9

Antimicrobials in Pediatric Dentistry

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OUTLINE

The second most commonly prescribed group of drugs for use in dentistry after the local anesthetics are the antibiotics. Infections involving the teeth and oral cavity can become quite severe and even life threatening if not properly managed. The management of infections usually involves a definitive dental or surgical procedure and often requires the use of antibiotics. Antimicrobials are substances that kill or suppress the growth or multiplication of microorganisms, either bacteria, viruses, fungi, or parasites. Antibiotics are substances produced by microorganisms or by synthetic chemical methods that can be used to treat bacterial infections. Antibiotics are indicated for diseases in which a specific bacterial pathogen has been identified, for clinical situations likely caused by a bacterial agent, and for use as a lifesaving measure in a severely ill patient. Prophylactic use of antibiotics is indicated in some specific instances, such as prophylaxis against bacterial endocarditis for patients with congenital heart disease. Antibiotic therapy is maximally successful if the causative pathogen is identified by culture or serologic testing and the therapeutic agent most active against that pathogen (confirmed by susceptibility testing) is administered in appropriate doses.

Antimicrobial Classification

A large number of antimicrobial agents are available for use in pediatric dentistry. There are multiple classification schemes for these agents, including differentiation by microbial target, mode of action, and effect on the bacterial pathogen.

Microbial Target

Antimicrobial agents are often categorized according to microbial target group. The principal emphasis of this chapter is on antibacterial agents—the antibiotics. Antibiotics are considered to be either of narrow or wide spectrum. Narrow-spectrum antibiotics are effective primarily against either gram-positive or gram-negative organisms. Broad-spectrum drugs are effective against a wider range of organisms (Table 9-1).

TABLE 9-1

Antimicrobial Spectrum and Preferred Therapeutic Agents

Microbial Spectrum	Class of Preferred Antimicrobial	Examples
Gram-positive aerobic bacteria	Natural penicillins	Penicillin G, Penicillin VK
	Penicillinase-resistant penicillins	Oxacillin, nafcillin, methicillin, dicloxacillin
	Aminopenicillins	Ampicillin, amoxicillin
	Macrolides	Erythromycin, clarithromycin, azithromycin
	Glycopeptides	Vancomycin, teicoplanin
	Cephalosporins	Cefazolin, cephalothin, cephalexin, cefaclor
	Lincosamides	Clindamycin
	Oxazolidinones	Linezolid
	Streptogramins	Quinupristin/dalfopristin
	Topicals	Bacitracin, mupirocin
Gram-negative aerobic bacteria	Aminoglycosides	Gentamicin, tobramycin, amikacin
	Extended-spectrum penicillins	Azlocillin, mezlocillin, piperacillin
	Antipseudomonal penicillins	Carbenicillin, ticarcillin
	Monobactams	Aztreonam
	Carbapenems	Imipenem, meropenem
	Cephalosporins	Ceftazidime
	Sulfonamides	Trimethoprim-sulfamethoxazole
Broad-spectrum antibacterial	Third/fourth-generation cephalosporins	Cefotaxime, ceftriazone, cefepime, cefdinir, ceftibuten, cefpodoxime
	β-lactam + β-lactamase inhibitor combinations	Ampicillin + sulbactam
		Amoxicillin + clavulanate
		Ticarcillin + clavulanate
		Piperacillin + tazobactam
	Quinolones	Ciprofloxacin, ofloxacin, sparfloxacin, norfloxacin
	Carbapenems	Imipenem + cilastin, ertapenem
	Tetracyclines	Tetracycline
Anaerobic bacteria	Penicillins	Penicillin G
	Cephalosporins	Cefotetan, cefoxitin
	Carbapenems	Imipenem + cilastin, ertapenem
	Lincosamides	Clindamycin
	Chloramphenicol	Chloramphenicol
	Metronidazole	Metronidazole
Fungal infections	Polyenes	Amphotericin B
	Azoles	Fluconazole, itraconazole, voriconazole
	Echinocandins	Caspofungin
	Topical antifungal agents	Nystatin, clotrimazole, miconazole, tolnaftate
Viral infections	Antiherpesvirus agents	Acyclovir, ganciclovir, foscarnet, famciclovir
	Topical antiherpes agents	Trifluridine, idoxuridine

Considerable overlap in effectiveness can exist with the broad-spectrum drugs. Efficacy against a particular microorganism is ideally determined by testing the susceptibility of the actual causative pathogen (obtained by culture) to specific antibiotics. Unfortunately, culture and susceptibility results may take 24 hours to several days and would delay initiation of antimicrobial therapy. This requires that a best guess be made for specific clinical situations as to which pathogen is most likely the causative agent and which antibiotic is usually most effective against it. This antibiotic, or combination of antibiotics, is used until culture and sensitivity results are available. Dental and periodontal infections are most commonly caused by bacteria that normally colonize the mouth, throat, and upper alimentary canal, for example, aerobic and anaerobic streptococci, *Micrococcus* species, anaerobic gram-negative bacteria (*Bacteroides, Fusobacterium,* and *Veillonella* species), and occasionally staphylococci or spirochetes.[3] Many of these organisms are sensitive to penicillins; hence penicillins remain the single most useful class of antibiotics for dental and periodontal infections. Occasionally, dental infections are caused by aerobic gram-negative bacteria, *Actinomyces,* or fungi. In these cases, other antimicrobials are needed for optimal therapy.

Convenient tables listing antimicrobial treatment recommended for various medical and dental clinical syndromes and sites of infection are published and updated periodically. *Nelson's Pocket Book of Pediatric Antimicrobial Therapy*[2] and the *Sanford Guide to Antimicrobial Therapy*[6] are two publications containing such guidelines. Data from local clinical microbiology laboratories can be consulted for information on local antibiotic susceptibility patterns of common pathogens.

Mode of Action

Antimicrobials may also be categorized according to their mode or site of action.[8] Common modes of action for antimicrobial agents are described in Box 9-1 and as follows: (1) inhibition of synthesis of the bacterial cell wall, a structure required for bacterial survival; (2) inhibition of protein synthesis, occurring at one of several possible steps; (3) interference with folic acid metabolism, thereby inhibiting bacterial growth; (4) interference with cell membrane permeability; (5) inhibition of nucleic acid synthesis; (6) inhibition of bacterial topoisomerase enzymes; and (7) inhibition of cytochrome P-450 sterol. By these mechanisms of action, the antimicrobial agents produce toxic effects that selectively interfere with the life cycle of the microbial agent while minimizing significant alterations in the cells of the human host.

Box 9-1 Antimicrobials

Mode of Action

Inhibition of Cell Wall Synthesis

Penicillins
Cephalosporins
Monobactams
Carbapenems
Glycopeptides
Echinocandins

Inhibition of Protein Synthesis

Bind 50S Ribosome

Macrolides
Chloramphenicol
Lincosamides
Oxazolidinones
Streptogramins

Bind 30S Ribosome

Aminoglycosides
Tetracyclines

Antimetabolites

Sulfonamides

Alteration of Cell Membrane Permeability

Polymyxins
Clotrimazole (antifungal)
Polyene antifungals

Inhibition of Nucleic Acid Synthesis

Rifampin
Griseofulvin
Nucleoside antivirals

Topoisomerase Inhibitors

Nalidixic acid
Quinolones

Inhibition of Cytochrome Sterol

Azoles (antifungal)

Bactericidal Versus Bacteriostatic Antibiotics

Antibiotics may also be classified as bactericidal or bacteriostatic. Bactericidal antibiotics actually kill the microorganisms, whereas bacteriostatic antimicrobials inhibit bacterial growth or multiplication and depend on the normal host defense mechanisms (immune system) to eliminate the microorganism. The same antibiotic may be bactericidal for some pathogens but bacteriostatic for others, or the activity may be concentration dependent. Bactericidal agents are preferable in most situations. Bacteriostatic agents should be avoided if possible in immunocompromised patients, because a compromised immune system may be unable to facilitate clearance of the offending microorganisms. Box 9-2 lists the agents in these categories.

Box 9-2 Bactericidal and Bacteriostatic Antibiotics

Bactericidal

Penicillins
Cephalosporins
Glycopeptides
Carbapenems
Monobactams
Aminoglycosides
Quinolones

Bacteriostatic

Macrolides
Tetracyclines
Chloramphenicol
Sulfonamides
Lincosamides
Rifampin
Oxazolidinones
Streptogramins

Antibiotic Resistance

Bacterial resistance to antibiotics is one of the most significant challenges in the management of infectious diseases. It has been exacerbated by widespread indiscriminate use of antibiotics in veterinary, medical, and dental applications.

Current issues in bacterial resistance include increasing resistance of staphylococci to penicillinase-resistant penicillins (e.g., methicillin, oxacillin), resistance of pneumococci to penicillins by alteration of bacterial penicillin-binding proteins, resistance of enterococci to glycopeptide antibiotics (i.e., vancomycin), and multidrug resistance among gram-negative bacteria due to bacterial modifying enzymes and extended-spectrum β-lactamases. The oral flora causing dental and periodontal infections may be affected by the growing problem of antibiotic resistance (Table 9-2).

TABLE 9-2
Mechanisms of Bacterial Resistance

Antibiotic Class	Common Mechanisms of Resistance
Penicillin	Hydrolysis by bacterial β-lactamases, altered bacterial binding proteins
Cephalosporins	Hydrolysis by extended-spectrum β-lactamases, cephalosporinases
Macrolides	Alteration of target sites, active efflux pump
Aminoglycosides	Alteration in uptake, modification by bacterial enzymes
Glycopeptides	Modification of bacterial cell wall precursors, with decreased binding
Trimethoprim-sulfamethoxazole	Resistant bacterial enzymes in folate pathway

The development of resistant bacterial strains may be minimized by consistently using an appropriate antibiotic dosage for an adequate period of time. For gram-negative infections, especially *Pseudomonas* infections, or infections with enterococci, treatment with combinations of antibiotics (e.g., a β-lactam and aminoglycoside) may help to prevent the emergence of resistant strains. Antibiotic combinations may also be necessary for infections with mixed types of bacteria. When planning combination drug therapy, it is important to select antibacterial agents that have synergistic or additive activity. Use of drugs that are antagonistic in combination may result in suboptimal clinical outcomes and an increased likelihood of the emergence of resistant strains.[7]

In most university-related clinical settings, the use of antibiotics is increasingly scrutinized by formulary committees and antibiotic stewardship programs. Multiple guidelines have been developed to provide recommendations for the appropriate use, and discourage inappropriate use, of antibiotics in various clinical situations. Hopefully, such efforts will promote an increase in the rational and appropriate use of antibiotics to minimize the spread of bacterial resistance.

Antibiotic Agents

The antibiotic agents that are used most commonly in pediatric dentistry include penicillins, clindamycin, macrolides, and cephalosporins.

Penicillins

In 1928, Sir Alexander Fleming discovered that penicillin mold lysed gram-positive microorganisms. This observation did not gain clinical usefulness until the 1940s, when the antibiotic era began. The penicillins are a group of antibiotics that differ in their pharmacologic properties. They are primarily active against gram-positive aerobic and anaerobic bacteria, but their spectrums of coverage can vary. As a group, they are the most allergenic antibiotics, and all exhibit cross-allergenicity.

Penicillin G

Penicillin G was the prototype of this group of antibiotic agents and continues to be the drug of choice for many infections. Its coverage is limited primarily to gram-positive organisms and selective gram-negative cocci. Penicillin G has two primary unfortunate properties. First, it is poorly absorbed orally, owing to its destruction by gastric acid, so that it is best given by the intramuscular or intravenous route. Second, it is readily destroyed by penicillinase-producing microorganisms. Semisynthetic penicillins have been developed to expand coverage and to overcome some of these disadvantages.

Penicillin V

The primary advantage of penicillin V is that it is stable at gastric pH, allowing for much improved absorption when it is administered orally. Its spectrum of coverage is the same as for penicillin G except it is slightly less effective against *Neisseria gonorrhoeae* and some anaerobes. However, it is also inactivated by penicillinase. Penicillin V is the primary oral antibiotic used to manage dental infections.

Ampicillin and Amoxicillin

Ampicillin has a broader spectrum of coverage than penicillin G or V, covering more gram-negative organisms, including some strains of *Escherichia coli, Haemophilus influenzae,* and *Salmonella.* It is, however, less effective against some gram-positive organisms. Although ampicillin is absorbed better orally than penicillin G, significant degradation occurs in the gut. Diarrhea or gastrointestinal upset is common, and 3% to 10% of children develop a maculopapular rash after receiving ampicillin. Amoxicillin has the same spectrum of coverage as ampicillin, but it is absorbed better orally and causes less diarrhea. Despite the usefulness of these drugs in pediatrics, they are not indicated over penicillin G or penicillin V for management of dental infection. Development of resistance to these agents, especially by *H. influenzae,* is becoming increasingly problematic.

Penicillinase-Resistant Penicillins

Most strains of staphylococci produce an enzyme, penicillinase, which destroys penicillins, resulting in drug resistance. Several penicillins have been developed that are resistant to destruction by penicillinase, including oxacillin, methicillin, nafcillin, cloxacillin, and dicloxacillin. These drugs should be reserved for infections involving penicillinase-producing staphylococci and are not indicated in common dental infections.

Clindamycin

Clindamycin has continued to gain favor as a useful antibiotic in the management of dental infections. It possesses good activity against most gram-positive bacteria as well as most anaerobic bacterial species associated with oral infections. The development of resistance to clindamycin has not been as common as resistance to the macrolides and other classes of antibiotics. Gastrointestinal upset, including diarrhea associated with *Clostridium difficile* toxin, is occasionally associated with this drug. However, the spectrum of activity, as well as the availability of oral and intravenous formulations, has made clindamycin a good option for management of oral infections.

Macrolides: Erythromycin, Azithromycin, and Clarithromycin

Erythromycin is a macrolide antibiotic that was introduced in 1952. Its spectrum of coverage is similar to that of penicillin, with the addition of some penicillinase-producing staphylococci, chlamydiae, *Legionella,* mycoplasma, and others. It is well absorbed orally. However, the free-base form is unstable at gastric pH, so it is administered with an enteric coating or in a salt form (stearate or estolate). Gastrointestinal upset in the form of diarrhea is a major disadvantage of erythromycin. Azithromycin and clarithromycin are structural derivatives of erythromycin that possess a broader spectrum of activity and improved bioavailability. The improved tolerability, specifically with less gastrointestinal upset, has resulted in greater use of these two agents compared with erythromycin. Macrolides are usually bacteriostatic rather than bactericidal. In addition, increasing resistance to macrolides has been a concern and presents another drawback to the routine use of these agents.

Cephalosporins

The cephalosporins are a varied group of bactericidal antibiotics that are chemically related to penicillin. They are broad spectrum in coverage and are divided into five "generations" by coverage. Many cephalosporins are similar to penicillins in their activity against gram-positive organisms (except *Streptococcus Enterococcus faecalis*) and are resistant to penicillinase. First-generation cephalosporins have limited activity against gram-negative enterobacteria, but the newer drugs have increasing activity against these agents. The cephalosporins exhibit some cross-sensitivity in patients who are allergic to penicillin. The oral cephalosporins include cephalexin, cefadroxil, cefaclor, and multiple other agents. They have fewer adverse effects than penicillins and are less bitter tasting when given orally. The cephalosporins are effective against oral pathogens, but they generally have less anaerobic activity than penicillins and at best have similar activity against aerobic oral floral. Therefore cephalosporins generally offer no advantage over penicillins for most dental infections and are usually more expensive. Cephalosporins should be reserved for severe infections involving gram-negative organisms or mixed infections.

Summary

Most dental and periodontal bacterial infections are caused by gram-positive aerobes, facultative streptococci, and, occasionally, staphylococci. Other occasional pathogens include anaerobic gram-negative organisms such as *Bacteroides, Veillonella, Fusobacterium,* gram-negative aerobes, and diphtheroids. Penicillins, clindamycin, and perhaps azithromycin are considered good choices for initial empirical therapy. Owing to the bactericidal action and narrow spectrum of activity, penicillin V (oral) or penicillin G (intramuscular) is often recommended as the primary drug of choice for dental and periodontal infections. Resistance to antibiotic agents presents an increasing threat to effective management of bacterial infections. Current editions of publications such as the *Drug Information Handbook for Dentistry*[4] and the *American Academy of Pediatric Dentistry Reference Manual*[1] can be consulted for updated recommendations on optimal therapy of infections in the oral cavity.

Antibiotic Prophylaxis

Endocarditis Prophylaxis

Bacterial endocarditis is a microbial infection of the endocardium (inner layer of the cardiac muscle). Certain patients with congenital heart disease or artificial heart valves are believed to be at high risk for developing this condition if a procedure or manipulation causes a transient bacteremia. The blood-borne bacteria may lodge on the abnormal endocardium or heart valves and cause serious endocardial infection. Recommended prophylactic antibiotic regimens are based on in vitro studies, clinical experience, animal models, and assessment of the bacteria common to a particular site and those most commonly identified with endocarditis.[9]

In 2007, an ad hoc writing group appointed by the American Heart Association for their expertise in prevention and treatment of infective endocarditis published updated recommendations regarding antibiotic prophylaxis of bacterial endocarditis.[3] The cardiac conditions for which antibiotic prophylaxis is recommended to prevent bacterial endocarditis are listed in Box 9-3. Antibiotic prophylaxis is recommended for *all* dental procedures that involved manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, in at-risk patients. Simple orthodontic adjustments that are unlikely to cause

bleeding and spontaneous shedding of deciduous teeth are thought not to present a significant risk of endocarditis; therefore prophylaxis is not recommended in these situations.

■ Box 9-3

Cardiac Conditions Associated with Endocarditis

Endocarditis Prophylaxis Recommended

Prosthetic cardiac valves or prosthetic material used for cardiac valve repair

Previous infective endocarditis

Congenital heart disease

- Unrepaired cyanotic congenital heart disease (including palliative shunts and conduits)
- Completely repaired congenital heart defect with prosthetic material or device (whether placed by surgery or by catheter intervention) during the first 6 months after the procedure
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or device

Cardiac transplantation recipients who develop cardiac valvulopathy

Endocarditis Prophylaxis Not Recommended

Isolated secundum atrial septal defect

Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 months)

Previous coronary artery bypass grafting

Mitral valve prolapse, with or without valvar regurgitation

Physiologic, functional, or innocent heart murmurs

Previous Kawasaki disease without valvar dysfunction

Previous rheumatic fever without valvar dysfunction

Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

Hypertrophic cardiomyopathy

Adapted from Wilson W, Taubert KA, Gewitz M et al: Prevention of infective endocarditis, *Circulation* 116:1736–1754, 2007.

Bacterial endocarditis after dental manipulations is most commonly caused by α-hemolytic streptococci. Therefore prophylaxis is specifically directed against these organisms. Gingivitis, periodontitis, and periapical infections can be the source of a bacteremia. Excellent oral hygiene and maintenance of dental health are important to reduce the potential for bacterial seeding in the bloodstream of at-risk patients.

The dental procedures for which antibiotic prophylaxis is, and is not, recommended are listed in Box 9-4. The antibiotic prophylaxis regimens for dental or respiratory treatment or procedures are described in Table 9-3.

■ Box 9-4 Dental Procedures and Endocarditis Prophylaxis

Endocarditis Prophylaxis Recommended	Endocarditis Prophylaxis Not Recommended
Dental extractions	Restorative dentistry† (operative and prosthodontic) with or without retraction cord‡
Periodontal procedures including surgery, scaling and root planing, probing, and recall maintenance	Local anesthetic injections (nonintraligamentary)
Dental implant placement and reimplantation of avulsed teeth	Intracanal endodontic treatment; post placement and buildup
Endodontic (root canal) instrumentation or surgery only beyond the apex	Placement of rubber dams
Subgingival placement of antibiotic fibers or strips	Postoperative suture removal
Initial placement of orthodontic bands but not brackets	Placement of removable prosthodontic or orthodontic appliances
Intraligamentary local anesthetic injections	Taking of oral impressions
Prophylactic cleaning of teeth or implants where bleeding is anticipated	Fluoride treatments
	Taking of oral radiographs
	Orthodontic appliance adjustment
	Shedding of primary teeth

†This includes restoration of decayed teeth (filling cavities) and replacement of missing teeth.

‡Clinical judgment may indicate antibiotic use in selected circumstances that may create significant bleeding.

■ TABLE 9-3

Prophylaxis Regimens for Dental, Oral, Respiratory Tract, or Esophageal Procedures

Situation	Agent	Regimen*
Oral	Amoxicillin	Adults: 2 g; children: 50 mg/kg orally 1 hr before
Unable to take oral medications	Ampicillin *or* Cefazolin or Ceftriaxone	Adults: 2 g IM or IV; children: 50 mg/kg IM or IV Adults: 1 g IM or IV; children: 50 mg/kg IM or IV
Allergic to penicillin or ampicillin oral	Clindamycin *or* Cephalexin† *or* Azithromycin or clarithromycin	Adults: 600 mg; children: 20 mg/kg orally Adults: 2 g; children: 50 mg/kg orally Adults: 500 mg; children: 15 mg/kg orally
Allergic to penicillin or ampicillin and unable to take oral medications	Clindamycin *or* Cefazolin† *or* Ceftriaxone	Adults: 600 mg IM or IV; children: 20 mg/kg IV or IM Adults: 1 g IM or IV; children: 50 mg/kg IM or IV

*Single dose 30-60 minutes before procedure. Total children's dose should not exceed adult dose.

†Cephalosporins should not be used in persons with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins.

Adapted from Wilson W, Taubert KA, Gewitz M et al: Prevention of infective endocarditis, *Circulation* 116:1736–1754, 2007.

Additional guidelines have also been provided, including those listed in Box 9-5.

■ Box 9-5 Additional Guidelines for Antibiotic Prophylaxis

1. In the case of delayed healing or of a procedure that involves infected tissue, additional doses of antibiotics may be needed.
2. Amoxicillin is the preferred oral antibiotic because it is better absorbed from the gastrointestinal tract and provides higher and more sustained serum levels.
3. If a patient is taking amoxicillin on a long-term basis for some reason (e.g., rheumatic fever prevention), a different

class of antibiotic, such as oral clindamycin, azithromycin, clarithromycin, or one of the other parenteral regimens, should be used for antibiotic therapy.
4. If a high-risk patient (e.g., a patient with a prosthetic valve) has maintained a "high level" of oral health, oral antibiotic prophylaxis may be used for simple dental procedures rather than the parenteral regimen. However, some physicians may still prefer parenteral antibiotic administration for these high-risk patients. The patient's physician should be consulted when planning dental care for high-risk individuals. Clindamycin phosphate is recommended for parenteral administration in individuals known to be allergic to amoxicillin or ampicillin.

Prophylaxis for Other High-Risk Patients

Children with a compromised immune system may be at increased risk of developing focal or systemic infection following transient bacteremia associated with dental procedures. Therefore antibiotic prophylaxis may be considered for patients with significant primary or acquired immune deficiency. Bacteremia in children with any form of indwelling hardware, including vascular shunt, ventricular shunt, central venous line, various orthopedic devices, and the like, may also provide a source of infection for the hardware. In addition to consulting current guidelines regarding prophylaxis, consulting with the child's physician is recommended for optimizing patient treatment.

Antifungal Agents

Candida species, and especially *Candida albicans*, can often be found on the healthy mucous membranes of the body. However, multiplication of the *Candida* species and invasion of the tissues rarely occur unless the immunity of the host is compromised. Candidiasis is common in children receiving oncology treatment, particularly during periods of severe immunosuppression and neutropenia. The extensive use of broad-spectrum antibiotics, steroids, chemotherapy-associated immunosuppression, and inadequate oral hygiene and nutrition alter the balance of the oral microflora and place children at risk for candidiasis.

The clinical management of oral candidiasis in children is similar to that in adults and consists principally of antifungal agents. Suspected *Candida* infections should be confirmed by culture and/or potassium hydroxide smear before initiating prompt and aggressive therapy in immunosuppressed patients. The medication and route of administration is determined by the severity of the infection. Oral and esophageal candidiasis is usually treated with topical suspensions or troches of antifungal agents, such as nystatin or clotrimazole. Several antifungal agents formulated for oral topical use contain sweeteners, which can promote caries if used for an extended period. Daily use of topical fluorides is recommended to reduce the caries potential.

Nystatin

Nystatin is the most common topical agent used for treatment of oral candidiasis in children. The drug is available as an oral suspension (100,000 U/ml) and a tablet (500,000 U). A dose of 800,000 to 2.4 million units per day in four divided doses for at least 48 hours after perioral symptoms disappear.

Clotrimazole

Clotrimazole is a fungicidal agent that is available only as a 10-mg troche for intraoral application. However, an oral suspension can be compounded from the vaginal tablets. The recommended dose is one troche dissolved slowly in the mouth five times a day for 14 days to achieve maximal effectiveness. The child must be of age and maturity to comprehend and follow instructions to use the troche vehicle. Liver toxicity has been reported in patients using clotrimazole, and clinical studies have not been conducted to establish the safety of the drug for children younger than 3 years.

Fluconazole and Other Azoles

Systemic antifungal therapy in oral candidiasis is usually reserved for children either not tolerating or failing topical treatment or those at risk of systemic infection. Fluconazole is a commonly used agent in these circumstances. The drug is available for oral or intravenous administration, and it achieves high levels in saliva. It has proved efficacious for the management of a variety of candidal species, although some species are resistant to the drug. Fluconazole is generally preferred over ketoconazole, which has a greater risk of associated hepatotoxicity. Itraconazole, posaconazole, and voriconazole are additional azoles with excellent activity against *Candida* and may eventually have a role in the management of infections associated with more resistant strains.

Amphotericin B and Caspofungin

Amphotericin has long been the primary drug of choice for systemic management of severe fungal infections. Efficacy of amphotericin has been demonstrated for infection caused by the majority of fungal pathogens. Adverse effects such as nephrotoxicity, metabolic disorders, and fever with administration are not uncommon. Caspofungin, a newer fungal cell wall inhibitor, has a narrower spectrum of activity but demonstrated efficacy in severe disease caused by certain fungal pathogens. This agent will likely have an increasing role in systemic antifungal therapy.

Antiviral Agents

Primary herpetic gingivostomatitis is the most commonly recognized manifestation of the herpes simplex virus type 1 (HSV-1). It is an acute illness often with concomitant fever, malaise, irritability, cervical lymphadenopathy, together with the characteristic oral and perioral ulcerative lesions involving the gingiva and mucous membranes of the mouth. HSV gingivostomatitis in healthy children resolves spontaneously within 10 to 14 days and requires only supportive therapy. However, primary or reactivation of latent HSV infections in immunosuppressed patients requires more aggressive therapy. Ulcerated herpetic lesions may be a portal for bacteria and fungi, resulting in serious disseminated infection.

Antiherpetic Agents

Effective agents for the management of HSV infection in immunocompromised patients include acyclovir, valacyclovir, and famciclovir. Drugs often used for management of cytomegalovirus are also efficacious for HSV but exhibit more toxicity. The route of therapy (e.g., oral versus intravenous acyclovir) is dependent on the host and site and severity of disease. Prophylactic therapy may be considered in patients seropositive for the HSV and at high risk for reactivation. Acyclovir is not indicated for patients at low risk for clinically significant disease or reactivation. Adverse effects on the central nervous system or kidneys may uncommonly be seen with intravenous acyclovir, whereas oral administration may be associated with headache, nausea, or neutropenia (the latter in infants). The likelihood of developing resistance to acyclovir is low but is more likely in immunocompromised hosts.

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