Yonsei Medical Journal
Vol. 39, No. 6, pp. 595-603, 1998

☐ Review Article ☐

Antibiotic Use at a Pediatric Age

Dong Soo Kim and Min Soo Park

For infections in infants and children, the successful antibiotic treatment depends primarily on rapid diagnosis of the disease, identification of pathogenic microorganisms, and appropriate application of specialized pharmacokinetic and pharmacodynamic knowledge of antibiotics in children. 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, the sulfonamides, and tetracycline should not be used in neonates. In this article, we describe these peculiarities of children and discuss the proper use of antibiotics in children.

Key Words: Antibiotics, pediatrics

In clinical practice a doctor needs to consider whether he should prescribe an antibiotic, and if so, which antibiotic to use for the safest, most effective, and most economical therapy. Many considerations must be made for the treatment of infectious diseases in general, including the emergence of new pathogens or old diseases in newly-recognized forms, changing virulence of pathogens, changing patterns of antimicrobial susceptibility, new diagnostic techniques, drugs or vaccines, as well as changing concepts of chemoprophylaxis must be considered (Klein, 1995; Kim, 1997; Kim, 1998).

Recently the incidence of infections caused by penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, ESBL-producing gram negative bacilli, and vancomycin-resistant enterococci has drastically increased in Korea as in other parts of the world (Chong and Lee, 1997). This poses a serious problem not only in adults but also in children.

Received October 20, 1998
Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea
Address reprint request to Dr. D.S. Kim, Department of Pediatrics, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul, Korea. Tel: 82-2-361-5524, Fax: 82-2-393-9118, E-mail: dskim6634@yumc.yonsei.ac.kr

As with other drugs antibiotic use in adults cannot be directly transferred to children. Even though most antibiotics used in adults have proven safety profiles in children and most times they are used in children with little problem, we must consider the peculiarities involving children.

Children are different from adults, even in obtaining test samples with added difficulty. As well, there is a large discrepancy from adults in absorption, distribution, metabolism and excretion of drugs. These peculiarities result in differences in therapeutic efficacy and toxicity of various antibiotics used in children. Because of known toxicity, certain drugs such as chloramphenicol in high doses, the sulfonamides, and tetracycline should not be used in neonates. Antibiotic therapy should be modified in neonates because of the biological immaturity of organs which are important for the termination of drug action. Because of poor conjugation, inactivation, or excretion, the serum concentrations of many antibiotics may be higher and their action may last longer in neonates than in older infants; thus, lower doses and longer intervals between doses may be necessary (Rhodes and Henry, 1992; Toyonaga, 1997). In this article, we will review these peculiarities of children and discuss the proper use of antibiotics in children.

In order to properly examine a patient and to

Table 1. 10 items to consider for proper antibiotic therapy

1. Is an antibiotic really needed?
2. Have you already obtained appropriate samples and culture?
3. Which is the most suspected organism?
4. Which antibiotic is most appropriate? (Most important for pediatric therapy)
5. Should we use a single antibiotic, or two or more antibiotics in combination?
6. What are the factors to be considered in relation to the host?
7. By which route should the antibiotic be administered?
8. What dosage?
9. Shall we change the antibiotic according to the culture result?
10. What is the appropriate duration of antibiotic therapy?

choose an appropriate antibiotic, we need to ask ourselves the following 10 questions (Table 1) (Reese and Betts, 1996).

IS AN ANTIBIOTIC REALLY NEEDED?

Infectious diseases in children are in general of viral origin rather than bacterial. However, in practice it is extremely difficult for pediatricians to differentiate viral and bacterial infections. Characteristic clinical signs and symptoms which are more often associated with a bacterial rather than a viral etiology include hyperpyrexia, chills, purulent tonsillopharyngitis, acute otitis media with or without effusions, tachypnea and urinary tract infections (Hull, 1989; Alpert *et al.* 1990). Also, we usually use the various findings listed in Table 2 to differentiate between viral and bacterial infections, but it is not as easy in reality as it seems (Helwig, 1997). We do not need to use antibiotics for viral infections, but once bacterial infection is confirmed, antibiotic therapy is absolutely required. For local infections like pneumonia, UTI, wound infection, soft tissue infection, etc. antibiotic therapy is necessary.

In fact, even though antibiotics are not needed for the treatment of URI or influenza, prescription of antibiotics for such viral infections is the main source of antibiotic abuses (Schaad, 1997). On the other hand, there are conditions when a quick decision for antibiotic therapy is mandated, such as local infections like pneumonia and UTI, neutropenic patients with fever, and when there is a possibility of acute endocarditis, bacterial meningitis, and acute necrotizing cellulitis.

Table 2. Differential diagnosis of viral and bacterial infection

Variable	Viral	Bacterial
Leukocytosis	Uncommon	Common
Shift to left (↑ bands)	Uncommon	Common
Neutropenia	Possible	Suggests overwhelming
↑ ESR	Unusual	Common
↑ CRP	Unusual	Common
↑ Elastase-α_1-protease	Uncommon	Common
Petechea	Present	Present

HAVE YOU ALREADY OBTAINED APPROPRIATE SAMPLES AND CULTURE?

Collecting appropriate test samples is extremely important even under emergency conditions and should be done before the initiation of antibiotic therapy. Unlikely adults, it is difficult to obtain test samples from children (Paisley and Laurer, 1994). However, obtaining the test samples is crucial in diagnosis as well as treatment of infectious diseases and should be given the best possible effort. In practice, especially in outpatient settings, pediatricians mainly rely on antibiotic therapy based on empiric regimen rather than that based on cultured organisms and their antibiotic susceptibility results. For empiric therapy to be effective, it is necessary for pediatricians to be aware of the most common organisms for local infections of various organs or parts of the body.

But if we do not perform cultures and the initial empiric antibiotic regimen is not helpful for the patient's clinical progress, we are placing ourselves

in a very difficult situation as for the determining an alternative antibiotic regimen. In such cases a (follow-up) culture test performed after the initiation of antibiotic therapy is not as reliable as the one done prior to antibiotic therapy.

WHICH IS THE MOST SUSPECTED ORGANISM?

In determining which antibiotic to use when there are several antibiotics available for treatment, it is important to consider which is the drug of choice for the specific infection and also to evaluate whether it may cause an adverse reaction or not. Furthermore, it is important to determine how easily the chosen antibiotic will reach the site of action. For example, clindamycin, aminoglycosides, as well as 1st- and some 2nd-generation cephalosporins do not penetrate into CNS. Also important is the pH of the infected tissues. If aminoglycosides, which are active under neutral pH, are used for abscesses, which are usually acidic, the antibiotic activity will be adversely affected. The possibility of adverse reactions to antibiotics must also be considered, and for long-term therapy one should be aware of the possibility of pseudomembranous enterocolitis for certain antibiotics. If possible, bactericidal agents are preferred to bacteriostatic agents. In view of the pharmacoeconomic aspect, it is better to use a cheaper antibiotic, all other things being equal. For empiric therapy, broad-spectrum antibiotics are usually selected; but for infections of proven bacterial organisms with known susceptibility, narrow-spectrum antibiotics are preferred.

WHICH ANTIBIOTIC IS MOST APPROPRIATE?

Unlike adults, children are constantly growing and developing. This fact should be taken into account whenever any drugs are given to children. From prematurity to adolescence, there is a large difference in body surface area, as well as hepatic and renal function depending on age. Therefore, the age factor is crucial in proper antibiotic therapy. First, we will examine various influences of age on pharmacokinetics of drugs.

Table 3. Host factors influencing drug absorption

Surface area available for absorption
Gastric and duodenal pH
Gastric emptying time
Size of bile salt pool
Bacterial colonization of gastrointestinal tract
Presence and extent of underlying disease

Absorption

When a drug is administered extravascularly, it must pass through various types of physiologic membranes before it enters the blood stream. After it is absorbed into the blood stream, it reaches the site of action. There are various factors influencing the rate and extent of drug absorption, and the host factors may vary for different ages (Table 3).

Distribution

The factors influencing the volume of distribution are the size of various body parts, protein-binding properties, hemodynamic factors including cardiac output, local blood flow, membrane permeability, which all vary with age (Besunder *et al.* 1988).

Body water: Body water and fat content vary with age (Friis-Hansen, 1983). The water content of full term neonates is about 75%, which rapidly falls to about 65% over the first year of life. It decreases gradually thereafter, reaching the adult level of 60% for men and 55% for women. This apparent change is mainly due to the change in extracellular water content. The relative ratio of the weight of each organ to body weight also varies with age.

Protein binding capacity: Plasma protein and drug-binding capacity vary according to the absolute amount of available protein, the number of available binding sites, protein-drug affinity, physiologic conditions of the patient, and the presence of endogenous substances competing for protein binding-sites, which are all closely related to age (Kurz *et al.* 1977).

Albumin, α_1-acid glycoprotein (orosomucoid), and lipoprotein are the circulating plasma proteins most important for binding with plasma drugs. Most basic drugs bind with albumin, α_1-acid glycoprotein, and lipoprotein, while acidic and neutral drugs bind with albumin. Plasma albumin and protein concentrations are diminished during infancy and reach adult values at about 10 – 12 months of age. α_1-acid glycoprotein, like albumin, is 3-fold lower than maternal level, but reaches adult level at 12 months of age (Wood and Wood, 1981).

There are differences in protein-binding capacity of ampicillin, α-azidobenzylpenicillin, and benzylpenicillin between neonates and adults. Free drug concentrations in neonatal cord blood are very high relative to those in adult blood. Among antibiotics, chloramphenicol, penicillin, and sulfonamides are present in high concentrations in cord blood compared to adult blood (Reed and Besunder, 1989).

In neonates, endogenous substances such as free fatty acid and bilirubin compete with drugs for albumin binding and influence drug-protein binding. Bilirubin is physiologically elevated during early neonatal period and in high concentrations can cause kernicterus (Reed and Besunder, 1989). Because the bilirubin-albumin binding affinity in neonates is very weak relative to adults and reaches adult level at about 5 months of age, newborn babies are at increased risk of kernicterus. Since the first report of kernicterus in a premature baby who was given sulfonamide, there have been a number of reports concerning in vitro antibiotic-albumin binding. Stutman *et al.* measured the competitive binding of several drugs and bilirubin to albumin (Stutman *et al.* 1985). Cefoperazone and moxalactam may cause a significant decrease in bilirubin-albumin binding in a dose-dependent manner; and moxalactam may cause such a phenomenon at a therapeutic concentration. A ceftriaxone-induced increase in free bilirubin concentration is a well-known phenomenon, and other cephalosporins such as cefonicid, cefotetan, and cefmetazole may also cause an increase in free bilirubin concentration in vitro. Cefotaxime, ceftazidime, and ceftizoxime do not influence bilirubin-albumin binding.

In the report of the extensive work done by Wadsworth and Suh, the drugs which cause displacement of bilirubin from the albumin-binding site, thus increasing the free bilirubin concentration, are sulfisoxazole, sulfamethoxazole, dicloxacillin, cefoperazone, ceftriaxone and moxalactam, in order of strength (Wadsworth and Suh, 1988). However, antibiotics commonly used in children such as cefotaxime, cefuroxime, cefaclor, gentamicin, clindamycin, trimethoprim, rifampin, chloramphenicol, ticarcillin, ceftazidime, piperacillin, netilmicin, amoxicillin, penicillin G, cefazolin, and amikacin rarely cause such a problem (Wadsworth and Suh, 1988).

Metabolism

As soon as a drug enters the body it begins to be eliminated. The overall rate of drug elimination from the body is expressed as pharmacokinetic parameter estimated clearance (CI), which is composed of total body, renal, and hepatic CI (Reed and Besunder, 1989). Many drugs are pharmacologically weakened or inactivated by being transformed into more polar water-soluble forms. On the other hand, there are some drugs (prodrugs) which are transformed into active forms in the body. For example, chloramphenicol succinate becomes active chloramphenicol base, while cefuroxime axetil becomes active cefuroxime.

Perhaps the most important organ for drug metabolism is the liver. Liver cells are involved in 2 types of enzyme reaction for the biotransformation of drugs. Phase I reaction is a nonsynthetic process and includes oxidation, reduction, hydrolysis, and hydroxylation for the functional preparation of drugs for phase II reaction. Phase II reaction is a synthetic process and includes conjugation with glycine, glucuronide, and sulfate for the enhancement of drug excretion (Reed and Besunder, 1989).

Ligandin or Y-protein is important for the uptake of substrates into metabolizing cells and reaches adult level 5 – 10 days after birth (Levi *et al.* 1969). The concentrations of drug oxidative enzymes in the liver at birth are similar to adults, but their activity is far lower than adults. The elimination of drugs by oxidative metabolism such as phenytoin and diazepam is delayed. The metabolic capacity of cytochrome P monooxygenase systems in the liver reaches adult level at 6 months of age (Neims *et al.* 1976), and that of alcohol dehydrogenase at 5 years of age (Pikkarainen and Raiha, 1967). Hydrolyzing

enzymes such as esterases are involved in the biotransformation of chloramphenicol succinate into active chloramphenicol base. These enzymes are in very low concentration in neonates and the metabolic rate of chloramphenicol succinate is highly variable and cannot be predicted (Echobichon and Stephens, 1973).

Phase II enzyme action helps the synthesis of water-soluble substances, thus enhancing drug elimination through the kideys and biliary system. Like cytochrome P involved in phase I reactions, enzymes involved in phase II reactions differ between children and adults and there exists high interindividual variability. Accumulation of chloramphenicol caused by immature chloramphenicol glucuronyl transferase activity in neonates results in gray baby syndrome in infants who were given chloramphenicol at high concentration, manifested by acute cellular toxicity causing dysfunction of cellular respiration (Leeder and Kearns, 1997). The activity of NAT2, another phase II enzyme, reaches adult level at 10−12 months of age and becomes fully mature at 3 years of age. Low activity of this enzyme increases the risk of sulfasalazine-induced hemolysis, sulfonamide-related Stevens-Johnson syndrome and toxic epidermal necrolysis (Leeder and Kearns, 1997).

However, it is not possible to generalize about the activity of all enzymes according to the stage of physical growth and development. It is manifested variably depending on the type of enzyme (Table 4).

Excretion

Most drugs are excreted through the kidneys and the amount of drug filtered by glomeruli in a unit time depends on the glomerular function, renal blood flow, and drug-protein binding. Renal blood flow reaches adult level between 5 and 12 months of age, and the glomerular filtration rate (GFR) between 3 and 5 months (Fitterman *et al.* 1965; Leake and Trygstad, 1977). The development and maturation of the glomerular filtration rate is important in determining the appropriate drug dosage. Renal tubular secretory function matures later than GFR, and this discrepancy between the maturation of glomerular and renal tubular functions may be a cause of diminished neonatal renal function (Fitterman *et al.* 1965; Hook and Bailie, 1979). Renal tubular function matures at about 30 weeks of age (Arant, 1978).

Drugs like penicillin stimulate renal function and increase renal clearance 2-fold with long-term administration. If dose frequency is not increased, drug efficacy may be decreased (Hook and Hewitt, 1977). This kind of organic stimulatory phenomenon by penicillin is observed only when the excretory pathway is not fully matured. On the other hand, renal immaturity may be beneficial in a way in which renal toxicity resulting from aminoglycoside

Table 4. Antibiotic-associated metabolizing enzymes in humans

Enzymes	Substrate	Inhibitors	Inducers	Developmental patterns
Phase I enzymes				
CYP2C9	Phenytoin etc.	Sufaphenazole	Rifampin	Peak at 3−4 yrs and
CYP2C19	Diazepam etc.	Tranylcypromine	Rifampin	↓ to adult level at puberty
CYP2E1	Acetaminophen	Disulfiram	Isoniazid	
CYP3A4	TAO	Erythromycin, TAO	Rifampin	Peak at 1−4 yrs, ↓ to puberty
CYP3A7	DHEA	Azol fungal (?)	Rifampin	
Phase II enzymes				
NAT2	INH, sulfamethoxazole	?	?	Adult activity by 1−3 yrs
UGTs*	Sulfisoxazole, C-M	?	Phenobarbital	Adult activity by 6−18 mos
STs†	C-M	Salicylic acid	Phenobarbital	Activity exceeds adult during infant and early childhood

*: Multiple isoforms of UDP glucuronyltransferase.
†: Multiple forms of sulfonyltransferase.

antibiotic accumulation in the kidneys can be prevented because the mass and function of proximal tubules in neonates are relatively decreased (Kuhl *et al.* 1985).

Other factors to be considered in the pediatric age group

Growth and development: Because childhood is a period of continuous growth and development, administration of antibiotics in children may cause peculiar neurologic and physical abnormalities which are not observed in adults. It may not be immediately evident but if becomes obvious after long-term administration. Especially since the central nervous system in children is continuously developing, antibiotics may cause severe neurodevelopmental dysfunction unlike adults. Various physical, developmental dysfunctions may result in growing children (Reed and Besunder, 1989).

The best-known adverse drug influence on physical development would be that of tetracycline when used in children under 10 years of age; tetracycline forms tetracycline-calcium orthophosphate complex and causes enamel dysplasia, hypoplasia and discoloration of teeth and dysfunction in bone growth (Reed and Besunder, 1989). Quinolones, nalidixic acid and ciprofloxacin, are reported to cause abnormalities in articular cartilage in young animals (Andersen and Goldstein, 1987). In children they are known to cause reversible arthralgia. Nalidixic acid has been used widely in children without special adverse reactions. Despite the safety shown through clinical experience with nalidixic acid in children, quinolones are contraindicated for use in children in whom growth is not completed (Schaad, 1994). Recently, a new quinolone which can be safely used in children has been developed and will be soon commercially available.

Decreased toxicity: A certain type of drug reaction may occur less in children than in adults, e.g. anaphylactic reaction to penicillin and cholestatic jaundice by erythromycin (Klein, 1995).

Drug administration: Intravenously administered drugs seem to reach the site of action quickly, but this is not always the case. It depends on the rate of intravenous fluid infusion, the dead space of the infusion set, and total volume of fluid in which the drug is diluted. Since most intravenous infusion sets are manufactured for adult use, they have a large dead space, and since the rate of infusion in neonates and infants is slow in general, intravenously-administered drugs reach the body only some time after infusion starts and it takes a relatively long time until the total amount of drug is completely delivered.

In order to resolve this problem, we need to standardize the total amount of time for drug administration and to keep a record. We have to record the amount and the content of fluid used for flushing the infusion set. Special infusion methods such as drug administration time and dosage for drugs with a narrow therapeutic index should be standardized as well as the method and volume of dilution of drugs which are intermittently given. In addition, we should avoid the simultaneous administration of two different drugs at different rates through a connector, and it is preferable to use an extending tube of the infusion set with as small a volume as possible and to inject the drug at the most proximal site to the intravenous line as possible (Axton and Hall, 1994).

Except for oral administration, the next most common route of administration of antibiotics in infants or children is intramuscular injection. In general, for severe infections it is recommended to administer drugs via an intravenous or intramuscular route in order to maintain adequate blood concentrations. However, except for drugs like benzathine penicillin, intramuscular injection is rarely used in pediatric practice. Obviously, IM injection may be used when there is no accessible venous route, but the site of injection should be chosen cautiously, unlike with adults. Antibiotics which can be given intramuscularly are cephalosporins such as cefazolin and ceftriaxone, aminoglycoside antibiotics and imipenem.

Like oral administration, there are a number of factors that influence the rate and amount of drug absorption when the intramuscular route is used. Especially in severely sick infants, the blood circulation at the site of injection is often poor and it may diminish the effect of intramuscularly-administered drugs (Losek and Gyuro, 1992).

In outpatient settings where relatively mild infections are treated, oral administration is preferred but

the special factors of children should be considered for the choice of antibiotics (Werk and Bauchner, 1998). An important factor to be considered for oral administration is in relation to meals. For antibiotics such as penicillin G, nafcillin, oxacillin, cloxacillin, dicloxacillin, ampicillin, and lincomycin, drug absorption is significantly decreased when given with food. Tetracyclines should not be given with milk, dairy products, or foods containing calcium or magnesium, which interfere with the absorption of drugs.

Percutaneous drug delivery is also frequently used. We should also be aware of the difference between children and adults in drug absorption through the skin. The stratum corneum of infants and children is relatively thin and the body surface area to body weight ratio of neonates is about 3 times that of adults (Reed and Besunder, 1989).

Drug Interaction: Infants and children who are given antibiotics also can be given other drugs at the same time. In this case, adverse drug reactions through drug interaction may develop and possibly lead even to death (Leeder and Kearns, 1997). Inhibitors of CYP3A4, one of the cytochrome P 450 enzymes, such as erythromycin and fluconazole, when given together with CYP3A4 substrate, such as cisapride, may develop toxic symptoms. Erythromycin competes with theophylline for the metabolic enzymes in the liver and causes elevation of theophylline peak plasma concentration to a toxic level and also hinders the elimination of carbamazepine. When chloramphenicol and phenytoin are simultaneously administered, both drug concentrations may reach a toxic level. On the other hand, phenobarbital and rifampin may induce the metabolism of chloramphenicol and lower the chloramphenicol concentration to a subtherapeutic level.

Prescription: Taste, smell, and color of drugs should not be overlooked when drugs are prescribed to children.

WHAT DOSAGE?

It is important to try to select the most effective and lowest possible dose, but at the same time minimize the possibility of adverse drug reactions and superinfections, as well as the patients' economic burden. Especially when PO drugs are prescribed in children, the dosage should be as little as possible. In general, the appropriate dosage in children is determined based on body weight. But some find body surface area to body weight to be more accurate in order to achieve reliable blood concentrations. For drugs like aminoglycosides, which are distributed mainly in extracellular body fluid compartment, the dosage calculation is more accurate when based on body surface area than on body weight. However, it is much more feasible in practice to use body weight for the calculation of the dosage.

SHALL WE CHANGE THE ANTIBIOTIC ACCORDING TO THE CULTURE RESULT?

In general, when results from the initial culture test are reported while the empiric regimen is being prescribed, we need to consider changing the antibiotics. To minimize the emergence of resistant strains, narrow-spectrum antibiotics are preferred to broad-spectrum ones, if possible. Especially for staphylococci or gram-negative organisms which are sensitive to penicillin, narrow-spectrum antibiotics are the best choice. Increasingly, more expensive, broad-spectrum antimicrobial drugs like second- and third-generation cephalosporins are being prescribed for common pediatric diseases and the use of less-expensive drugs such as penicillins has been decreasing (McCaig and Hughes, 1995). Perhaps this trend is fuelled by concerns about bacterial resistance, by effective promotion by pharmaceutical companies of their newest antimicrobial, or by attempts to ensure treatment compliance. However, with the new beta-lactam drugs demonstrating efficacy similar to that of amoxicillin against many diseases, it is often difficult to justify the use of newer, more broad-spectrum and expensive antimicrobial agents (Kunin, 1985; Harrison, 1995).

When the culture result is negative and the patient's condition is not improving, we should consider the possibility of other organisms or of noninfective causes. But the most important point for the selection of antibiotics is the clinical progress of the

patient, not the culture results. When the patients' condition is improving while on antibiotics to which the organism found in the culture result is resistant, there is no need to change the antibiotics.

WHAT IS THE APPROPRIATE DURATION OF ANTIBIOTIC THERAPY?

The appropriate duration of antibiotic therapy should be individualized rather than uniformly conformed to a set of guidelines. However, certain specific agents have shorter recommended courses; for example, in treating acute otitis media, ceftriaxone is pending approval in the US as a single intramuscular injection (Green and Rothrock, 1993), and azithromycin has been approved as a single dose daily for 5 days (Lorlertratna and Cunningham, 1997).

REFERENCES

Alpert G, Hippert E, Fleisher GR: Case control study of hyperpyrexia in children. *Pediatr Infect Dis J 9: 161-163, 1990*

Andersen RC, Goldstein EJC: The introduction of the quinolones: a new class of antiinfectives. *Hosp Formul 22: 36-43, 1987*

Arant BS Jr : Developmental patterns of renal functional maturation compared in the human neonate. *J Pediatr 92: 705-712, 1978*

Axon SE, Hall B: An innovative method of adminstering i.v. medications to children. *Pediatr Nursing 20: 341-344, 1994*

Besunder JB, Reed MD, Blumer JL: Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface. *Clin Pharmacokinet 14: 189-216, 1988*

Chong Y, Lee K: *Antimicrobial resistance and its mechanisms.* Suhung Publishing Co., Seoul, *1997*

Echobichon DJ, Stephens DS: Perinatal development of human blood esterases. *Clin Pharmacol Ther 14: 41-47, 1973*

Fitterman GH, Shuplock NA, Phillip FJ: The growth and maturation of human glomeruli and proximal convolutions from term to. childhood. *Pediatrics 35: 601-619, 1965*

Friis-Hansen B: Water distribution in the foetus and newborn infant. *Acta Paediatr Scand 305(Suppl): 7-11, 1983*

Green SM, Rothrock SG: Single-dose intramuscular ceftriaxone for acute otitis media in children. *Pediatrics 91: 23-39, 1993*

Harrison CJ: Perspectives on newer oral antimicrobials; what do they add? *Pediatr Infect Dis J 14: 436-444, 1995*

Helwig H : Contemporary issues in the management of pediatric infections. *Pediatr Infect Dis J 16: S39-42, 1997*

Hook JB, Bailie MD: Perinatal renal pharmacology. *Ann Rev Pharmacol Toxicol 19: 491-509, 1979*

Hook JB, Hewitt WR: Development mechanisms for drug excretion. *Am J Med 62: 497-506, 1977*

Hull D: Fever: the fire of life. *Arch Dis Child 64: 1741-1747, 1989*

Kim DS: *Antibiotic use in pediatric patients: The antibiotics.* Seoul, Yonsei Unversity Graduate School *1998, 34-55*

Kim KH: Antimicrobial therapy for pediatric patients. *Korean J Chemother 15: 179-192, 1997*

Klein JO: Antimicrobial therapy issues facing pediatricians. *Pediatr Infect Dis J 14: 415-419, 1995*

Kuhl PG, Soeding K, Seyberth HW: Aminoglycoside treatment and renal prostaglandin excretion in premature infants. *Dev Pharmacol Ther 8: 61-67, 1985*

Kunin CM: The responsibility of the infectious disease community for the optional use of antimicrobial agents. *J Infect Dis 151: 388-398, 1985*

Kurz, Mauser-Ganshorn A, Stickel HH: Differences in the binding of the drugs to plasma proteins from newborns and adult man. I. *Eur J Clin Pharmacol 11: 463-467, 1977*

Leake RD, Trygstad CW: Glomerular filtration rate during the period of adaptation to extrauterine life. *Pediatr Res 11: 959-962, 1977*

Leeder JS, Kearns GL: Pharmacogenetics in pediatrics. *Pediatr Clin North Am 44: 55-77, 1997*

Levi AJ, Gatmaiton Z, Arias IM: Two hepatic cytoplasmic fractions, y and z, and their role in the hepatic uptake of bilirubin, sulfobromophthalein, and other anions. *J Clin Invest 48: 2156-2167, 1969*

Lorlertratna N, Cunningham CK: Erythromycin and beyond: using macrolide antibiotics. *Contemp Pediatr 14: 27-55, 1997*

Losek JD, Gyuro J: Pediatric intramuscular injections: do you know the procedure and complications? *Pediatr Emerg Care 8: 79-81, 1992*

McCaig LF, Hughes JM: Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA 273: 214-219, 1995*

Neims AH, Warner M, Loughnan PM, Aranda JV: Developmental aspects of the hepatic cytochrome P_{450} mono-oxygenase system. *Ann Rev Pharmacol Toxicol 16: 427-445, 1976*

Paisley JW, Laurer BA: Pediatric blood cultures. *Clin Lab Med 14: 17-30, 1994*

Pikkarainen PH, Raiha NCR: Development of alcohol dehydrogenase activity in the human liver. *Pediatr*

Res 1: 165-168, 1967

Reed MD, Besunder JB: Developmental pharmacology: ontogenic basis of drug disposition. *Pediatr Clin North Am 36: 1053-1074, 1989*

Reese RE, Betts RF: *Antibiotic use.* In Reese RE, Betts RF, eds. *A practical approach to infectious diseases,* 4th ed. Boston, Little Brown and Company, *1996, 1059-1395*

Rhodes KH, Henry NK: Antibiotic therapy for severe infections in infants and children. *Mayo Clin Proc 67: 59-68, 1992*

Schaad UB: Use of the new quinolones in pediatrics. *Isr J Med Sci 30: 463-468, 1994*

Schaad UB : Toward an integrated program for patient care in pediatric infections. *Pediatr Infect Dis J 16: S34-38, 1997*

Stutman HR, Parker KM, Marks MI: Potential of moxalactam and other new antimicrobial agents for bilirubin-albumin displacement in neonates. *Pediatrics 75: 294-298, 1985*

Toyonaga Y: Pharmacokinetics of antibiotics in children. *Acta Paediatr Jpn 39: 114-123, 1997*

Wadsworth SJ, Suh B : In vitro displacement of bilirubin by antibiotics and 2-hydroxybenzoylglycin in new borns. *Antimicrob Agents Chemother 32: 1571-1575, 1988*

Werk LN, Bauchner H: Practical considerations when treating children with antimicrobials in the outpatient setting. *Drugs 55: 779-790, 1998*

Wood M, Wood AJ: Changes in plasma drug binding and α_1-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther 29: 522-526, 1981*