Antibacterial Agents in Pediatrics

Susana Chavez-Bueno, MD[a], Terrence L. Stull, MD[b],*

Antibiotics are the therapeutic agents most frequently used in pediatrics. The majority of prescriptions for antibacterial drugs are to treat common pediatric infections such as otitis media, pharyngitis, pneumonia, and other respiratory infections that are diagnosed primarily in the ambulatory setting.[1] In many of these cases, however, antimicrobials are inappropriately prescribed; thus, antibiotic overuse is a persistent problem, especially in outpatient pediatric practices.[2] Antibiotics are also widely used to treat infections of the skin and soft tissues, genitourinary tract, bones and joints, central nervous system (CNS), and other sites in patients who require hospitalization.

Despite their widespread use in pediatrics, few antibiotics have been studied adequately to be considered safe and effective for use in children. Unfortunately, data regarding antibiotic pharmacokinetics, efficacy, and side effects are often extrapolated from studies performed in adults or animals when selecting dosing regimens for children. The US Food and Drug Administration (FDA) addressed the issue with the Pediatric Rule, which became effective in 1999. Under this rule, any application for approval of a human drug or biologic agent is expected to contain data assessing the safety and effectiveness in pediatric patients. Two recent laws, which were reauthorized in 2007, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, further encourage the research and development of drugs in children.

When using antibiotics in children, many factors that are different from those for adults should be considered. A discussion of the general principles of pharmacokinetics and pharmacodynamics pertinent to the pediatric population is included in this article, followed by a discussion of selected antibiotics that are most commonly used in pediatrics.

[a] Department of Pediatrics, Section of Pediatric Infectious Diseases, University of Oklahoma Health Sciences Center, 940 NE 13th Street, Room 2B 2311, Oklahoma City, OK 73104, USA
[b] Department of Pediatrics, University of Oklahoma Health Sciences Center, 940 NE 13th Street, Room 2B 2308, Oklahoma City, OK 73104, USA
* Corresponding author.
E-mail address: terrence-stull@ouhsc.edu (T.L. Stull).

PHARMACOKINETICS

Antibiotic pharmacokinetics describe their absorption, metabolism, elimination, and distribution. Gestational and chronologic age are factors to consider when administering antibiotics to children because various organs mature at different rates as children grow, affecting the pharmacokinetics.[3] Other factors affecting pharmacokinetics include underlying diseases, drug interactions, and tissue distribution.

Parenteral antibiotic administration often results in higher and more predictable serum concentrations compared with the oral route. Oral bioavailability of most beta-lactam antibiotics, for example, is approximately 5% to 10% compared with the intravenous (IV) route. However, certain antibiotics, including clindamycin, trimethoprim/sulfamethoxazole, and linezolid, on the other hand, have excellent bioavailability after administration by the oral route, and the serum concentrations are similar to those found after an IV dose.

Hepatic function changes over time as the result of variations in blood flow and the maturation of enzyme systems. In neonates, both phase I (primarily oxidation) and phase II enzymes (conjugation) may be reduced, although they are more active by 2 months of age.[4] After the first year of life, the levels of most liver enzymes are similar to the levels in adults.[5,6] Besides the changes in hepatic metabolism, it is also important to consider the protein binding properties of different antibiotics at different stages of life. The bilirubin-albumin binding capacity in neonates is very low, and it does not reach adult levels until approximately 5 months of age. Excess unconjugated bilirubin can result in bilirubin encephalopathy (kernicterus). Certain antibacterial agents (eg, ceftriaxone and the sulfonamides) can increase toxic bilirubin levels as the result of displacement from albumin. Because the risk for kernicterus is directly related to the serum concentration of unbound, unconjugated bilirubin, these agents should be avoided in newborns and young infants. Cefotaxime and ceftazidime pose less risk.

Renal function also is determined by gestational and chronologic age.[7] The glomerular clearance of drugs in neonates is slow compared with that in older children and adults. Aminoglycosides and glycopeptide antibiotics are almost exclusively eliminated by the renal route, and adjusted gestational age is the best predictor of their clearance. The glomerular filtration rate increases during infancy to approach an adult rate by 6 months of age.[8,9] Antibiotic dosing in neonates is further complicated because neonates have larger total-body-water content and a higher proportion of extracellular fluid compared with older children, which translates into a larger volume of distribution.

Although age correlates with body weight as the child grows, pharmacokinetic parameters do not necessarily follow. In many cases, body-weight-normalized drug clearance in children exceeds that of adults; therefore, a higher dosage based on body weight may be necessary. Maximum-body-weight dosages prevent overdosing in adolescents and overweight children. Adjusting dosages based on body surface area may help to avoid overdosing of certain antibiotics, especially in older children. Monitoring of antibiotic serum concentrations is sometimes indicated to assess both efficacy and toxicity.

In addition, adherence to oral antibiotic therapy is another relevant issue to consider in children. For those who can only take liquid formulations, palatability plays an important role in compliance with therapy (**Table 1**).[10–14]

PHARMACODYNAMICS

Pharmacodynamics describes the effects, activity, or toxicity of a pharmaceutical agent within the body. When selecting an antibiotic for pediatric use, knowledge about

Table 1
Comparative palatability of selected antibiotic suspensions used in pediatrics[10–14]

Pleasant Taste	Inconsistent Preference	Unpleasant Taste
Amoxacillin	Amoxacillin/clavulanic acid	Cefpodoxime
Cefdinir	Azithromycin	Cefuroxime
Cefixime	Ciprofloxacin	Clarithromycin
Cephalexin	Erythromycin	Clindamycin
Loracarbef/rifampin	Trimethoprim/sulfamethoxazole	Linezolid

the specific causative organism and its susceptibility to different antibiotics is crucial. Early isolation of the organism by obtaining appropriate clinical samples for laboratory testing before beginning antibiotic therapy is ideal, although sometimes empiric selection of an antibiotic is necessary. The site of infection is another factor to consider when choosing a particular agent because antibiotic concentrations vary in different compartments.

The minimum inhibitory concentration (MIC) determines the susceptibility of a particular pathogen to a specific antibiotic. The MIC is the lowest concentration of the antibiotic that inhibits the growth of the pathogen in vitro. Not all isolates of a pathogen have the same MIC for a given antibiotic.[15]

Resistance to antibiotics varies greatly depending on the specific bacterial mechanisms of resistance and host factors. Local epidemiologic data are key to assessing the prevalent patterns of resistance in a community and are helpful in selecting the most appropriate initial empiric antibiotic therapy.

Two main patterns of bactericidal activity exist. Antibiotics such as penicillins and cephalosporins demonstrate time-dependent killing, that is, the duration that the concentration of the drug is greater than the MIC of the target organism is directly related to bacterial killing.[16] Vancomycin, clindamycin, and the macrolides also show time-dependent antibacterial activity. Bacterial killing by such antibiotics as the aminoglycosides and fluoroquinolones, on the other hand, is concentration dependent, that is, a higher drug concentration leads to a greater rate and extent of bacterial killing.

The duration of therapy is determined in many cases by common practice and general experience because critical evaluations of therapy duration have been performed for only a few diseases. In general, a longer duration of therapy should be used (1) for tissues in which antibiotic concentrations may not be high (eg, bone), (2) when the organisms are less susceptible to antibiotic therapy, (3) when a relapse of infection is unacceptable (eg, CNS infections), or (4) when the host is immunocompromised in some way.[17]

BETA-LACTAMS

Penicillin was discovered more than 5 decades ago, and the beta-lactam antibiotics have been synthetically modified. They continue to be widely used in pediatrics. Despite the development of resistance by several organisms, this group of antibiotics continues to be used against a variety of infections in children.

Penicillins

Penicillins are the most frequently prescribed antibacterials in the United States and many other parts of the world. Amoxicillin accounts for ~50% of all oral liquid

antibacterials and ~75% of all oral liquid penicillins prescribed in primary care settings in England.[18]

In the 1950s, the entire beta-lactam family of antibiotics included only penicillin G and penicillin V. Today, these antibiotics remain the first-line therapy for infections caused by susceptible streptococci, including group A streptococcal pharyngitis. They are also the drugs of choice in syphilis, meningococcal, *Listeria*, and neonatal group B streptococcal infections.

Broad-spectrum penicillins, the aminopenicillins, were developed in the 1960s. Ampicillin, and later amoxicillin, provided activity against gram-negative bacteria and enterococci.[19] Amoxicillin is structurally related to ampicillin and has the same spectrum of activity and potency. It is much better absorbed when given orally, achieving blood concentrations approximately twice as high as those obtained with ampicillin. Initially, aminopenicillins were active against many gram-negative strains of bacteria, including *Escherichia coli*, *Proteus* spp, *Salmonella* spp, and beta-lacta-mase–negative *Haemophilus influenzae*. Unfortunately, these organisms have developed various mechanisms of resistance, and the aminopenicillins no longer remain the first choice for many of these infections, although they continue to be used against susceptible isolates. *Streptococcus pneumoniae,* the most common etiologic agent of otitis media, is another example of the development of bacterial resistance to penicillins. Through selection of strains producing penicillin-binding proteins with decreased affinity for penicillins, the resistance of many strains of *S pneumoniae* has progressively increased. However, because the mutations in the penicillin-binding proteins usually result in only modestly reduced susceptibility, higher doses of aminopenicillins result in serum concentrations that exceed the MIC for a greater portion of the dosing interval, thus allowing effective killing.[20] Therefore, the currently recommended dosage of amoxicillin is 80 to 90 mg/kg/d instead of 40 mg/kg/d when treating otitis media caused by some penicillin-nonsusceptible *S pneumoniae* isolates.[21]

Another mechanism of resistance became evident in the mid-1960s with the identification of bacteria-producing beta-lactamases. The first semisynthetic penicillin that was stable to staphylococcal penicillinase was methicillin. This was followed by other semisynthetic penicillins that had increased activity and the option of oral administration, such as cloxacillin, flucloxacillin, and dicloxacillin. Dicloxacillin has excellent bioavailability as an oral agent, but is poorly palatable, and for treating infections caused by beta-lactamase–producing organisms in children, it has been replaced by other antibiotics. Penicillinase-resistant parenteral semisynthetic penicillins that are more commonly used than methicillin include nafcillin and oxacillin. These antibiotics are effective for treating methicillin-susceptible *Staphylococcus aureus* (MSSA) infections in children. The emergence of methicillin-resistant *S aureus* (MRSA) in the pediatric population has caused a decrease in their use in children.

A different approach to counteract beta-lactamase has been the development of beta-lactamase inhibitors such as clavulanic acid.[22] The combination of amoxacillin and clavulanic acid became available in 1980, and it has been widely used in children to treat otitis media, community-acquired pneumonia, sinusitis, infections of the skin and subcutaneous tissues, urinary tract infections, and animal and human bites. This combination has an expanded activity to include MSSA, beta-lactamase–positive *H influenzae*, and many anaerobes as well. Sulbactam is another beta-lactamase inhibitor. In combination with ampicillin for IV administration, it is FDA-approved for use in children aged 1 year and older for treatment of skin and subcutaneous tissue infections. Its spectrum of activity is similar to that of amoxicillin/clavulanic acid, and there is evidence that it is an effective therapy for intra-abdominal infections and meningitis caused by susceptible organisms.[23]

Extended-spectrum penicillins were also developed with the goal of treating infections caused by *Pseudomonas aeruginosa.* These penicillins include the carboxypenicillins and ureidopenicillins. Side effects unique to these two groups include hypokalemia and hypernatremia. The carboxypenicillins consist of carbenicillin and ticarcillin. Compared with ampicillin, both have enhanced activity against *P aeruginosa* and other gram-negative bacteria. Ticarcillin has greater antipseudomonal activity compared with carbenicillin in vitro. However, the aminopenicillins continue to have superior activity against enterococci compared with the carboxypenicillins. Ticarcillin is approved for use in pediatrics to provide treatment for intra-abdominal infections, skin and subcutaneous tissue infections, respiratory tract infections, septicemia, and urinary tract infections caused by susceptible organisms. The combination of ticarcillin and clavulanic acid is also approved for use in children older than 3 months of age for similar indications, there is also evidence for its efficacy as an empiric therapy in febrile neutropenic pediatric patients.[24] The ureidopenicillins have enhanced aerobic gram-negative activity, including antipseudomonal activity. They have a decreased frequency of side effects and are active against *Enterococcus* spp. Included in this group are mezlocillin, azlocillin, and piperacillin. Piperacillin is the ureidopenicillin most commonly used in pediatrics, and its combination with tazobactam, another penicillinase inhibitor, has been approved to provide therapy for appendicitis and peritonitis in children aged 2 months and older.[25] Evidence supports its efficacy as an empiric therapy for febrile episodes in pediatric neutropenic patients.[26]

Cephalosporins

Cephalosporins are among the most commonly used beta-lactam antibiotics in children. Various cephalosporins are derived by doing modifications of the prototype molecule, cephalosporin C, which is produced by the fungus *Cephalosporium acremonium*. These antimicrobials are routinely classified into "generations," based mainly on their spectrum of activity. Both oral and parenteral agents are available within each category (**Table 2**).[27] In general, first-generation cephalosporins are most active against aerobic gram-positive cocci. Second-generation cephalosporins are more active against selected gram-negative organisms; additionally, cefoxitin and cefotetan (both cephamycins, the latter not FDA-approved for use in children) are active against anaerobic bacteria. Third-generation cephalosporins are the most active against gram-negative organisms, including some with activity against *P aeruginosa* (ceftazidime and, to a lesser extent, cefoperazone). Fourth-generation cephalosporins include cefepime and cefpirome, the latter not FDA-approved for use in adults or children.

Some organisms, including all enterococci, *Listeria* monocytogenes, and atypical pneumonia organisms such as *Legionella*, *Mycoplasma*, and *Chlamydia* spp, are always resistant to all cephalosporins.

Cephalosporins are generally well tolerated. Orally administered cephalosporins may cause gastrointestinal complaints such as nausea, vomiting, or diarrhea. Thrombophlebitis occurs in about 1% to 2% of patients who receive cephalosporins intravenously. Hypersensitivity or allergic reactions occur in 1% to 3% of patients who receive cephalosporin drugs, and skin testing helps confirm such reactions.[28] The rate of cross-reactive cephalosporin allergy in patients who have known penicillin allergy is poorly defined, but it appears to be low.[29,30] Other side effects include occasional leukopenia and thrombocytopenia; eosinophilia may occur. Cephalosporins can also cause hypoprothrombinemia and transient elevation of transaminases; they are rarely nephrotoxic or neurotoxic.

Table 2 FDA-approved cephalosporins for use in children		
Generation	**Oral**	**Parenteral[b]**
First generation	Cefadroxil Cephalexin[a] Cephradine	Cefazolin[a] Cephalothin Cephradine
Second generation	Cefaclor Cefprozil Cefuroxime	Cefoxitin Cefuroxime
Third generation	Cefditoren Cefixime[a] Cefpodoxime Ceftibuten Cefdinir[a]	Cefotaxime[a] Ceftazidime[a] Ceftizoxime Ceftriaxone[a]
Fourth generation	—	Cefepime

[a] Most commonly used in pediatrics.
[b] All parenterally administered cephalosporins are available in intramuscular and IV forms.

Newer cephalosporins under investigation and with broader activity, including activity against MRSA, are ceftobiprole[31] and ceftaroline.[32]

First-generation oral cephalosporins are mainly used to treat skin and soft-tissue infections caused by susceptible organisms (they are not active against MRSA), streptococcal tonsillopharyngitis, and urinary tract infections. Cephalexin is most commonly used for these indications. At higher doses, oral cephalosporins are useful to treat bone and joint infections in children. The most common side effects include skin reactions and gastrointestinal upset.

Parenteral first-generation cephalosporins are for the most part used to treat bone, urinary tract, respiratory tract, and skin and soft-tissue infections, and for preoperative prophylaxis when indicated.

Cefuroxime is the most commonly used *second-generation* cephalosporin used in children. It is available for oral and parenteral administration. Cefuroxime is the only cephalosporin of this group that has demonstrable penetration into the CNS. However, its use for treatment of bacterial meningitis was associated with delayed sterilization and a higher incidence of hearing loss.[33] Other indications include pharyngitis, otitis media, lower respiratory tract infections, soft-tissue infections, and urinary tract infections. Other oral second-generation cephalosporins include cefaclor and cefprozil, both with a spectrum of activity similar to cefuroxime axetil. Cefaclor has been associated with serum sickness–like reactions that have limited its use in this patient population. Cefprozil is better tolerated and is more palatable. Loracarbef and cefamandole are second-generation cephalosporins that are no longer available in the United States.

Oral *third-generation* cephalosporins used commonly in pediatrics include cefixime, cefpodoxime, ceftibuten, and cefdinir. Cefixime is FDA-approved for use in children older than 6 months of age and is commonly used in urinary tract infections and for the treatment of *Salmonella* infections. Cefpodoxime may be dosed once or twice daily and is approved for use in children older than 2 months of age, but it is poorly palatable. Ceftibuten has similar coverage to cefpodoxime, and is approved only for treatment of respiratory tract infections, sinusitis, and otitis media in children aged 6 months and older. Cefdinir has a broader spectrum of activity, with activity against MSSA and streptococci that is comparable with that of the first-generation agents. It may be dosed once or twice daily, and it has a favorable taste.

The most widely used parenteral third-generation cephalosporins in children are ceftriaxone, cefotaxime and ceftazidime. These agents have enhanced activity compared with second-generation agents against Enterobacteriaceae. In general, they have activity against penicillin nonsusceptible *S pneumoniae* and *Haemophilus, Neisseria*, and *Moraxella* spp. Third-generation parenteral cephalosporins are the drugs of choice for the treatment of many types of bacterial meningitis. Ceftriaxone has the convenience of dosing once daily for the treatment of most infections. It can be given either intravenously or intramuscularly. Its affinity to bind albumin can cause displacement of bilirubin; therefore, it is not recommended for use in neonates, particularly for those who have hyperbilirubinemia. Ceftriaxone achieves excellent peak serum concentrations and efficacy against resistant nonmeningeal *S pneumoniae* infections. However, with the increase in the number of nonsusceptible isolates, the use of vancomycin plus a third-generation cephalosporin is recommended when initiating antibiotic therapy for bacterial meningitis, until culture and susceptibility results are available. Cefotaxime has equivalent coverage to that of ceftriaxone, and has no restrictions for use during the newborn period. Ceftazidime is the only third-generation agent that has activity against susceptible strains of *P aeruginosa.* Overall, these agents are well tolerated. They, like other beta-lactams, can be associated with agranulocytosis, thrombocytopenia, pseudomembranous colitis, and hypersensitivity reactions. Ceftriaxone has been associated with reversible pseudocholelithiasis. Its administration with any calcium-containing IV solutions should be avoided.[34]

Cefepime is a parenterally administered *fourth-generation* cephalosporin that was first approved by the FDA in 1997. It has good activity against gram-positive bacteria, including MSSA and α-hemolytic streptococci. Also, it has the best activity against penicillin-resistant pneumococcus among the cephalosporins. In addition, its gram-negative activity against *H influenzae, Neisseria* spp, and *Pseudomonas* spp is excellent. It is also more active against Enterobacteriaceae, including strains that produce extended-spectrum beta-lactamases, than third-generation cephalosporins are.[35] Cefepime is FDA-approved for use in children older than 2 months of age for empiric therapy of febrile neutropenia, and to treat skin and soft-tissue infections, moderate to severe pneumonia, and urinary tract infections. Adverse effects associated with cefepime use include headache, gastrointestinal upset, local reactions, and rash that occur in less than 2% of individuals. More serious adverse effects include encephalopathy and seizures.

Carbapenems and Monobactams

Carbapenems are a class of antibiotics that have one of the broadest spectra of antimicrobial activity for use in pediatrics. The chemical structure of the carbapenems is very similar to that of the penicillin ring, with the side chain providing resistance to most beta-lactamase enzymes. Imipenem, meropenem and ertapenem have activity against most gram-negative and gram-positive organisms, with differences in activity that depend on the particular beta-lactamase produced by the pathogen. Meropenem is less active against gram-positive organisms and more active against gram-negative organisms than imipenem. Ertapenem has decreased activity against *Pseudomonas* isolates compared with imipenem and meropenem. Carbapenems are not active against MRSA, *Enterococcus faecium*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Chlamydia* spp, and *Mycoplasma* spp.

Imipenem is approved for use in pediatrics to treat endocarditis, septicemia, and intra-abdominal, bone, and urinary tract infections. Meropenem is approved for use in children older than 3 months of age to provide therapy for meningitis (recommended dose for this indication of 120 mg/kg/day, maximum dose of 6 g/day), complicated

skin and soft-tissue infections, and intra-abdominal infections. Ertapenem is approved for use in children older than 3 months of age to provide therapy for severe pneumonia, complicated skin and soft-tissue infections, and intra-abdominal and pelvic infections.

Carbapenems are administered parenterally, and their excretion is predominantly by glomerular filtration. Imipenem must be administered with cilastatin to avoid hydrolysis and to reduce nephrotoxicity. In general, tolerability to carbapenems is good.[36] Seizures are a well-known side effect of imipenem/cilastatin, especially in patients who have meningitis. Seizures occur in approximately 3% of patients who are treated with imipenem and who do not have CNS infections, but the incidence of seizures can be as high as 33% in patients who have bacterial meningitis.[37]

Despite their broad-spectrum activity, resistance to carbapenems, especially by gram-negative organisms, has been reported.[38]

Aztreonam is the only monobactam approved for pediatric use. Its spectrum of activity resembles that of the aminoglycosides, and it has activity against most aerobic gram-negative bacilli, including *P aeruginosa*. When used for empiric therapy, aztreonam must be given in combination with other antimicrobial agents that are active against gram-positive and anaerobic species.[39] It is approved for use in children 9 months of age and older to provide therapy for lower respiratory tract infections, urinary tract infections, septicemia, and intra-abdominal infections caused by susceptible organisms. Aztreonam may be administered intramuscularly or intravenously; the primary route of elimination is by urinary excretion. The drug is not nephrotoxic and has not been associated with disorders of coagulation. Anaphylactic reactions have been reported in less than 1% of individuals who receive the drug.

AMINOGLYSCOSIDES

Aminoglycosides are one of the oldest groups of antibiotics still in use. Streptomycin, the first aminoglycoside available, was discovered in the mid-1940s and was used to treat tuberculosis. The aminoglycosides are bactericidal inhibitors of protein synthesis. They are not available for oral administration, so they are mainly used in parenteral form, although inhaled tobramycin is FDA-approved for use in children older than 6 years of age who have cystic fibrosis.[40,41]

Aminoglycosides are predominantly used to treat gram-negative bacillary infections. They have some activity against *S aureus* and are synergistic against *Enterococcus* spp, but their gram-positive activity as single agents is very limited. In pediatrics, they remain key agents to treat gram-negative bacteria, including *E coli*, *Salmonella* spp, *Shigella* spp, *Enterobacter* spp, *Citrobacter* spp, *Acinetobacter* spp, *Proteus* spp, *Klebsiella* spp, *Serratia* spp, *Morganella* spp, *Pseudomonas* spp, and mycobacteria. Therefore, they are useful in the treatment of urinary tract infections, intra-abdominal infections, neonatal sepsis, complicated infections in cystic fibrosis, and as empiric therapy for febrile neutropenic patients. They are also used to treat plague, tularemia, and brucellosis.

The three most commonly used aminoglycosides in children are gentamicin, tobramycin, and amikacin. In general, tobramycin has greater antipseudomonal activity, and amikacin is more active against resistant gram-negative bacilli.

Because the aminoglycosides are concentration-dependent antibiotics, their bactericidal effect depends on an adequate peak concentration. Adult studies have shown enhanced bactericidal effect and minimized toxicity using once-daily dosing of aminoglycosides. Pediatric studies of once-daily dosing have been conducted and also support this dosing regimen.[42]

Ototoxicity and nephrotoxicity are the most notable adverse effects. However, studies have failed to demonstrate a consistent correlation between aminoglycosides and hearing loss in pediatric patients[43]; the risk for nephrotoxicity in pediatric patients also has rarely been demonstrated.

MACROLIDES

Macrolides inhibit RNA-dependent protein synthesis by reversibly binding to the 50S ribosomal subunit of susceptible microorganisms. Besides their direct antimicrobial activity, clinical trials in patients who have chronic inflammatory lung diseases have suggested an anti-inflammatory effect by documenting significant improvement in lung function and quality of life along with fewer exacerbations when macrolides are used.[44] The mechanism of action mediating these effects is currently under investigation.[45]

Erythromycin is the oldest agent in this group; it has been available since the mid-1950s. The antimicrobial activity of erythromycin includes various gram-positive organisms, and *Legionella, Mycoplasma*, and *Chlamydia* spp. Its disadvantages include poor gastrointestinal tolerance and a short half-life. Erythromycin was commonly used as an alternative therapy for penicillin-allergic children who were afflicted with streptococcal pharyngitis, sinusitis, or acute otitis media; however, recent increases in macrolide-resistant *S pneumoniae* and *H influenzae* have decreased its utility in children.[46–48] Macrolide resistance is mainly due to either an alteration of the drug-binding site on the ribosome that is caused by methylation (macrolide-lincosamide-streptogramin B resistance) or to active drug efflux. Macrolide hydrolysis caused by esterases is a resistance mechanism in Enterobacteriaceae.

Newer macrolides for use in children include azithromycin and clarithromycin. They are used for the treatment of respiratory tract infections, sexually transmitted diseases, and infections caused by *Helicobacter* or *Mycobacterium avium* complex. The bioavailability of the azithromycin suspension is not affected by meals, and its half-life allows once-daily administration. Azithromycin is also available for IV dosing. Clarithromycin possesses increased acid stability, which results in improved oral bioavailability and reduced gastrointestinal intolerance.[49]

Ketolides are semisynthetic derivatives of the 14-membered ring macrolide antibiotics that have an expanded spectrum of activity.[50] Telithromycin, a member of this group, is approved for the treatment of mild to moderate pneumonia in adults, but its safety and efficacy in children have not yet been established.

Side effects of macrolides include alteration of gastrointestinal motility, potential for cardiac arrythmia, and inhibition of drug metabolism that leads to clinically relevant drug–drug interactions.[51] Erythromycin stimulates gastric motility more so than clarithromycin and azithromycin do. The association of erythromycin with increased risk for hypertrophic pyloric stenosis in newborns has prompted some clinicians to use azithromycin instead to treat pertussis and chlamydia infections in these patients.[52]

LINCOSAMIDES

Lincomycin and clindamycin are clinically useful lincosamide antibiotics. They are bacteriostatic and act by inhibiting protein synthesis.[53] Clindamycin is usually more active than lincomycin in the treatment of bacterial infections, particularly those caused by anaerobic species. Among aerobic gram-positive bacteria, it is active against most strains of pneumococcus, group A *Streptococcus*, *Streptococcus viridans*, and many *Staphylococcus* strains. Clindamycin also inhibits the production of

exotoxin associated with toxic shock syndromes, and it also affects some protozoa. Clindamycin is available for oral, intramuscular, and IV administration.

Clindamycin use is on the increase in pediatrics because of the increase in community-acquired MRSA infections. Evidence to support the use of clindamycin to provide therapy for community-acquired MRSA in children is limited,[54] and there is currently no specific indication by the FDA for the use of clindamycin to treat MRSA infections in children.

The most common adverse effect of clindamycin is diarrhea, which is reported in 2% to 20% of patients. Antibiotic-associated pseudomembranous colitis is possible as well. Hypersensitivity reactions are also common, presenting as a morbilliform rash; erythema multiforme and Stevens-Johnson syndrome are rare.[55] Less common adverse effects include liver toxicity, bone marrow suppression, and muscle weakness, all of which are reversible after drug discontinuation. Clindamycin can prolong the effect of neuromuscular blocking agents.

GLYCOPEPTIDES

Vancomycin and teicoplanin are the two glycopeptides that have been used clinically for the treatment of multidrug-resistant infections that are caused by gram-positive organisms. Vancomycin is more widely used in pediatrics.

Vancomycin is a glycopeptide that inhibits synthesis of the bacterial cell wall. It is commonly used for infections that are caused by MRSA, coagulase-negative staphylococci, ampicillin-resistant enterococci, and *Bacillus* and *Corynebacterium* spp. It has become an important agent used in combination with other antibiotics when initiating therapy for biologic hardware infections (eg, central venous catheters, ventriculoperitoneal shunts) because of its activity against coagulase-negative staphylococci. It is also used in bacterial meningitis because of its activity against penicillin-nonsusceptible *S pneumoniae*, and in selected episodes of febrile neutropenia because of the possibility of resistant viridans streptococci.[56] Oral vancomycin is used to treat pseudomembranous colitis caused by *Clostridium difficile.* This use carries the potential risk for the development of vancomycin-resistant enterococci (VRE).[57,58]

Unfortunately, resistance to vancomycin by several organisms, including *S aureus* and enterococci, continues to increase. Although the incidence of strains that have a reduced susceptibility to vancomycin seems low, the true incidence may be much higher because of technical difficulties with common methods of detection. Current methods for testing vancomycin are not completely reliable in many laboratories. One concern is that vancomycin treatment failures are related to the presence of vancomycin-resistant subpopulations of MRSA strains that seem to be vancomycin susceptible in the laboratory.[59] Reduced clinical efficacy of vancomycin has been reported in patients who have clinical isolates that have a MIC of more than 1 μg/mL, even though the MIC is still within the susceptible range (MIC $\leq$ 2 μg/mL).[60]

In general, vancomycin is well tolerated, but reported adverse effects include gastrointestinal, hypotension, and cardiovascular effects after rapid infusion; drug-mediated skin reactions; thrombophlebitis; and rarely, ototoxicity. Also, previous preparations of vancomycin were associated with nephrotoxicity, but this occurrence is infrequent with the newer preparation. Red man syndrome is probably histamine-mediated and responds to antihistamine or corticosteroid administration and a slowing of the infusion rate.

Dalbavancin and telavancin are new lipoglycopeptides that are undergoing clinical trials, but the FDA has not yet granted approval for their use in adults or children.[61,62]

OXAZOLIDINONES, STREPTOGRAMINS, AND LIPOPEPTIDES

Linezolid is the first oxazolidinone approved for use in the United States, including use in children. The drug is predominately bacteriostatic, and it has antimicrobial activity against gram-positive organisms such as streptococci, staphylococci, and enterococci, including species that are resistant to conventional antibacterials.[63] Linezolid has activity against rapidly growing mycobacterial species, multiple *Nocardia* spp, and *Mycobacterium tuberculosis*. It has excellent bioavailability, both intravenously and orally, and a very good safety profile in children.[64] There is also evidence for its safety in neonates.[65,66] It is approved for use in adults and children for the treatment of serious infections caused by *Enterococcus faecium* or *E fecalis*, including VRE; *S aureus*, including MRSA; coagulase-negative staphylococci; and streptococci, including penicillin-resistant *S pneumoniae*. It is used for complicated soft-tissue and skin-structure infections caused by MRSA, nosocomial pneumonia caused by MRSA, bacteremia caused by VRE, and bacteremic community-acquired pneumonia caused by penicillin-resistant *S pneumoniae*. Its most common adverse reactions are diarrhea, headache, vomiting, nausea, elevated serum transaminase concentrations, and rash. Thrombocytopenia is common in adults, so it is recommended to monitor blood counts in children weekly while they are receiving therapy with linezolid.

Dalfopristin/quinupristin is a streptogramin combination approved for use in patients aged 16 years and older for treatment of complicated skin and soft-tissue infections and VRE infections.[67] This antibiotic is active against MRSA, coagulase-negative staphylococci, resistant pneumococcus, and vancomycin-resistant *Enterococcus faecium*. However, it has no activity against vancomycin-resistant *E faecalis.* It is available for parenteral use. Adverse effects include infusion site reactions (eg, pain, edema), nausea and vomiting, diarrhea, headache, mylagias, and arthralgias.[68]

Daptomycin is a novel cyclic lipopeptide, approved for use in the United States in 2003, that is bactericidal against gram-positive bacteria, including MRSA and VRE. Daptomycin kills gram-positive bacteria by the disruption of multiple bacterial plasma membrane functions, without penetrating the cytoplasm.[69] Daptomycin is also effective against a variety of streptococci, such as beta-hemolytic streptococci and other *Streptococcus* spp. Synergy with daptomycin has been described in vitro for aminoglycosides such as gentamicin, oxacillin, other beta-lactams, and rifampicin.[70] The drug is highly protein bound (92%); excretion is primarily renal. Daptomycin is approved to treat skin and soft-tissue infections,[71] *S aureus* bacteremia, and right-sided endocarditis in adults. It is not approved for the treatment of pneumonia. Its safety and efficacy in patients younger than 18 is under study.

SULFONAMIDES

The combination of trimethoprim/sulfamethoxazole (TMP/SMX) is one of the most commonly used antibiotics within this group in pediatrics. The antibiotics act by inhibiting folic acid synthesis in bacteria at two different enzymatic steps.[72] After oral administration, 85% of the drug is absorbed readily, regardless of the presence of food or other medications; there is also an IV form available.

TMP/SMX is approved for use in children older than 2 months of age to provide therapy for urinary tract infections, selected gastrointestinal infections caused by gram-negative organisms, acute otitis media (not as a first line agent for this indication), and *Pneumocystis jiroveci* pneumonia. TMP/SMX is also an alternative to treat *Listeria* meningitis in penicillin-allergic patients.

The rapid emergence of community-acquired MRSA in children has changed the empiric choice for outpatient antibiotic therapy, especially in cases of localized

infections such as cellulitis and abscesses.[73] In these cases, and although it is not FDA approved for this specific indication, TMP/SMX may be the antibiotic of choice, especially if the rate of inducible clindamycin resistance is high in the community (>15%).[74] TMP/SMX may not be active against group A streptococci; therefore, when this organism is suspected as a copathogen, other effective therapies need to be considered. The rates of TMP/SMX resistance for community-acquired MRSA in the United States have remained low; however, in Europe the TMP/SMX resistance rates to MRSA in general have been reported to be between 53% and 76%.[75] Most of the experience with using TMP/SMX to provide therapy for S aureus infection in children is anecdotal; therefore, more studies are needed to ascertain its efficacy as a first-line therapy in this population.[76]

Adverse effects for TMP/SMX include mild to severe dermatologic conditions and various gastrointestinal symptoms. Bone marrow suppression can occur with prolonged use. Aseptic meningitis has occurred as well. TMP/SMX competes with bilirubin for plasma protein-binding sites, thereby increasing the risk for kernicterus, particularly in preterm or already jaundiced neonates. Patients who have glucose 6-phosphate-dehydorgenase (G-6-PD) deficiency, including fetuses and preterm neonates, may develop dose-related acute hemolytic anemia if treated with TMP/SMX.

QUINOLONES

The fluoroquinolones are bactericidal agents that are derivatives of nalidixic acid. They are inhibitors of DNA replication by binding to the topoisomerases of their target bacteria. They are broad-spectrum agents that have activity against gram-positive organisms, including some penicillin-nonsusceptible pneumococci and MRSA. They exhibit excellent activity against gram-negative bacteria, including the Enterobacteriaceae, *Moraxella catarrhalis*, beta-lactamase–producing *H influenzae*, and *Shigella*, *Salmonella*, and *Neisseria* spp. In addition, they have activity against *P aeruginosa*, with ciprofloxacin being most active. Atypical organisms, including *Mycoplasma* and *Chlamydia* spp, *Legionella pneumophila, Ureaplasma urealyticum,* and strains of *Mycobacterium* are also susceptible.

Ciprofloxacin is the only quinolone approved for use in children, and it is only approved to provide therapy for complicated urinary tract infections, pyelonephritis, and postexposure treatment of inhalation anthrax. Other older quinolones that are approved for use in adults include levofloxacion, ofloxacin, and norfloxacin. Newer agents include gatifloxacin, gemifloxacin, and moxifloxacin.

Early in their development, fluoroquinolones were found to affect cartilage in juvenile animals, resulting in arthropathy. Although the pathogenesis remains unknown, the potential for arthropathy in children is a concern that has limited the use of these drugs in pediatrics. Case reports and retrospective cohort studies, mostly in children who have cystic fibrosis, have failed to demonstrate an association with irreversible arthropathy; however, although the association between quinolones and pediatric arthropathy is weak, it is prudent to use these antibiotics only when safer alternatives are not available.[77]

Despite their limited approval for use in children, it is estimated that more than one-half million prescriptions for quinolones are written in the United States every year for patients younger than 18 years of age.

The use of fluoroquinolones in children should be limited to patients who have cystic fibrosis and life-endangering infections, resistant gram-negative neonatal meningitis, *Salmonella* and *Shigella* spp infections, chronic suppurative otitis media, and some cases of complicated acute otitis media.[78] The unskilled use of fluoroquinolones in

children, particularly in community-acquired lower respiratory infections, could accelerate the problem of pneumococcal resistance.[79]

SUMMARY

Many antibacterial agents are safe and effective in pediatrics. Unfortunately, microbial pathogens have continued to develop new mechanisms of resistance that limit the treatment options for infections in children. Reducing antibiotic overuse in pediatrics by prescribing antibiotics responsibly and by encouraging people to follow their physician's instructions about dosing and duration would likely delay the development of resistance. Research on antibiotic development and the clinical applications in children will continue to meet the need for better therapeutic options in this population.

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