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Management of Typhoid Fever and Bacterial Meningitis by Chloramphenicol in Infants and Children

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Abstract

Chloramphenicol inhibits protein synthesis in bacteria and is usually bacteriostatic, but is bactericidal against Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitis. Chloramphenicol penetrates all body tissues well. The cerebrospinal fluid concentration averages 60% of the serum level, while brain levels are 9 times higher because of high lipid solubility of this drug. Chloramphenicol acts primarily by binding reversibly to the 50S ribosomal subunit. This antibiotic is the drug of choice for the treatment of typhoid and paratyphoid fevers and bacterial meningitis. Chloramphenicol possesses a broad-spectrum of antimicrobial activity. Strains are considered sensitive if they are inhibited by chloramphenicol concentrations of ≤ 8 µg/ml. Neisseria gonorrhea, Brucella species, Bordetella pertussis, gram-positive cocci, Clostridium species, and gram-negative rods including Bacteroides fragilis are inhibited by chloramphenicol. Most anaerobic bacteria including Mycoplasma, Chlamydia, Rickettsiae, Vibrio cholera, Escherichia coli and Klebsiella pneumoniae are inhibited by this antibiotic.

The doses of chloramphenicol are 40.5 mg/kg/day for neonates and 75.5 mg/kg/day for older children. The therapeutic concentrations of chloramphenicol are 10-25 µg/ml. Peak therapeutic concentrations are obtained in 60% and therapeutic trough concentrations are found in 42% of children. Children affected by typhoid fever are cu red by chloramphenicol and the sensitivity to this antibiotic is 100%. Acute bacterial meningitis is the most dangerous infections disease in children. The causative organisms are gram-positive and gram-negative bacteria, and chloramphenicol is effective in killing these microorganisms. The aim of this study was to review the management of typhoid fever and bacterial meningitis in infants and children by chloramphenicol.

Key Words: Children, Chloramphenicol, Effects, Infants, Meningitis Typhoid-Fever.

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1-INTRODUCTION

Chloramphenicol is used to treat the typhoid and paratyphoid fevers, bacterial meningitis and ventriculitis because of good penetration in the cerebrospinal fluid. It is also used for sepsis and pneumoniae in some countries because most alternatives remain expensive. Chloramphenicol penetrates all body tissues well: the cerebrospinal concentration averages 60% (range, 45% to 99%) of the serum levels, while brain levels are 9 times higher because of high lipid solubility of this antibiotic. The oral chloramphenicol (chloramphenicol palmitate) also requires prior hydrolysis by pancreatic enzymes that makes it unwise to give the drug by mouth when first starting treatment in early infancy. Much of the inactive ester is excreted by renal tubules, most of the drug is first metabolized to the inactive glucuronide, so the dose does not usually need to be modified in renal failure. Excretion and metabolic inactivation are, however, influenced by postnatal age. The half-life decreases from a mean of 27 hours in the first week of life to 8 hours by 2 to 4 weeks and 4 hours in children over 4 months old (1).

Chloramphenicol inhibits protein synthesis in bacteria, and to a less extent, in eukaryotic cells. The drug readily penetrates cells, probably by facilitated diffusion. Chloramphenicol acts primarily by binding reversibly to the 50S ribosomal subunit (near the binding site for the macrolide antibiotics and clindamycin, which chloramphenicol inhibits competitively). Although binding of transfer RNA (tRNA) at the codon recognition site on the 30S ribosomal subunit is undisturbed, the drug apparently prevents the binding of the amino acid-containing end of the aminoacyl tRNA to the acceptor site on the 50S ribosomal subunit. Chloramphenicol also can inhibit mitochondrial protein in mammalian cells, perhaps because mitochondrial ribosomes resemble bacterial ribosomes (both are 70S) more than they do the 80S cytoplasmic ribosomes of mammalian cells. The peptidyl transferase of mitochondrial ribosomes, but not of cytoplasmic ribosomes, is inhibited by chloramphenicol. Mammalian erythropoietic cells are particularly sensitive to this drug (2). Due to the chloramphenicol toxic profile, which includes aplastic anemia, and gray baby syndrome and the availability of other less toxic but equally effective drugs used for similar indications, chloramphenicol is not extensively used. It nevertheless remains the drug of choice for the treatment of typhoid and paratyphoid fevers, life-threatening rickettsial disease, bacterial meningitis and aerobic and anaerobic gram-negative and gram-positive bacterial infections in patients who have life-threatening allergy to penicillins (3).

Chloramphenicol is usually bacteriostatic but is bactericidal against Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitis, and chloramphenicol clinical efficacy against these meningeal pathogens is well established (4). Chloramphenicol can be used to treat serious pediatric infections when Haemophilus influenzae is a likely pathogen, as well as typhoid fever, anaerobic infections, bacterial meningitis in patients allergic to penicillin, brain abscesses, and rickettsial infections. The use of chloramphenicol is limited because of its toxicity. Aplastic anemia is very rare but can occur after either oral or intravenous administration. Chloramphenicol remains an important inpatient antibiotic that can be invaluable for treating certain life-threatening infections.

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports:

MEDLINE, CINAHL, EMBASE, Google scholar and Medline (via PubMed) as search engines; September 2017 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "chloramphenicol dosing neonates", "chloramphenicol typhoid fever neonates", "chloramphenicol meningitis neonates", and "chloramphenicol effects neonates", were used. In addition, the books Neonatal Formulary (1) and NEOFAX by Young and Mangum (5) were consulted.

3-RESULTS

3-1. Dose and administration of chloramphenicol in infants and children

3-1-1. Loading dose

Give 20 mg/kg intravenous infusion by syringe pump over 30 min (5).

3-1-2. Maintenance dose: (begin 12 hours after the loading dose).

Premature infants under 1 month of age: give 2.5 mg/kg every 6 hours. Fullterm infants under 1 week of age and premature infants over 1 month of age: give 5 mg/kg per dose every 6 hours. Fullterm infants over 1 week of age: give 12.5 mg/kg per dose every 6 hours (5).

3-2. Monitoring

Close monitoring of serum concentration is mandatory. Small changes in dose and interval can lead to disproportionately large changes in serum concentration. Therapeutic peak serum concentration is 10 to 25 µg/ml. Monitor complete blood count and reticulocyte counts. Assess hepatic and renal functions (5).

3-3. Antimicrobial activity of chloramphenicol

Chloramphenicol possesses a broad-spectrum of antimicrobial activity. Strains are considered sensitive if they are inhibited by chloramphenicol concentrations of ≤ 8 µg/ml, except Streptococcus pneumoniae where the breakpoint is ≤ 4 µg/ml, and Haemophilus influenzae, which has a breakpoint of 2 µg/ml. Chloramphenicol is bacteriostatic against most bacteria, although it is bactericidal against Haemophilus influenzae, Neisseria meningitides, and Streptococcus pneumoniae. More than 95% of strains of the following gram-negative bacteria are inhibited in vitro by 8 µg/ml or less of chloramphenicol: Haemophilus influenzae, Neisseria meningitides, Neisseria gonorrhea, Brucella species, and Bordetella pertussis. Likewise, most anaerobic bacteria, including gram-positive cocci and Clostridium species, and gram-negative rods including bacillus fragilis, are inhibited by ≤ 8 µg/ml of this drug.

Strains of Streptococcus aureus tend to be less susceptible, with MICs > 8 µg/ml. Chloramphenicol is active against Mycoplasma, Chlamydia, and Rickettsiae. The Enterobacteriacae are variably sensitive to chloramphenicol. Most strains of Escherichia coli (≥ 75%), Klebsiella pneumoniae, Proteus mirabilis and indole-positive Proteus species are susceptible. Strains of Vibrio cholera are largely susceptible to chloramphenicol. Pseudomonas aeruginosa, Shigella and Salmonella are resistant to multiple drugs, including chloramphenicol. Of special concern is the increasing prevalence of multiple-drug-resistant strains of Salmonella serotype typhi, particularly for strains acquired outside United States (2).

3-4. Absorption, distribution, fate and excretion of chloramphenicol

Chloramphenicol is absorbed rapidly from the gastrointestinal tract. The preparation of chloramphenicol for parenteral use is

the water-soluble, inactive prodrug sodium succinate. Similar plasma concentrations of chloramphenicol succinate are achieved after intravenous and intramuscular administration. Hydrolysis of chloramphenicol succinate by esterases occurs in vivo. Chloramphenicol succinate is rapidly cleared from plasma by kidneys; this may reduce overall bioavailability of the drug because as much as 30% of the dose may be excreted before hydrolysis. Decreased esterase activity has been observed in the plasma of neonates and infants, prolonging time to peak concentrations of active chloramphenicol (up to 4 hours) and extending the period over which renal clearance of chloramphenicol succinate can occur. Chloramphenicol is widely distributed in body fluids and readily reaches therapeutic concentrations in the cerebrospinal fluid, where values are about 60% (range, 45-99%) of those in plasma in the presence or absence of meningitis. Hepatic metabolism to the inactive glucuronide is the major route of elimination. The half-life of chloramphenicol correlates with plasma bilirubin concentration. About 50% of chloramphenicol is bound to plasma proteins; such binding is reduced in neonates (2).

3-5. Therapeutic uses of chloramphenicol

Therapy with chloramphenicol must be limited to infections for which the benefits of the drug outweigh the risk of the potential toxicities. When other antimicrobial drugs that are equally effective and potentially less toxic are available, they should be used instead of chloramphenicol (6). The typhoid fever should be treated with third-generation cephalosporins and quinolones because they are less toxic and because strains of Salmonella typhi are resistant to chloramphenicol (7).

Despite concerns about adverse effects, chloramphenicol continues to be used in certain situations and, due to its low therapeutic index and variable pharmacokinetics, therapeutic drug monitoring is often recommended (8). Chloramphenicol finds applications in typhoid fever and bacterial meningitis and therapeutic drug monitoring is routinely performed. In Malaysia, however, chloramphenicol is used without therapeutic drug monitoring. Ismail et al. (8) therefore decided to evaluate their therapeutic drug monitoring for chloramphenicol in relation to its role in chloramphenicol therapy in children, who constitute most of the patients. The objective of Ismail et al. (8) was also to develop strategies to improve the therapeutic drug monitoring for chloramphenicol use. Data were collected from 168 children given chloramphenicol for various indications and monitored by the therapeutic service. The dose of chloramphenicol was used to maintain plasma concentrations within a range of 10 to 25 µg/ml. Outcomes measured included daily temperature and hematological indices. Daily doses and plasma chloramphenicol varied greatly.

Doses averaged 40.5 mg/kg/day for neonates and 75.5 mg/kg/day for older children. Average peak concentrations were therapeutic in 60% of subjects and therapeutic trough concentrations were found in 42% of subjects. Average duration of typhoid fever was 6.3 days and it was unaffected by plasma chloramphenicol concentrations. Typhoid was eradicated in 97% of children, but 9 children with other diagnoses died. Side-effects were confined to mild reversible hematological abnormalities which developed in 11% of children at plasma concentrations which tended to be high. Ismail et al. (8) concluded that chloramphenicol remains useful in children with typhoid fever, and its use for

other indications, however, should be reviewed. Routine therapeutic drug monitoring for chloramphenicol is probably not warranted, at least until a clearer role is defined by well-designed prospective studies. Chloramphenicol has certain notable characteristic: it penetrates reliably into the central nervous system; it is usually bacteriostatic, but is bactericidal against Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitides. It is metabolized in the liver, and levels of drug in serum need to be monitored in patients with liver disease and in neonates (9). Potential toxicity limits the use of this drug. It has been estimated that death from aplastic anemia occurs in one of 24,500-40,800 courses of treatment. The incidence of aplastic anemia after parenteral therapy is almost unknown; however, a few cases have been reported. The gray baby syndrome has occurred in premature and newborn infants receiving high doses of chloramphenicol. This condition can be avoided by reduction of dosage and by monitoring levels of drug in the serum of these infants. The most common toxicity is a reversible, dose-related bone marrow suppression, which is identified by serial monitoring of reticulocyte and complete blood cell counts. Many of the identifications for use of this drug are still controversial because studies comparing the toxicity and efficacy of chloramphenicol and of alternative antibiotics have not been done.

3-6. Management of typhoid fever by chloramphenicol in infants and children

Between September 2008 and April 2015, Obaro et al. (10) screened 10,133 children in regional sites in central and northwest Nigeria. Clinically significant bacteremia was detected in 609 of 4,051 (15%) in the Northwest and 457 of 6,082 (7.5%) in the central region of Nigeria. Across both regions, Salmonella species account for 24% to 59.8% of bacteremias and are the commonest cause of childhood bacteremia, with a predominance of Salmonella enterica serovar Typhi. The prevalence of resistant to ampicillin, chloramphenicol, and cotrimoxazole was 38.11%, with regional differences in susceptibility to different antibiotics but high prevalence of resistance to readily available oral antibiotics. Salmonella Typhi is the leading cause of childhood bacteremia in central Nigeria. Expanded surveillance is planned to define the dynamics of transmission. The high prevalence of multidrug-resistance calls for improvement in environmental sanitation in the long term and vaccination in the short term.

Blood, stool and urine samples were collected from 100 patients diagnosed as having typhoid in 5 hospitals in Akwa Ibom State and analyzed for the presence of Salmonella species and other bacteria (11). Of the 100 blood samples screened, 55 (55%) were positive with the Widal test and 39 (39%) were positive on blood culture. Thirteen (14.1%) out of 92 urine samples were positive for bacterial growth, while 22 (26.8%) of the stool cultures were positive out of 82 samples screened. Those within the age range 11 to 20 years old were infected most frequently (33%), followed by the age range 21 to 30 years (19%) and 41 to 50 years (18%).

Those in the age range of 0 to 2 years old (4%) were least infected. Female subjects were more infected than males. The commonest organisms isolated from blood samples were Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Streptococcus faecalis, Salmonella paratyphi and Salmonella typhi, Streptococcus aureus, Streptococcus epidermis, Escherichia coli, Klebsiella aerogenes, Streptococcus faecalis, Proteus mirabilis were isolated from urine; while those isolated from stool were Streptococcus aeruginosa, Escherichia coli, Salmonella typhi, Salmonella paratyphi, Shigella species, Klebsiella

pneumoniae, Proteus vulgaris, Streptococcus aureus, Streptococcus epidermis, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa and Vibrio cholera 01. The isolates were sensitive to peflacine, ceftazidime, ciprofloxacin, ceftriaxone, cefotaxime and chloramphenicol. These antibiotics are recommended as the drugs of choice in therapy. These results suggest the existence of symptomless carriers of enteric fever bacilli in the state. This is worrisome, since some Salmonella typhi isolates exhibited multiple resistance to commonly used antibiotics.

From 1982 to 1995, 71 children admitted in the medical center of Chiu et al. (12) were diagnosed to have typhoid fever by culture or serology. Of the 71 children, most (83%) were aged 5 to 15 years. These children usually presented with fever and gastrointestinal symptoms, including abdominal pain, diarrhea, nausea, and constipation. Hepatosplenomegaly was the most common physical sign observed and abdominal tenderness ranked the second. Thrombocytopenia occurring in 9 patients (13%) was the most common mode of complication. Other complications included intestinal perforation (3%), rectal bleeding (3%), ascites or pleural effusion (4%, each), and meningitis (1%).

The incidence of complications tended to be higher among children 5 years of age than older ($p = 0.31$). Most patients responded well to appropriate antimicrobial therapies. There was no mortality. Relapse was observed in two children, although both had received 10 days of chloramphenicol therapy. The clinical isolates of Salmonella typhi were susceptible in vitro to all the antibiotics tested, including chloramphenicol, which, however, showed a higher MIC_{90} (Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms) level than the other drugs tested. In conclusion, there were age-specific differences of typhoid fever in children in terms of the incidence and morbidity and antibiotic resistance of Salmonella typhi has not been a problem in this area at least up to 1995. Salmonella is an important pathogen for infants and children of which multiple resistant strains were recently reported. Yang and Chi (13) reviewed the records of documented patients who had positive culture for Salmonella in the author's Pediatric Department from September 1982 to September 1992. Those patients with acute gastroenteritis were divided into two groups: I, those complicated with bacteremia and II, non-bacteremic cases.

Then these authors compared the age, body temperature, severity of clinical symptoms, white blood cell count and Salmonella serotype of these two groups. There were 180 cases of Salmonella infection in the author Pediatric Department during the past decade. The mean age was 14.8 months. Most patients (88.9%) were under two years old and 146 subjects were victims of acute gastroenteritis. Six cases had infection of the central nervous system. Five cases presented typhoid fever. Of three mortal cases, two died from meningitis with sepsis and one was victim of malignant lymphoma and septic arthritis complicated with sepsis. Salmonella group B was the most common pathogen. There were no cases of typhoid after 1989.

The sensitivity to ampicillin, chloramphenicol, and ceftriaxone for Salmonella group B were 25.7%, 26.1%, and 100%, respectively. Multiply resistant Salmonella species were not present in the examined cases. The severity of clinical symptoms varied significantly between those who had acute gastroenteritis with bacteremia (Group I), and those who had acute gastroenteritis without bacteremia (Group II). However, there was a significant distinction in the average age of

the two groups (p = 0.005). Although the annual number of cases did not decrease in recent years, the number of cases of typhoid fever did decrease. Most patients were infants and acute gastroenteritis was the most common. In the investigated cases, the relative sensitivity for ampicillin and chloramphenicol was small over the past decade. Multiply resistant Salmonella species were not found, which may be due to the small sample size. Over a period of 12 years, 109 children with Salmonella enteric fever were treated with chloramphenicol: 65 children were given the drug at 50 mg/kg/day (Group A), and 44 children received 100 mg/kg/day (Group B) (14). Treatment failed in 63% of cases with the lower dose and in 24% of children treated with the higher dose ($p < 0.001$). The children who received the higher dose produced a clinical response in 5.4 ± 1.8 days compared with 7 ± 2.6 days with the lower dose ($p < 0.01$). Chloramphenicol in an initial dose of 100 mg/kg/day is recommended in the treatment of typhoid and paratyphoid fevers in children. Ninety-seven Nigerian children under 5 years of age had typhoid or paratyphoid fever proven by blood culture (15). They presented with fever, anemia, gastrointestinal or neurological disturbances, and typhoid and paratyphoid fevers appeared clinically indistinguishable.

In this holoendemic malaria area, malaria was the most important differential diagnosis, and may have contributed to the concomitant anemia seen in the majority of patients. Despite vigorous therapy with chloramphenicol or trimethoxazole, and blood transfusion where indicated, the mortality in both typhoid and paratyphoid fevers was 18% in both groups.

3-7. Management of bacterial meningitis by chloramphenicol in infants and children

Acute bacterial meningitis is still considered one of the most dangerous infectious diseases in children. Cerebrospinal fluid samples from 179 patients (aged from 3 days to 12 years) with positive culture results were collected (16). Isolated pathogens were identified using the VITEK 2 system. The antimicrobial susceptibility of isolates was determined using the disc diffusion method. Of the isolates, 50.8% were gram-positive bacteria, and 49.2% were gram-negative bacteria. The most prevalent pathogens were Escherichia coli (28.5%), Streptococcus pneumoniae (17.8%), Staphylococcus epidermidis (10.0%), Haemophilus influenzae type b (9.5%), and group B streptococcus (7.2%). In young infants aged ≤ 3 months, Escherichia coli was the organism most frequently isolated from the cerebrospinal fluid (39/76; 51.3%), followed by group B streptococcus (13/76; 17.1%) and Streptococcus pneumoniae (8/76; 10.5%). However, in young infants aged > 3 months, the most frequently isolated organism was Streptococcus pneumoniae (24/103; 23.3%), followed by Staphylococcus epidermidis (18/103; 17.5%) and Haemophilus influenzae type b (16/103; 15.5%). The susceptibility rate of Streptococcus pneumoniae isolate to chloramphenicol was 87.5%.

Cronobacter sakazakii (formerly Enterobacter sakazakii) is an opportunistic pathogen that causes meningitis, sepsis, and necrotizing enterocolitis in neonates and infants through consumption of contaminated milk-based foods (17). The prevalence of Cronobacter sakazakii in 705 retail milk-based infant and baby food samples were investigated in 12 cities in Shaanxi, China, in 2010 and 2012. One hundred and nineteen samples (16.9%) were Cronobacter sakazakii positive. The isolates were further characterized for antimicrobial susceptibility to 14 antibiotics, pulsed-field gel electrophoresis

profiles, and presence of virulence genes. Samples of brand W, Y, A, and G in 2010 and 2012 were Cronobacter sakazakii positive. All isolates recovered in 2010 and 2012 were susceptible to chloramphenicol. Antibiotic resistance of isolates was most commonly found to rifampicin, amoxicillin-clavulanic acid, streptomycin, tetracycline, and ampicillin in both 2010 and 2012, except to trimethoprim/sulfamethoxazole in 2012. Pulsed-field gel electrophoresis profiles indicated that Cronobacter sakazakii isolates were genotypically diverse, although these isolates were prevalent in infant and baby foods with the same brand. A total of 34 virulence gene profiles of the Cronobacter sakazakii isolates were detected in 2010 and 2012. Isolates that co-carried hly-ompX-eitCBAD-iucABCD/iutA genes in 2012 were significantly ($p < 0.05$) more prevalent than those in 2010. These results added new epidemiological evident for the widespread occurrence of Cronobacter in retail milk-based infant and baby foods and this should be an indicator of potential health risk for consumers.

Neisseria meningitides is a leading etiologic agent of severe invasive disease. Skoczynska et al. (18) characterized the invasive meningococcal disease epidemiology in Poland during the last decade, based on laboratory confirmed cases. The study encompassed all invasive meningococci collected between 2002 and 2011 in the National Reference Centre for Bacterial Meningitis. The isolates were re-identified and characterized by susceptibility testing, MLST analysis, PorA and FetA sequencing. A Polymerase chain reaction (PCR) technique was used for meningococcal identification directly from clinical materials. In the period studied, 1,936 cases of invasive meningococcal disease were confirmed, including 75.6% identified by culture. Seven invasive meningococcal disease outbreaks, affecting mostly adolescents, were reported; all were caused by serogroup C meningococci of ST-11. The highest incidence was observed among children under one year of age (15.71/100,000 in 2011). The general case fatality rate in the years 2010 to 2011 was 10%. Meningococci of serogroup B, C, Y and W-135 were responsible for 48.8%, 36.6%, 1.2% and 1.2%, of cases, respectively. All isolates were susceptible to third generation cephalosporins, chloramphenicol, ciprofloxacin, and 84.2% were susceptible to penicillin. Multilocus sequence typing (MLST) analysis (2009-2011) revealed that among serogroup B isolates the most represented were clonal complexes (CC) ST-32CC, ST-18CC, ST-41/44CC, ST-213CC and ST-269CC, and among serogroup C: ST-103CC, ST-41/44CC and ST-11CC. The disease was mostly attributed to changes in the surveillance system including an expanded case definition and inclusion of data from non-culture diagnostic.

Acute bacterial meningitis remains an important cause of mortality among African children. Roca et al. (19) strengthened hospital-based surveillance of acute bacterial meningitis among children admitted to Manhica District Hospital (Maputo, Mozambique). Cerebrospinal fluid samples were collected from children admitted to the hospital who met clinical criteria of acute bacterial meningitis. Laboratory determinations were performed. Clinical information and outcome of cases were recorded. During the first 12 months of surveillance, which began in January 2006, cerebrospinal fluid samples were collected from 642 children < 15 years of age with suspected meningitis (18% of all pediatric patients admitted to the hospital during that time). Acute bacterial meningitis was confirmed in 43 (7%) of the 642 cases. Haemophilus influenzae type b (14 cases), pneumococcus (9 cases), and

meningococcus (7 cases) represented approximately 70% of confirmed cases. Four of 9 pneumococci cases were serotypes covered by the 7-valent pneumococcal conjugate vaccine. The case fatality rate among patients with acute bacterial meningitis was 24% (8 of 33 with known outcome); and additional 8 patients left the hospital before discharge. The incidence of acute bacterial meningitis was 85 per 100,000 subjects, which peaked at 2 to 12 months of age at 1,078 cases per 100,000 subjects. All 9 pneumococci isolates were susceptible to chloramphenicol, and 8 were susceptible to penicillin (the additional 1 patient had intermediate resistance). For 10 Haemophilus influenzae type b isolates tested, only 1 patient was susceptible to chloramphenicol, and 5 patients were susceptible to ampicillin. These data reinforce the importance of acute bacterial meningitis as cases could have been prevented by current pneumococcal and Haemophilus influenzae type b conjugate vaccines.

During June 1998 to November 2003, 475 cerebrospinal fluid samples were collected from 20,173 children < 15 years of age admitted to hospital (20). Culture results confirmed 71 (15%) cases of acute bacterial meningitis. The most prevalent bacterial etiologies were Streptococcus pneumoniae (n = 31), Haemophilus influenzae (n = 13), and Neisseria meningitis (n = 8). Other important bacteria were Streptococcus species (n = 7), Salmonella Species (n = 4) and Staphylococcus aureus (n = 3). Crude incidence rates of acute bacterial meningitis and pneumococcal meningitis were 20/100,000 and 10/100,000 children-year-at risk, respectively. Incidences were more than three times higher in the < 1 year age group. Overall case fatality rate was 36%, and was highest for Haemophilus influenzae and pneumococcal meningitis (55% and 45%, respectively, p-level = 0.044). Pneumococcal susceptibility was 81% for oxacillin and 93% for chloramphenicol. For Haemophilus influenzae isolates, susceptibility was 54% for ampicillin, and 62% for chloramphenicol. Streptococcus pneumoniae and Haemophilus influenzae were the main etiologies responsibly for the high burden of mortality associated with acute bacterial meningitis in rural Mozambique. A total of 989 infants and children 0 to 59 months old with suspected meningitis using standardized guidelines based on clinical signs and symptoms were prospectively enrolled from April to May 2000 in a rural general hospital in the Philippines (21). Blood, cerebrospinal fluid, antigen testing and cell count were drawn on admission for culture. All had blood cultures and 623 (63%) had cerebrospinal fluid samples. Bacterial etiology was found in 54 (5%). The most common bacterial pathogens were Haemophilus influenzae type b (20, 37%) and Streptococcus pneumoniae (10, 18%).

All of the Haemophilus influence type b infections and 8 (80%) Streptococcus pneumoniae infections were in infants less than 1 y old. Twelve (22%) of the subjects with bacterial meningitis died. All strains of Streptococcus pneumoniae, and Haemophilus influenzae were sensitive to chloramphenicol, cotrimoxazole and ampicillin. In conclusion, Streptococcus pneumoniae and Haemophilus influenzae type b are the most common etiological agents of bacterial meningitis in a rural area in the Philippines, and occur especially in infants less than 1 year old. Etiological agents were susceptible to the currently recommended antimicrobial agents. As group B streptococci prevalence varies from place to place and this organism is responsible for serious infections in newborns such as septicemia and meningitis, the present study was carried out to find the prevalence of group B streptococci in pregnant women and

their neonates (22). From June 1998 to April 1999 a total of 317 pregnant women and neonates were examined for group B streptococci. Group B streptococci colonization rate was 2.52% and 1.26% in pregnant women and their neonates, respectively. Four sites - viz. throat, external ears, external nares and stump of umbilicus from neonates were found to be equally colonized by group B streptococci immediately after birth and at the time of discharge from hospital, except the umbilicus which was not swabbed at the time of discharge. None of the neonates developed group B streptococci related sepsis. Selective broth medium was found to be a superior transport method over Stuart transport and filter paper method. The isolates were sensitive to chloramphenicol at a percentage of 66.6 (12/18). Enterococcal meningitis is a rare complication of neurosurgical procedure of high technology treatment of children and occurs mainly in immunocompromised neonates with very-low-birth weight, and severe prematurity. It complicates sometime ventriculoperitoneal (VP) shunt insertion or perinatal trauma (23). Enterococcal faecalis caused 10 nosocomial meningitis and all strains were susceptible to chloramphenicol. Mortality in this cohort of 10 children was 20% which is insignificantly higher than overall mortality in the whole cohort of meningitis within last 15 years.

Sixty-eight children with systemic Streptococcus pneumoniae infection were identified by hospital chart review between 1989 and 1997 (24). The age distribution varied from 2 days to 15 years, with a mean age of 3.3 years. There were 35 boys and 33 girls. Four clinical entities included 30 cases of meningitis, 20 cases of pneumonia, 10 cases of peritonitis and 8 cases of septicemia/bacteremia. Forty patients (58.8%) had underlying disease. Seventeen patients (25.0%) developed early complications and the mortality rate was 8.8%. The susceptibility isolates to chloramphenicol was 91.3%. Skoczynska et al. (25) reported the results of the first two years (1997-1998) of activity of the National Reference Centre for Bacterial Meningitis on the etiologic agents of bacterial meningitis in Poland. Of 220 isolates sent to the National Reference Centre for Bacterial Meningitis, the most frequently identified was Neisseria meningitides (n = 90, 40.9%), followed by Haemophilus influenzae (n = 58, 26.4%), and Streptococcus pneumoniae (n = 46, 20.9%). Of meningococcal isolates, 88.9% belonged to serogroup B and 10.0% to serogroup C, and the most prevalent serotype was 22 (43.3%). Most meningococci were highly sensitive to penicillin; however, 10% of them, had decreased susceptibility to penicillin. More than 90% of Haemophilus influenzae belonged to serotype B, and all were susceptible to third-generation cephalosporin and chloramphenicol. A broad distribution of serotypes was found among pneumococcal isolates, of which the most common were serotype 3 and 8. Penicillin nonsusceptible isolates constituted 13% of all pneumococcal isolates. Three of the resistant pneumococci belonged to serotype 23F. These findings demonstrate the current epidemiological situation of bacterial meningitis in Poland.

Sixty-one episodes of Salmonella meningitis were identified during the 3-year period from February 1996 to January 1999 inclusive (26). These accounted for 6.8% of all the acute bacterial meningitis cases seen during this time. In contrast, only two children were admitted with Salmonella meningitis in 1982. The increase may reflect the rise in HIV disease and the associated increase in Salmonella septicemia. All but one child were under 2 years of age, only six children were well nourished and anemia was common. The prognosis was poor: 33

(58%) died, 19 made a full recovery and 5 developed sequelae. Two children relapsed, one of whom died. Patients were routinely treated with chloramphenicol, to which all isolates were sensitive in vitro. The poor outcomes suggest that an alternative antibiotic policy is required. Nik Khairulddin et al. (27) conducted a retrospective study of 65 children who had invasive of Haemophilus influenzae disease from June 1985 to December 1994. The age distribution varied from 1 day to 72 months with a mean of 13 months. Peak incidence occurred in the 7 to 12 months age group. The majority (89.1%) was below two years of age. The relative frequencies of the 75 clinical entities documented were as follows: meningitis 64%, pneumoniae 29.3%, septicemia 5.4%, and abscess 1.3%. In addition, 13.5% of cases had meningitis associated with pneumoniae. Serotype B accounted for all strains in cases where serotyping was done. Anemia (Haemoglobin < 10%) was seen in 71.4% of cases. Long term complications were noted in 41.5% cases of meningitis. Case fatality rate was 12.3%. The Haemophilus influenzae sensitive to chloramphenicol was 98.2%.

Review of the management of neonatal infections is done with the aim of guiding the clinician on appropriate therapy (28). Minimum investigations should include a white blood cell count and a blood culture. The bulk of infections at Kenyatta National Hospital newborn unit are caused by Klebsiella, Citrobacter and Staphylococcus aureus. During the 1990's considerable resistance to gentamicin was developed. Currently, cephalosporins and chloramphenicol have the best sensitivity pattern. The diagnosis must be carefully verified at different stages of treatment to ensure that only those requiring antimicrobial therapy get it. Indiscriminate use is thus avoided. This in turn minimizes development of antibiotic resistant organisms. Failure of response to antimicrobials sometimes means a noninfectious cause of illness or poor supportive management. Continuous surveillance is recommended with emphasis on primary prevention as well as cross infections. Catania et al. (29) valuated the incidence and clinical therapeutic aspects of Haemophilus influenzae type b meningitis in children. They reported a retrospective study from January 1982 to December 1994, in children aged from 1 month to 14 years suffering from acute purulent meningitis. Particular attention was directed to Haemophilus influenzae type b meningitis (20 cases). The incidence rate of Haemophilus influenzae type b meningitis in the overall cases (n = 89) was 22.47% (n = 20), while among children younger than 5 years, Haemophilus influenzae type b was the most frequent pathogen isolated (20/58, 34.7%). In 1/4 of cases, particularly in children younger than 1 year, exordium was nonspecific and unclear. At admission culture and examination of cerebrospinal fluid were performed. Cerebrospinal fluid was cultured on blood agar and chocolate plates. A latex agglutination test was used for rapid detection of the bacterial antigens. In some cases, Catania et al. (29) looked for bacterial antigens in urine. Twenty percent of children had complications and 10% had sequelae (1 year follow-up). No children died. Antibiotic treatment was principally with ampicillin, cephalosporin and chloramphenicol.

The clinical and microbiological data of 60 neonates, 23 from the Neonatal Unit (group I), and 37 (group II) from the General Pediatric Wards with bacterial meningitis were presented by Adhikari et al. (30). The overall prevalence/1,000 was significantly lower in group I (0.36) than in group II (1.11; $p < 0.0001$). This low incidence follows the introduction of amikacin for the treatment of the ill

neonates in 1986. Streptococcus agalactiae (n = 21, 35%), Klebsiella pneumoniae (n = 17, 28%), and Escherichia coli (n = 10, 17%) were the commonest pathogens accounting for 80% of cases. Streptococcus agalactiae isolates were uniformly susceptible to penicillin and chloramphenicol. Gram-negative isolates showed resistance to ampicillin, chloramphenicol and sulphamethoxazole-trimethoprin. Fifty patients with systemic Haemophilus influenzae disease were identified by hospital chart review between 1980 and 1992. The age distribution varied from 8 days to 14 years; the mean age was 12.7 months (31). The peak incidence was between 4 and 6 months of age. The relative frequencies of 79 clinical entities encountered in 50 patients were as follows: meningitis 55.7%, bacteremia 13.9%, pneumoniae 25.3%, cellulites 2.5%, and arthritis 1.3%. There were 23 patients (46%) who had more than one disease entity. Most of the patients were anemic (Hemoglobin < 10 %) when hospitalization. Sixty-four percent of the patients had early complications. The mortality rate was 8%. Although serotyping was not done from the isolates, at least 33 cerebrospinal fluid samples were positive for Haemophilus influenzae type b capsular antigen by Counterimmunoelectrophoresis. The susceptibility of Haemophilus influenzae to chloramphenicol was 87.5%.

During a two-year period, from January 1989 to January 1991, 39 (12%) of 331 children admitted to various hospitals and health centers in Enugu and Nsukka areas of Eastern Nigeria with symptoms of meningitis had Haemophilus influenzae isolated from their cerebrospinal fluids (32). Ninety percent were aged 24 months and below. Out of the 39 isolates, 37 were Pittman serotype b while the remaining 2 were typed. More males (61.5%) had Haemophilus influenzae meningitis in comparison with 38.5% of females. A percentage of 69.2 of the cases occurred during the dry season while 30.7% occurred during the rainy season. All the isolates were sensitive to chloramphenicol. The leading role of Haemophilus influenzae meningitis in children who were 7 to 24 months of age in this part of the world and the increasing resistance of this organism to ampicillin was hereby stressed. A total of 10,466 samples from cases of meningitis in different age groups were cultured during the period 1988 and 1991 (33). Acinetobacter calcoaceticus was isolated in 12 (5.6%) of 211 positive cultures. The strains were 100% susceptible to chloramphenicol, and 100% resistant to ampicillin, cotrimoxazole and tetracycline and 50% resistant to cephalotin, gentamicin, and kanamycin.

A survey of 303 urban and 156 rural children showed nasopharyngeal carriage of relatively resistant Streptococcus pneumoniae organisms in 14.2% and 19.2% of children, respectively (34). These organisms have a MIC for penicillin in the range of 0.12 to 1 µg/ml. An analysis of 40 relatively resistant Streptococcus pneumoniae strains showed resistance to co-trimoxazole in 47.5%, trimethoprim in 42.5%, fusidic acid in 20%, and in 5% rifampicin. All the strains were susceptible to chloramphenicol and vancomycin. Eighty-three per cent of the strains tested belonged to serogroup 6 and 19.

Of 155 highlands children with purulent culture-positive meningitis, 84% were aged 12 months or less and 92% were infected with either Haemophilus influenzae, Streptococcus pneumoniae or both organisms. Other pathogens were Streptococcus pyogenes (2 isolations) and Streptococcus agalactiae and Klebsiella species (1 of each). Neisseria meningitides (8 isolations), Streptococcus pyogenes (2 isolations) and Streptococcus agalactiae and Klebsiella species (1 of each). Among Haemophilus influenzae isolates, serotype b strains predominated (83%) and most

(96%) belonged to biotype I or II (35). Infections due to non-serotype B hemophilia included serotype a (9 strains), biotype I or II. Infections due to non-serotype B hemophilia included serotype a (9 strains), serotype f (1 strain) and non-serotypeable variants (3 strains). Of 67 Streptococcus pneumoniae strains 22% were resistant to benzylpenicillin, with a MIC of 0.1 to 1.0 µg/ml. The commonest serotypes were 5 (11 isolates), type 7 (9 isolates) and types 2, 6 and 46 (6 of each). No resistance to chloramphenicol was detected in either Haemophilus influenzae or Streptococcus pneumoniae. The known case fatality rate was 37%. A percentage of 46 of children with pneumococcal infection died (46%) whereas those infected with Haemophilus influenzae (30%) died, though the difference was not statistically significant; 79% of all deaths occurred in children aged less than 12 months. There is an urgent need for Haemophilus influenzae and Streptococcus pneumoniae vaccines that are effective in young children.

A total of 131 children with Haemophilus influenzae infection was studied over a 5 years period. Of these, 92% and of those who died from this disease, 94% were 2 years old or less (36). Mortality was 26% and morbidity among the survivors was 36%. Most of the children studied were marasmic. The seasonal incidence is discussed since incidence peaked mainly the dry season with a secondary peak in the raining season. Hemoglobin (H6) electrophoresis, done in respect of a few children, showed a significantly higher incidence of hemoglobin (Hb) SS among patients than in the general population. This relationship is being studied further. The prognosis did not appear to be significantly affected by the choice between a combination of penicillin and chloramphenicol on the one hand and ampicillin alone on the other. A combination of penicillin and chloramphenicol is preferred to chloramphenicol alone in initiating therapy because 100% of strains of Haemophilus influenzae isolated in the laboratory of Nottidge (36) are susceptible to chloramphenicol but 75% of strains of Streptococcus pneumoniae are susceptible to this drug. Serum chloramphenicol levels were evaluated in 52 children with severe infection treated intravenously with chloramphenicol monostearoylglycolate or chloramphenicol in capsules (37). Effective serum levels were recorded with all chloramphenicol preparations. The variability was largest with chloramphenicol monostearoylglycolate. In a case of neonatal Escherichia coli meningitis good serum levels of chloramphenicol were achieved with chloramphenicol palmitate orally, supporting the view that oral chloramphenicol palmitate can be used to treat serious infections in this age group.

The absorption and disposition of orally administered chloramphenicol palmitate was studied in 7 neonates (four preterms and three terms). The highest measured chloramphenicol serum concentrations occurred more than or equal to 4 hours after the dose, and ranged from 5.5 to 23 µg/ml after a dose of chloramphenicol palmitate of 50 mg/kg per day orally (38). The dosage had to be increased in all preterm neonates from 25 mg/kg per day to 50 mg/kg per day to obtain adequate serum levels during therapy. In four neonates the apparent half-life could not be estimated, because there was no decline in serum concentrations. The apparent half-life was 3 and 6 hours in two neonates in whom the serum concentration declined during the dosing interval. Urinary excretion of chloramphenicol and the glucuronide ester in three neonates varied from 24% to 55% of the dose administered. There was a considerably variability in serum chloramphenicol levels when chloramphenicol palmitate

was administered orally. The delay in achieving the maximum serum concentration, non-declining serum curve, and low renal recovery is indicative of incomplete, prolonged, and erratic absorption, possibly related to delayed gastric empting or decreased intraluminal hydrolysis of the palmitate ester.

3-8. Chloramphenicol toxicity in infants and children

Chloramphenicol was initially designed for the treatment of typhoid fever, but it has fallen out of favor due to the ubiquity of antibiotic-resistant Salmonella typhi. It was also historically used for the empiric treatment of pediatric patients presenting with petechial rash and fever for its excellent coverage of meningococcal sepsis and rickettsial diseases (39). Due to its low-cost, wide spectrum of coverage, and low incidence of toxicity, chloramphenicol has been added to the World Health Organization's list of Essential Medicines, and the growing problem of antimicrobial resistance to current broad-spectrum antibiotics has brought back interest in its use worldwide.

A decade after its discovery, the first case reports of a potentially fatal adverse reaction to chloramphenicol was discovered in neonates, with a prediction towards preterm infants. Neonates born at less than 37 weeks gestation were given chloramphenicol in an intravenous or oral formulation within 2 days of birth when they began to develop abdominal distention, vomiting, hypothermia, cyanosis, and cardiovascular instability. Vasomotor collapse resulting in mottling skin and eventual ashen-gray discoloration led to the naming of this reaction as "gray baby syndrome". Recent work on the toxicology of chloramphenicol suggests that its propensity to cause damage to the blood forming organs may be related to its potential for nitro-reduction and the subsequent production of nitric oxide (40). Aerobic and anaerobic nitro-reduction of chloramphenicol by human fetal and neonatal liver results in the production of the amine derivative. However intermediates of the reaction nitroso-or glutathionesulphinamido-chloramphenicol could not be detected by hplc. Perfusion of chloramphenicol through isolated lobules of human placenta caused a decrease in blood pressure at a time which coincided with a peak of nitric oxide production. However, although the pressure drop could be reversed by an inhibitor of nitric oxide synthesize, the nitric oxide profile remained the same. These observations suggest that involvement of the para-nitro group of chloramphenicol could cause both hemotoxicity and hypotension in susceptible individuals.

For infections in infants and children, the successful antibiotic treatment depends primarily on rapid diagnosis of the disease, identification of pathogenetic microorganisms, and appropriate application of specialized pharmacokinetic and pharmacodynamic knowledge of antibiotics in children (41). In infants and children, the absorption, distribution, metabolism, and excretion of drugs may differ considerably in comparison with adults. Because of known toxicity, certain drugs such as chloramphenicol in high doses, sulfonamides, and tetracycline should not be used in neonates.

Although high concentrations of chloramphenicol are related to toxicity, as shown experimentally and during treatment, the mechanism of toxicity remains unclear (42). Published works suggest that relatively minor metabolites may be causally related to toxic reactions in vitro and some of these metabolites have been detected in sera from treated patients. It is possible that all the major toxic manifestations of chloramphenicol may be explained by attack by free radicals. Depletion in compounds acting as cellular antioxidants, such as glutathione

and vitamin E, may conceivably increase the vulnerability of an individual to chloramphenicol toxicity, while supplementation with an antioxidant might protect against it. Research into the metabolism of chloramphenicol and the mechanism of its toxicity has declined since early work in the 1950s and 1960s, but its continuing use worldwide means that there is justification for renewed interest in the toxicology of this useful antibiotic.

The incidence of dose related chloramphenicol toxicity was determined in 64 neonates from 12 hospitals. Ten of 64 neonates exhibited symptoms attributed clinically to chloramphenicol toxicity (43). Nine received the dose prescribed and one an overdose. The grey baby syndrome was observed in 5 of 10 neonates; four babies suffered reversible hematological reactions; and 1 neonate was described as very grey. Peak serum chloramphenicol concentrations in these 10 neonates ranged from 28 to 180 µg/ml and trough concentrations ranged from 19 to 47 µg/ml. Serum chloramphenicol concentrations above the therapeutic range (15-25 µg/ml) were observed in a further 27 neonates (2 had received a 10-fold overdose), none of whom showed signs of toxicity. Serious toxicity was associated with either prescription of dosages greater than that recommended or overdose of chloramphenicol. High concentrations in young neonates may be avoided by giving the recommended dose and then careful monitoring; concentrations should be maintained between 15 and 25 µg/ml. No neonates with concentrations within this range showed clinical signs of toxicity.

Because of known toxicity, certain drugs such as chloramphenicol in high doses, sulfonamides, and tetracycline should not be used in neonates. Antibiotic therapy should be modified in neonates because of biologic immaturity of organs important for the termination of drug action (44). Because of poor conjugation, inactivation, or excretion, the serum concentrations of many antibiotics may be higher and more prolonged in neonates than in infants. Thus, the dosages of many antibiotics must be lower and the intervals between administrations must be longer. The appearance of strains of ampicillin-resistant Haemophilus influenzae, the slow development of resistance to chloramphenicol among gram-negative and gram-positive bacteria, and the development of improved analytic methods to measure chloramphenicol have all resulted in the use of this drug in selected cases of serious infection in children beyond the neonatal age. Third-generation cephalosporins have an important role in the empiric treatment of pediatric bacterial meningitis because of their ability to penetrate in the central nervous system and their effectiveness against penicillin- or chloramphenicol-resistant Haemophilus strains and against many gram-negative bacteria in the Enterobacteriacae group.

Nahata (45) studied the relationship between steady-state chloramphenicol serum concentration and hematologic adverse effects in 45 pediatric patients. The mean peak serum concentration of chloramphenicol in patients with and without toxicity were not different ($p < 0.01$): 22.7 µg/ml in neutropenic patients versus 23.1 µg/ml in those without neutropenia; 18.2 µg/ml in patients with leucopenia versus 23.3 µg/ml in those without leucopenia; 22.2 µg/ml in patients with eosinophilia versus 23.9 µg/ml in those without eosinophilia; 23.7 µg/ml in patients with anemia versus 22.1 µg/ml in those without anemia. None of the patients developed thrombocytopenia. These data clearly demonstrated that chloramphenicol toxicity may not be predictable by serum concentration in pediatric patients receiving therapeutic doses of chloramphenicol succinate. Thus, frequent

monitoring of chloramphenicol serum concentration does not appear warranted unless a patient appears unresponsive to a therapeutic dose or has received an excessive dose. Because of the immature excretory and/or metabolic processes of infants, it was recognized that detailed pharmacokinetic studies were necessary before these drugs could be used safely and effectively in young infants, but it was only with experience that it became obvious that toxicity remained relatively unpredictable (46). Neonates were found to be more resistant to certain types of adverse reactions (e.g., renal damage by aminoglycosides, bacitracin, methicillin, etc.), but more susceptible to others (sulfonamides, chloramphenicol, tetracycline, nitrofurantoin, and so forth).

In many instances, toxic effects encountered could have been predicted by experimental data in animals, but in other cases, this was not possible. Thus, the use of new antimicrobial agents in neonates may expose them to unpredictable dangers. For that reason, new drugs should only be administered to young infants if they clearly have a therapeutic advantage over older ones. Therapeutic trials must await adequate pharmacokinetic studies, and the investigator must be prepared to follow the treated infants (along with a group of matched control patients) for a sufficient length of time to be certain that any organ damage caused by the drug would have become clinically detectable. In some cases this requires a period of several years.

3-9. Resistance to chloramphenicol

Several bacteria, such as Pseudomonas aeruginosa, Shigella and Salmonella, are resistant to multiple drugs, including chloramphenicol. The resistance to this antibiotic usually is caused by a plasmid-encoded chloramphenicol acetyltransferase that inactivate the drug. Resistance also can result from decreased permeability and from ribosomal mutation. Acetylated derivatives of chloramphenicol fail to bind to bacterial ribosomes (2).

4-DISCUSSION

Chloramphenicol is used to treat typhoid and paratyphoid fevers and bacterial meningitis. The penetration of chloramphenicol in tissues is good, its concentration in cerebrospinal fluid is 60% (range, 45-99%) of the serum levels and in brain is 9 times higher because of the high lipid solubility of this antibiotic. Chloramphenicol palmitate may be administered orally but this requires prior hydrolysis by pancreatic enzymes that makes it unwise to give the drug by mouth when first starting treatment in early infancy. The elimination rate of chloramphenicol is influenced by postnatal age and the half-life of this antibiotic is 27 hours in the first week of life, 8 hours by 2 to 4 weeks and 4 hours in children over 4 months of age (1). Hepatic metabolism to the inactive glucuronide is the major route of elimination. In adults, about 50% of chloramphenicol is bound to plasma proteins and in neonates the bound fraction is reduced (2). Chloramphenicol inhibits protein synthesis in bacteria.

This antibiotic acts primarily by binding reversibly to the 50S ribosomal subunit. Chloramphenicol also can inhibit mitochondrial protein in mammalian cells. Due to chloramphenicol toxic effects, which includes aplastic anemia and gray baby syndrome, this antibiotic is not extensively used. It nevertheless remains the drug of choice for the treatment of typhoid and paratyphoid fevers, life-threatening rickettsial disease, bacterial meningitis, and patients who have life-threading allergy to penicillins (3). Chloramphenicol possesses a broad-spectrum of antimicrobial activity. This antimicrobial agent is usually bacteriostatic, but it is bactericidal against Haemophilus influenzae, Streptococcus

pneumoniae, and Neisseria meningitis (4). Strains are considered sensitive if they are inhibited by concentrations of chloramphenicol ≤ 8 µg/ml. Streptococcus pneumoniae and Haemophilus influenzae have a breakpoint of ≤ 4 µg/ml and ≤ 2 µg/ml, respectively. More than 95% of gram-negative bacteria are inhibited in vitro by 8 µg/ml or less of chloramphenicol. Chloramphenicol is active against Mycoplasma, Chlamydia, and Rickettsiae. Most strains of Escherichia coli (≥ 75%) and Klebsiella pneumoniae are susceptible. Strains of Vibrio cholera are largely susceptible to chloramphenicol. Strains of Streptococcus aureus tend to be less susceptible, with MICs > 8 µg/ml and strains of Pseudomonas aeruginosa, Shigella and Salmonella are resistant to chloramphenicol (2).

The potential toxicity of chloramphenicol suggests that other drugs equally effective and potentially less toxic should be used (6). Despite concerns about adverse effects, chloramphenicol continues to be used in certain situations and, due to its low therapeutic index and variable pharmacokinetics, therapeutic drug monitoring of this antibiotic is often recommended (8). The typhoid fever should be treated with third-generation cephalosporins and quinolones because they are less toxic and because strains of Salmonella typhi are resistant to chloramphenicol (7).

Daily doses and plasma concentration of chloramphenicol varied greatly. Therapeutically plasma chloramphenicol concentrations range from 10 to 25 µg/ml. The recommended doses of chloramphenicol are 40.5 mg/kg/day for neonates and 75.5 mg/kg/day for older children. Average peak concentrations are therapeutic in 60% of cases and trough concentrations are therapeutic in 42% of cases (8). Average duration of fever was 6.3 days and it was unaffected by plasma concentration of chloramphenicol. Typhoid was eradicated in 97% of cases and side-effects are confined to mild reversible hematological abnormalities which develops in 11% of children at plasma concentrations which tended to be high (8). Potential toxicity limits the use of this drug. It has been estimated that death from aplastic anemia occurs in one of 24,500-40,800 courses of treatment (9). The gray baby syndrome occurred in premature and newborn infants receiving high doses of chloramphenicol. This condition can be avoided by reduction of dosage and by monitoring levels of drug in the serum of these infants. The most common toxicity is a reversible, dose-related bone marrow suppression, which is identified by serial monitoring of reticulocyte and complete blood cell counts. Many of the indications for use of this drug are still controversial because studies comparing the toxicity and efficacy of chloramphenicol and of alternative antibiotics have not been done. Salmonella species account for 24% to 59.8% of bacteremias and are the commonest cause of childhood bacteremia, with a predominance of Salmonella enterica serovar Typhi (10).

The prevalence of resistance to chloramphenicol was 38.11%. Salmonella Typhi is the leading cause of childhood bacteremia in central Nigeria. The high prevalence of multidrug-resistant strains calls for improvement in environmental sanitation in the long term and vaccination in the short term. Blood, stool and urine samples were collected from 100 patients diagnosed as having typhoid in 5 hospitals in Akwa Ibom State and analyzed for the presence of Salmonella species and other bacteria (11). A percent of 55 were positive with the Widal test; 39% were positive for blood culture; 14.1% of urine samples were positive for bacterial growth, while 26.8% of stool cultures were positive for bacterial growth. The isolates

were sensitive to peflacine, ceftazidime, ciprofloxacin, ceftriaxone, cefotaxime and chloramphenicol. These antibiotics are recommended as the drugs of choice in therapy. These results suggest the existence of symptomless carriers of enteric fever bacilli in the state. This is worrisome, since some of the Salmonella typhi isolates exhibited multiple resistance to commonly used antibiotics. Seventy-one children were diagnosed to have typhoid fever by culture or serology (12). These children usually presented with fever and gastrointestinal symptoms, including abdominal pain, diarrhea, and nausea or vomiting, and constipation. Hepatosplenomegaly and thrombocytopenia were the most common physical signs observed and abdominal tenderness ranked the second. Other complications included intestinal perforation, rectal bleeding, ascites or pleural effusion, and meningitis. The clinical isolates of Salmonella typhi were susceptible in vitro to all the antibiotics tested, including chloramphenicol, which, however, showed a higher MIC_{90} level than other drugs tested. Antibiotic resistance of Salmonella typhi was not a problem at least up to 1995.

Salmonella group B was the most common pathogen (13). There were no cases of typhoid fever after 1989. The sensitivities to ampicillin, chloramphenicol, and ceftriaxone for Salmonella group B were 25.7%, 26.1% and 100%, respectively. The severity of clinical symptoms varied significantly between those who had acute gastroenteritis with bacteremia (Group I), and those who had acute gastroenteritis without bacteremia (Group II). However, there was a significant distinction in the average age of the two groups ($p = 0.005$). Although the annual number of cases did not decrease in recent years, the number of cases of typhoid fever decreased. Most patients were infants and acute gastroenteritis was the most common complication. The relative sensitivity for ampicillin and chloramphenicol was small over the past decade. Multiply resistant Salmonella species were not found, which may be due to the small sample size. Over a period of 12 years, 109 children with salmonella enteric fever were treated with chloramphenicol: 65 children were given the drug at 50 mg/kg/day (Group A), and 44 received 100 mg/kg/day (Group B) (14). Treatment failed in 63% of cases with the lower dose and in 24% of children treated with the higher dose ($p < 0.001$). In the children who received only chloramphenicol, the higher dose produced a clinical response in 5.4 ± 1.8 days compared with 7 ± 2.6 days with the lower dose ($p < 0.01$). Chloramphenicol in an initial dose of 100 mg/kg/day is recommended in the treatment of typhoid and paratyphoid in children.

Ninety-seven Nigerian children under 5 years of age had typhoid or paratyphoid fever proved by blood culture (15). They had fever, anemia, gastrointestinal or neurological disturbances, and typhoid and paratyphoid appeared clinically indistinguishable. In this holoendemic malarial area, malaria was the most important differential diagnosis, and may have contributed to the concomitant anemia seen in the majority of patients. Despite vigorous therapy with chloramphenicol or trimethoxazole, and blood transfusion when indicated, the mortality in both typhoid and paratyphoid was 18%. Acute bacterial meningitis is still considered one of the most dangerous infectious diseases in children (16). Jiang et al. (16) investigated the prevalence and antibiotic resistance profiles of cerebrospinal fluid pathogens in 179 children with acute bacterial meningitis. The children with meningitis were aged between 3 days and 12 years. Isolated pathogens were identified using the Vitek 32 system. Of the isolates, 50.8% were gram-positive bacteria, and 49.2% were

gram-negative bacteria. Meanwhile, the susceptibility rates of Streptococcus pneumoniae isolates to penicillin G, erythromycin, chloramphenicol, ceftriaxone and tetracycline were 68.8%, 0.0%, 87.5%, 81.3% and 0.0%, respectively. Gentamicin, ofloxacin, linezolid and vancomycin were identified as the most effective antibiotics for Streptococcus pneumoniae, each with susceptibility rates of 100%.

Cronobacter sakazakii was investigated in 705 retail milk-based infant and baby food samples. One hundred and nineteen samples (16.9%) were positive Cronobacter sakazakii (17). The isolates were further characterized for antimicrobial susceptibility to 14 antibiotics, and the presence of the virulence genes. Samples of brand W, Y, A, and G in 2010 and 2012 were Cronobacter sakazakii positive. All isolates recovered in 2010 and 2012 were susceptible to levofloxacin and cefoperazone. In 2012, no isolate was resistant to gentamicin, cefoxitin, chloramphenicol, gatifloxacin, ciprofloxacin, and ceftriaxone.

Antibiotic resistance of isolates was most commonly found to rifampicin, amoxicillin-clavulanic acid, streptomycin, tetracycline, and ampicillin in both 2010 and 2012, except to trimethoprim/sulfamethoxazole in 2012. Pulsed-field gel electrophoresis profiles indicated that Cronobacter sakazakii isolates were genotypically diverse, although these isolates were prevalent in infant and baby foods with the same brand. A total of 34 virulence gene profiles of the Cronobacter sakazakii isolates in 2010 and 2012 were detected. Isolates that co-carried hly-ompX-eitCBAD-iucABCD/iutA genes in 2012 were significantly ($p < 0.05$) more prevalent than those in 2010. These results added new epidemiological evidence for the widespread occurrence of Cronobacter sakazakii retail milk-based infant and baby foods and this should be an indicator of potential health risk for consumers. Samples of cerebrospinal fluid were collected from 642 children aged < 15 years with suspected meningitis (19). Haemophilus influenzae type b, pneumococcus, and meningococcus represented approximately 70% of confirmed cases. The case fatality rate among patients with acute bacterial meningitis was 24%. The incidence of acute bacterial meningitis was 85 cases per 100,000 subjects, which peaked at 2 to 12 months of age at 1,078 cases per 100,000 subjects. All pneumococci isolates were susceptible to chloramphenicol. For the Haemophilus influenzae type b isolates (n = 10) tested, only 1 was susceptible to chloramphenicol, and 5 were susceptible to ampicillin. These data reinforce the importance of acute bacterial meningitis as a cause of hospital admission and death in rural sub-Saharan Africa.

A total of 475 cerebrospinal fluid samples were collected from 20,173 children aged < 15 years (20). Culture results confirmed 71 (15%) cases of acute bacterial meningitis. Streptococcus pneumoniae, pneumococcus, Haemophilus influenzae, and Neisseria meningitis were the most prevalent bacterial etiologies. Streptococcus pneumoniae and Haemophilus influenzae are the main etiologies responsible for the high burden of morbidity and mortality associated with acute bacterial meningitis in rural Mozambique. Streptococcus species, Salmonella species, and Staphylococcus aureus were also isolated. Crude incidence rates of acute bacterial meningitis were 20 cases per 100,000 subjects. Incidences were more than three times higher in infants aged < 1 years. Pneumococcal susceptibility was 81% for oxacillin and 93% for chloramphenicol. For Haemophilus influenzae isolates, susceptibility was 54% for ampicillin and

62% for chloramphenicol. These findings are important to evaluate treatment guidelines and potential impact of control measures. A total of 989 infants and children 0 to 59 months old with suspected bacterial were prospectively enrolled (21). All had blood cultures and cerebrospinal fluid was sampled from 623 (63%). The most common bacterial pathogens were Haemophilus influenzae type b and Streptococcus pneumoniae. All of the Haemophilus influenzae type b infections and 8 (80%) Pneumococcus pneumoniae were sampled from infants aged < 1 year. All strains of Streptococcus pneumoniae and Haemophilus influenzae were sensitive to chloramphenicol, cotrimoxazole and ampicillin.

Enterococcal meningitis is a rare complication of neurosurgical procedure which occurs mainly in immunocompromised neonates with very low birth weight and severe prematurity (23). Enterococcal faecalis caused 10 nosocomial meningitis infections and all were susceptible to vancomycin, chloramphenicol, gentamicin and ampicillin. Early empiric therapy should include also ampicillin or vancomycin, if enterococcal etiology is suspected.

Streptococcus pneumoniae infections (n = 68) were identified by hospital chart review between 1986 and 1997 (24). The patient's age distribution varied from 2 days to 15 years, with a mean age of 3.3 years. Four clinical entities included 30 cases of meningitis, 20 cases of pneumonia, 10 cases of peritonitis and 8 cases of septicemia/bacteremia. Forty patients (58.8%) had underlying diseases. Seventeen patients (25.0%) developed early complications and the mortality rate was 8.8%. The percentage of susceptible isolates to penicillin, chloramphenicol, cefotaxime/ceftriaxone, ciprofloxacin, imipenem and vancomycin were 69.6, 91.3, 100.0, 87.2, 100.0, and 97.1, respectively. There were 6 cases of drug-resistant Streptococcus pneumoniae; 3 cases of meningitis, 1 case of pneumonia, 1 case of infective endocarditis and 1 case of purpura fulminans. The present data indicate that Streptococcus pneumoniae infection is relatively serious and life-threatening. The number of bacterial meningitis isolates in children was 220 (25). The most frequently identified isolates were Neisseria, followed by Haemophilus influenzae serotype b, and Streptococcus pneumoniae. Of the meningococcal isolates, 88.9% belonged to serogroup B and 10.0% to serogroup C, and the most prevalent serotype was 22 (43.3%). More than 90% of Haemophilus influenzae were susceptible to third generation cephalosporins and chloramphenicol.

Sixty-one episodes of Salmonella meningitis were identified during a 3-year period (26). These accounted for 6.8% of all the acute bacterial meningitis cases seen during this time. Only two children were affected by Salmonella meningitis in 1982. The prognosis was poor: 33 (58%) died, 19 made a full recovery and five developed sequelae. Patients were routinely treated with chloramphenicol, to which all isolates were sensitive in vitro. The poor outcomes suggest that an alternative antibiotic policy is required.

Nik Khairulddin et al. (27) conducted a retrospective study of 65 children who had invasive Haemophilus influenzae disease from June 1985 to December 1994. The age distribution varied from one day to 72 months with a mean age of 13 months. Peak incidence occurred in the 7 to 12 months age group, and the majority (89.1%) were below two years of age. The relative frequencies of the clinical entities documented were as follows: meningitis 64%, pneumonia 29.3%, septicemia 5.4%, and abscess 1.3%. In addition, 13.5% of cases had meningitis associated with pneumonia. Long term complications were noted in 41.5% of cases of meningitis.

Case fatality rate was 12.3%. The percentage of high invasive Haemophilus influenzae strains were sensitive to penicillin, ampicillin, chloramphenicol and co-trimoxazole were 83.7%, 87.7%, 98.2% and 89.7%, respectively. The bulk of infections at Kenyatta National Hospital newborn unit are caused by Klebsiella, Citrobacter and Staphylococcus aureus (28). During the 1990's considerable resistance to gentamicin was developed. Cephalosporins and chloramphenicol had the best sensitivity pattern. Continuous surveillance is recommended with emphasis on primary prevention of infection as well as cross infections.

The investigation was carried out on a group of 270 children, aged between 3 months and 12 years (29). The cultures of the throat swabs and urines were performed on the admission of the children before the beginning of the therapy. The throat-swab cultures showed pathogen microorganisms in 232 samples (85.9%). The gram-negative bacteria were 122 and the gram-positive were 110. Strains of saprophytic microbial flora were 38. The urine cultures proved to be positive in 81 cases (30%), the gram-negative isolates were 56 and the gram-positive isolates were 25. A few isolates either from the throat or from urine, showed resistance to the common antibacterial agents.

Streptococcus agalactiae (n = 21; 35%), Klebsiella pneumoniae (n = 17; 28%), and Escherichia coli (n = 10; 17%) were the commonest pathogens accounting for 80% of cases (30). Streptococcus agalactiae isolates were uniformly susceptible to penicillin and chloramphenicol. Gram negative isolates showed resistance to ampicillin, chloramphenicol and Sulfamethoxazole / Trimethoprim.
Klebsiella pneumoniae isolates showed resistance to gentamicin and amikacin. All isolates were fully susceptible to cefotaxime.

Fifty patients aged from 8 days to 14 years (mean age, 12.7 months) had systemic Haemophilus influenzae disease (31). The peak incidence was between 4 and 6 months of age. The children were affected by meningitis, bacteremia, pneumoniae, cellulites, arthritis and septic shock. Sixty-four percent of patients had early complications. The mortality rate was 8%. At least 33 (66%) cerebrospinal fluid samples were infected by Haemophilus influenzae type b. The percentage of susceptible Haemophilus influenzae to penicillin, ampicillin, chloramphenicol, and co-trimoxazole were 57.1%, 76.4%, 87.5% and 54.2%, respectively. There was no strain resistant to third generation cephalosporin. For prevention of infection, an appropriate strategy for vaccination is required.

A total of 331 Nigerian children, aged 24 months or below, with symptoms of meningitis had Haemophilus influenzae isolates from their cerebrospinal (32). The leading role of meningitis caused by Haemophilus influenzae was 7 to 24 months. Out of the 39 isolates, 37 were Pittman serotype b while the remaining 2 were type d. A percentage of 69.2% of cases occurred during the dry season while 30.7% occurred during the rainy season. All isolates were sensitive to chloramphenicol and erythromycin, while 90% were sensitive to ampicillin and penicillin.

A total of 10,468 cerebrospinal fluid was sampled from patients of different age suffering from bacterial meningitis (33). Acinetobacter calcoaceticus was isolated in 12 (5.6%) of 211 positive cultures. The strains were 100% resistant to ampicillin, cotrimoxazole and tetracycline and 50% were resistant to cefazolin and gentamicin and kanamycin, but 100% was susceptible to chloramphenicol. A percentage of 14.2 and 19.2 of children residing in urban and rural environments, respectively, were suffering from nasopharyngeal carriage of

relatively resistant Streptococcus pneumoniae organisms (34). The MICs for penicillin ranged from 0.12 to 1.0 µg/ml. An analysis of 40 relatively resistant Streptococcus pneumoniae strains showed resistance to co-trimoxazole in 47.5%, trimethoprim in 42.5%, fusidic acid in 20%, tetracycline in 2.5%, and rifampicin in 5%. All strains were susceptible to chloramphenicol and vancomycin.

Purulent culture-positive meningitis was observed in 155 highlands children aged 12 months or less (35). The causative infections were Haemophilus influenzae, Streptococcus pneumoniae or both organisms. Other pathogens were Neisseria meningitides, Streptococcus pyogenes, Streptococcus agalactiae, and Klebsiella species. Among Haemophilus influenzae isolates, serotype b strains predominated (83%) and most (96%) belonged to biotype I or II. No resistance to chloramphenicol was detected in either Haemophilus influenzae or Streptococcus pneumoniae. There is an urgent need for Haemophilus influenzae and Streptococcus pneumoniae vaccines that are effective in young children.

A total of 131 children were affected by Haemophilus influenzae (36). The incidence peaked mainly in the dry season with a secondary peak in the rainy season. The prognosis did not appear to be significantly affected by the choice between a combination of penicillin and chloramphenicol on the one hand and ampicillin alone on the other. A combination of penicillin and chloramphenicol is preferred to chloramphenicol alone in initiating therapy because 100% of strains of Haemophilus influenzae are susceptible to chloramphenicol and penicillin but only 75% of strains of Streptococcus pneumoniae are susceptible to chloramphenicol alone. Serum chloramphenicol levels were evaluated in 52 children with severe infection treated intravenously with chloramphenicol succinate and orally with chloramphenicol palmitate, chloramphenicol monostearoylglycolate or chloramphenicol in capsules. Effective serum levels were recorded with all chloramphenicol preparations. The variability was largest with chloramphenicol monostearoylglycolate (37). Effective serum levels were recorded with all chloramphenicol preparations. The variability was largest with chloramphenicol monostearoylglycolate. Monitoring of serum chloramphenicol levels in neonates is necessary. After the neonatal period monitoring of serum chloramphenicol levels is useful in avoiding too high concentrations.

The highest chloramphenicol serum concentrations ranged from 5.5 to 23 µg/ml after 50 mg/kg/day chloramphenicol palmitate orally to seven neonates (38). The dosage had to be increased in all preterm neonates from 25 mg/kg/day to 50 mg/kg/day to obtain adequate serum levels during therapy. The apparent half-life was 3 and 6 hours in two neonates in whom the serum concentrations declined during the dosing interval. Urinary excretion of chloramphenicol and glucuronide ester ranged from 24% to 55% of the dose administered to 3 neonates. There was considerable variability in serum chloramphenicol levels when chloramphenicol palmitate was administered orally.

The delay in achieving the maximum serum concentration, non-declining serum curve, and low renal recovery is indicative of incomplete, prolonged, and erratic absorption, possibly related to delayed gastric emptying or decreased intraluminal hydrolysis of the palmitate ester. The toxicology of chloramphenicol suggests that its propensity to cause damage to the blood forming organs may be related to its potential for nitro-reduction and the subsequent production of nitric oxide (40).

Both aerobic and anaerobic nitro-reduction of chloramphenicol by human fetal and neonatal liver results in the production of the amine derivative. Perfusion of chloramphenicol through isolated lobules of the human placenta causes a decrease in blood pressure at a time which coincides with a peak of nitric oxide production. However, although the pressure drop could be reversed by an inhibitor of nitric oxide synthesize, the nitric oxide profile remains the same. The para-nitro group of chloramphenicol could cause both hemotoxicity and hypotension in susceptible individuals. Chloramphenicol may damage the organs because it is related to the nitro-reduction and the subsequent production of nitric oxide.

The successful antibiotic treatment in infants and children depends primarily on rapid diagnosis of the disease, identification of pathogenic microorganisms, and appropriate application of specialized pharmacokinetic and pharmacodynamic knowledge of antibiotics. In infants and children, the absorption, distribution, metabolism, and excretion of drugs may differ considerably in comparison with adults (41). Because of known toxicity, certain drugs such as chloramphenicol in high doses, sulfonamides, and tetracycline should not be used in neonates.

Nine neonates received the dose prescribed and one an overdose (43). The grey baby syndrome was observed in 5 of 10 neonates; four neonates suffered reversibly from hematological reactions; and one neonate was described as very grey. Peak serum chloramphenicol concentrations in these 10 neonates ranged from 28 to 180 µg/ml and trough concentrations from 19 to 47 µg/ml. Serum chloramphenicol concentrations above the therapeutic range (15 to 25 µg/ml) were observed in a further 27 neonates (two had received a 10-fold overdose), none of whom showed signs of toxicity. Serious toxicity was associated with either prescription of dosages greater than that recommended or over dosage of chloramphenicol. High concentrations in young neonates may be avoided by prescribing a recommended dose and then careful monitoring; concentrations should be maintained between 15 and 25 µg/ml. Because of known toxicity, certain drugs such as chloramphenicol in high doses, sulfonamides, and tetracycline should not be used in neonates (44). The dosages of many antibiotics must be lower and the intervals between administrations must be longer in neonates. The appearance of strains of ampicillin-resistant Haemophilus influenzae, the slow development of resistance to chloramphenicol among gram-negative and gram-positive bacteria, and the development of improved analytic methods to measure chloramphenicol have all resulted in the use of this drug in select cases of serious infection in children beyond the neonatal age. Third-generation cephalosporins have an important role in the empiric treatment of pediatric bacterial meningitis because of their ability to penetrate the central nervous system and their effectiveness against ampicillin- or chloramphenicol-resistant Haemophilus influenzae strains and against many gram-negative bacteria in the Enterobacteriacae group.

The mean peak serum concentration of chloramphenicol in patients with and without toxicity were not different (45). Therefore, chloramphenicol toxicity may not be predictable by serum concentration in pediatric patients receiving therapeutic doses of chloramphenicol succinate. Thus, frequent monitoring of chloramphenicol serum concentration does not appear warranted unless a patient appears unresponsive to a therapeutic dose or has received an excessive dose. The use of new antimicrobial agents in neonates may expose them to unpredictable dangers (46). For that reason, new drugs should only be

administered to young infants if they clearly have a therapeutic advantage over older ones. Therapeutic trials must await adequate pharmacokinetic studies, and the investigator must be prepared to follow the treated infants for a sufficient length of time to be certain that any organ damage caused by the drug would have become clinically detectable.

5- CONCLUSION

In conclusion, chloramphenicol is used to treat typhoid and paratyphoid fevers and bacterial meningitis. This antibiotic acts primary by binding reversibly to the 50S ribosomal subunit. Chloramphenicol apparently prevents the binding of the amino acid-containing end of the aminoacyl tRNA to the acceptor site on the 50S ribosomal subunit. Chloramphenicol inhibits protein synthesis in bacteria and is usually bacteriostatic but it is bactericidal against Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria Meningitis. The antimicrobial activity of chloramphenicol requires that microorganisms be sensitive to this antibiotic at a concentration $\leq$ 8 μg/ml. Chloramphenicol possesses a broad-spectrum of antibacterial activity against gram-negative and gram-positive bacteria. Strains of Vibrio cholera are largely susceptible to chloramphenicol, whereas strains of Pseudomonas aeruginosa, Shigella and Salmonella are resistant to multiple antibiotics including chloramphenicol.

The dose of chloramphenicol is 40.5 mg/kg/day in neonates and 75.5 mg/kg/day in older children and the therapeutic plasma concentrations of chloramphenicol range from 10 to 25 μg/ml. The half-life of chloramphenicol is affected by the postnatal age and is 27 hours in the first week of life, 8 hours by 2 to 4 weeks and 4 hours in children over 4 months old. The penetration of this antibiotic in tissues is good and it reaches a concentration of 60% (range, 45-99%) in the cerebrospinal fluid of that in plasma. In the brain the chloramphenicol concentrations are 9 times higher because of the high lipid solubility of this antibiotic. Chloramphenicol is toxic and therapy with chloramphenicol must be limited to infections for which the benefits of the drug outweigh the risk of the potential toxicities. When other antibacterial drugs that are equally effective and potentially less toxic are available, they should be used instead of chloramphenicol.

6- CONFLICT OF INTERESTS

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