin had a total resistance. With the increasing incidence of antimicrobial resistance, which poses a clinically significant risk to vulnerable patients, it is important that clinical microbiology laboratories have accurate and timely information concerning the strains of bacteria present to enable them to predict which antibiotics are likely to be effective in treating the infections they may cause. Thirteen neonates with hypoxic-ischemic encephalopathy undergoing controlled hypothermia received 100 mg/kg/dose every 8 hours (59).

The half-life, the clearance and the distribution volume were 18.1$\pm$7.1 hours, 0.43$\pm$0.11 ml/min/1.73 m^2, and 0.50$\pm$0.27 l/kg, respectively. The distribution volume of the central compartment was 0.35$\pm$0.46 l/kg, the calculated population estimate for the total distribution volume was 0.52$\pm$0.28 l/kg. The ampicillin clearance increased with gestational and postnatal ages and consequently the half-life decreased with the increases of gestational and postnatal ages. Thus, the half-life and the clearance are influenced by neonatal maturation. The median distribution volume of ampicillin was 0.40 l/kg in all neonates and it is influenced neither by gestational age nor by postnatal age. Tremoulet et al. (60) suggested the following simplified dosing regimen for ampicillin in neonates. Fifty mg/kg ampicillin administered every 12 hours to neonates with a gestational age $\leq$ 34 weeks

and a postnatal age ≤ 7 days, 75 mg/kg every 12 hours administered to neonates with a gestational age of ≤ 34 weeks and a postnatal age of ≥ 8 to ≤ 28 days, and a 50 mg/kg every 8 hours administered to neonates with a gestational age > 34 weeks and a postnatal age ≤ 28 days. This ampicillin regimen achieved the efficacy target in 90% of subjects. Yoshioka et al. (61) administered ampicillin to 3 full-term infants. The rates of infusion in the three neonates per min were 210, 192, and 108. The ampicillin serum level rose rapidly, then rose more slowly, and approached a plateau 3 to 6 hours after ampicillin administration. At 6 hours, the level of ampicillin in serum ranged from 23.5 mg/ml to 7.8 mg/ml.

5- CONCLUSION

In conclusion, ampicillin is a bactericidal antibiotic, it penetrates into the bacterial wall better than penicillin G and is active against gram-negative bacteria that are resistant to penicillin G. Ampicillin is the most widely used antibiotic against the infections caused by Listeria, β-lactamase-negative Haemophilus, enterococci, Shigella, streptococci, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Neisseria gonorrhea, Neisseria meningitis and many coliform organisms. In neonates with a gestational age ≤ 34 weeks and a postnatal age ≤ 7 days, the half-life, the clearance and the distribution volume of ampicillin are 5.0 hours, 0.055 l/h/kg, and 0.40 l/kg, respectively. The ampicillin half-life decreases and the clearance increases with neonatal maturation whereas the distribution volume is not affected by neonatal maturation. The recommended dose of ampicillin is 50 mg/kg every 12 hours in the first week of life, every 8 hours in neonates 1-3 weeks old, and every 6 hours in neonates 4 or more weeks old. Bacteremia, caused by the group B Streptococcus is treated with 150 to 200 mg/kg/day ampicillin, and meningitis is treated with 300 to 400 mg/kg/day ampicillin in divided doses. In literature there is not a review on the effects and pharmacokinetics of ampicillin in neonates and infants. Some bacteria are resistant to ampicillin and a combination of gentamicin and a third-generation cephalosporin is recommended.

6- 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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