Premedication for Dental Procedures, 2nd Edition
Mark Donaldson

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By
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3 clock hours will be awarded upon successful completion of this course.
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Mark Donaldson has disclosed that he has no significant financial or other conflicts of interest pertaining to this course book.

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Toni M. Roucka has disclosed that she has no significant financial or other conflicts of interest pertaining to this course book.

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INTRODUCTION

COURSE OBJECTIVES

After completing this course, the learner will be able to:

1. Discuss the pathogens most commonly associated with orofacial infections.
2. Explain how antibiotics are classified.
3. Differentiate among specific antibiotics.
4. Explain the appropriate timing of antibiotics.
5. Explain indications for antibiotic use in premedicating for dental procedures.

Oral healthcare professionals (OHCPs) are routinely involved with the selection and prescription of antibiotics to either therapeutically manage an existing orofacial infection or prevent an infection prophylactically. In fact, there are only three major prophylactic uses of antimicrobial agents in the practice of dentistry: prophylaxis in patients at risk for development of infective endocarditis (IE), prophylaxis in orthopedic patients, and prophylaxis in patients with compromised immune systems caused by certain diseases or medications (Goodchild & Donaldson, 2009). OHCPs are required to stay current with published guidelines because they represent standards of care; however, the evidence in support of these recommendations can be controversial. Regardless of these issues, the appropriate prescribing of antibiotics when indicated, although challenging for both dental and medical professionals alike, is vitally important in the overall management of patients.

The practice of overprescribing antibiotics in certain medical and dental situations, as well as development of antibiotic-resistant strains of bacteria, could be greatly abated with closer attention to basic prescription-writing principles. The purpose of this course is to review the pharmacology of antimicrobial agents and present current guidelines and therapeutic choices to optimize antibiotic prescribing practices. Because the goal of antibiotic therapy is to ensure selection of the right drug at the right time and at the right dose, for the right patient and the right procedure, the information presented in this course should be considered essential knowledge for all OHCPs, including those just starting their careers and those needing a midcareer refresher.

After completing this intermediate-level course, the participant will be able to discuss the differences among antibiotics typically prescribed for orofacial infections. In the case of special patient populations such as orthopedic, cardiac, and immunosuppressed patients, the selection and timing of appropriate prophylactic antibiotics will be made clear. The principles learned will also be directly applicable to the appropriate selection of antimicrobial therapy for the
pregnant or breast-feeding patient. These principles will also assist in recognizing those patients with a significant allergic history and determining how to best, and safely, treat them. This course is specifically designed for all members of the dental healthcare team – dentists, dental hygienists, and dental assistants.
PREMEDICATION FOR DENTAL PROCEDURES

PATHOGENS MOST COMMONLY ASSOCIATED WITH OROFACIAL INFECTIONS

Most cases of oral pathology seen by oral health professionals (OHCPs) involve inflammatory conditions associated with pain, and a significant percentage of dental pain originates from either acute or chronic infections, which necessitate operative intervention followed by analgesic therapy, rather than antibiotics alone. Clinical situations that require antibiotic therapy are limited and typically include oral infections accompanied by elevated body temperature and evidence of systemic spread such as lymphadenopathy and trismus (muscle spasm that locks the mouth in a closed position). In general, antibiotics are required for either treatment of an existing infection or prophylaxis for a potential infection depending on the immunocompetency of the patient. Figure 1 outlines the stepwise guidelines for prescribing antibiotics.

Treatment of an existing infection with systemic antimicrobials should be employed only in acute conditions for which OHCPs know the most commonly associated pathogens. Correctly diagnosing the infecting microorganism(s) and choosing the most targeted and effective antibiotic will help ensure clinical

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Figure 1: Stepwise Guidelines in Considering the Prescribing of an Antibiotic

- **Does the patient have an active infection?**
  - **NO**
  - **YES**
    - **Is the patient at risk for infection due to a cardiac, orthopedic, or immuno-compromised situation?**
      - **NO**
        - Antibiotics not indicated
      - **YES**
        - **Does the patient still require antibiotic coverage after oral examination and definitive treatment?**
          - **NO**
          - **YES**
            - **Did the patient’s signs/symptoms improve within 72 hours of beginning antibiotics?**
              - **NO**
              - **YES**
                - **Continue antibiotic for at least 48 hours after symptoms have resolved**

See appropriate section on antibiotic prophylaxis

effectiveness. Although bacteriological assessment and identification ideally should be completed before treatment is begun, an acutely ill patient cannot have antibiotic treatment delayed while clinicians wait for the results of bacteriological testing, which can take 48 hours or more. For this reason, the choice of antibiotic must be based empirically on the OHCP’s knowledge of the common causative microorganisms and the antibiotic(s) to which these organisms are typically susceptible (Goodchild & Donaldson, 2009). Drawing from the seminal work of Paster and colleagues (2001), Table 1 outlines the predominant cultivable flora associated with orofacial infections. The most common pathogens associated with orofacial infections, according to their prevalence, are

- **Streptococcus**;
- **Actinomyces, Eubacterium, and Leptotrichia**;
- **Fusobacterium, Bacteroides, Prevotella, and Porphyromonas**;
- **Peptostreptococcus**;
- **Lactobacillus**; and
- **Veillonella**.

(Han & Wang, 2013)

Therefore, in treating an acute orofacial infection or providing prophylaxis for a potential infection, it is reasonable to select an antibiotic to which the probable organisms (gram-positive aerobes and intraoral anaerobes) are susceptible.

| TABLE 1: PREDOMINANT CULTIVABLE FLORA FROM VARIOUS SITES OF THE ORAL CAVITY |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Group** | **Predominant Organism** | **Prevalence** |
|          |                              | **Tongue** | **Saliva** | **Gingival Crevise** | **Dental Plaque** |
| **Anaerobes** |                              |          |          |                   |                   |
| Gram + cocci | Peptostreptococcus | Rare | ++ | + | ++ |
| Gram – cocci | Veillonella | ++ | ++ | ++ | + |
| Gram + rods | Actinomyces, Eubacterium, Lactobacillus, Leptotrichia | + | Rare | +++ | ++ |
| Gram – rods | Fusobacterium, Bacteroides, Prevotella, Porphyromonas | + | Rare | ++ | ++ |
| **Aerobes** |                              |          |          |                   |                   |
| Gram + cocci | Streptococcus | ++++ | +++++ | +++ | +++ |
| Gram – cocci | Moraxella | Rare | Rare | Rare | Rare |
| Gram + rods | Lactobacillus, Corynebacterium | ++ | ++ | ++ | +++ |
| Gram – rods | Enterobacteriaceae | Rare | Rare | Rare | Rare |

*Note that gram-negative aerobes are the least commonly encountered organisms in the normal oral flora.

CLASSIFICATION OF ANTIBIOTICS

Antibiotics can be classified in many ways. The most familiar classification is based on their chemical structure. One of the most common clinical approaches is to consider an antibiotic's mechanism of action, which will determine the types of microbes against which the particular antibiotic may be most effective. This characteristic is sometimes called an antibiotic's spectrum of activity. Another classification system for antibiotics depends on how effective they are at halting microbial reproduction and ultimately eliminating an infection (i.e., bacteriostatic versus bactericidal). Finally, a third approach is to consider how they may be most effective at eradicating an infection based on their ability to work via concentration-dependent or time-dependent killing. Each of these classifications will be discussed in the following section.

Spectrum of Activity

Antibiotics are often classified according to their spectrum of activity. Narrow-spectrum antibiotics typically cover either gram-positive or gram-negative bacteria, but they are usually not effective against both, whereas extended-spectrum antibiotics are effective against a variety of both gram-positive and gram-negative bacteria. Broad-spectrum antibiotics are effective against both gram-positive and gram-negative bacteria and, often, other bacteria such as anaerobes as well. Table 2 categorizes the spectrum of activity for the most common antibiotics used to treat orofacial infections (Soares et al., 2012). Table 3 lists typical prescriptions for the antibiotics most commonly employed in treating orofacial infections.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Narrow</th>
<th>Extended</th>
<th>Broad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lincosamides (clindamycin)</td>
<td>Cephalosporins (cephadrine, cepalexin, cefadroxil, cefaclor, cefuroxime)</td>
<td>Augmentin (amoxicillin plus clavulanate)</td>
<td></td>
</tr>
<tr>
<td>Macrolides (erythromycin, clarithromycin, azithromycin)</td>
<td>Extended-Spectrum Penicillins (ampicillin, amoxicillin)</td>
<td>Sulfonamides and trimethoprim (Bactrim, Septra, Co-Trimoxazole)</td>
<td></td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)</td>
<td>Tetracyclines (tetracycline, doxycycline)</td>
<td></td>
</tr>
<tr>
<td>Penicillin G, V</td>
<td>β-Lactamase-resistant penicillins (cloxacillin, dicloxacillin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Name (Brand Name)</td>
<td>Available Formulations</td>
<td>Usual Adult Dosage</td>
<td>Usual Pediatric Dosage</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------</td>
<td>-------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Amoxicillin (Amoxil, generics)</td>
<td>250, 500, 875 mg tablets 250, 500 mg capsules 125, 250 mg chewable tablets 125 mg/5 mL oral solution 200 mg/5 mL oral solution 250 mg/5 mL oral solution 400 mg/5 mL oral solution</td>
<td>250-500 mg q8h or 500-875 mg q12h</td>
<td>20-90 mg/kg/d divided q8-12h</td>
</tr>
<tr>
<td>Azithromycin (Zithromax, generics)</td>
<td>250, 500 mg tablets 100 mg/5 mL oral solution 200 mg/5 mL oral solution</td>
<td>500 mg day 1, then 250 mg once daily x 4 days</td>
<td>5-10 mg/kg once daily x 4 days</td>
</tr>
<tr>
<td>Cephalexin (Keflex, generics)</td>
<td>250, 500, 750 mg capsules</td>
<td>250 mg-1 g q6-12h</td>
<td>25-100 mg/kg/d divided q6-8h</td>
</tr>
<tr>
<td>Ciprofloxacin (Cipro, generics)</td>
<td>100, 250, 500, 750 mg tablets 250 mg/5 mL oral solution 500 mg/5 mL oral solution</td>
<td>250-750 mg q12h</td>
<td>10-20 mg/kg q12h</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin, generics)</td>
<td>250, 500 mg tablets 500 mg extended-release (XL) tablets 250 mg/5 mL oral solution 500 mg/5 mL oral solution</td>
<td>250-500 mg q12h 1,000 mg once a day</td>
<td>7.5 mg/kg q12h XL tablets are not for pediatric use</td>
</tr>
<tr>
<td>Generic Name (Brand Name)</td>
<td>Available Formulations</td>
<td>Usual Adult Dosage</td>
<td>Usual Pediatric Dosage</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td><strong>Clindamycin</strong> (Cleocin, generics)</td>
<td>75, 150, 300 mg capsules 75 mg/5 mL oral solution</td>
<td>150-450 mg q6-8h</td>
<td>10 mg/kg q8h</td>
</tr>
<tr>
<td><strong>Doxycycline</strong> (Vibramycin, generics)</td>
<td>50, 75, 100, 150 mg capsules 25 mg/5 mL oral solution 50 mg/5 mL oral syrup</td>
<td>100 mg q12h</td>
<td>2-4 mg/kg/d divided q12h</td>
</tr>
<tr>
<td><strong>Erythromycin</strong> (multiple generics)</td>
<td>250 mg capsules 200 mg/5 mL oral solution 400 mg/5 mL oral solution</td>
<td>250-500 mg q6h</td>
<td>7.5-12.5 mg/kg q6h</td>
</tr>
</tbody>
</table>
Antibiotics in Treating Orofacial Infections (3 of 3)

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Available Formulations</th>
<th>Usual Adult Dosage</th>
<th>Usual Pediatric Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin (Levaquin, generics)</td>
<td>250, 500, 750 mg tablets 125 mg/5 mL oral solution</td>
<td>250-750 mg once daily</td>
<td>Not recommended for routine use in children or adolescents &lt;18 years old.</td>
<td>Take at least 2 hours before, or 6 hours after, the dose of a multivitamin that contains polyvalent cations (i.e., calcium, iron, magnesium, selenium, zinc).</td>
</tr>
<tr>
<td>Metronidazole (Flagyl, generics)</td>
<td>250, 500 mg tablets 375 mg capsules 750 mg ER (extended-release) tablets</td>
<td>500 mg q6-12h</td>
<td>30 mg/kg/d divided q6h</td>
<td>Key adverse event(s) related to dental treatment: unusual/metallic taste, glossitis, stomatitis, xerostomia (normal salivary flow resumes upon discontinuation), and furry tongue. Do not take with alcohol as a disulfiram-like reaction may occur.</td>
</tr>
<tr>
<td>Moxifloxacin (Avelox)</td>
<td>400 mg tablets</td>
<td>400 mg once daily</td>
<td>Not recommended for routine use in children or adolescents &lt;18 years old.</td>
<td>Take at least 2 hours before, or 6 hours after, the dose of a multivitamin that contains polyvalent cations (i.e., calcium, iron, magnesium, selenium, zinc).</td>
</tr>
<tr>
<td>Penicillin (Pen VK, generics)</td>
<td>250, 500 mg tablets 125 mg/5 mL oral solution 250 mg/5 mL oral solution</td>
<td>250-500 mg q6-8h</td>
<td>25-50 mg/kg/day divided q6-8h</td>
<td>Also available as a suspension that may not be equivalent on an mg/mg basis to the tablets.</td>
</tr>
<tr>
<td>Tetracycline (multiple generics)</td>
<td>250, 500 mg tablets 250, 500 mg capsules</td>
<td>250-500 mg q6h</td>
<td>25-50 mg/kg/d divided q6h</td>
<td>Tetracyclines are not recommended for use during pregnancy or in children ≤8 years of age since they have been reported to cause enamel hypoplasia and permanent teeth discoloration. Take at least 2 hours before, or 6 hours after, the dose of a multivitamin that contains polyvalent cations (i.e., calcium, iron, magnesium, selenium, zinc).</td>
</tr>
</tbody>
</table>


Bacteriostatic Versus Bactericidal

Another classification system for antibiotics depends on whether they are bacteriostatic or bactericidal. Bacteriostatic antibiotics prevent the growth of bacteria, keeping them in a stationary phase of growth. Bactericidal antibiotics kill bacteria regardless of where they may be in their growth cycle. In reality, there are not two distinct categories of antimicrobial agents (one that exclusively kills bacteria and another that only inhibits bacterial growth). Some bactericidal antibiotics may fail to kill every organism within 24 hours (if the inoculum is large), and some bacteriostatic antibiotics will kill some bacteria within 24 hours (often more than 90% to 99% of the inoculum), but not enough (more than 99.9%) to be
called **bactericidal**. These in vitro microbiological determinations are based on laboratory findings in which bactericidal or bacteriostatic antibiotics can be influenced by test duration, growth conditions, extent of reduction in bacterial numbers, and bacterial density (Pankey & Sabath, 2004). The more pertinent in vivo or clinical definitions are more arbitrary, and most antibiotics may be better classified as being potentially both bactericidal and bacteriostatic because bacteriostatic agents are often bactericidal against susceptible organisms at high concentrations.

There are certainly clinical situations in which bactericidal action is considered necessary over bacteriostatic treatments – for example, in cases of endocarditis, meningitis, osteomyelitis, and neutropenia. In general, OHCPs should remember that bacteriostatic and bactericidal antibiotics are equivalent for the treatment of most infectious diseases in immunocompetent patients, whereas bactericidal agents are preferred when patient immune defenses are impaired or if the infection is particularly deep-seated (Pankey & Sabath, 2004). Table 4 summarizes which antibiotics most commonly prescribed for the treatment of orofacial infections fall into which category.

**Concentration-Dependent Versus Time-Dependent Killing**

Often, antibiotic failures are the result of inappropriately prescribing bacteriostatic antibiotics for the wrong indication or at the wrong (too low) dose. In the case of bactericidal agents, antibiotic failures primarily result from inappropriate prescribing, typically a mismatch between an antibiotic's spectrum of activity and the pathogens intended to be eradicated (in other words, the wrong drug for the right bug). Bactericidal antibiotics exert either **concentration-dependent killing** (e.g., the fluoroquinolones and metronidazole) or **time-dependent killing** (e.g., all β-lactam antibiotics: penicillins, cephalosporins, and amoxicillin/clavulanic acid). Concentration-dependent killing occurs with antibiotics that can achieve high concentrations at the infection site (greater than 10 times the minimum inhibitory concentration of the infecting organism). Their rate and extent of microbial killing increase with increasing drug concentration, and these antibiotics can typically be administered just once or twice a day. Antibiotics that exert time-dependent killing must be given more frequently because their bactericidal activity does not rely so much on the size of the dose administered as on how long the drug concentration is maintained above the minimum bactericidal concentration. This time requirement explains why even today penicillin G and penicillin VK cannot be given as one large dose, once a day, but require redosing every 6 to 8 hours to be effective.

**THE DRUGS**

Even though many antibiotics are available, in the case of orofacial infections, the prudent prescriber needs to focus on only a handful of pertinent drug classes – penicillins, cephalosporins, tetracyclines, macrolides, fluoroquinolones, and nitroimidazoles – based on their spectrum of activity and the anticipated pathogens. Table 2 describes the spectrum of activity for these most commonly used antibiotics in treating orofacial infections and the most common individually prescribed drugs within each drug class. Table 4 further categorizes these drug classes and the individual specific drugs in each category as either bactericidal or bacteriostatic in their action.
Penicillins

Penicillin, which is the original drug within the broader penicillin drug class, is a narrow-spectrum antibiotic because it mainly targets gram-positive aerobic and facultative bacteria (Staphylococcus spp., Streptococcus spp., Listeria), most anaerobes (with certain exceptions, such as Bacteroides), and spirochetes (Brachyspiraceae, Leptospiraceae, and Spirochaetaceae). Penicillin, which is still considered the drug of choice for streptococcal infections, causes bacterial lysis by interfering with the synthesis of peptidoglycan, which is necessary for the formation of the bacterial cell wall. Penicillin G, from which this class of drugs derives its name, is the progenitor and is considered the gold standard. It is typically given parenterally (typically intravenously), bypassing the alimentary tract, because it is unstable in the highly acidic environment of the stomach. Penicillin VK (penicillin V potassium) is the orally stable formulation of penicillin G. The “V” comes from the Latin word vesco/vescar, meaning “eat.”

Penicillins are sometimes referred to as β-lactam antibiotics because their chemical structure contains a β-lactam ring. The β-lactam antibiotics inhibit the formation of peptidoglycan cross-links in the bacterial cell wall, causing bacterial death via inhibition of cell wall synthesis.

Cephalosporins

Cephalosporins such as cephalaxin are also called β-lactam antibiotics, based on their similar chemical structure. Their mechanism of action, therefore, is analogous to that of the penicillins. Although all β-lactam antibiotics kill bacteria by the same mechanism of action, it is their individual chemical structures that determine their spectrum of activity. Ampicillin and amoxicillin are extended-spectrum penicillins, but they can be combined with other antibiotics to create a broad-spectrum antibiotic. An example is amoxicillin combined with the β-lactamase inhibitor clavulanate. (Some bacteria have developed the enzyme β-lactamase to help them resist the effects of β-lactam antibiotics.)

Nitroimidazoles, Clindamycin, and the Macrolides
Narrow-spectrum antibiotics include metronidazole, a nitroimidazole antibiotic; clindamycin, a lincosamide antibiotic; and the macrolide antibiotics erythromycin, clarithromycin, and azithromycin. Metronidazole is active only against obligate anaerobic bacteria such as Bacteroides, Campylobacter, Clostridium, Fusobacterium, Peptococcus, Peptostreptococcus, Prevotella, and Veillonella, in which the drug interferes with nucleic acid synthesis, causing microbial death. Clindamycin and the macrolide antibiotics inhibit bacterial protein synthesis by affecting the function of 30S or 50S ribosomal subunits, leading to bacterial cell death. Clindamycin has better activity against most strains of Staphylococcus aureus and is more active against gram-positive and gram-negative anaerobes; however, the macrolides are more effective against Streptococcus pneumoniae, as well as other typical (Haemophilus influenzae and Moraxella catarrhalis) and atypical (Legionella pneumophila, Mycoplasma pneumonia, and Chlamydophila pneumoniae) upper respiratory tract pathogens (Bennett et al., 2014).

**Fluoroquinolones and Tetracyclines**

The fluoroquinolones (e.g., ciprofloxacin, levofloxacin, and moxifloxacin) are extended-spectrum antibiotics that act by interfering with bacterial nucleic acid synthesis. These agents are not typically used as first-line agents for orofacial infections, although ciprofloxacin may have a role in treating susceptible species of Pseudomonas (Bennett et al., 2014). The fluoroquinolones and broad-spectrum agents such as sulfamethoxazole/trimethoprim and the tetracyclines (tetracycline, doxycycline, and minocycline) can cause collateral damage such as superinfection by resistant pathogens or selection for antibiotic resistance, because these agents are less targeted in their microbial selection compared with the narrow-spectrum antibiotics. Low-dose tetracyclines such as subantibiotic doses of doxycycline have been used to treat periodontal disease; however, this activity is based on anti-inflammatory properties of the medication rather than on antibacterial properties (Bretz, 2012).

**APPROPRIATE TIMING OF ANTIBIOTICS**

Antibiotic timing is an important consideration in determining both when to begin an antibiotic and when to discontinue an antibiotic. The consensus with respect to prophylaxis is that antibiotics should be started 30 to 60 minutes before the start of the dental procedure in those patients at risk for infective endocarditis (IE; Gould et al., 2006; Roberts, Ramsdale, Lucas, & British Cardiac Society Working Group, 2004; Wilson et al., 2007). In 1990, Berney and Francioli evaluated the efficacy of single-dose amoxicillin in rats with catheter-induced aortic vegetations either 30 minutes before or 30 to 240 minutes after bacterial challenge. These vegetations were introduced intravenously with various inoculum sizes of tolerant Streptococcus sanguis or Streptococcus faecalis. This work verified the effectiveness of the antibiotic as being protective even when given up to 2 hours postoperatively, underscoring the importance of considering empiric preoperative antibiotics the gold standard for IE prophylaxis (Berney and Francioli, 1990; Beck, 2013).

If a patient is already receiving chronic therapy with an antibiotic that is also recommended for IE prophylaxis for a dental procedure, the clinician should select an antibiotic from a different class (Meyer, 2015; Wilson et al., 2007). For example, patients who take an oral penicillin for secondary prevention of rheumatic fever are likely to harbor viridans group streptococci that are relatively
resistant to penicillin and amoxicillin. Clindamycin, azithromycin, or clarithromycin is appropriate for IE prophylaxis for a dental procedure in such cases, but only in the class of patients for which prophylaxis is indicated.

In patients already undergoing parenteral antibiotic therapy for IE, that therapy should be continued and the timing of the dosage adjusted to be administered 30 to 60 minutes before the dental procedure (Meyer, 2015; Wilson et al., 2007).

INDICATIONS FOR USE OF ANTIBIOTICS AS PREMEDICATION FOR DENTAL PROCEDURES

Although oral bacterial pathogens may be responsible for cases of IE or late-prosthetic joint infections, it is unclear to what extent these infections result from dental office procedures versus bacteremia from routine daily activities such as tooth brushing and chewing food. There is very little evidence demonstrating that dental office procedures cause distant site infections (Skaar, O’Connor, Hodges, & Michalowicz, 2011); therefore, the driving force behind the practice of antibiotic prophylaxis is the improbable, yet possible, devastating impact of a bacteremia-induced infection of a cardiac valve, prosthetic joint, or indwelling medical device such as an implantable defibrillator or pacemaker.

When antibiotics are considered for prophylaxis, the same drugs used to treat orofacial infections are used prophylactically; however, depending on the indication, they may be administered in a slightly different manner – either as a one-time preoperative prophylactic dose, in the case of cardiac and orthopedic patients, or as a routine prescription of several days’ duration for an immunocompromised patient (e.g., a patient with cancer, a patient receiving hemodialysis, or an organ transplant recipient).

Antibiotic Prophylaxis for Cardiac Patients

Endocarditis is a life-threatening disease that involves an infection of the endocardium or the heart valves. It occurs when bacteria in the bloodstream lodge on abnormal heart valves or other damaged heart tissue. Endocarditis usually develops in individuals with underlying structural cardiac defects who develop bacteremia involving organisms likely to cause endocarditis. The following sequence of events is thought to result in IE:

1. Nonbacterial thrombotic endocarditis (NBTE) forms on the surface of a cardiac valve with endothelial damage.

2. Transient bacteremia is caused by viridans group streptococci and other oral microflora, often in association with dental procedures or routine daily activities.

3. Bacteria in the bloodstream adhere to the site of the NBTE. In animal models of experimental endocarditis, numerous bacterial surface components in streptococci, staphylococci, and enterococci have been shown to act as adhesins.

4. Sequestered microorganisms proliferate, multiplying as rapidly as in broth cultures.

(Wilson et al., 2007).
Sequestered high-bacterial-density infections such as those observed with endocarditis are often difficult to eradicate. Problems with antibiotic penetration, the so-called\textit{ inoculum effect}, and stationary-phase organisms make these infections difficult to treat. For example, vancomycin, penicillin, and other β-lactams interact with and inhibit synthesis of the cell wall in the bacterial cytoplasmic membrane. However, when the number of bacteria is overwhelming and the core of the infection lacks nutrients (placing organisms in stationary phase), these agents are unable to reach their target site on a growing cell wall (Tan et al., 2012). More than 90% of microorganisms in mature left- or right-sided valvular vegetations are metabolically inactive and are therefore less responsive to the bactericidal effects of antibiotics (Durack, 1972).

In summary, the development of IE results from the complex interaction between the bloodstream pathogen with matrix molecules and platelets at sites of endocardial cell damage (Wilson et al., 2007). In addition, the host’s immune response to the infecting microorganism is responsible for many of the clinical manifestations of IE. Without treatment, endocarditis has a lethality approaching 100%. Moreover, despite improvements in outcome brought about by advances in antimicrobial therapy and the enhanced ability to diagnose and treat complications, substantial morbidity and mortality (rates of 5% to 76%) still result from endocarditis infections (Wilson et al., 2007). Consequently, prevention of IE has been a major goal of OHCPs.

Antibiotic prophylaxis for IE in dentistry has been a subject of debate and controversy since 1955 when the American Heart Association (AHA) began developing recommendations for prophylactic antibiotics to prevent IE. These recommendations have set the standard of care for decades; however, there remains confusion regarding which patients are at risk for distant site infections and which dental procedures and bacteria may be of greatest concern. Further complicating the issue is the ongoing emergence of resistant bacterial pathogens created by the indiscriminate use of antibiotics, the costs to the healthcare system, the small risk for fatal allergic reactions, and the reported low compliance rate on the part of physicians and OHCPs with respect to these guidelines. Clearly what drives prophylactic antibiotic prescribing in dentistry is a combination of the AHA guidelines, long-standing dogma, practice habits, and medicolegal considerations.

The latest AHA recommendations for the dental management of patients with cardiac abnormalities were published in 2007 (Wilson et al., 2007). These guidelines define patients at risk (Table 5) and the appropriate antibiotic regimen for which they should receive prophylaxis (Table 6). The dental procedures most likely to put patients at risk include all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. In contrast, the procedures and events that do not require prophylaxis are

- routine anesthetic injections through noninfected tissue (although intraligamentary and intraosseous anesthetic injections do require antibiotic prophylaxis),
- dental radiographs,
- placement of removable prosthodontic or orthodontic appliances,
- adjustment of orthodontic appliances,
- placement of orthodontic brackets,
• shedding of deciduous teeth, and
• bleeding from trauma to the lips or oral mucosa.

The primary reasons for revision of the IE prophylaxis guidelines follow:

• IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, gastrointestinal tract, or genitourinary tract procedure.

• Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, gastrointestinal tract, or genitourinary tract procedure.

• The risk for antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.

• Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure in reducing the risk for IE.

(Wilson et al., 2007)

### TABLE 5: CARDIAC CONDITIONS* FOR WHICH ANTIBiotic PROPHYLAXIS IS RECOMMENDED

| 1. Cardiac transplantation recipients who develop cardiac valvulopathy |
| 2. Prosthetic cardiac valve |
| 3. Previous infective endocarditis |
| 4. Three specific types of congenital heart disease (CHD); ** |
| i. Unrepaired cyanotic CHD, including palliative shunts and conduits |
| ii. 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*** |
| iii. Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization) |

*These cardiac conditions are associated with the highest risk of adverse outcomes from endocarditis.

**Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

***Prophylaxis is recommended because endotheialization of prosthetic material occurs within 6 months after the procedure.

The AHA does not recommend secondary antibiotic prophylaxis for patients with nonvalvular cardiovascular devices (i.e., a pacemaker implantation) who are undergoing dental, respiratory, gastrointestinal, or genitourinary procedures (Baddour et al., 2011). When there is any doubt concerning whether antibiotic prophylaxis is necessary for any given patient, it is always best to consult with the patient’s physician before initiating any invasive dental treatment.

**Antibiotic Prophylaxis for Orthopedic Patients**

Guidelines published in 2013 by the American Dental Association and American Academy of Orthopedic Surgeons for the dental management of orthopedic patients fell short in clearly delineating the specific subpopulations that may be at highest risk or the dental procedures that may carry a higher risk for bacteremia as outlined in the earlier 2003 guidelines (Tables 7 and 8; American Dental Association & American Academy of Orthopedic Surgeons, 2003; Rethman et al., 2013). These 2013 guidelines stated, “Treatments and procedures applicable to the individual patient rely on mutual communication between patient, physician, dentist, and other healthcare practitioners” (p. 3). The guidelines proposed a shared decision-making tool designed to help the patient who has undergone an orthopedic procedure determine, with the assistance of his or her dentist or physician, whether taking an antibiotic before a dental procedure is prudent or necessary (Jevsevar, 2013). The final recommendations state that the clinician might consider discontinuing the practice of routinely

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**TABLE 6: AMERICAN HEART ASSOCIATION ANTIMICROBIAL REGIMENS FOR ENDOCARDITIS PROPHYLAXIS**

<table>
<thead>
<tr>
<th>Usual oral drug and dose</th>
<th>If patient is unable to take oral medication</th>
<th>If patient is allergic to penicillin but able to tolerate oral therapy</th>
<th>If patient is allergic to penicillin and unable to tolerate oral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin 2 gm</td>
<td>Ampicillin 2 g IM or IV* or cefazolin or ceftriaxone 1 g IM or IV</td>
<td>Cefalexin**† 2 g or clindamycin 600 mg or azithromycin 500 mg or clarithromycin 500 mg</td>
<td>Cefazolin 1 g IM or IV or ceftriaxone 1 g IM or IV or clindamycin</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin 50 mg/kg</td>
<td>Ampicillin 50 mg/kg IM or IV* or cefazolin 50 mg/kg IM or IV or ceftriaxone 50 mg/kg IM or IV</td>
<td>Cefalexin**† 50 mg/kg or clindamycin 20 mg/kg or azithromycin 15 mg/kg or clarithromycin 15 mg/kg</td>
<td>Cefazolin 50 mg/kg IM or IV or ceftriaxone† 50 mg/kg IM or IV or clindamycin 20 mg/kg IM or IV</td>
</tr>
</tbody>
</table>

*IM – intramuscular; IV – intravenous.
**Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of aspiration, angioedema, or anaphylaxis with penicillins.
††Single dose 30 to 60 minutes prior to procedure.

prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants who are undergoing dental procedures because the evidence in support of this practice is limited (Rethman et al., 2013).

### TABLE 7: PATIENTS AT POTENTIAL INCREASED RISK OF EXPERIENCING HEMATOGEOUS TOTAL JOINT INFECTION

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Condition Placing Patient at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients during the first two years</td>
<td>Not applicable</td>
</tr>
<tr>
<td>following joint replacement</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised or</td>
<td>Inflammatory arthropathies such as rheumatoid arthritis,</td>
</tr>
<tr>
<td>immune suppressed patients</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>Drug- or radiation-induced immunosuppression</td>
<td></td>
</tr>
<tr>
<td>Patients with comorbidities*</td>
<td>Previous prosthetic joint injections</td>
</tr>
<tr>
<td></td>
<td>Malnourishment</td>
</tr>
<tr>
<td></td>
<td>Hemophilia</td>
</tr>
<tr>
<td></td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>Insulin-dependent (type 1) diabetes</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
</tr>
</tbody>
</table>

*Conditions shown for patients in this category are examples only; there may be additional conditions that place such patients at risk of experiencing hematogenous total joint infection.


### TABLE 8: DENTAL PROCEDURES THAT MAY CARRY A HIGHER BACTEREMIC RISK

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Dental Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher incidence*</td>
<td><strong>Dental extractions</strong>&lt;br&gt;Periodontal procedures, including surgery, subgingival placement of antibiotic fibers/straps, scaling and root planing, probing, recall maintenance&lt;br&gt;Dental implant placement and re plantation of avulsed teeth&lt;br&gt;Endodontic (root canal) instrumentation or surgery only beyond the apex&lt;br&gt;Initial placement of orthodontic bands but not brackets&lt;br&gt;Intraligamentary and intraosseous local anesthetic injections&lt;br&gt;Prophylactic cleaning of teeth or implants where bleeding is anticipated</td>
</tr>
<tr>
<td>Lower incidence**</td>
<td><strong>Restorative dentistry (operative and prosthodontic) without retraction cord</strong>*&lt;br&gt;Local anesthetic injections (non-intraligamentary and non-intraosseous)&lt;br&gt; Intracanal endodontic treatment; post placement and buildup&lt;br&gt;Placement of rubber dam&lt;br&gt;Postoperative suture removal&lt;br&gt;Placement of removable prosthodontic/orthodontic appliances&lt;br&gt;Taking of oral impressions&lt;br&gt;Fluoride treatments&lt;br&gt;Taking of oral radiographs&lt;br&gt;Orthodontic appliance adjustment</td>
</tr>
</tbody>
</table>

*Prophylaxis should be considered for patients with total joint replacement who meet the criteria in Table 7. No other patients with orthopedic implants should be considered for antibiotic prophylaxis prior to dental treatment/procedure.

**Prophylaxis not indicated, although clinical judgment may indicate antibiotic use in selected circumstances that may create significant bleeding.

***Includes restoration of carious (decayed) or missing teeth.


Given this lack of clear and distinct recommendations in consistently managing these patients, a panel of experts was specifically convened by the American Dental Association Council on Scientific Affairs in 2014. The panel developed the most recent evidence-based clinical practice guideline on the use
of prophylactic antibiotics in patients with prosthetic joints who are undergoing dental procedures (Sollecito et al., 2015). The 2014 panel concluded that, in general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended before dental procedures to prevent prosthetic joint infection. The clinical reasoning for the recommendation includes the following:

- Evidence exists that dental procedures are not associated with prosthetic joint implant infections.
- Evidence exists that antibiotics provided before oral care do not prevent prosthetic joint implant infections.
- Antibiotics can cause harms, including anaphylaxis, antibiotic resistance, and opportunistic infections such as *Clostridium difficile*.
- The benefits of antibiotic prophylaxis may not exceed the harms for most patients.
- The OHCP should consider the individual patient’s circumstances and preferences when deciding whether to prescribe antibiotics before dental procedures (Sollecito et al., 2015).

For patients with a history of complications associated with their joint replacement surgery who are undergoing dental procedures that include gingival manipulation or mucosal incision, the OHCP should consider prophylactic antibiotics only after consultation with the patient and orthopedic surgeon (Rethman et al., 2013). In cases in which antibiotics are deemed necessary, it is most appropriate that the orthopedic surgeon recommend the antibiotic regimen and, when the circumstances make it reasonable, write the prescription. The appropriate antibiotic regimen for which the patient should receive prophylaxis matches the AHA cardiac recommendations previously described in Table 6.

**Antibiotic Prophylaxis for Immunocompromised Patients**

Numerous medical conditions – such as diabetes, cancer, hemodialysis, and organ transplantation – are associated with suppression of the immune system either directly or as a result of treatments involving medications such as insulin, chemotherapy, prednisone, or antirejection medications. A primary concern for an immunocompromised patient is the risk of poor wound healing and systemic involvement from an orofacial infection. Therefore, consideration for appropriate antibiotics to treat an active dental infection is vital to enhance healing of an orofacial infection and to avoid a systemic infection that could lead to a necrotizing fasciitis in the case of a fragile diabetic patient (Camino Junior, Naclerio-Homem, Cabral, & Luz, 2014). In addition to treatment of active infections, prophylactic antibiotics before invasive dental procedures have been suggested for cardiac and orthopedic patients, including patients with numerous medical conditions such as those mentioned above (diabetes, cancer, hemodialysis, and organ transplantation), in which they may not be able to mount an appropriate immune system response.

The use of appropriate antibiotics for the *treatment* of an oral infection is vital, particularly in immunocompromised patients with cancer. The timing of dental treatment is complicated in patients being treated with cytotoxic cancer therapy because the definitive treatment (e.g., endodontic therapy or extraction) should be timed before the onset of chemotherapy-induced neutropenia (low white blood cell count, generally defined as 1,700 or fewer neutrophils per microliter of blood)
or after the white blood cell counts return to an appropriate level (Donaldson, Goodchild, & Wrobel, 2015). The development of an orofacial infection during chemotherapy-induced neutropenia is uncommon, possibly partly because of a decreased inflammatory response from deficient numbers of white blood cells. Use of antibiotics and a delay of definitive dental treatment until white blood cell counts increase is a rational treatment plan for patients with cancer and the associated chemotherapy-associated neutropenia.

Topical antibiotics such as chlorhexidine 0.12% solution (the patient swishes and expectorates 10 mL twice daily) are appropriate for localized gingival inflammation during neutropenia. The use of broad-spectrum antibiotics is also appropriate for the treatment of active orofacial infections in patients with neutropenia, although ideally the antibiotic regimen should be based on appropriate susceptibility of bacterial isolates as identified through the culturing of draining pus, if available. Outpatient cancer patients or patients without severe neutropenia may respond well to oral antibiotics such as penicillin VK or amoxicillin, clindamycin, azithromycin, tetracycline, or amoxicillin with the β-lactamase inhibitor clavulanate (Donaldson et al., 2015).

The use of antibiotics for prophylaxis before an invasive dental procedure has been suggested for patients with a variety of other immunocompromised conditions, including patients with cancer and the associated neutropenia, patients with end-stage renal disease treated with hemodialysis, patients who have undergone organ transplantation, and patients with poorly controlled diabetes. The evidence to support the practice of routine antibiotic prophylaxis before invasive dental procedures in these populations continues to evolve, however, and decisions to prescribe are often based on medicolegal concerns rather than literary evidence, which remains poor (Lockhart, Hanson, Ristic, Menezes, & Baddour, 2013; Seymour, 2013). For these reasons, dental prescribers need to understand that the negative consequences of repeated antibiotic use, such as increased antibiotic resistance, costs, and potential allergic reactions, must always be weighed against the perceived benefit of infection prevention, and that they should therefore practice only evidence-based dentistry.

**Patients With Cancer and Associated Neutropenia**

Patients with cancer may be neutropenic from their chemotherapy treatment or their underlying cancer. Despite the lack of substantial scientific evidence, the National Cancer Institute recommends that the AHA-recommended regimen for prophylactic antibiotics be employed for patients with indwelling venous access lines and an absolute neutrophil count between 1,000 and 2,000 mcL before any invasive dental procedure (National Cancer Institute, n.d.). Further consideration should be given to a more aggressive antibiotic therapy in the presence of infection, which the prudent OHCP should discuss with the patient's oncologist.

**Patients on Hemodialysis**

Vascular access sites used for patients receiving hemodialysis are at increased risk of becoming infected (Bennett et al., 2014). Treatment may require hospitalization, systemic antibiotics, and possible shunt removal. The most common infectious agents are gram-positive bacteria, followed by gram-negative and polymicrobial bacteria. Orofacial bacteria are infrequently the source of vascular access site infections (Bennett et al., 2014). IE can result from a vascular access infection, with up to 25% of these patients requiring heart valve
replacement (Kiefer et al., 2011). The need for antibiotic prophylaxis for the prevention of shunt infections is controversial, and currently there are no specific guidelines. However, one review suggests that prophylaxis is warranted at all times for recipients of hemodialysis arteriovenous shunts (after implantation/revision) when dental procedures capable of inducing high-level bacteremia are planned (Guay, 2012). Still, the AHA guidelines do not discuss whether antibiotic prophylaxis is recommended for all hemodialysis shunts, and no well-designed clinical trials have been published on these patients to provide further guidance. Therefore, the best strategy is to consult with the patient’s nephrologist to determine whether the physician considers antibiotics to be necessary.

**Patients With Organ Transplants**

Patients are routinely prescribed immunosuppressive medications to prevent rejection of transplanted organs. These medications may include long-term prednisone, mycophenolate, cyclosporine, azathioprine, or others, which function by moderating the T-cell response of the patient to prevent graft rejection. Unfortunately, an increased risk for infection is one negative side effect of these immunosuppressive medications. Even given this information, the use of antibiotic prophylaxis for invasive dental procedures in these patients is controversial. Discussion with the patient’s transplant physician regarding the use of antibiotics is recommended. It is reasonable to use prophylactic antibiotics in the first few months after transplantation, when the patient has the highest risk for infection and acute graft rejection (Bennett et al., 2014). Dosing of antibiotics recommended by the AHA for prevention of IE, listed earlier in Table 6, is also reasonable.

**The Dental Patient Who Is Pregnant or Breast-Feeding**

The dental patient who is pregnant represents two significant challenges to the dental professional. First, although most dental procedures are elective and can be postponed until after the baby is delivered, dental treatment for a pregnant woman who has oral pain, advanced disease, or infection should not be delayed. Second, not all women of childbearing age know that they may be pregnant, and when selecting and prescribing a medication for any woman of childbearing age, the clinician should always consider the possibility of the patient conceiving while she is still taking the medication. Balancing the risks of the drug’s potential adverse effects (usually on the fetus) with the benefit (usually to the mother) of treating the disease is the goal when prescribing medication to a patient who is pregnant (Donaldson & Goodchild, 2012).

The U.S. Food and Drug Administration (FDA) traditionally has used a letter system to classify drugs on the basis of the level of risk they pose to the fetus to determine the risks associated with the use of drugs in pregnancy (Table 9; U.S. Food and Drug Administration, n.d.). Although the letter categories are being replaced according to the FDA Pregnancy and Lactation Labeling Final Rule, medications that have displayed the letters in their package inserts will in many cases retain them for the next few years (FDA, 2015). In the lettered system, drugs in categories A and B are considered safe for use, whereas drugs in category C may be used only if the benefits outweigh the risks. Drugs in category D should be avoided except in certain exceptional circumstances (i.e., a condition
that threatens the mother’s life). The use of category X drugs in pregnant women is contraindicated.

| TABLE 9: U.S. FOOD AND DRUG ADMINISTRATION PREGNANCY RISK FACTOR DEFINITIONS |
|---------------------------------|------------------------------------------------------------------|
| Category | Definition |
| A | The results of controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote. |
| B | Either the results of animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women OR the results of animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of risk in later trimesters. |
| C | Either the results of studies in animals have revealed adverse effects (teratogenic, embryocidal, or other) on the fetus and there are no controlled studies in women OR results of studies in women and animals are not available; drug should be given only if the potential benefit justifies the potential risk to the fetus. |
| D | There is positive evidence of human fetal risk, but the benefits of use in pregnant women may be acceptable despite the risk (for example, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). |
| X | Results of studies in animals or humans have demonstrated fetal abnormalities or evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit; use of the drug is contraindicated in women who are or may become pregnant. |


The letter system is being replaced because the FDA deemed it too simplistic for dealing with the complexities of pregnancy and lactation. Furthermore, although information concerning “males and females of reproductive potential” did appear on labeling, its location on the label was inconsistent. The Final Rule is meant to fix that problem as well as to make the pregnancy and lactation instructions more helpful for prescribers (FDA, 2015).

Some antibiotics can cross the placenta and deposit in the embryo’s teeth and bones (sites of active calcification). Members of the tetracycline drug class (tetracycline, minocycline, and doxycycline) exhibit this effect: As little as 1 g/day of tetracycline taken during the third trimester of pregnancy produces yellow staining of both the primary and secondary teeth in the developing fetus (Lochary, Lockhart, & Williams, 1998; Tredwin, Scully, & Bagan-Sebastian, 2005). Therefore, the FDA letter system classifies all of the tetracyclines as category D drugs. Topical minocycline oral powder, indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis, bears a black box warning to avoid use of the medication during pregnancy and in nursing women. While all tetracyclines, including doxycycline, are excreted in breast milk, short-term use by lactating women is not necessarily contraindicated, but the pharmaceutical manufacturers do emphasize that the effects of prolonged exposure to doxycycline in breast milk are unknown (Pfizer, 2016a, 2016b). The LactMed database (2016c, 2016g), which is supported by
the American Academy of Pediatrics as a reliable source of drug safety for breast-feeding infants (Sachs and American Academy of Pediatrics Committee on Drugs, 2013), states that

although a number of reviews have stated that tetracycline is contraindicated during breastfeeding because of possible staining of infants’ dental enamel or bone deposition of tetracyclines, a close examination of available literature indicates that there is not likely to be harm in short-term use of tetracycline during lactation because milk levels are low and absorption by the infant is inhibited by the calcium in breastmilk. Short-term use of tetracycline is acceptable in nursing mothers. As a theoretical precaution, avoid prolonged or repeat courses during nursing. (LactMed, 2016g)

This statement applies to tetracycline, minocycline, and doxycycline, as well as to other antibiotics not commonly used in dentistry.

Based on results from animal studies, the progenitor manufacturer of clarithromycin has stated that this antibiotic should not be used in pregnant women except in clinical circumstances in which no alternative therapy is appropriate (Abbott Laboratories, n.d.; Andersen et al., 2013). In the traditional lettering system, the FDA classifies clarithromycin as pregnancy category C. Although the LactMed database (2016b) states that low levels of clarithromycin are secreted into breast milk and are safe for the infant, the manufacturer recommends that caution be exercised when administering clarithromycin to breast-feeding women (Abbott Laboratories, n.d.). Other macrolides, such as erythromycin and azithromycin, are also considered compatible with breast-feeding (Arbor Pharmaceuticals, 2012; LactMed, 2016a, 2016d; Pfizer, 2016b). When in doubt, the OHCP should consult with the patient’s family physician or pediatrician before prescribing drugs in the tetracycline family to a nursing mother.

In the FDA’s traditional lettering system, all of the other antibiotics commonly used in dentistry (amoxicillin, azithromycin, cephalexin, clindamycin, erythromycin, metronidazole, and penicillin) are classified as pregnancy risk category B. All of these antibiotics are also compatible with breast-feeding, except metronidazole, which is an in vitro mutagen. Clinicians should recommend that the patient stop breast-feeding for 12 to 24 hours (pump and discard) after taking the single-dose therapy of metronidazole, to minimize pediatric exposure (LactMed, 2016f). Erythromycin is also incompatible with breast-feeding as it concentrates in human milk, and there are published cases of pyloric stenosis being induced in the breast-fed newborn (Lund et al., 2014; Sorensen, 2003).

Although antifungal agents are not commonly prescribed by dentists, the appearance of oral thrush may at times necessitate the use of these drugs. In the case of oral thrush, oral nystatin (FDA pregnancy category C) is the safest agent to use both in pregnant patients and in patients who are breast-feeding because absorption after oral use is poor, greatly reducing the risk to the fetus or the breast-fed newborn (Czeizel, Kazy, & Puhó, 2003). The other common indication for antifungals is for the female dental patient who develops a vaginal yeast infection secondary to one of the previously listed antibiotic treatments. Vaginal candidiasis (moniliasis or thrush) is a common and distressing infection for many women, and it is even more common during pregnancy (Mashburn, 2012). The Cochrane Pregnancy and Childbirth Group’s Trials Register has reviewed the Cochrane Central Register of Controlled Trials (CENTRAL/CCTR) and concluded that topical treatments with either terconazole or clotrimazole not only are
preferred in pregnant women, given the decreased systemic absorption, but also appear to be more effective than oral therapies such as nystatin for treating symptomatic vaginal candidiasis during pregnancy (Soong & Einarson, 2009). Patients may self-medicate because many of these preparations are available over the counter. However, the Cochrane Review on this topic suggests that pregnant women may require a longer treatment course compared with the courses more commonly used in women who are not pregnant; longer courses (7 days) cured more than 90% of women, whereas standard (4-day) courses cured only about half of the affected women (Soong & Einarson, 2009). Newer oral agents, such as fluconazole, provide for equally efficacious, short-course treatment (from a single 150-mg dose up to a once-daily, 3-day course) and may be preferred for compliance reasons. The traditional FDA listing places fluconazole in pregnancy category C for the single-dose vaginal candidiasis regimen and in category D for all other indications. Regardless, the investigators in a 2008 trial in Denmark who examined the maternal use of fluconazole and risk for congenital malformations found no overall increased risk for congenital malformations after fetal exposure to short-course treatment with fluconazole in early pregnancy (Nørgaard et al., 2008). The American Academy of Pediatrics considers fluconazole safe to use while breast-feeding as levels excreted into breast milk are lower than the neonatal dosage normally employed (LactMed, 2016e).

Table 10 summarizes the recommendations for antibiotic use in the dental patient who is pregnant or breast-feeding. Notably, patients who are pregnant should receive the full adult dose of medication and for the usual length of treatment. Serious infections should be treated aggressively. Penicillins and cephalosporins are considered safe, and the use of higher-dose regimens (e.g., cephalexin 500 mg three times per day rather than 250 mg three times per day) should be elected because these β-lactam antibiotics are cleared from the system more quickly as a result of the increase in glomerular filtration rate in pregnancy. In the patient who is breast-feeding, antibiotics may cause altered bowel flora, causing diarrhea in the infant. If the infant develops a fever, the clinician should consider whether it could be the result of drug exposure from maternal antibiotic treatment.
Allergy Status

Many patients report an allergic history to certain antibiotics. Such a history limits the treatment options in managing oral infections. The prudent practitioner should first validate the patient’s allergic status by inquiring into the circumstances and the allergic response reported by the patient. In every case in which the patient reports a reaction that has affected his or her breathing (e.g., tongue or throat swelled up, acutely compromising the airway) or has required treatment at the hospital, the condition should be considered a true allergy. This is a type of immediate, type I immunoglobulin E (IgE)-mediated anaphylactic reaction, and future exposure to the related medication must be avoided. Some patients, however, will report an intolerance or delayed-type reaction, such as diarrhea, itchiness, or other mild cutaneous reactions. In these patients, re-exposure to the medicine may not necessarily be life-threatening and may in fact be considered if the benefit of treatment outweighs the potential risk of the reaction. However, when any doubt exists, it is always prudent to contact the patient’s physician for consultation.

Penicillin-induced anaphylaxis is uncommon, occurring with an incidence of between 1 and 4 episodes per 10,000 administrations (Macy, 2014). Still, amoxicillin and penicillin were the leading cause of severe antibiotic-induced anaphylaxis in one report, probably because these drugs are so commonly administered (Renaudin, Beaudouin, Ponvert, Demoly, & Moneret-Vautrin, 2013). There is cross-reactivity between the penicillins and cephalosporins (because of the shared β-lactam-containing structure) in patients with a true allergic history. Therefore, a reported allergy to an antibiotic in either drug class would make the prescribing of an antibiotic from the other class a contraindication. The clinician should treat these patients more appropriately, with a macrolide antibiotic (erythromycin, clarithromycin, or azithromycin) or a lincosamide antibiotic such as clindamycin.
Among patients who report penicillin reactions (but do not undergo confirmatory testing), between 0.17% and 8.4% will also react if given a cephalosporin such as cephalaxin (Lee, 2014; Pichichero & Zagursky, 2014). Regardless, given this relatively low rate of cross-reactivity, if a patient reports an intolerance or delayed-type reaction to an antibiotic in a specific drug class, use of an antibiotic from the other class may be possible.

In the atopic patient, it may be valuable to note that the macrolides, the tetracyclines, clindamycin, and metronidazole cause hypersensitivity reactions much less frequently than the penicillins, cephalosporins, sulfonamides, and other classes of antimicrobials (Bennett et al., 2014). Macrolides can cause delayed-onset maculopapular exanthems (a type of widespread rash characterized by flat red areas on the skin covered with small confluent bumps) in about 1% of treated patients, which is close to the rate in placebo-treated patients in many drug studies (Lee, 2014). Anaphylaxis and serious non-IgE-mediated reactions are rare. Patients who have reacted to one macrolide (e.g., erythromycin) in the past may tolerate other macrolides (e.g., clarithromycin or azithromycin; Araújo & Demoly, 2008). Immunoglobulin E-mediated reactions caused by the tetracyclines are rare, with only a few published reports of single patients (Jang et al., 2010; Ogita, Takada, & Kawana, 2011). Allergic reactions to clindamycin are uncommon, although clindamycin is a frequent cause of gastrointestinal side effects and is one of the more common causes of Clostridium difficile colitis (Thornhill et al., 2015). Frequently, patients may report these types of side effects as allergies, although they are not immunological reactions. Hypersensitivity reactions due to metronidazole are rare, with only a small number of case reports in the published literature (Asensio Sánchez et al., 2008; García-Rubio, Martínez-Cócera, Santos Magadán, Rodríguez-Jiménez, & Vázquez-Cortés, 2006).

**SUMMARY**

Antibiotics are employed regularly in dentistry, whether to treat and manage existing oral disease or to prevent an infection prophylactically. There are only three major prophylactic uses of antimicrobial agents in the practice of dentistry: prophylaxis in patients at risk for development of IE (cardiac patients), prophylaxis in orthopedic patients, and prophylaxis in patients with compromised immune systems caused by certain diseases or medications. In prescribing antibiotics, the OHCP must consider the type of infection, the patient’s allergy status, other medications the patient is taking, and other physical conditions that may affect treatment (e.g., pregnancy, immune disorders, cardiac conditions). Some of these factors can be addressed in a straightforward manner. Others, such as allergies, require clinical judgment and can be challenging for both dental and medical professionals alike. This course has reviewed the key factors—those that are vitally important in the overall management of patients—that OHCPs must assess.

In addition, this course has reviewed the current guidelines and regimens for the use of antibiotic prophylaxis before dental procedures for patients with cardiac abnormalities. It also reviewed specific conditions that do not justify prophylactic treatment and addressed the current recommendations for patients with joint replacements. Using the information covered in this course, OHCPs will be able to determine the best treatment and preventive management options for their patients.
The appropriate prescribing of antibiotics when indicated, although challenging for dental and medical professionals alike, is vitally important in the overall management of patients.
EXAM QUESTIONS

PREMEDICATION FOR DENTAL PROCEDURES

This is for your reference only. To complete the exam, login to your account at http://www.westernschools.com

Questions 1–20

Note: Choose the one option that BEST answers each question.

1. Clinical situations that require antibiotic therapy are limited and typically include oral infections accompanied by evidence of systemic spread such as
   a. spontaneous pain.
   b. elevated body temperature.
   c. sensitivity to palpation.
   d. localized swelling.

2. The most common pathogen associated with orofacial infections is
   a. *Actinomyces*.
   b. *Streptococcus*.
   c. *Fusobacterium*.
   d. *Lactobacillus*.

3. Bacteriological testing of a dental infection can take up to
   a. 2 to 4 hours.
   b. 12 to 18 hours.
   c. 24 to 36 hours.
   d. 48 hours or more.

4. Which spectrum of antibiotics is effective against both gram-positive and gram-negative bacteria, as well as other bacteria such as anaerobes?
   a. Narrow
   b. Wide
c. Extended  
d. Broad

5. Antibiotics that prevent the growth of bacteria, keeping them in a stationary phase of growth, are referred to as  
   a. bacteriostatic.  
   b. bactericidal.  
   c. antibistatic.  
   d. antibicidal.

6. Bactericidal antibiotics that exert concentration-dependent killing include  
   a. amoxicillin/clavulanic acid.  
   b. cephalosporin.  
   c. metronidazole.  
   d. penicillin.

7. The antibiotic class of choice for dental management of streptococcal infections is the  
   a. penicillins.  
   b. cephalosporins.  
   c. nitroimidazoles.  
   d. tetracyclines.

8. Penicillin acts by causing bacterial lysis by interfering with the synthesis of peptidoglycan, which is necessary for the formation of the bacterial  
   a. cell wall.  
   b. nucleus.  
   c. proteins.  
   d. RNA.

9. Penicillin G is the progenitor form of penicillin and is typically given  
   a. parenterally.  
   b. enterally.  
   c. by mouth.  
   d. rectally.

10. Metronidazole, a nitroimidazole antibiotic, has a spectrum of activity that is considered
11. Clindamycin and the other macrolide antibiotics work by inhibiting the synthesis of bacterial
   a. RNA.
   b. peptidoglycan cross-links.
   c. cell wall.
   d. protein.

12. Low-dose tetracyclines such as subantibiotic doses of doxycycline have been used to treat
   a. endodontic infections.
   b. candidiasis.
   c. herpes simplex.
   d. periodontal disease.

13. When dealing with patients at risk for infective endocarditis (IE), the consensus with respect to prophylaxis is that antibiotics be started
   a. 30 to 60 minutes before the dental procedure.
   b. 60 to 90 minutes before the dental procedure.
   c. 30 to 60 minutes after the dental procedure.
   d. 60 to 90 minutes after the dental procedure.

14. If a patient is already receiving chronic antibiotic therapy with an antibiotic that is also recommended for IE prophylaxis for a dental procedure, the antibiotic selected should be
   a. from the same class.
   b. from a different class.
   c. of a lower strength.
   d. of a higher strength.

15. The term for a life-threatening infection of the endocardium or the heart valves is
   a. endocarditis.
   b. pericarditis.
   c. myocarditis.
   d. peritonitis.
16. Which of the following dental procedures requires antibiotic prophylaxis?
   a. Routine anesthetic injections through noninfected tissue
   b. Intraligamentary or intraosseous injections
   c. Placement of orthodontic brackets
   d. The taking of dental radiographs

17. Definitive dental treatment such as endodontic therapy or extraction should be timed before chemotherapy-induced
   a. pancytopenia.
   b. anemia.
   c. thrombocytopenia.
   d. neutropenia.

18. Among the antibiotics that can cross the placenta and deposit in the embryo’s teeth and bones is
   a. metronidazole.
   b. penicillin.
   c. tetracycline.
   d. amoxicillin.

19. Clinicians should recommend that the patient stop breast-feeding for 12 to 24 hours (pump and discard) after taking the single-dose therapy of
   a. amoxicillin.
   b. tetracycline.
   c. metronidazole.
   d. clindamycin.

20. Although allergic reactions to clindamycin are uncommon, this antibiotic frequently causes
   a. maculopapular exanthems.
   b. respiratory issues.
   c. delayed-type reactions.
   d. gastrointestinal side effects.

This concludes the final examination. To complete the exam, login to your account at http://www.westernschools.com
RESOURCES

WEB SITES

American Dental Association: Oral Health Topics
This ADA website concerns topics such as dental materials, medical conditions with oral manifestations, medications with potential impact on dental treatment, infection control, and so on. Refer to the Oral Health Topics section of ADA.org to find clinically relevant, evidence-based summaries related to scientific concerns that may come up for you.

Infectious Diseases Society of America
“The Infectious Diseases Society of America (IDSA) represents physicians, scientists, and other healthcare professionals who specialize in infectious diseases. IDSA's purpose is to improve the health of individuals, communities, and society by promoting excellence in patient care, education, research, public health, and prevention relating to infectious diseases.”
http://www.idsociety.org

LactMed
Maintained by the National Institutes of Health’s Toxicology Data Network (TOXNET), “the LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency. ... LactMed is updated monthly.”

Motherisk
Motherisk counselors talk to hundreds of women and their healthcare providers each day, providing guidance, support, and peace of mind, as well as supporting research in this field.
http://www.motherisk.org

SafeFetus
SafeFetus.com is a website set up for pregnant mothers and their physicians and pharmacists to protect the baby, whether during pregnancy or during lactation, from any harmful effects of medication (whether prescribed or over the counter). The site also provides information on maternal exposures to physical agents, infectious agents,
and diseases, and how they may affect the unborn child. SafeFetus.com is maintained by physicians and pharmacists in an attempt to produce a worldwide database.
http://www.safefetus.com

TEXTBOOKS


REFERENCES


